JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

Data-driven HIV prevention: the HIV prevention cascade and beyond

Guest Editors: James R Hargreaves, Judith D Auerbach, Bernadette Hensen, Simon Gregson
Supplement Editor: Marlène Bras, Elisa de Castro Alvarez

Volume 23, Supplement 3, June 2020
WILEY

Acknowledgements

The Guest Editors - James R Hargreaves, Judith D Auerbach, Bernadette Hensen and Simon Gregson - would like to thank all of the authors and reviewers who responded to our request for contributions, prepared manuscripts, and participated in the rigorous review and selection process. We wish that many more studies could have been included, but hope that this effort to strengthen HIV prevention programmes through innovation in the collection, analysis and interpretation of data will continue. We also thank the editors and staff of the *Journal of the International AIDS Society* for thoughtful guidance, rigorous support, and encouragement throughout the process.

Support

This supplement was funded by the Bill & Melinda Gates Foundation. The content is solely the responsibility of the authors and does not necessarily represent the views of the funding agency.

Disclaimer

The authors of the papers are responsible for the views expressed in these articles and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

Data-driven HIV prevention: the HIV prevention cascade and beyond

Guest Editors: James R Hargreaves, Judith D Auerbach, Bernadette Hensen, Simon Gregson
Supplement Editors: Marlène Bras, Elisa de Castro Alvarez

Contents

Volume 23, Supplement 3
June 2020

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

Hargreaves JR et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25538
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25538/full | https://doi.org/10.1002/jia2.25538

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

EDITORIAL

Strengthening primary HIV prevention: better use of data to improve programmes, develop strategies and evaluate progress

James R Hargreaves[1,§], Judith D Auerbach[2], Bernadette Hensen[3], Saul Johnson[4] and Simon Gregson[5]

[§]**Corresponding author:** James Hargreaves, 15-17 Tavistock Place, London WC1H 9SH, United Kingdom. Tel: +44 207 927 2955. (james.hargreaves@lshtm.ac.uk)

Keywords: HIV prevention; primary prevention; cascades; HIV prevention programmes; data; programme monitoring

Received 7 May 2020; **Accepted** 8 May 2020

It is heartening to learn from recent data in multiple settings that decreasing community viral load through "universal test and treat" programmes is having a significant impact on HIV morbidity, mortality and the rate of new HIV infections in some settings [1-3]. However, focusing only on preventing *transmission* from a person already living with HIV to one who is not, is only half of the equation and will by itself not "end HIV." A crucial focus remains preventing *acquisition* of HIV infection among people at risk. Achieving this requires that we strengthen primary HIV prevention programmes because HIV incidence declines attributable to treatment may be slower than required to meet global goals [4]; treatment as prevention may have less impact where a high proportion of transmission involves those in early stage HIV infection [5]; and, critically, because it is essential that individuals and communities have the autonomy to avoid acquiring HIV if at all possible.

Happily, the range of efficacious tools for primary prevention of HIV infection has increased in recent years. These include condoms, voluntary medical male circumcision, oral pre-exposure prophylaxis (PrEP), clean needles and associated drug use paraphernalia, as well as a range of behaviours, such as information sharing between partners about HIV serostatus, use of antiretroviral therapy (ART), or HIV viral load before making decisions about sex and drug-using activities. However, optimism must be tempered by the fact that, although some tools have been with us for some time, their population impact has been limited by individual, interpersonal, social (including cultural, economic and political) and structural factors.

The aim of a primary HIV prevention programme is to increase the uptake and continued use of efficacious HIV prevention tools and other safe behaviours among those who may be at risk of infection. Achieving this requires strategies that are appropriate, acceptable and reach those in need. Programmers can only know how well they are doing in this regard by collecting and using data in a systematic way. This special issue of *Journal of the International AIDS Society* showcases current thinking on how data can be used to support decision makers in deploying their resources to maximize the impact of primary HIV prevention programmes.

Formulating an HIV prevention strategy includes a range of considerations: whether and how to focus efforts to particular populations versus implementing a general population approach; which prevention tools to offer; and, the extent to which the programme should focus on strengthening motivation for HIV prevention behaviours, improving supply channels, and/or supporting the capacity of individuals to enact HIV avoidance behaviours. Data-informed insights are needed to support these decisions. The data must go beyond an assessment of where and among whom new HIV infections are occurring. Only by understanding the modifiable determinants of risk and barriers to prevention can programmers select, implement, monitor and strengthen the most appropriate interventions and policies.

This is not a new call. More than 10 years ago, "know your epidemic, know your response" was positioned as a "rallying cry" for an intensified HIV prevention response [6]. The need to renew this message periodically reflects the reality that the measurement challenges we face in HIV prevention are formidable, the determinants of HIV risk are multiple, complex and interacting, and the barriers to sustained behaviour change significant. It is clear that interdisciplinary research and data-driven multi-sectoral planning remain critical to strengthening primary HIV prevention. The papers in this special issue reflect the effort, innovation, and challenges faced by those who share this vision today.

In responding to our call for papers on "Data-driven HIV prevention," many (though not all) of the papers attempt to operationalize an HIV prevention cascade. HIV prevention cascades are a promising framework that can be used to generate insights from data in many instances. We were pleased to see the innovation and thought reflected in the papers that provided cascade models: nevertheless, there remains work to do. As Auerbach *et al.* [7] outline, debates about the merits

and pitfalls of HIV prevention cascades are ongoing, but there is general agreement that a standardized programme monitoring tool (like the treatment cascade) would be helpful. As the authors note, emerging consensus identifies the core steps of primary prevention cascade models for programme monitoring and research as first characterizing the priority population at risk, and then tracking motivation, access, uptake and/or effective use of prevention tools among this population. We use this prevention cascade structure to provide a brief overview of the content of this special issue.

Identifying priority populations for whom primary prevention efforts are to be strengthened is the first job for any HIV prevention strategy. Rice *et al*. [8] reflect on a pilot of tests of recent HIV infection in diverse routine HIV testing settings in Kenya and Zimbabwe and consider the potential use of these tests to help focus prevention activities. Virkud *et al*. [9] generate cascades that show the need for HIV prevention to be strengthened among those who visit bars, hotels and guest houses in cross-border areas in East Africa. Sibanda *et al*. [10] show that new HIV infections among pregnant mothers are a critical driver of infant infections in Zimbabwe and highlight the need to strengthen prevention cascades among HIV-negative women.

HIV prevention programmes seek to increase individuals' motivation to undertake behaviours that will protect them and others from HIV infection. [11] The HIV prevention cascade recognizes that the range of relevant behaviours include decisions such as to avoid sex, take PrEP, suggest condom use to a sexual partner, and be circumcised. An individual's behavioural intention is also influenced by perceived social norms. Hill *et al*. [12] present data from one priority population – adolescent girls and young women (AGYW) in Malawi – and carefully examine the relationships between risk perception, "epidemiological" risk, and the motivation of these young women to take PrEP. They conclude that motivation remains lower than optimal and more efforts are needed as PrEP rolls out. Similarly, Ramautarsing *et al*. [13] used programmatic data to document PrEP roll-out among transgender women and men who have sex with men (MSM) in Thailand. They found that the biggest gap in the cascade for both population groups was in demand: many clients who were offered PrEP did not initiate PrEP because they did not perceive themselves to be at risk for HIV acquisition.

When people are motivated to use existing HIV prevention methods, lack of access to them can have population-level impacts on infection rates. The implications of poor access are shown by a modelling exercise of couples' voluntary counselling and testing programmes, which can facilitate prevention choices, in six African countries presented by Wall *et al*. [14] When new methods, such as PrEP, are introduced, gains in HIV prevention can be made through strengthening supply channels and breaking down access barriers; but uptake takes time and is influenced by attitudes and behaviours of providers and clients. Were *et al*. [15] use data from the first two years of PrEP roll-out in Kenya to construct prevention cascades and to highlight missed opportunities in PrEP delivery and uptake among three priority populations – female sex workers (FSW), MSM and AGYW. For AGYW, the biggest missed opportunity was screening. For MSM and FSW, the biggest missed opportunity was that, among those who were screened and found eligible for PrEP, the majority did not initiate PrEP despite its availability.

Even when people are motivated, have access to, and initiate HIV prevention measures, social and structural barriers may impede their capacity to use them consistently. Programmatic innovation in addressing these barriers remains critical. Chabata *et al*. [16] show that knowledge of condom efficacy is high and availability good among young women who sell sex in Zimbabwe, and yet consistent use is low, especially among those young women who recently experienced violence from a sexual partner. Holmes *et al*. [17] characterize the relationship environments of young women in South Africa and how these influence PrEP use/adherence, secondary distribution of HIV self-tests to partners, and of sharing information about HIV status. In a modelling study, Bershteyn *et al*. [18] demonstrate how implementation challenges along the prevention cascade differentially influence the population-level impacts of the use of oral PrEP and long-acting PrEP in Kenya. Wilson *et al*. [19] report on social and structural determinants and patterns of PrEP use among two sexual minority populations – transgender women and MSM in the United States. They find differences in the PrEP cascades for the two populations, with transgender women being more affected by social-structural issues of poverty, homelessness and unemployment than MSM. Their paper underscores the need to distinguish and specify priority populations, and to identify the particular HIV prevention gaps, barriers and approaches relevant to each.

As Auerbach *et al*. [7] note, and the aforementioned examples attest, while the cascade model has proven to be useful for monitoring progress and gaps in HIV prevention programming in many settings, it does have limitations. Dumchev *et al*. [20] present an analysis of data from an integrated bio-behavioural survey in Ukraine to assess the HIV prevention cascade for people who inject drugs. They find that in their context there was little consistency between their "access to services" and "effective use" measures, given that people who inject drugs often obtain sterile syringes from sources other than the programmes being monitored.

Across the papers included in this special issue, authors are striving for a strengthened feedback loop, from data to programming decisions, for primary HIV prevention to support implementers and managers to deploy the interventions that are most needed to address the determinants of risk in their settings. Most papers use existing data streams to populate their cascade models, and many identify significant measurement and interpretation challenges in operationalizing key elements of the cascade. Further innovation remains essential to strengthen our capacity to track cascades and thereby strengthen the right intervention mix. Generally, it is not feasible to create new data sources or make fundamental changes to existing data sources to inform prevention programming. However, more work would be useful to establish the extent to which minor changes to routine data systems, including further integration of qualitative enquiry, would be feasible for different settings, populations and methods that would improve the validity and utility of the cascades that can be generated.

Most of the papers submitted for the special issue focussed on single methods of prevention. To some extent this may reflect the continuing siloing of programmes for different prevention methods despite the common call for combination prevention approaches [21]. In principle, it is quite possible to create HIV prevention cascades for combination prevention

[22] and we would encourage more attempts to do this. We would also like to see a greater effort to bring HIV prevention cascade thinking into modelling efforts that often guide programme decision making. Again, a greater focus on qualitative and participatory data enquiry that unpacks the reasons for drop offs in the cascade, could also accelerate the loop from data to programmatic improvement.

We applaud the authors of the papers in this series for grappling with some thorny issues in primary HIV prevention data collection and, particularly, cascade analysis. We hope readers find this special issue helpful in their own efforts to strengthen ongoing monitoring, evaluation and advocacy of HIV prevention to meet global goals by 2030.

AUTHORS' AFFILIATIONS

[1]Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom; [2]Department of Medicine, University of California San Francisco, San Francisco, CA, USA; [3]Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom; [4]Health Practice, Genesis Analytics, Johannesburg, South Africa; [5]Faculty of Medicine, Imperial College London, London, United Kingdom

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

JRH drafted the initial manuscript. JDA provided substantial revisions and finalized the draft manuscript. All authors critically reviewed the manuscript, suggested revisions and editorial changes, and approved the final version.

ACKNOWLEDGEMENT

We thank the Editors in Chief and the team in the editorial office at the *Journal of the International AIDS Society* for their excellent support with this supplement.

FUNDING

This supplement was funded by the Bill & Melinda Gates Foundation. The content is solely the responsibility of the authors and does not necessarily represent the views of the funding agency. Research contribution, by Professor James Hargreaves, was covered in part from OPP1120138 'MeSH Consortium', and the contribution by Saul Johnson was funded through Gates Foundation Investment 47698.

REFERENCES

1. Peterson ML, Larmarange J, Wirth K, Skalland T, Ayles H, Kamya MR, et al. Population-level viremia predicts HIV incidence across universal test & treat sites. [CROI Abstract 47]. In special issue: Abstracts from the 2020 conference on retroviruses and opportunistic infections. Top Antivir Med. 2020 [cited 2020 May 29];28(1):16. Available from: https://croiconference.org
2. Callander DJ, Stoové M, McManus H, Carr A, Gray R, Hoy J, et al. Decreasing community viremia is associated with decreasing HIV incidence in Australia. [CROI Abstract 48]. In special issue: Abstracts From the 2020 conference on retroviruses and opportunistic infections. Top Antivir Med. 2020 [cited 2020 May 29];28:17. Available at: https://croiconference.org
3. Barnabas RV, van Rooyen H, Asiimwe S, van Heerden A, Pillay D, Szpiro A, et al. Community ART increases viral suppression and eliminates disparities for African men. [CROI Abstract 49LB]. In special issue: Abstracts from the 2020 conference on retroviruses and opportunistic infections. Top Antivir Med. 2020;28[cited 2020 May 29]:17. Available at: https://croiconference.org
4. UNAIDS. 2016–2021 Strategy: on the fast-track to end AIDS. Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2015 [cited 2020 Mar 14]. Available from: https://www.unaids.org/sites/default/files/media_asset/20151027_UNAIDS_PCB37_15_18_EN_rev1.pdf
5. Hayes RJ, Donnell D, Floyd S, Mandla N, Bwalya J, Sabapathy K, et al. Effect of universal testing and treatment on HIV incidence—HPTN 071 (PopART). N Engl J of Med. 2019;381:207–18.
6. UNAIDS. Annual Report: Knowing your epidemic. Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva. 2008 [cited 2020 Mar 14]. Available from: https://www.unaids.org/sites/default/files/media_asset/jc1535_annual_report07_en_1.pdf
7. Auerbach JD, Gerritsen AAM, Dallabetta G, Morrison M, Garnett GP. A tale of two cascades: promoting a standardised tool for monitoring progress in HIV prevention. J Int AIDS Soc. 2020;23(S3):e25498.
8. Rice B, de Wit M, Welty S, Risher K, Cowan F, Murphy G, et al. Can HIV recent infection surveillance help us better understand where primary prevention efforts should be targeted? Results of three pilots integrating a Recent Infection Testing Algorithm into routine programme activities in Kenya and Zimbabwe. J Int AIDS Soc. 2020;23(S3):e25513.
9. Virkud AV, Arimi P, Ssengooba F, Mulholland GE, Herce M, Markiewicz M, et al. Access to HIV prevention services in East African cross-border areas: a 2016–2017 cross-sectional bio-behavioural study. J Int AIDS Soc. 2020;23(S3):e25523.
10. Sibanda EL, Webb K, Fahey C, Kang Dufour MS, McCoy SI, Watadzaushe C, et al. Use of data from various sources to evaluate and improve the prevention of mother to child transmission of HIV program in Zimbabwe: a data integration exercise. J Int AIDS Soc. 2020;23(S3):e25524.
11. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett RB, Hargreaves J. HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades. Lancet HIV. 2019;6:60–6.
12. Hill LM, Maseko B, Chagomerana M, Hosseinipour MC, Bekker LG, Pettifor A, et al. HIV risk, risk perception, and PrEP interest among adolescent girls and young women in Lilongwe, Malawi: operationalizing the PrEP cascade. J Int AIDS Soc. 2020;23(S3):e25502.
13. Ramautarsing RA, Mekensa R, Sungsing T, Chinbunchorn T, Sangprasert T, Fungfoosri O, et al. Evaluation of a pre-exposure prophylaxis program for men who have sex with men and transgender women in Thailand: learning through the HIV prevention cascade lens. J Int AIDS Soc. 2020;23(S3):e25540.
14. Wall KM, Inambao M, Kilembe W, Karita E, Chomba E, Vwalika B, et al. Cost-effectiveness of couples' voluntary HIV counselling and testing in six African countries: a modelling study guided by an HIV prevention cascade framework. J Int AIDS Soc. 2020;23(S3):e25522.
15. Were D, Musau A, Mutegi J, Ongwen P, Manguro G, Kamau M, et al. Using an HIV prevention cascade for identifying missed opportunities in PrEP delivery in Kenya: results from a programmatic surveillance study. J Int AIDS Soc. 2020;23(S3):e25537.
16. Chabata ST, Hensen B, Chiyaka T, Mushati P, Busza J, Floyd S, et al. Condom use among young women who sell sex in Zimbabwe: a prevention cascade analysis to identify gaps in prevention programming. J Int AIDS Soc. 2020;23(S3):e25512.
17. Holmes L, Kaufman R, Casella A, Mudavanhu M, Mutunga L, Polzer T, et al. Qualitative characterizations of relationships among South African adolescent girls and young women and male partners: implications for engagement across HIV self-testing and pre-exposure prophylaxis prevention cascades. J Int AIDS Soc. 2020;23(S3):e25521.
18. Bershteyn A, Sharma M, Akullian AN, Peebles K, Sarkar S, Braithwaite RS, et al. Impact along the pre-exposure prophylaxis "cascade of prevention" in western Kenya: a mathematical modelling study. J Int AIDS Soc. 2020;23(S3):e25527.
19. Wilson EC, Turner CM, Arayasirikul S, Lightfoot M, Scheer S, Raymond HF, et al. Disparities in the PrEP continuum for trans women compared to MSM in San Francisco, California. J Int AIDS Soc. 2020;23(S3):e25539.
20. Dumchev K, Sazonova Y, Smyrnov P, Cheshun O, Paskchuk O, Saliuk T, et al. Operationalizing the HIV prevention cascade for PWID using the integrated bio-behavioural survey data from Ukraine. J Int AIDS Soc. 2020;23(S3):e25509.
21. UNAIDS. Combination HIV prevention: tailoring and coordinating biomedical, behavioural and structural strategies to reduce new HIV infections. Joint United Nations Programme on HIV/AIDS. 2010 [cited 2020 Mar 14]. Available from: https://www.unaids.org/sites/default/files/media_asset/JC2007_Combination_Prevention_paper_en_0.pdf
22. Fearon E, Phillips A, Mtetwa S, et al. How Can Programs Better Support Female Sex Workers to Avoid HIV Infection in Zimbabwe? A Prevention Cascade Analysis. J Acquir Immune Defic Syndr. 2019;81:24–35. doi:10.1097/QAI.0000000000001980

Auerbach JD et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25498
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25498/full | https://doi.org/10.1002/jia2.25498

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

COMMENTARY

A tale of two cascades: promoting a standardized tool for monitoring progress in HIV prevention

Judith D Auerbach[1,§], Annette AM Gerritsen[2], Gina Dallabetta[3], Michelle Morrison[4] and Geoffrey P Garnett[5,6]

[§]**Corresponding author:** Judith D Auerbach, 550 16th Street, San Francisco 94143, USA. Tel: +1 415 476 6288. (judith.auerbach@ucsf.edu)

Abstract

Introduction: To achieve significant progress in global HIV prevention from 2020 onward, it is essential to ensure that appropriate programmes are being delivered with high quality and sufficient intensity and scale and then taken up by the people who most need and want them in order to have both individual and public health impact. Yet, currently, there is no standard way of assessing this. Available HIV prevention indicators do not provide a logical set of measures that combine to show reduction in HIV incidence and allow for comparison of success (or failure) of HIV prevention programmes and for monitoring progress in meeting global targets. To redress this, attention increasingly has turned to the prospects of devising an HIV prevention cascade, similar to the now-standard HIV treatment cascade; but this has proven to be a controversial enterprise, chiefly due to the complexity of primary prevention.

Discussion: We address a number of core issues attendant with devising prevention cascades, including: determining the population of interest and accounting for the variability and fluidity of HIV-related risk within it; the fact that there are multiple HIV prevention methods, and many people are exposed to a package of them, rather than a single method; and choosing the final step (outcome) in the cascade. We propose two unifying models of prevention cascades - one more appropriate for programme managers and monitors and the other for researchers and programme developers - and note their relationship. We also provide some considerations related to cascade data quality and improvement.

Conclusions: The HIV prevention field has been grappling for years with the idea of developing a standardised way to regularly assess progress and to monitor and improve programmes accordingly. The cascade provides the potential to do this, but it is complicated and highly nuanced. We believe the two models proposed here reflect emerging consensus among the range of stakeholders who have been engaging in this discussion and who are dedicated to achieving global HIV prevention goals by ensuring the most appropriate and effective programmes and methods are supported.

Keywords: HIV prevention cascades; HIV prevention programmes; prevention monitoring; programme improvement; key and vulnerable populations; public health; intervention

Received 1 October 2019; **Accepted** 6 April 2020

1 | INTRODUCTION

The UN Political Declaration of 2016 outlined key *2020 Global Prevention Targets and Commitments* that included reducing the numbers of people newly infected with HIV to fewer than 500,000 per year (a 75% reduction against 2010 targets), reducing the number of adolescent girls and young women newly infected with HIV globally to below 100,000 per year, and ensuring that 90% of people at risk of HIV infection have access to comprehensive HIV prevention services. Notwithstanding a 16% reduction in HIV incidence overall between 2010 and 2018, it is clear that, as we have entered the year 2020, these global targets will not be met. To achieve significant progress from 2020 onward, it is essential to ensure that appropriate HIV prevention programmes are being delivered with high quality and sufficient intensity and scale and taken up by the people who most need and want them to have public health and epidemic impact.

Yet, currently, there is no standard way of assessing this. To redress this, attention increasingly has turned to the prospects of devising an HIV prevention cascade, similar to the now-standard HIV treatment cascade; but this has proven to be a controversial enterprise, chiefly due to the complexity of primary prevention. We believe there is a way forward with two versions of a prevention cascade—a basic model that can be used by programme managers applying routine data, and an expanded model that can be used by researchers (working with programme managers) and public health policy makers who have access to and can generate additional types of data.

2 | DISCUSSION

2.1 | The value of prevention cascades

Prevention cascades have multiple, potential and somewhat overlapping uses. They can provide: a logical framework summarizing actions taken by individuals across a population that can prevent HIV acquisition; a management tool to focus on gaps and related barriers and bottlenecks and identify potential for programmatic improvement; and an advocacy tool for indicating points for intervention to enhance programme effectiveness.

2.2 | Issues in devising a prevention cascade framework

Notwithstanding their potential value, a number of core issues and nuances have made it difficult to reach consensus in the field about how to devise HIV prevention cascades and to agree on one shared model. We address some of these below.

2.2.1 | Presentation of Cascade

Two different models of presenting the elements (or steps) in cascades have been used in the field, making comparisons in HIV treatment progress across locales difficult [1]. In one, the denominator remains the same for each step - for example all people living with HIV; in the other, the denominator of each step is derivative from the step before—for example people living with HIV who know their status, of those, the proportion on ART, of those, the proportion who are virally suppressed [2]. The choice of model will, of course, influence its interpretation. Many in the HIV prevention field have been using "cascade" to signify models that show derivative denominators [3-7], as we do in the remainder of this commentary.

2.2.2 | *The initial denominator*

Determining the beginning denominator - the population of interest - in an HIV prevention cascade can be challenging. For HIV prevention, there is no uniform, clearly defined population in need (as compared with all people living with HIV for the treatment cascade), but several populations that have different characteristics and vulnerabilities to HIV infection. Moreover, HIV prevention is neither a uniform nor a linear process; people move in and out of situations of risk affected by a range of psycho-social, interpersonal and demographic characteristics. This also means that within populations that are defined as "at risk" because of their overall HIV incidence or prevalence, for example female sex workers (FSW), there is heterogeneity of risk [8]. As with any group categorised according to epidemiological risk factors there is an averaging of risk across a heterogeneous population. In choosing a population focus there is a trade-off in the level of risk and the number of people covered.

Although primary prevention cascades focus on those who are HIV negative, many HIV prevention programmes do not begin with HIV testing to determine who definitely is uninfected in order to focus the promotion of primary prevention methods on them. In some cases, prevention programmes are even intentionally delivered to a population that includes both HIV-positive and HIV-negative individuals with a specific type of risk for either transmission or acquisition, for example all people with non-regular partners, for whom condoms would be recommended, which can complicate the denominator. With all these nuances in mind, size estimates of the population of interest provide the best, albeit imperfect method for determining the initial cascade denominator.

2.2.3 | *Time covered by the cascade*

Risk of HIV acquisition is cumulative over exposures occurring over time. The timeframe that the prevention cascade covers could vary depending on the intensity of risk and the duration prevention programmes are in place. In assessing HIV prevention programmes, it makes sense to track cohorts or to sample populations cross-sectionally with time periods short enough to measure changes in appropriate use of interventions. In treatment cascades it is not always clear whether the 90:90:90 target refers to a specific moment in time, or is cumulative diagnosis, ART initiation and viral suppression for the cohorts of those infected. For prevention, the cascade should be assessed as a function of time; using convenient durations, such as a month or a year, as a standard timeframe will allow for comparability across prevention cascades.

2.2.4 | *Multiple prevention options*

People at risk of HIV often are presented with more than one option of prevention method, unlike the fairly singular ART option that is monitored through the treatment cascade [9]. Sometimes prevention method options are delivered simultaneously in a package, for example one that promotes condoms and pre-exposure prophylaxis (PrEP) and provides economic support for adolescent girls and young women. Measuring the effect of a prevention package as a whole, while desirable, becomes tricky. The prevention package can be thought of as the activities undertaken to ensure that prevention methods are effectively used. Looking at the combined cascades generated by a prevention package allows the effectiveness of the package to be assessed. These realities of prevention programming mean that multiple, differentiated prevention cascades - by population and prevention method - are necessary. These can follow a uniform framework, but their characteristics and data points will be different. Fearon and colleagues [10] provide an example of a cascade, based on routine programme data, for each of two prevention methods provided to female sex workers - condoms and PrEP - showing where they overlap. This may be as close to assessing combination packages as we can come, outside of a large-scale randomized community trial comparing the efficacy of different packages within similar populations, which, in fact, have not proven fruitful in the test and treat arena [11-14].

2.2.5 | *The final outcome*

Deciding what exactly is and should be the ending point (the measured and reported outcome) for prevention cascades fundamentally depends upon the purpose of the cascade. If the focus is on programme coverage and the uptake and use of the prevention method(s) promoted by that programme, then the endpoint would be correct and consistent use (adherence or persistence) of the prevention method(s). If the

focus is on evaluation or impact of the programme on HIV infection rates (incidence), then the endpoint would be remaining HIV negative. The latter is much more difficult to measure directly in a cascade model, as it requires a combination of programme data, behavioural surveys or interviews and HIV testing. But it can be based on estimates of efficacy when correct and consistent use is known. This is similar to how viral suppression - not decreased morbidity, mortality, and/or onward transmission - is used as the final outcome in the treatment cascade.

Because cascades measure the reduction in risk across individuals but do not account for reduced exposures as the prevalence of infection falls, they provide a partial population level measure of the impact of prevention interventions. Where capacity exists, researchers can work with programme implementers to estimate infections averted through mathematical modelling of the acquisition and transmission of HIV and the population dynamics of infections and other extrapolation methods.

2.3 | Two unifying cascade models

While the issues noted above continue to be debated, a few consensus meetings have reached the conclusion that HIV prevention programme managers at national and sub-national levels and from government and non-governmental organisations who are involved in the implementation, administration, monitoring and evaluation of HIV prevention programmes would benefit from having a standardised cascade model, like the treatment cascade, to monitor their progress and identify gaps and opportunities for improvement [15]. The advantage of a relatively simple, generic model is that it promotes comparability over time, across populations, between sub-groups of a population, across geographical areas and between prevention methods. Moreover, it can be populated with routine programme data and survey data.

A collaboration of global partners, including the authors and representatives from UNAIDS, WHO, and a number of national HIV prevention programmes, are developing operational guidance for creating basic HIV prevention cascades that can be used as a programme management tool [16] that can describe what is being provided and used by a given population and determine where the gaps lie for the purposes of informing programme improvement, as shown in Figure 1 (model a). This basic cascade model begins with identification and quantification of a population group that is the focus of a prevention programme. Ideally, this population will be comprised of those most at risk of getting infected as well as most

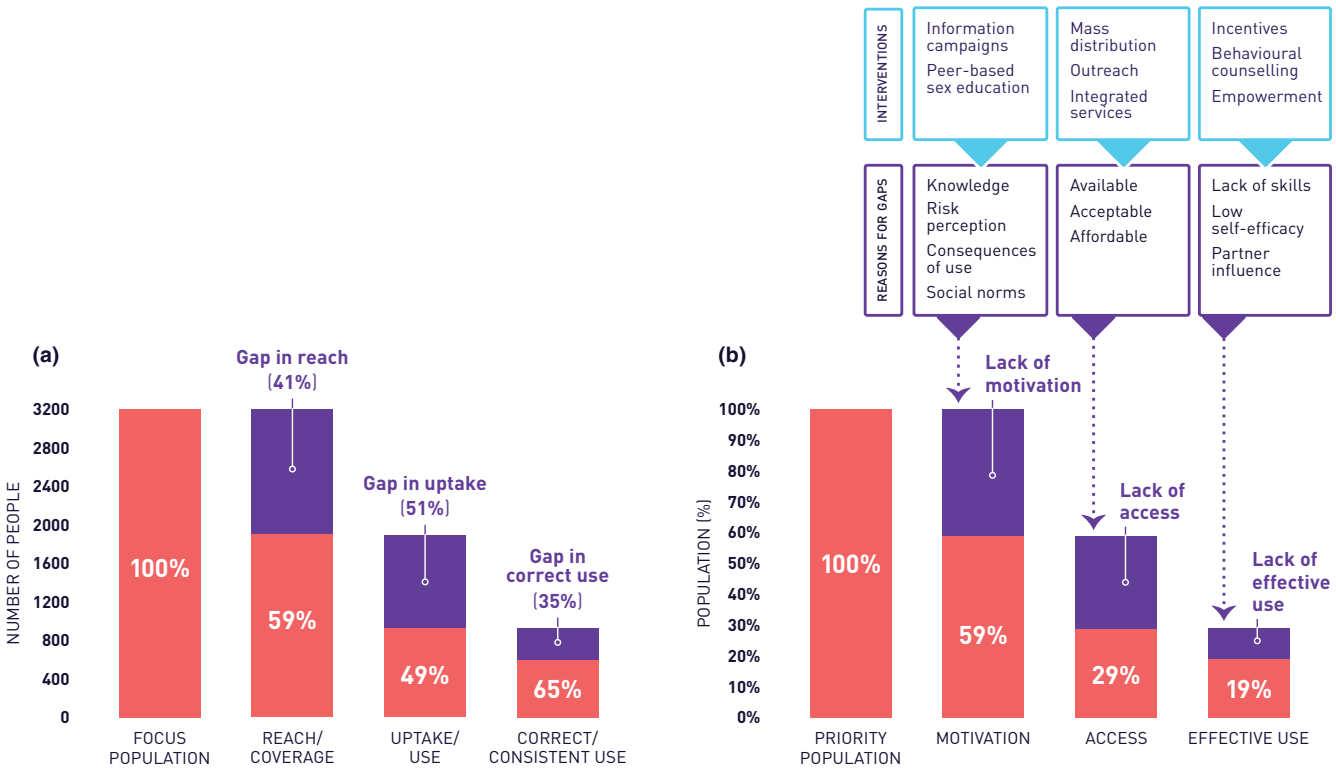

Figure 1. Two unifying prevention cascade models. In the basic model **(a)**, the bars represent the programme success, showing, sequentially, the number and proportion of the focus population that is covered by the intervention (59%), the number and proportion of those covered by the intervention that take it up (49%) and the number and proportion of those who take up the intervention that use it correctly (65%) (e.g. in the past 12 months). The purple area and proportion above each red section of the bar represents the gap in each step. This cascade is recommended for assessing basic programme performance. In the expanded model **(b)**, using the same data, but a format adapted from Schaefer and colleagues [5] and Manicaland Centre [15] (whereby the percentages across the red bars are based upon the priority population), the gaps are in motivation, access and consistent use, and the reasons for these can be further explored and potential interventions identified. This alternative approach is more attuned to research and the design of programmes than to the monitoring of programme implementation.

in need of the particular prevention method(s) being provided by the programme, although, as noted above, this may not always be the case. It can best be determined using size estimation methods, for example census, enumeration, behavioural surveillance, mapping, etc. [17] The next step, reach or coverage, is defined as the extent to which a prevention method is delivered or made accessible to the focus population. The third step measures uptake and initial use of the prevention method among those reached by the programme; and the fourth step assesses the extent to which those who take up a prevention method use it correctly and consistently. Reach, uptake and use may be measured with routine programme data, polling booth survey data, and, if feasible, behavioural surveillance data. This basic model has been adopted for prevention programme monitoring in Kenya [18,19], India [20] and Zimbabwe [21].

The basic prevention cascade, effectively, is the first step in a three-step framework that would subsequently involve qualitative and quantitative research to understand the individual and social-structural causes (i.e. the why) of these gaps, and then the development and testing of appropriate solutions to improve the effectiveness of HIV prevention efforts, as demonstrated ultimately by reductions in HIV incidence, although that may not be represented in the cascade itself. A version of this extended framework, modified from that proposed by Schaefer and colleagues [5] and informed by earlier work [3-4,15], is also shown in Figure 1 (model b). It includes a step related to "motivation" to denote the importance of "demand" as a facilitator in uptake and use of a prevention method. This model, recently applied in Manicaland, Zimbabwe [22], is most feasible to use in contexts with research capacity and infrastructure, as it requires collection and analysis of quantitative and qualitative data that go beyond the data regularly collected by prevention programme implementers and managers. It is worth noting that in some circumstances, the order of the motivation and access steps in the Schaefer et al. model would differ. For example when everyone in a focus population has access to a prevention method, "motivation" might come after "access" to better convey who in the end actually takes up the prevention method because they want to use it when availability is not an obstacle.

Furthermore, in Figure 1 model b, the proportion shown in the final step (effectively using the method) represents the overall success of the programme vis-à-vis the total focus population. This value could be multiplied by known efficacy of the prevention method(s) promoted in the programme to estimate the proportional reduction in HIV incidence achieved. The difference in the two methods of cascade illustration is important for the immediate visual impression it makes on how well a programme is performing, but the information on the scale and relative importance of gaps is similar.

2.4 | Data quality and improvement

A prevention cascade will only be as good as the data that comprise it. Since most data are not perfect, neither will be the prevention cascade. What is most important is to use the best available data, while continuing to find ways to improve them, and to use these data to inform decisions about programme improvement. When engaging in cascade analysis, it is important to be clear about the sources, quality and limitations of the data used, as each has its strengths and limitations, and each can be improved [23-25].

For example when no valid size estimates are available for members of a key population group who are most at risk, multiple estimates may have to be generated and triangulated to reach both a point estimate and a range. Integrated bio-behavioural surveillance (IBBS), while employing a consistent sampling method and ensuring representativeness, still relies on self-report, which is subject to bias. Similarly, polling booth and small areas surveys, which are more easily used in programmes also may be subject to sampling bias. This can be improved by introducing innovative, and potentially more valid, data collection methods, such as digital methods. Additionally, programmes may not routinely collect all the data needed to populate a cascade, nor disaggregate them by key population. But these data can be triangulated with other sources, including IBBS and focused qualitative surveys, where feasible. In sum, efforts should be made to assure that the highest quality data available are used in cascade development and analysis, and, simultaneously, to improve upon their quality in new and innovative ways.

3 | CONCLUSIONS

The HIV prevention field has been grappling for years with the idea of developing a standardised way to regularly assess progress and to monitor and improve programmes accordingly. The cascade framework, already universally adopted for HIV treatment, provides the potential to do this, but it is complicated and highly nuanced. We have proposed that two models be employed—one chiefly for programme managers, and the other chiefly for programme developers, researchers and policy makers—to move the field forward. We believe these models reflect emerging consensus among the range of stakeholders who have been engaging in this discussion and who are dedicated to achieving global HIV prevention goals by ensuring the most appropriate and effective programmes and methods are supported.

AUTHORS' AFFILIATIONS

[1]Department of Medicine, University of California San Francisco, San Francisco, CA, USA; [2]EpiResult, Pietermaritzburg, South Africa; [3]HIV Delivery, TB/HIV Team, Bill & Melinda Gates Foundation, Washington, DC, USA; [4]HIV Epidemiology and Surveillance, Bill & Melinda Gates Foundation, Seattle, WA, USA; [5]Data and Metrics, TB/HIV Team, Bill & Melinda Gates Foundation, Seattle, WA, USA; [6]Department of Global Health, University of Washington Seattle, Seattle, WA, USA

COMPETING INTERESTS

J.D.A: none, A.A.M.G.: none, G.D.: none, M.M.: none, G.P.G.: none.

AUTHORS' CONTRIBUTIONS

J.D.A., A.A.M.G., G.D., M.M. and G.P.G. conceived the idea for this commentary: J.D.A. and A.A.M.G. prepared the manuscript. All authors reviewed, provided feedback and approved the final manuscript.

ACKNOWLEDGEMENTS

We thank all the participants of the UNAIDS and Bill & Melinda Gates Foundation HIV Prevention Cascades Meeting, held 2-3 May, 2018, Geneva, Switzerland, for contributing greatly to our thinking about prevention cascades. We also thank Janie Vinson for her assistance with preparing Figure 1.

FUNDING

This commentary is supported by the Bill & Melinda Gates Foundation. The draft operational guidance for creating HIV prevention cascades document on which this work is based was funded by UNAIDS and the Bill & Melinda Gates Foundation. JDA: received support from BMGF for work related to this commentary. AAMG: received support from UNAIDS and BMGF for work related to this commentary.

REFERENCES

1. Godfrey-Faussett P. The HIV prevention cascade: more smoke than thunder? Lancet HIV. 2016;3:e286–8.
2. Granich R, Gupta S, Hall I, Aberle-Grasse J, Hader S, Mermin J. Status and methodology of publicly available national HIV care continua and 90–90-90 targets: a systematic review. PLoS Med. 2017;14:e1002253.
3. UNAIDS. Global AIDS Update 2017. Ending AIDS: Progress Towards the 90–90-90 Targets. Joint United Nations Programme on HIV/AIDS (UNAIDS), Geneva. 2017 [cited 2019 Sep 8]. Available from: http://www.unaids.org/sites/default/files/media_asset/Global_AIDS_update_2017_en.pdf
4. Garnett GP, Hallett TB, Takaruza A, Hargreaves J, Rhead R, Warren M, et al. Providing a conceptual framework for HIV prevention cascades and assessing feasibility of empirical measurement with data from east Zimbabwe: a case study. Lancet HIV. 2016;3:e297–306.
5. Hargreaves JR, Delany-Moretlwe S, Hallett TB, Johnson S, Kapiga S, Bhattacharjee P, et al. The HIV prevention cascade: integrating theories of epidemiological, behavioural, and social science into programme design and monitoring. Lancet HIV. 2016;3:e318–22.
6. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett RB, Hargreaves J. HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades. Lancet HIV. 2019;6:60–6.
7. Chan PA, Glynn TR, Oldenburg CE, Montgomery MC, Robinette AE, Almonte A, et al. Implementation of pre-exposure prophylaxis for HIV prevention among men who have sex with men at a New England sexually transmitted diseases clinic. Sex Transm Dis. 2016;43(11):717–23.
8. Kelley CF, Kahle E, Siegler A, Sanchez T, del Rio C, Sullivan PS, et al. Applying a PrEP continuum of care for men who have sex with men in Atlanta, Georgia. Clin Infect Dis. 2015;61(10):1590–7.
9. McKinnon LR, Izulla P, Nagelkerke N, Munyao J, Wanjiru T, Shaw SY, et al. Risk factors for HIV acquisition in a prospective nairobi-based female sex worker cohort. AIDS Behav. 2015;19(12):2204–13.
10. Fearon E, Phillips A, Mtetwa S, Chabata ST, Mushati P, Cambiano V, et al. How can programs better support female sex workers to avoid HIV infection in Zimbabwe? a prevention cascade analysis. J Acquir Immune Defic Syndr. 2019;81(1):24–35.
11. Havlir DV, Balzer LB, Charlebois ED, Clark TD, Kwarisiima D, Ayieko J, et al. HIV testing and treatment with the use of a community health approach in rural Africa. N Engl J Med. 2019;381:219–229.
12. Hayes RJ, Donnell D, Floyd S, Mandla N, Bwalya J, Sabapathy K, et al. Effect of universal testing and treatment on HIV incidence—HPTN 071 (PopART). N Engl J Med. 2019;381:207–218.
13. Iwuji CC, Orne-Gleimann J, Larmarange J, Balestre E, Thiebaut R, Tanser F, et al. Universal test and treat and the HIV epidemic in rural South Africa: a phase 4, open-label, community cluster randomised trial. Lancet HIV. 2018;5(3):e116–E125.
14. Makhema J, Wirth KE, Pretorius Holme M, Caolathe T, Mmalane M, Kadima E, et al. Universal testing, expanded treatment, and incidence of HIV infection in Botswana. N Engl J Med. 2019;381(3):230–42.
15. Manicaland Centre for Public Health Research. HIV prevention cascades: stakeholder consultation meeting and workshop. 2017 [cited 2019 Sep 8]. Available from: http://www.manicalandhivproject.org/uploads/4/7/1/9/4719905/hpc_consultation_workshop_report_final.pdf
16. Operational guidance for creating HIV prevention cascades: A tool for monitoring programmes 2020. Draft in review.
17. UNAIDS/WHO. Guidelines on estimating the size of populations most at risk to HIV. 2010 [cited 2019 Sep 8]. Available from: http://unaids.org/sites/default/files/media_assett/2011_Estimating_Populations_en-0.pdf
18. Bhatachargee P, Musyoki HK, Becker M, Musimbi J, Kaosa S, Kioko J, et al. HIV prevention programme cascades: insights from HIV programme monitoring for female sex workers in Kenya. J Int AIDS Soc. 2019;22:e25311.
19. Mugambi C. Example of a prevention cascade at country level. Invited presentation TUSY09; IAS 2019, Mexico City, Mexico. Available from author.
20. Reza-Paul S, Steen R, Maiya R, Lorway R, Elvira T, Wheeler T, et al. Sex worker community-led interventions interrupt sexually transmitted infection/human immunodeficiency virus transmission and improve human immunodeficiency virus cascade outcomes: a programme review from South India. Sex Transm Dis. 2019;46(8):556–62.
21. Weiner R, Sisimayi C. Development and institutionalizing HIV prevention cascades in the national monitoring system in Zimbabwe. UNAIDS, Zimbabwe Ministry of Health and Child Care, Zimbabwe National AIDS Council. June 2019. Available from authors.
22. Moorehouse L, Schaefer R, Thomas R, Nyamukapa C, Skovdal M, Hallett TB, et al. Application of the HIV prevention cascade to identify, develop and evaluate interventions to improve use of prevention methods: examples from a study in east Zimbabwe. J Int AIDS Soc. 2019;22:e25309.
23. LINKAGES. Monitoring guide and toolkit for key population HIV prevention, care, and treatment programmes. 2016 [cited 2019 Sep 8]. Available from: https://www.fhi360.org/sites/default/files/media/documents/resource-linkages-monitoring-tools.pdf
24. WHO. Consolidated strategic information guidelines for HIV in the health sector. Geneva: WHO. 2015 [cited 2019 Sep 8]. Available from: https://www.who.int/hiv/pub/guidelines/strategic-information-guidelines/en/
25. WHO. HIV strategic information for impact. Cascade data use manual: To identify gaps in HIV and health services for programme improvement. Geneva: WHO. 2018 [cited 2019 Sep 8]. Available from: http://www.who.int/hiv/pub/toolkits/hiv-cascade-data-use-manual/en

Rice BD et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25513
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25513/full | https://doi.org/10.1002/jia2.25513

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Can HIV recent infection surveillance help us better understand where primary prevention efforts should be targeted? Results of three pilots integrating a recent infection testing algorithm into routine programme activities in Kenya and Zimbabwe

Brian D Rice[1,§], Mariken de Wit[1], Susie Welty[2], Kathryn Risher[1], Frances M Cowan[3], Gary Murphy[4], Sungai T Chabata[3], Wanjiru Waruiru[2], Sitholubuhle Magutshwa[3], John Motoku[5], Daniel Kwaro[6], Benard Ochieng[6], Georges Reniers[1] and George Rutherford[2]

[§]**Corresponding author**: Brian D. Rice, 15-17 Tavistock Place, London, WC1H 9SH, UK. Tel: +44 (0) 20 7927 2567. (brian.rice@lshtm.ac.uk)

Abstract

Introduction: Surveillance of recent HIV infections in national testing services has the potential to inform primary prevention programming activities. Focusing on procedures required to accurately determine recent infection, and the potential for recent infection surveillance to inform prevention efforts, we present the results of three independent but linked pilots of recency testing.

Methods: To distinguish recently acquired HIV infection from long-standing infection, in 2018 we applied a Recent Infection Testing Algorithm that combined a laboratory-based Limiting Antigen Avidity Enzyme Immunoassay with clinical information (viral-load; history of prior HIV diagnosis; antiretroviral therapy-exposure). We explored potential misclassification of test results and analysed the characteristics of participants with recent infection. We applied the algorithm in antenatal clinics providing prevention of mother-to-child transmission services in Siaya County, Kenya, outreach sites serving female sex workers in Zimbabwe, and routine HIV testing and counselling facilities in Nairobi, Kenya. In Nairobi, we also conducted recency testing among partners of HIV-positive participants.

Results: In Siaya County, 2.3% (10/426) of HIV-positive pregnant women were classified as recent. A risk factor analysis comparing women testing recent with those testing HIV-negative found women in their first trimester were significantly more likely to test recent than those in their second or third trimester. In Zimbabwe, 10.5% (33/313) of female sex workers testing HIV-positive through the outreach programme were classified recent. A risk factor analysis of women testing recent versus those testing HIV-negative, found no strong evidence of an association with recent infection. In Nairobi, among 532 HIV-positive women and men, 8.6% (46) were classified recent. Among partners of participants, almost a quarter of those who tested HIV-positive were classified as recent (23.8%; 5/21). In all three settings, the inclusion of clinical information helped improve the positive predictive value of recent infection testing by removing cases that were likely misclassified.

Conclusions: We successfully identified recently acquired infections among persons testing HIV-positive in routine testing settings and highlight the importance of incorporating additional information to accurately classify recent infection. We identified a number of groups with a significantly higher proportion of recent infection, suggesting recent infection surveillance, when rolled-out nationally, may help in further targeting primary prevention efforts.

Keywords: HIV; surveillance; recent infection; prevention; Kenya; Zimbabwe

Received 2 October 2019; **Accepted** 22 April 2020

1 | INTRODUCTION

Knowing where and among whom new HIV infections are occurring is helpful in estimating HIV incidence and also, potentially, in guiding prevention programmes and evaluating their impact [1-7]. Identifying hotspots, at the population-level, of recently acquired HIV infection could help programmes identify where and among whom primary prevention efforts such as pre-exposure prophylaxis (PrEP) and voluntary medical male circumcision (VMMC) should be intensified. Information on recently acquired HIV may also inform primary prevention efforts at the individual level. For example prioritizing partner notification services among newly diagnosed persons who have acquired HIV recently may minimize recall bias relating

to partner information [8], and assist efforts to reach a person's most recent partners to encourage them to seek testing and preventative services.

A number of laboratory-based assays have been developed that can identify recent HIV infections through the testing of blood specimens [9,10]. These assays utilize specific antibody markers that evolve in the months following infection. When interpreted as part of a Recent Infection Testing Algorithm (RITA) (where laboratory test results are combined with other information to classify an HIV infection), these assays are able to distinguish recently acquired infection from long-standing infection among persons being diagnosed with HIV [6,10]. They have been used in national population-based HIV impact assessment (PHIA) surveys in 12 high-burden African countries to estimate national HIV incidence [11-13]. In 2018, the United States President's Emergency Plan for AIDS Relief (PEPFAR) called for recent infection surveillance to be implemented at scale in supported countries [14,15]

We present the results of three independent but linked pilots of HIV recency testing in routine service-provision settings in Kenya and Zimbabwe.

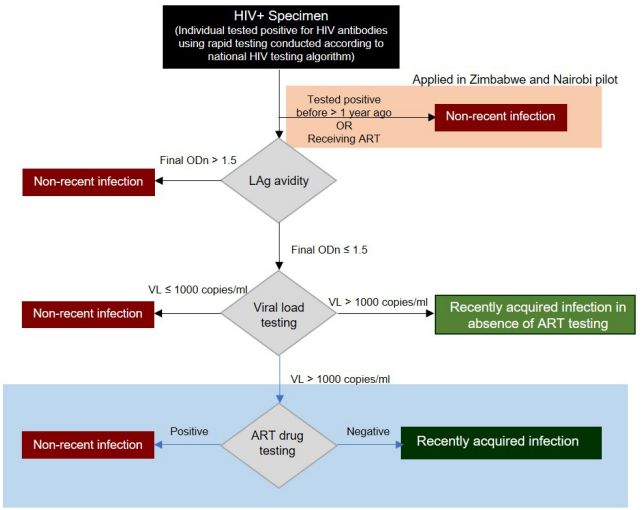

Figure 1. Recency testing algorithm (RITA) as applied in the three pilots.

2 | METHODS

To explore whether RITAs can be applied in routine service setting in sub-Saharan Africa, and whether the information generated can be used to inform prevention activities, we chose a variety of routine service-provision contexts in Kenya and Zimbabwe to conduct recency testing. These settings were as follows: antenatal clinics providing prevention of mother-to-child transmission (PMTCT) services in Siaya County, Kenya, a national programme for female sex workers in Zimbabwe, and HIV testing and counselling (HTC) facilities in Nairobi, Kenya.

2.1 | Data collection and sample processing

Prior to the commencement of our pilots, all study staff underwent training on good clinical practice, ethics and the handling of confidential information as per our study protocols. Eligible participants were asked to read and sign a consent form and were probed for their understanding. For illiterate participants, study staff read the forms out and sought consent in the presence of an independent witness. Data were collected between February and November 2018.

In all three pilots, anti-HIV-1-positive specimens were classified as either recent or long-standing using a RITA that combined a LAg Avidity EIA (a single-well avidity assay that provides a measure of antibody avidity as normalized optical density (ODn)) with information on viral-load, history of prior HIV diagnosis and/or exposure to antiretroviral therapy (ART)) (Figure 1). This RITA gives an indication as to whether or not a person being diagnosed with HIV is likely to have been infected within the last four to six months.

The Maxim HIV-1 LAg-Avidity EIA Dried Blood Spot (DBS) Kit was used in Nairobi on DBS samples, with the Maxim HIV-1 LAg-Avidity EIA being used in Siaya County and Zimbabwe on plasma samples. As per manufacturer guidance, LAg tests with an initial ODn value ≤ 2.0 were retested in triplicate from a fresh dilution of the specimen to confirm the result, and confirmatory anti-HIV serology was performed on specimens with an ODn value < 0.4. Viral-load was measured using the Abbott m2000, Roche Cobas Ampliprep/Cobas Taqman or similar automated platform, according to manufacturers' instructions. Internal quality control checks were run according to manufacturers' instructions. Persons with a final ODn ≤ 1.5 and a viral-load> 1000 copies/ml were classified as recent infection positive in the absence of ART testing.

As the inclusion of information on ART-exposure could improve RITA performance through lowering false-recent misclassification [4,16], samples assessed as recent in Nairobi were sent to the Pharmacokinetic Laboratory at the University of Cape Town to test for the presence of ART metabolites in the blood (metabolites, including Lopinavir, Ritonavir, Nevirapine, Efavirenz, Indinavir, Saquinavir, Zidovudine, Lamivudine and Stavudine, were quantified by a robust simultaneous liquid chromatography/tandem mass spectrometry method)[17,18].

In Siaya County, recent samples were linked to a woman's antenatal clinic record to explore ART-exposure, and were also linked to their antenatal clinic and Health and Demographic Surveillance Site (HDSS) record to explore testing history for prevalent infection. Evidence of ART-exposure or previous HIV-positive test would potentially result in a recent infection being reclassified as long-standing. Table 1 summarizes our recruitment and testing approach per pilot.

For all three pilots we collected information on participants' sex, age, marital status and testing facility. In Zimbabwe and Nairobi, level of education was also collected. In addition, number of pregnancies and pregnancy trimester was collected in Siaya County, and employment status, HIV testing history and pregnancy status was collected in Nairobi.

2.2 | Statistical analysis

We developed a flowchart to show the flow of participants and sample testing for all three pilots together, starting with all those presenting for testing, and ending with final classification of recent and long-standing HIV infection. We present

Table 1. Three pilots of HIV recent infection testing in routine service settings

Siaya County, Kenya	Nairobi, Kenya	Sisters with a Voice, Zimbabwe
Setting Estimated HIV prevalence of 21% in 2017 [26]. Fertility rate> five children per woman, and almost all women (94%) access antenatal care at some point during pregnancy [27].	**Setting** Estimated HIV prevalence of 12% in population served by participating clinics in Eastern Nairobi [28].	**Setting** Across participating facilities, prevalence of HIV among FSW is on average 58% [20,29,30]. HIV incidence rates are poorly understood, but may be as high as 10% per year [31].
Collaborative partner Kenya Medical Research Institute (KEMRI) and the KEMRI/CDC Siaya HDSS	**Collaborative partner** Eastern Deanery AIDS Relief Programme (EDARP)	**Collaborative partner** Centre for Sexual Health and HIV AIDS Research Zimbabwe (CeSHHAR-Zimbabwe)
Study population Pregnant women seeking antenatal care in fourteen medical facilities	**Study population** Clients attending any of the fourteen EDARP HTC facilities	**Study population** FSW attending one of six static facilities of the Sisters with a Voice Programme that provide a range of services including testing and referral to government ART services [31].
Study period February – November 2018	**Study period** March – November 2018	**Study period** June – November 2018
Assay Maxim HIV-1 LAg-Avidity EIA venous blood	**Assay** Maxim HIV-1 LAg-Avidity EIA Dried Blood Spot	**Assay** Maxim HIV-1 LAg-Avidity EIA venous blood
Inclusion criteria • Women aged 13 or older seeking antenatal care in one of the selected medical facilities in Siaya County • Provides informed consent • Received an HIV-positive test result	**Inclusion criteria** • Aged 18 or older • Unknown HIV status prior to visit • Attending an EDARP HTC facility • Willing and able to provide informed consent • Received an HIV-positive test result, or presumptive positive	**Inclusion criteria** • FSW aged 18 or older • Provides informed consent • Received an HIV-positive test result
	Exclusion criteria • Indeterminate HIV result • Not willing to enrol on follow-up at facility • Taking pre-exposure prophylaxis	**Exclusion criteria** • Indeterminate HIV result • Prior history of testing HIV-positive (>1 year ago) • On ART
Specimen collection and testing • Study nurse or laboratory phlebotomist drew a maximum of 10ml of venous blood • Samples packed and transferred to KEMRI-Centre for Global Health Research HIV Research Laboratory in Kisumu on a daily basis where they were tested (or stored for testing)	**Specimen collection and testing** Study nurse drew 6mL of venous blood collected in an ethylenediaminetetraacetic (EDTA) tube and a pipette was used to dispense venous blood on two Whatman™ 903 Snap-Apart Cards with 5 dried blood spots (DBS) of 70 µL each, for a total of 10 filled spots per participant	**Specimen collection and testing** • Study nurse drew venous blood (where study nurse not available, then a clinic nurse drew blood) • Samples packed and transferred to laboratory in Harare within 36 hours and stored at −20C or below for testing

Inclusion and exclusion criteria for each pilot reflect the routine practice of the facilities within which recruitment was conducted. FSW, Female Sex Workers; HDSS, Health and Demographic Surveillance System; HTC, HIV Testing and Counselling; EIA, Enzyme-linked Immunosorbent Assay.

the number of people testing recent prior and subsequent to viral-load testing and ART investigations. In relation to ART-exposure, we detail each misclassification case.

Using the Siaya county and, separately, the Zimbabwe data we describe the characteristics of those testing HIV-positive and classified as recent. To look for risk factors for recent HIV infection, we applied logistic regression where women testing HIV-positive and recent were compared with those testing HIV-negative. In Siaya County, due to a small number of recent cases, it was

not possible to apply logistic regression adjusting for multiple variables.

Using the Nairobi HTC data, we describe the characteristics of HIV-positive women and men with recent and long-standing infection. We applied logistic regression to compare the characteristics of those with recent infection with those with long-standing infection (it was not possible to compare to persons testing HIV-negative as these data were not available). To account for facility clustering, a generalized estimated equation (GEE) model that includes age at diagnosis, gender, and HIV testing history was applied. In Nairobi, participants confirmed to be HIV-positive, were counselled on index-testing and asked to bring their sexual partners to the facility for HIV and recent infection testing. We describe the characteristics of these partners.

Due to small cell counts, and to avoid deductive disclosure, testing facility was either anonymized or combined in our analysis. Percentages are presented as among persons for whom information was available, confidence intervals are presented at the 95% level, and Wald and likelihood-ratio tests were applied for logistic regression. In Zimbabwe (only pilot for which the necessary data were available), we assessed recent infection clustering by sample collection date and testing facility. STATA15 (Stata Corp, College Station, TX) was used for analyses.

2.3 | Ethical approval

Local approval was provided by KEMRI Scientific Ethics Review Unit (SERU application 3589) and London School of Hygiene & Tropical Medicine (LSHTM) (reference number 14458) for the pilot in Kisumu, by the ethical committee of Medical Research Council of Zimbabwe for the Zimbabwe pilot and by Kenyatta National Hospital-University of Nairobi Ethical Review Board for the pilot in Nairobi. Ethical approval was also obtained at the LSHTM for the Zimbabwe pilot (reference number 14542) and Nairobi pilot (reference number 14585).

3 | RESULTS

3.1 | Siaya County, Kenya: antenatal clinics providing PMTCT services

Over the study period, 2409 eligible women presented at participating antenatal clinics, of whom 2364 (98.1%) consented to participate in the study (Figure 2). Of these women, 1806 (76.4%) were under 30 years of age, 1792 (75.8%) were married and 1157 (48.9%) had experienced three or more pregnancies. In total, 444 (18.8%) women tested HIV-positive, of whom 426 (95.6%) had a valid LAg and viral-load test (18 women did not consent to recency testing). Among these 426 women, 106 (24.9%) tested recent prior to viral-load being considered, with 11 (2.6%) testing recent with a viral-load> 1000 copies/mL.

Of the 11 women classified as recent based on their LAg and viral-load tests, one was reclassified as long-standing when clinical documentation of treatment was also considered (recency misclassification of 9.1% (1/11)). For this woman there was clinical documentation of her having initiated treatment almost four years prior to their sample collection date

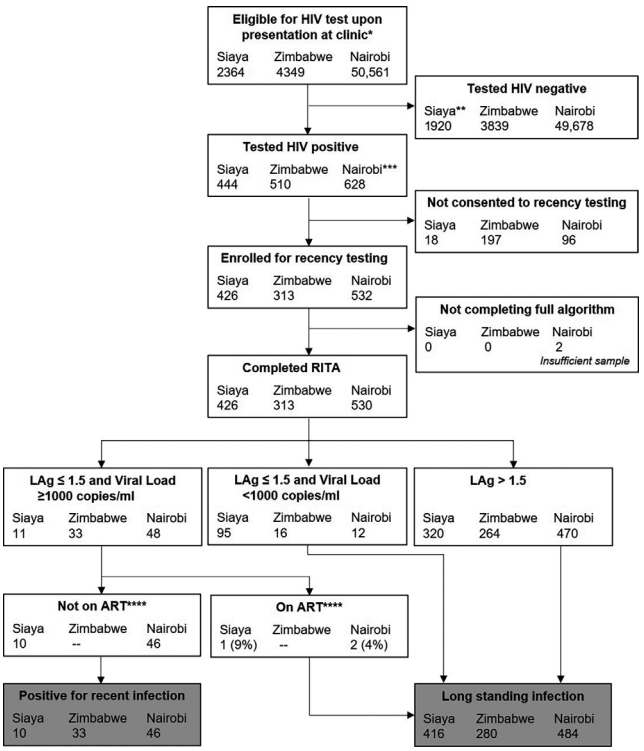

Figure 2. Recruitment and testing flowchart for the three pilots. *Eligibility criteria: providing consent for HIV testing & in Zimbabwe: not having been tested in previous three months or taking ART. **1914 tested HIV-negative, six had unknown HIV status. ***883 tested HIV-positive, but 255 of these tested HIV+ before. ****In Siaya County, ART status was determined using clinic records; in Nairobi, ART status was determined using ARV metabolite testing; in Zimbabwe, ART status was not determined. RITA, recency testing algorithm

within the study. Of the remaining ten women, one initiated treatment 78 days prior to her study sample draw date. As her first known HIV-positive date was on the same date as ART initiation, she remained classified as recent. Another woman initiated ART three days prior to her study sample draw, and again remained classified as recent. Of the remaining eight women, four initiated treatment on the same day as their study sample draw, three initiated within 16 days of their sample draw, and one did not have documented date of ART initiation. Exploration of the women's HIV testing history for prevalent infection from the HDSS and ANC record, provided no further evidence of misclassification. In total 2.3% (10/426) of women were classified recent.

A total of 10 women classified as recent were identified at seven of the 14 clinics and had sample collection dates evenly distributed across the study period. Nine (90%) of the 10 women were under 30 years of age, and half (55.6%; 5/9 (1 missing record)) were in their first trimester of pregnancy.

Comparing HIV-positive women testing recent with women testing HIV-negative found women in their first trimester to have nearly a ten times increased odds of testing recent compared to those in their second or third trimester (Table 2). There were no notable differences in age, marital status, study facility, or number of pregnancies between HIV-negative women and HIV-positive women testing recent.

3.2 | Zimbabwe: national programme for female sex workers

In Zimbabwe, 9138 women presented at one of the six participating facilities, of whom 4349 (47.6%) were tested for HIV (routinely, women who have tested for HIV within the past three months, or who report ART use, are not offered an HIV test). Of these 4349 women, 511 (11.7%) tested HIV-positive, and of these, 313 (61.3%) agreed to have a sample taken for viral-load and recent infection testing. Almost half (141; 46.7%) of these women were aged between 25 and 34 years, and the majority attained a secondary school education (247; 81.8%) and/or were separated or divorced (177; 58.6%).

Among the 313 women who tested HIV positive, and for whom both a viral-load and a recent infection test was available, 15.7% (49/313) tested recent based on their LAg test result alone. Based on their LAg and viral-load (>1000 copies/mL), 33 (10.5%) of these women were classified as recent (Figure 2). Among the 313 women testing HIV-positive, by age, those aged 18 or 19 years had the highest percentage of recent infection (5/23; 21.7%). By education, HIV-positive women for whom secondary education was their highest attainment were most likely to test recent (31/246; 12.6%), whereas by marital status, those who were single or never married presented with the highest percentage of recent infection (17/87; 19.5%).

Table 3 characterizes HIV positivity among the 4349 women tested for HIV, and also presents a risk factor analysis of recent infection, comparing HIV-positive women with recent infection to HIV-negative women, adjusting for age and study facility. There was no strong evidence of an association between having a recent infection and any of the variables.

A visual assessment of the data suggested some clustering by sample collection date and testing facility. On one day during week five of recruitment, six women tested positive for recent infection. Three of these women tested at the same facility, and three were aged between 20 and 24 years. A statistical analysis of clustering over time (logistic regression with sample collection date as covariate) found no evidence of an association between recency test results and week ($p = 0.74$) or month ($p = 0.21$).

3.3 | Nairobi, Kenya: routine HIV testing and counselling clinics

In Nairobi, 50,561 eligible women and men presented at one of the fourteen participating facilities. Of these, 883 (1.75%) tested HIV-positive, of whom 255 (28.9%) were subsequently found on enquiry (self-reported test history) to have tested HIV-positive before and were therefore ineligible for recency testing (Figure 2). In total, 532 (84.7%; 628) of those eligible consented to test for recent infection. Among these, 316 (59.4%) were female, of whom 57 (18%) were pregnant. The majority of participants (64.1%; 341) had previously tested for HIV, with a third (33.6%; 179) having tested in the past 12 months.

Two of the 532 people consenting to participate were subsequently found to have insufficient sample to test. Of the remaining 530 people testing for recent infection and viral-load, 60 (11.3%) tested recent based on the LAg test result

Table 2. Characterization of HIV and recent infection among antenatal clinic attendees in Siaya County testing for HIV

	HIV positivity	Risk factor analysis for recent infection		
Characteristics	**n/N[a] (%)**	**n/N[b] (%)**	**Crude OR (95% CI)**	***p*-value**
Age (years)				
<20	30/503 (6.0)	2/475 (0.4)	0.74 (0.10 to 3.8)	0.72
20 to 24	100/794 (12.6)	4/698 (0.6)	1	-
25+	314/1060 (29.6)	4/750 (0.5)	0.93 (0.22 to 3.9)	0.92
Study site				
1[c]	102/522 (19.5)	3/423 (0.7)	1.5 (0.33 to 5.5)	0.54
Other	342/1836 (18.6)	7/1501 (0.5)	1	
Marital status				
Married	364/1787 (20.4)	7/1430 (0.5)	1	
Single	40/500 (8.0)	2/462 (0.4)	0.88 (0.13 to 3.7)	0.88
Separated/ divorced/ widowed	39/69 (56.5)	1/31 (3.2)	6.8 (0.36 to 39.8)	0.08
Trimester				
1st	74/289 (25.6)	5/215 (2.3)	9.6 (2.5 to 39.2)	<0.001
2nd & 3rd	347/2005 (17.3)	4/1658 (0.2)	1	-
Pregnancies				
1	39/663 (5.9)	3/627 (0.5)	1	
2	91/519 (17.5)	5/433 (1.2)	2.4 (0.59 to 11.9)	0.22
3+	302/1157 (26.1)	2/857 (0.2)	0.49 (0.06 to 2.9)	0.43

[a]n = testing HIV-positive; N = testing for HIV; [b]n = testing recent; N = testing HIV-negative + testing recent; [c]Testing facility 1is the largest facility by patient volume.

Table 3. Characterization of HIV and recent infection among female sex workers testing for HIV in Zimbabwe

	HIV positivity	Risk factor analysis for recent infection				
	n/N[a] (%)	n/N[b] (%)	Crude OR (95% CI)	*p*-value	Adjusted OR[c] (95% CI)	*p*-value
Age (years)				0.37		0.3
18 to 19	39/405 (9.6)	5/372 (1.4)	1		1	
20 to 24	143/1309 (10.9)	13/1180 (1.1)	0.82 (0.29 to 2.31)		0.79 (0.28 to 2.25)	
25 to 34	232/1679 (13.8)	13/1460 (0.9)	0.66 (0.23 to 1.86)		0.60 (0.21 to 1.74)	
35+	78/676 (11.5)	2/600 (0.3)	0.24 (0.05 to 1.27)		0.22 (0.04 to 1.16)	
Study site				0.18		0.12
1	89/744 (12.0)	6/661 (0.9)	1		1	
2	57/414 (13.8)	1/358 (0.3)	0.31 (0.04 to 2.55)		0.33 (0.04 to 2.79)	
3	228/1518 (15.0)	11/1302 (0.9)	0.93 (0.34 to 2.53)		1.04 (0.38 to 2.87)	
4	37/357 (10.4)	5/325 (1.5)	1.71 (0.52 to 5.63)		2.08 (0.62 to 6.94)	
5	61/477 (12.8)	7/423 (1.7)	1.84 (0.61 to 5.50)		2.08 (0.69 to 6.28)	
6	39/839 (4.7)	3/803 (0.4)	0.41 (0.10 to 1.64)		0.42 (0.10 to 1.69)	
Education				0.15		0.15
Primary or less	87/635 (13.7)	2/550 (0.4)	1		1	
Secondary or higher	400/3374 (11.9)	31/3005 (1.0)	2.87 (0.68 to 12.01)		2.89 (0.68 to 12.24)	
Marital status				0.12		0.07
Single/ never married	148/1341 (11.0)	17/1210 (1.4)	1		1	
Married/ living together as if married	30/149 (20.1)	2/121 (1.7)	1.18 (0.27 to 5.17)		1.82 (0.39 to 8.45)	
Divorced/ separated	290/2372 (12.2)	13/2098 (0.6)	0.44 (0.21 to 0.90)		0.38 (0.17 to 0.84)	
Widowed	24/188 (12.8)	1/165 (0.6)	0.43 (0.06 to 3.24)		0.50 (0.06 to 4.18)	

[a]n = testing HIV-positive (of the 511 women testing HIV positive, regardless of viral-load and recency test); N = testing for HIV; [b]n = testing recent; N = testing HIV-negative + testing recent; [c]Adjusted for age and study site. OR, odds ratio; CI, confidence interval.

alone, with 48 (9.1%) testing recent with a viral-load> 1000 copies/ml (Table 4). ART metabolite testing identified one woman and one man among these 48 to have been wrongly classified (misclassification of 4.2%). In total, 8.7% (46/530) of people were classified as recent. Among women this percentage was 12.4% (39/315) and among men 3.3% (7/215).

Around half (45.7%; n = 21) of the 46 people newly testing HIV-positive who also tested recent were aged under 25 years and the proportion with a recent infection declined with increasing age, see Table 4. Just over half of those testing recent were married or co-habiting (52.2%; n = 24), and had tested HIV-negative in the past 12 months (54.3%; n = 25). The percentage of people newly testing HIV-positive who had previously tested for HIV during the past 12 months was higher among those classified as recent (54.3%; n = 25) than among those classified as having long-standing infection (31.6%; 153/484).

Among people newly testing HIV-positive (recent and long-standing infection), being a woman, being under 25 years of age, having tested for HIV in the last 12 months, and presenting at the facility with the largest catchment area and largest corresponding patient volume were shown to be individually predictive of recent infection (Table 4). Testing for interactions indicated an interaction between age at diagnosis and gender (Table 5). Young women (15 to 29 years old) had 3.85 times the odds of recent infection than men in the same age group. Participants reporting having tested for HIV in the past 12 months had 1.72 times the odds of recent infection compared to those reporting having last tested more than 12 months ago.

Following an HIV-positive test result and counselling, 144 (27.1%) of participants subsequently brought a sexual partner to the clinic for HIV testing. Of these 144, two brought in two partners, making the total 146. Among the 146 sexual partners of index cases testing for HIV, 61 (41.8%) tested positive for HIV. Among these 61 HIV-positive partners, 21 subsequently enrolled in the pilot, of whom five (5/21; 23.8%) were classified as recent. The percentage of partners testing HIV-positive, and being classified as recent, were significantly higher than the corresponding percentages among all non-partner (i.e. the recruitment figures presented above less the 146 partners) participants ($p < 0.001$ & $p = 0.019$ respectively).

4 | DISCUSSION

We successfully conducted three independent but linked pilots in routine programme setting in Kenya and Zimbabwe to identify people with recently acquired HIV infection. Among HIV-positive participants, we report 2.3% of pregnant women in Siaya County, 10.5% of FSW in Zimbabwe and 12.4% of women and 3.3% of men attending HTC facilities in Nairobi to have been diagnosed with recent infection. Among partners of participants in Nairobi, the percentage was 23.8%.

In Siaya County we found women in their first trimester to be significantly more likely to test recent compared to those in their second or third trimester. While inference with small numbers is challenging, this finding may relate to increased

Table 4. Characterization of recent and long-standing infection among women and men newly testing HIV-positive in HIV testing and counselling facilities in Nairobi

Characteristics[a]	Recent		Long-standing		Recency[b]
N = 530	N = 46	%	N = 484	%	%
Sex					
Male	7	15.2	208	43.0	3.3
Female	39	84.8	276	57.0	12.4
Age (years)					
15 to 19	5	10.9	13	2.7	27.8
20 to 24	16	34.8	79	16.3	16.8
25 to 29	13	28.3	102	21.1	11.3
30 to 34	7	15.2	100	20.7	6.5
35 to 39	2	4.3	80	16.5	2.4
40+	3	6.5	110	22.7	2.7
Testing facility					
1[c]	9	19.6	36	7.5	20.0
Other	37	80.4	447	92.5	7.6
Marital status					
Single	15	32.6	97	20.0	13.4
Married/co-habiting	24	52.2	269	55.6	8.2
Separated	6	13.0	74	15.3	7.5
Divorced	0	0.0	10	2.1	0.0
Widowed	1	2.2	31	6.4	3.1
Unknown	0	0.0	3	0.6	0.0
Highest level of education					
None	2	4.3	7	1.4	22.2
Primary	16	34.8	251	51.9	6.0
Secondary	21	45.7	176	36.4	10.7
Tertiary	7	15.2	48	9.9	12.7
Unknown	0	0.0	2	0.4	0.0
Employment status					
Employed	28	60.9	347	71.7	7.5
Unemployed	18	39.1	135	27.9	11.8
Unknown	0	0.0	2	0.4	0.0
Ever tested for HIV					
Yes	35	76.1	305	63.0	10.3
No	11	23.9	179	37.0	5.8
Tested for HIV in last 12 months					
Yes	25	54.3	153	31.6	14.0
No	21	45.7	329	68.0	6.0
Unknown	0	0.0	2	0.4	0.0
Pregnancy status (n = 316)					
Pregnant	10	25.6	47	17.0	17.5
Not-pregnant	29	74.4	229	83.0	11.2

[a]Excludes two participants for whom there was insufficient sample to test; [b]Calculated as recent infection/ newly testing HIV-positive (recent & long-standing infections); the denominator only includes new HIV-positives as repeat testers were excluded; [c]Testing facility 1 is the largest facility by catchment area and patient volume

risk of HIV infection during unprotected sex leading to pregnancy, and/or may be due to lowered coital frequency among women later in pregnancy. The former of these two potential explanations would support the targeting of women trying to get pregnant, particularly those in sero-discordant couples, with interventions such as PrEP and partner testing. In Kenya, the offering of HTC to the partners of persons diagnosed with HIV is already encouraged [19].

Among FSW in Zimbabwe, there was no strong evidence of associations with testing recent when comparing HIV-positive women with recent infection to HIV-negative women. One likely reason for this is the relatively small number of women found to have a recent infection. Despite a lack of association, and despite FSW in Zimbabwe being a known high-risk group [20,21], we would argue that ongoing efforts to differentiate prevention needs among FSW are applicable. These efforts should include the expanded roll-out of recency testing at venues utilized by FSW and, where possible, through the collection of more detailed information on previous HIV test history.

In Nairobi, we found young women newly testing HIV-positive were significantly more likely to test recent than their male counterparts. The observed difference by sex is probably due to women presenting earlier in their course of infection than men. Among those newly testing HIV-positive, women, as compared to men, were younger at age of HIV diagnosis, and were more likely to have ever tested and to have tested within the last 12 months. We were unable to investigate why women may present earlier than men. We also found participants newly testing HIV-positive who had tested for HIV in the past 12 months were significantly more likely to test recent than those having tested over a year ago. This probably reflects that people who are HIV-negative that test more frequently (potentially due to engaging more frequently in risk behaviour) will test recent when first diagnosed with HIV. Interestingly, we found significantly higher yields of HIV and recent infection among partner, as compared to non-partner, participants in Nairobi. Although based on small numbers, these results provide support for recency test results among index cases informing partner testing strategies [15].

In two of our three pilots there was some suggestion of clustering by sample collection date or testing facility. In Zimbabwe, six of the 33 women testing recent did so on the same day, with three also testing at the same facility. In Nairobi, the facility with the largest catchment area and patient volume presented with a significantly higher percentage of recent infections than at smaller facilities. Although we only present suggestive evidence, information on recent infection clustering in time and space could be used to target prevention efforts in specific geographical areas and specific populations; for example mobilizing outreach teams to promote HIV testing or deliver PrEP.

Several studies have explored recent infection testing in sub-Saharan Africa. A number of these studies conducted recency testing as a means to estimate HIV incidence rather than an end in itself [22,23]. However, a couple of studies provide details on recency testing and present recency percentages similar to those we report. Among participants aged 15 to 49 years providing DBS samples as part of the 2012 national population-based household surveys in Kenya and South Africa, 4.5% (21/470) and 3.3% (73/2,202) tested recent respectively [4]. The authors of this study conclude that information on viral-load and ART-exposure in their RITA potentially improved the predictive value of the RITA [4]. Another study tested the

Table 5. Predictors of recent infection, disaggregated by gender, among women and men newly testing HIV-positive in HIV testing and counselling facilities in Nairobi

	Male			Female		
	N	aOR (95%CI)	*p*-value	N	aOR (95%CI)	*p*-value
Aged 15 to 29 years	58	1	-	171	1	-
Aged 30+ years	158	0.99 [0.94, 1.06]	0.87	145	0.23 [0.16, 0.32]	<0.01
Tested over 12 months ago	162	1	-	189	1	-
Tested within last 12 months	53	1.05 [1.01, 1.08]	0.01	126	2.12 [1.83, 2.45]	<0.01

DBS stored samples of people aged 15 to 64 years participating in the 2007 Kenya AIDS Indicator Survey for recent infection. Among these participants, 6.2% (64/1,025) were classified as recent [3]. Compared to persons testing HIV-negative, factors associated with recent infection in this population included being widowed or currently married (compared to being never married), having had two or more sexual partners in the last year, not using a condom at last sex in the past year, and reporting a sexually transmitted infection diagnosis or symptoms in the past year [3].

There were a number of limitations to our study. In Siaya county and Zimbabwe recency testing was conducted on venous blood samples whereas in Nairobi DBS was used. As we did not compare the performance of these two methods, results across the three pilots should be compared with caution. We planned to conduct ART metabolite testing in all three pilots. Due to challenges in attaining import and export licences to transport samples to the University of Cape Town we were only successful in carrying out ART testing in our Nairobi pilot. In Zimbabwe, routinely applied criteria for conducting an HIV test reduced the number of women eligible for inclusion in our study, thereby potentially reducing the number of women found to be HIV-positive and recent. Furthermore, the fairly low participation rate in recency testing (61.3%) among the women testing HIV-positive ensures our results should be interpreted with caution, given the possibility for selection bias. In Nairobi, we were unable to attain detailed information on people testing HIV-negative. Therefore, in contrast to Siaya County and Zimbabwe, we compare persons testing recent with long-standing infection rather than HIV-negativity.

For programmes to include recency testing as part of routine HIV service delivery for the purpose of identifying priority populations for primary prevention efforts (the first step of a unifying HIV prevention cascade framework described by Schaefer *et al*) [24], there are a number of considerations. Programmes can anticipate additional costs resulting from test assays and logistics related to sample handling [25], needing to make modifications to client flows (e.g. to draw additional amounts of blood for laboratory-based testing), and providing additional training to healthcare workers. The collection, transportation, storage and testing of samples (DBS and plasma) will need to be closely monitored to ensure assay manufacturer's instructions for use are being followed, and testing laboratories will require training in the performance of the assay and should partake in an external quality-assurance scheme. To guarantee the inclusion of ART metabolite testing in the interpretation of LAg test results, the process for transporting samples outside of country should be reviewed prior to commencement of testing, and simpler assays should be developed so that blood samples may be tested at in-country laboratory facilities. Finally, programmes will need to consider potential prevention interventions resulting from recent infections, such as partner testing, PrEP delivery and community prevention initiatives.

5 | CONCLUSIONS

At a time when the national surveillance of recent infection is being promoted across sub-Saharan Africa [14,15], we show that integrating recency testing into routine programme activities in Kenya and Zimbabwe is feasible. In identifying recently acquired infections among persons testing HIV-positive, we highlight the importance of incorporating information on viral-loads and ART to accurately classify recent infection. Having identified a number of groups with a significantly higher proportion of recent infection, we highlight how recency surveillance may help us in further targeting primary prevention efforts. The identification of hotspots of transmission and characteristics associated with new infection, even among high-incidence populations, could inform where and among whom primary prevention efforts should be strengthened.

AUTHORS' AFFILIATIONS

[1]London School of Hygiene & Tropical Medicine, London, UK; [2]University of California, San Francisco, USA; [3]Centre for Sexual Health and HIV/AIDS Research, Harare, Zimbabwe; [4]Independent consultant in HIV laboratory diagnostics, London, UK; [5]Eastern Deanery AIDS Relief Programme, Nairobi, Kenya; [6]Kenya Medical Research Institute, Kisumu, Kenya

COMPETING INTERESTS

We, the authors, have no conflicts of interest to declare.

AUTHORS' CONTRIBUTION

BR wrote the paper and conceived, organized and led the study. MdW, SW, KR and SC analysed the data. WW, SM, JM, DK and BO coordinated the study. FC, GReniers and GRutherford implemented the work. GM supported the laboratory analyses. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

We gratefully acknowledge all the members of the MeSH Working Group on routine HIV recent infection testing for their contributions to running these three pilots of recency testing. We also wish to thank the many individuals who participated in our pilots.

REFERENCES

1. Janssen RS, Satten GA, Stramer SL, Rawal BD, O'Brien TR, Weiblen BJ, et al. New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. JAMA. 1998;280(1):42–8.
2. UNAIDS/WHO Working Group on Global HIV/AIDS and STI surveillance. When and how to use assays for recent infection to estimate HIV incidence at a population level. 2011 [cited 2019 Sept 19]. Available from: https://www.who.int/diagnostics_laboratory/hiv_incidence_may13_final.pdf
3. Mastro TD, Kim AA, Hallett T, Rehle T, Welte A, Laeyendecker O, et al. Estimating HIV incidence in populations using tests for recent infection: issues, challenges and the way forward. J HIV AIDS Surveill Epidemiol. 2010;2(1):1–14.
4. Xu Y, Laeyendecker O, Wang R. Cross-sectional human immunodeficiency virus incidence estimation accounting for heterogeneity across communities. Biometrics. 2019;75(3):1017–28.
5. Kim AA, Rehle T. Short communication: assessing estimates of HIV incidence with a recent infection testing algorithm that includes viral load testing and exposure to antiretroviral therapy. AIDS Res Hum Retroviruses. 2018;34(10):863–6.
6. Kim AA, Parekh BS, Umuro M, Galgalo T, Bunnell R, Makokha E, et al. Identifying risk factors for recent HIV infection in Kenya using a recent infection testing algorithm: results from a Nationally representative population-based survey. Plos One. 2016;11:e0155498.
7. Kim AA, Behel S, Northbrook S, Parekh BS. Tracking with recency assays to control the epidemic: real-time HIV surveillance and public health response. AIDS. 2019;33(9):1527–9.
8. Brown LB, Miller WC, Kamanga G, Kaufman JS, Pettifor A, Dominik RC, et al. Predicting partner HIV testing and counseling following a partner notification intervention. AIDS Behav. 2012;16(5):1148–55.
9. Sempa JB, Welte A, Busch MP, Hall J, Hampton D, Facente SN, et al. Performance comparison of the Maxim and Sedia limiting antigen avidity assays for HIV incidence surveillance. PLoS ONE. 2019;14:e0220345.
10. World Health Organization. WHO working group on HIV incidence measurement and data use: 3–4 March 2018, Boston, MA, USA: meeting report. 2018 [cited 2020 Mar 5]. Available from: https://apps.who.int/iris/bitstream/handle/10665/272940/WHO-CDS-HIV-18.9-eng.pdf
11. International Center for AIDS Care and Treatment Program CU. What is PHIA? 2020. [cited 2020]. Available from: https://phia.icap.columbia.edu/about/
12. Centers for Disease Control and Prevention. Frequently Asked Questions: Population-based HIV Impact Assessments. 2017 [cited 2020 Mar 5]. Available from: https://www.cdc.gov/globalhivtb/images/PHIA-FAQs.pdf
13. Justman JE, Mugurungi O, El-Sadr WM. HIV population surveys - bringing precision to the global response. N Engl J Med. 2018;378(20):1859–61.
14. President's Emergency Plan for AIDS Relief. PEPFAR 2019 Country Operational Plan Guidance for all PEPFAR Countries. 2019 [cited 2019 Sept 19]. Available from: https://www.state.gov/wp-content/uploads/2019/08/PEPFAR-Fiscal-Year-2019-Country-Operational-Plan-Guidance.pdf
15. President's Emergency Plan for AIDS Relief. Surveillance of Recent HIV Infections: Using a Point-of-Care Recency Test to Rapidly Detect and Respond to Recent Infections. 2018 [cited 2019 Sept 19]. Available from: https://www.pepfarsolutions.org/emerging-technologies-innovations/2018/7/11/surveillance-of-recent-hiv-infections-using-point-of-care-recency-tests-to-rapidly-detect-and-respond-to-recent-infections
16. Aghaizu A, Murphy G, Tosswill J, DeAngelis D, Charlett A, Gill ON, et al. Recent infection testing algorithm (RITA) applied to new HIV diagnoses in England, Wales and Northern Ireland, 2009 to 2011. Eurosurveillance. 2014;19(2):20673
17. Jung BH, Rezk NL, Bridges AS, Corbett AH, Kashuba AD. Simultaneous determination of 17 antiretroviral drugs in human plasma for quantitative analysis with liquid chromatography-tandem mass spectrometry. Biomed Chromatogr. 2007;21(10):1095–104.
18. University of Cape Town. Division of Clinical Pharmacology. 2020 [cited 2020 Mar 12]. Available from: http://www.medicine.uct.ac.za/med/divisions/pharmacology
19. Kenya Ministry of Health. AIDS Strategic Framework. 2019 [cited 2019 Sept 19]. Available from: http://nacc.or.ke/wp-content/uploads/2015/09/KASF_Final.pdf
20. Cowan FM, Davey CB, Fearon E, Mushati P, Dirawo J, Cambiano V, et al. The HIV Care cascade among female sex workers in Zimbabwe: results of a population-based survey from the sisters antiretroviral therapy programme for prevention of HIV, an integrated response (SAPPH-IRe) Trial. J Acquir Immune Defic Syndr. 2017;74(4):375–82.
21. Fearon E, Phillips A, Mtetwa S, Chabata ST, Mushati P, Cambiano V, et al. How can programmes better support female sex workers to avoid HIV infection in Zimbabwe? a prevention cascade analysis. J Acquir Immune Defic Syndr. 2019.
22. Grebe E, Welte A, Johnson LF, van Cutsem G, Puren A, Ellman T, et al. Population-level HIV incidence estimates using a combination of synthetic cohort and recency biomarker approaches in KwaZulu-Natal, South Africa. PLoS ONE. 2018;13:e0203638.
23. Rehle T, Johnson L, Hallett T, Mahy M, Kim A, Odido H, et al. A comparison of South African National HIV incidence estimates: a critical appraisal of different methods. Plos One. 2015;10:e0133255.
24. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett TB, Hargreaves JR. HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades. Lancet HIV. 2019;6(1):e60–e6.
25. Grebe E, Welte A, Hall J, Busch MP, Facente SN, Keating SM, et al. Recency staging of HIV Infections Through Routine Diagnostic Testing [abstract]. Conference on Retroviruses and Opportunistic Infections; 2017; Seattle. Abstract nr 511.
26. Kenya Ministry of Health. Kenya HIV estimates report 2018. 2018 [cited 2019 Sept 19]. Available from: https://nacc.or.ke/wp-content/uploads/2018/11/HIV-estimates-report-Kenya-20182.pdf.
27. Kohler PK, Okanda J, Kinuthia J, Mills LA, Olilo G, Odhiambo F, et al. Community-based evaluation of PMTCT uptake in Nyanza Province, Kenya. Plos One. 2014;9:e110110. https://doi.org/10.1371/journal.pone.0110110. eCollection.
28. Eastern Deanery AIDS Relief Program. Our Background. 2019 [cited 2019 Sept 19]. Available from: www.edarp.org
29. Cowan FM, Davey C, Fearon E, Mushati P, Dirawo J, Chabata S, et al. Targeted combination prevention to support female sex workers in Zimbabwe accessing and adhering to antiretrovirals for treatment and prevention of HIV (SAPPH-IRe): a cluster-randomised trial. Lancet HIV. 2018;5(8):e417–e26.
30. Ndori-Mharadze T, Fearon E, Busza J, Dirawo J, Musemburi S, Davey C, et al. Changes in engagement in HIV prevention and care services among female sex workers during intensified community mobilization in 3 sites in Zimbabwe, 2011 to 2015. J Int AIDS Soc. 2018;21 Suppl 5:e25138.
31. Hargreaves JR, Mtetwa S, Davey C, Dirawo J, Chidiya S, Benedikt C, et al. Implementation and operational research: cohort analysis of program data to estimate HIV incidence and uptake of HIV-related services among female sex workers in Zimbabwe, 2009–2014. J Acquir Immune Defic Syndr. 2016;72(1):e1–8.

Virkud AV et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25523
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25523/full | https://doi.org/10.1002/jia2.25523

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Access to HIV prevention services in East African cross-border areas: a 2016-2017 cross-sectional bio-behavioural study

Arti V Virkud[1,§], Peter Arimi[2], Freddie Ssengooba[3], Grace E Mulholland[1], Michael E Herce[4], Milissa Markiewicz[5], Sharon Weir[1,5] and Jessie K Edwards[1]

[§]**Corresponding author**: Arti V Virkud, 135 Dauer Dr., 2101 McGavran-Greenberg Hall, Chapel Hill, North Carolina 27599, USA. (avirkud@unc.edu)

Abstract

Introduction: East African cross-border areas are visited by mobile and vulnerable populations, such as men, female sex workers, men who have sex with men, truck drivers, fisher folks and young women. These groups may not benefit from traditional HIV prevention interventions available at the health facilities where they live, but may benefit from services offered at public venues identified as places where people meet new sexual partners (e.g. bars, nightclubs, transportation hubs and guest houses). The goal of this analysis was to estimate availability, access and uptake of prevention services by populations who visit these venues.

Methods: We collected cross-sectional data using the Priorities for Local AIDS Control Efforts sampling method at cross-border locations near or along the land and lake borders of Kenya, Rwanda, Tanzania and Uganda from June 2016–February 2017. This bio-behavioural survey captured information from a probability sample of 11,428 individuals at 833 venues across all areas. Data were weighted using survey sampling weights and analysed using methods to account for the complex sampling design.

Results: Among the 85.6% of persons who had access to condoms, 60.5% did not use a condom at their last anal or vaginal sexual encounter. Venues visited by high percentages of persons living with HIV were not more likely than other venues to offer condoms. In 12 of the 22 cross-border areas, male or female condoms were available at less than 33% of the venues visited by persons having difficulty accessing condoms. In 17 of the 22 cross-border areas, education outreach visits in the preceding six months occurred at less than 50% of the venues where participants had low effective use of condoms.

Conclusions: Individuals visiting venues in cross-border areas report poor access to and low effective use of condoms and other prevention services. Availability of HIV prevention services differed by venue and population type and cross-border area, suggesting opportunities for more granular targeting of HIV prevention interventions and transnational coordination of HIV programming.

Keywords: HIV; Africa; Eastern; border crossing; condoms; female; vulnerable populations

Additional Supporting Information may be found online in the Supporting Information tab for this article.

Received 30 September 2019; **Accepted** 23 April 2020

1 | INTRODUCTION

Achieving the UNAIDS 2030 goals to reduce new HIV infections to 200,000 per year will require optimization of HIV prevention and testing [1]. While HIV treatment has been crucial in reducing the number of new infections, combination HIV prevention to reduce transmission risk is still necessary to meet these goals [2]. Primary HIV prevention interventions include routine HIV testing services (HTS), provision of condoms and sexual lubricants, pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), voluntary medical male circumcision, sexually transmitted infection (STI) screening and treatment, and needle and syringe programmes. These primary prevention interventions have all been shown to reduce new infections [1,3-6].

East African cross-border areas are important mixing grounds for populations at risk of acquiring HIV and may be underserved by national prevention efforts. Social venues, like bars and nightclubs, in these areas are visited by a diverse population often looking to meet new sexual and needle-sharing partners, and are exposed to a unique blend of national and local HIV prevention programming. These areas are visited by traditionally defined key populations, such as female sex workers, men who have sex with men and persons who

inject drugs, as well as other populations at elevated risk for HIV, such as truck drivers, fisher folk (persons who self-identify as engaged in fishing industry) and young women [7-10]. The presence of these key and priority populations make cross-border areas important focal points for HIV prevention efforts [11,12].

While national HIV strategic plans across East African countries recommend similar prevention interventions, the prioritization of key populations differs across national plans [7-9,13]. Key and mobile populations visiting cross-border venues may not be reached by recommended facility-based prevention services near where they reside [14,15]. Better specifying gaps in HIV prevention programming using a cascade analysis and geographically targeting effective services to the places where mobile and key populations meet and socialize can help ensure that these populations are not neglected in regional cross-border HIV prevention efforts [16].

The availability and effective use of HIV prevention services at East African cross-border areas is not well understood. A deeper understanding of how these services are distributed and where gaps exist can help drive improvement of existing HIV prevention programmes and the introduction of future interventions. In this paper, we describe the distribution and uptake of primary HIV prevention services, specifically condom availability, at venues identified as places where people meet new sexual partners in cross-border areas. We highlight the extent to which HIV prevention service availability aligns with the presence of high-risk behaviours and HIV prevalence. We also examine gaps in prevention access and utilization through the lens of a programmatically relevant "prevention cascade" framework [17-21] and map disparities between services nominally offered at cross-border venues and their availability as reported by venue patrons.

2 | METHODS

2.1 | Study population

We examine the distribution of prevention services in East Africa cross-border areas using data from the Cross-Border Integrated Health Study (CBIHS), described in detail elsewhere [15]. Briefly, the CBIHS collected data describing the health status and behaviours of populations living in and/or travelling through 14 cross-border areas, representing 22 unique locations in the East African countries of Kenya, Rwanda, Tanzania and Uganda between June 2016 and February 2017. The selected cross-border areas were chosen based on high level of cross-border traffic and/or trade and sizeable populations. Of the selected areas, eight surrounded international border posts on major transport corridors, and six were situated around fishing villages on Lake Victoria that serve as points of international commerce.

2.2 | Study data collection

In each selected area, the Priorities for Local AIDS Control Efforts (PLACE) method was used to collect information on venues where people socialize and meet new sexual partners and to collect health behaviour and outcome data for people at these venues [14,22-25]. The PLACE method, explained in Data S1, aims to help local officials prioritize and allocate resources by identifying and characterizing populations that may benefit from HIV prevention and treatment services and venues where these populations can be reached.

2.3 | Ethics

Study protocol (IRB number 15-3234) and activities were reviewed and approved by the Institutional Review Board at the University of North Carolina in Chapel Hill; Makerere University Higher Degrees, Research, and Uganda National Council of Science and Technology; the Kenya Medical Research Institute Ethics Review Committee; the National Institute for Medical Research in Tanzania; and the Rwanda National Ethics Committee. All participants in the bio-behavioural survey provided written informed consent.

2.4 | Variable coding

Characteristics of the venues were defined by responses from informants at the venue, hereafter: "informants." Prevention services examined include distribution of free condoms (male and female), free sexual lubricants, condoms for sale, availability of HIV testing, safer sex education by outreach workers, availability of needle exchange programmes, availability of male circumcision programmes and visits by outreach workers, sex worker peer educators, men who have sex with men peer educators, and/or mobile HIV-care clinics, as reported by informants. Education outreach was defined as present if informants reported the presence of safer sex education by outreach workers and visits by outreach workers, sex worker peer educators, men who have sex with men peer educators, and/or mobile HIV-care clinics at venues.

Characteristics of the population in this study were defined by responses to bio-behavioural survey questions provided by venue participants, hereafter: "participants." Condom availability was measured by an affirmative response to "If you wanted a condom, would it be easy for you to get one?", "In the past six months, has an outreach worker such as a peer educator given you a condom?", or "Do you have a condom with you now and can you show it to me [the interviewer]?". Effective condom use was measured from a series of four questions asking about the participation in vaginal sex in the prior year, the use of condom at last vaginal sex, the participation in anal sex in the prior year and the use of condom at last anal sex, where "I have never had penis to vagina/anal sex" was a response option.

Venues were classified as having a high percentage of persons living with HIV if prevalence among participants at the venue was in the top 33% of HIV prevalence estimates across all study venues. Similarly, venues were classified as having a high percentage of persons with unsuppressed viral load if the prevalence of unsuppressed viral load at the venue was in the top 33% of the prevalence distribution among study venues. HIV status was defined by the result from a rapid HIV test, except among those who refused the test or had a missing test result; in such cases, participants who reported a positive test result within the prior year were classified as living with HIV. Viral suppression was determined through analysis of dried blood spots and was defined as a viral load measurement under 1,000 copies/mL (see details in Data S1).

Table 1. Characteristics of venues in the East Africa Cross-Border Integrated Health Study, 2016-2017

	All venues (n = 883)		
	Count	Weighted %	95% CI
Venue type			
Bar/pub/restaurant	407	45.3	41.7, 48.9
Commercial venue[a]	74	9.4	7.2, 11.7
Hotel/guest house/lodge	266	29.9	26.6, 33.1
Nightclub/disco/brothel	22	2.4	1.3, 3.6
Outside venue[b]	39	4.5	3.0, 6.1
Transportation hub[c]	13	1.6	0.7, 2.6
Other	62	6.8	5.0, 8.6
Populations visiting venue			
Fisher folk	386	44.7	41.1, 48.3
Truck drivers	609	69.7	66.5, 73.0
Young women	282	34.0	30.5, 37.5
Homeless people	297	35.2	31.7, 38.7
Injection drug users	51	6.2	4.4, 8.0
Years in operation			
Less than 1 year	117	12.7	10.4, 15.1
More than 1 year	742	87.3	84.9, 89.6
Sale of alcohol	576	63.8	60.3, 67.3
Sex at venue	438	49.1	45.6, 52.6
Persons looking to pay for or sell sex at venue	471	55.0	51.4, 58.7
Female sex worker lives at venue	155	17.9	15.0, 20.7

[a]Commercial venues included markets, hair salons, shops, cinemas, recreation and game centres and schools; [b]Outdoor venues included beaches, parks, construction sites and streets; [c]Transportation hubs included truck stops and lorry/railway stations. CI, confidence interval.

2.5 | Statistical analysis

Two types of data were analysed: venue-level data and participant-level data. Venues were weighted to represent the distribution of characteristics across all venues at the selected cross-border areas. Participant-level data were weighted to represent the distribution of behaviours and other characteristics that would be observed among a random sample of individuals at venues at the selected cross-border areas. The participant-level data weights used to generate weighted estimates for behaviours, characteristics and viral suppression are described in the Data S1.

Applying weights and adjusting standard errors to account for the complex survey design, we estimated the distribution of venue characteristics, including type of venue and availability of HIV prevention services. At the participant level, using person-level weights and accounting for survey design, we estimated the distribution of demographic characteristics among populations found at venues in these cross-border areas and the distribution of HIV prevention behaviours, such as condom use, access to condoms and lubricants, and receipt of information about HIV prevention.

We estimated the weighted mean number of prevention services and the proportion of participants reporting high-risk behaviours for venues where a high percentage of persons living with HIV or unsuppressed HIV were found. We generated prevention cascades for condom availability, and effective use using weighted percentages for men, women, female sex workers and men who have sex with men. Among uninfected persons visiting venues, HIV testing history was categorized by ever been tested for HIV, testing in the prior year and receipt of test result. Finally, we generated maps of cross-border areas depicting the weighted percentage of venues with condoms available where visitors had difficulty accessing condoms and the percentage of venues visited by education outreach where visitors had low effective use of condoms. Analyses were conducted using SAS 9.4 software (SAS institute, Cary, NC) and R (version 3.5.4).

3 | RESULTS

3.1 | Study sample

Of 1161 venues sampled for venue verification, 883 were found operational with an informant willing to answer questions about the venue. Overall, 45.3% of venues were bars or pubs (Table 1). According to venue informants, 94.8% of venues were visited by members of at least one key or priority population, men or women visited the venue to pay for or sell sex at 55.0% of the venues, and among the venues where women and men were having sex, 71.9% (95% CI: 67.3, 76.4) had condoms available at the venue.

Among the 883 venues, 452 were sampled for the bio-behavioural interviews. At sampled venues, 11,410 individuals participated in the survey. The average age of participants was 30 years, 66.2% were male, 75.3% were employed and 46.1% had at least some secondary education (Table 2). Among women at venues, 21.3% (95% CI: 19.3, 23.2) reported that they had ever experienced physical violence and 12.4% (95% CI: 10.7, 14.1) had ever been forced to have sex. Among participants who were not living with HIV, 89.7% had previously received an HIV test, however, 20.9% of participants reported their last test was more than one year prior to the survey, not including the test offered at the time of the survey (Data S1).

3.2 | The condom cascade

The HIV prevention cascades for condoms demonstrate that the principal obstacle to condom use was lack of effective use (Figure 1). Among the 85.6% of participants who reported being able to obtain a condom, 60.5% reported not using a condom at their last sexual encounter (51.8% of the total uninfected population). However, a subset of participants reported difficulty accessing condoms (14.4%), with women (18.8%) more likely to report lack of access as a barrier to condom use than men (12.3%, Figure 2). Female sex workers at venues were more likely to report having access to and using condoms than other participant populations. Most men who have sex with men at venues reported access to condoms but low effective use.

Table 2. Demographics of participants in the East Africa Cross-Border Integrated Health Study, 2016-2017

	All participants (n = 11,410)		
	Unweighted mean/frequency	Weighted %	95% CI
Age – Mean (min, max)	30.2	30.4 (15, 85)	30.0, 30.7
Female	4175	33.8	32.1, 35.4
Pregnant[a]	244	8.2	6.8, 9.6
Education			
Less than primary school	2326	21.4	19.8, 23.1
Primary school	3827	32.5	30.8, 34.1
Some secondary or more	5241	46.1	44.1, 48.2
Employment			
Full, partial or informal	8511	75.3	73.4, 77.3
Not employed	2793	24.7	22.7, 26.6
Key populations			
Young women	1653	13.0	11.9, 14.1
Female sex workers	655	5.3	4.7, 6.0
Men who have sex with men	92	0.8	0.6, 1.0
Persons who inject drugs	55	0.6	0.4, 0.8
Fisher folk	1279	9.9	7.7, 12.1
Truck drivers	192	1.9	1.3, 2.4

[a]Weighted percentage of women who were pregnant at the time of interview among all women. Ci, confidence interval.

3.3 | Access to prevention services

Among participants, 92.6% of women and 92.4% of men reported having received information about HIV/AIDS either at the venue, on the radio, or from a health worker in the year prior to their interview (Table 3). Among participants who came to venues to find a sex partner (n = 1,040), 11.4% (95% CI: 7.6, 15.2) carried a condom with them. While 54.0% (95% CI: 47.7, 60.2) of those engaged in anal sex in the prior 12 months (n = 183) reported using a condom at their last anal sexual encounter, only 36.7% (95% CI: 34.9, 38.6) of those participating in vaginal sex (n = 9275) in the prior 12 months reported using a condom at last vaginal sex. Among participants reporting both anal and vaginal sex in the prior 12 months (n = 161), 44.0% reported consistent use of a condom at last anal and vaginal sexual encounter. Among participants reporting receipt of any HIV information and vaginal sex in the prior 12 months, 37.4% reported using condoms at last vaginal sexual encounter.

3.4 | Alignment of prevention services and high-risk venues

Venues visited by high percentages of people living with HIV, overall or unsuppressed, were not substantially more likely to have condoms available, according to venue informants than all venues combined (Table 4, 54.8% and 58.3% vs. 51.8%). Informants at venues in outside areas and transportation hubs, like railway stations and truck stops, reported an average of at least three prevention services across all cross-border areas (Table 5). The average number of prevention services offered per venue ranged from 0.1 to 3.4 at each cross-border area with notable differences in available services across border areas in Malaba, Katuna/Gatuna and Mutukula (Data S1). The most commonly reported prevention services included distribution or sale of male condoms and availability of HIV testing.

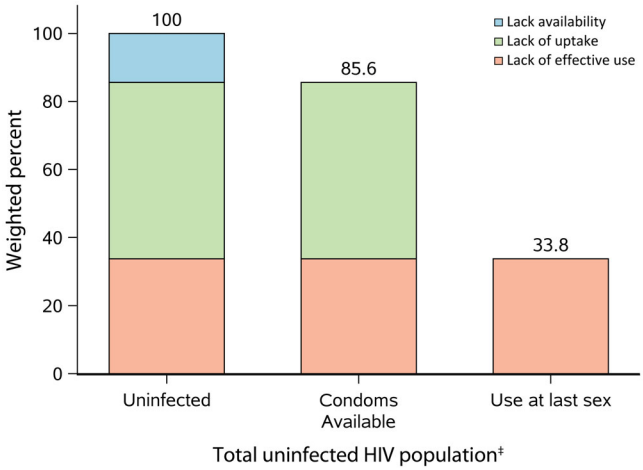

Figure 1. HIV intervention-centric prevention cascade among an uninfected HIV population in the East Africa Cross-Border Integrated Health Study, 2016-2017. [a]Color categories were generated using existing HIV prevention cascade frameworks [17]. [b]Uninfected are those who had sex in the prior year and were not infected with HIV.

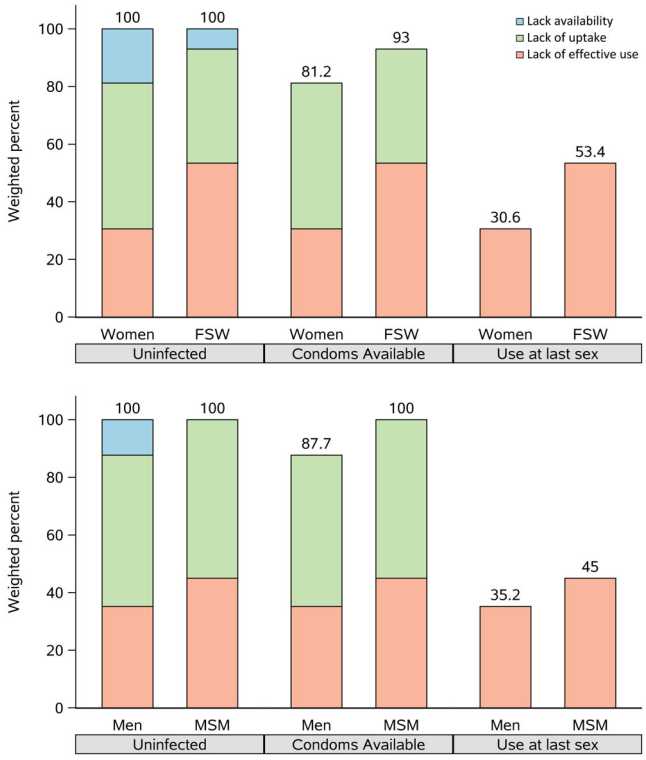

Figure 2. HIV intervention-centric prevention cascade in select populations in the East Africa Cross-Border Integrated Health Study, 2016-2017[a]. [a]Colour categories were generated using existing HIV prevention cascade frameworks [17]. [b]Uninfected are those who had sex in the prior year and were not infected with HIV.

3.5 | Disparities in availability and use of services

In 12 of the 22 cross-border areas, informants reported that free male or female condoms were available in the prior six months at less than 33.0% of the venues where participants reported difficulty accessing condoms at the venue (Figure 3). For 17 of the 22 cross-border areas, informants reported that, in the past six months, education outreach had visited less than 50.0% of the venues where participants reported low effective use of condoms (Figure 4). Many cross-border areas had large disparities in condom availability and use across the international border; in these areas, one side of the border may have many venues with both a high need for condoms (i.e. many participants who reported low access or effective use of condoms) and few services to address this gap (i.e. many informants reported no free condoms available and no education outreach at venues) despite high reported levels of access to/effective use of condoms and outreach activities at venues just across the border.

4 | DISCUSSION

The CBIHS identified important successes and opportunities for improving HIV prevention programming at cross-border areas in East Africa. We described a study population that was composed mostly of young men, suggesting that outreach to venues in cross-border areas may be a suitable strategy to reach men with HIV testing and other prevention services. Our analysis used novel HIV prevention cascades to visually represent data on HIV prevention intervention delivery. With this prevention cascade framework, we found that effective use at last sex was low despite generally high access to condoms. Our approach provides an illustrative example for how prevention cascades can be applied to guide assessment of other HIV prevention commodities, like PrEP and personal lubricants [17-20]. Lastly, we observed important differences in the availability of prevention services by venue type and within the same cross-border areas, suggesting opportunities for more granular targeting of venue-based prevention services and transnational coordination of HIV prevention programming.

Application of the cascade framework provides programme planners with a standardized way to visualize barriers to targeted HIV prevention delivery. The cascade format enables quick visualization of important opportunities (or the lack thereof) to prioritize and provide HIV prevention interventions. In our study, the application of the cascade framework identified adherence to condom use as a major barrier to overall effective use in cross-border areas. The cascade framework also creates a standardized way to compare efforts across different populations at risk, such as between men and men who have sex with men and between women and female sex workers as was done in our study. Based on such comparisons, it appears additional work must be done to reach men and women at venues who are not men who have sex with men or female sex workers, but who may nonetheless be at higher risk for HIV acquisition than people in the general population. Finally, while we focused on condoms for the prevention cascade in our study, the framework can extend to other prevention commodities, like PrEP [26].

Table 3. Access to prevention services among participants in the East Africa Cross-Border Integrated Health Study, 2016-2017

	Women (n = 4175)			Men (n = 7235)		
	Unweighted mean/ frequency	Weighted %	95% CI	Unweighted mean/ frequency	Weighted %	95% CI
Condom access and use						
Feel it is easy to get condom	2960	71.1	68.7, 73.5	5823	80.1	78.7, 81.6
Given condom by outreach worker in prior six months	1650	37.5	34.6, 40.4	3017	41.6	38.8, 44.4
In possession of a condom	192	4.3	3.3, 5.4	323	4.1	3.4, 4.9
Used condom at last anal sex (among those who had anal sex in the prior 12 months, **n = 183**)	44	48.9	41.9, 55.8	32	43.9	36.0, 51.8
Used condom at last vaginal sex (among those who had vaginal sex in the prior 12 months, **n = 9275**)	1173	35.7	32.9, 38.6	2200	37.3	35.2, 39.3
Other prevention services						
HIV testing in prior 12 months	3138	74.0	71.9, 76.1	4909	67.3	65.5, 69.2
Feel it is easy to get sexual lubricants	201	4.6	3.0, 6.1	305	4.0	3.1, 4.9
Circumcised (among men)	-	-	-	5506	77.0	75.1, 78.9
Received information about HIV/AIDS at the venue in the prior 12 months	2189	50.3	47.5, 53.2	3597	48.7	45.6, 51.8
Received information about HIV/AIDS on the radio in the prior 12 months	3652	86.2	84.7, 87.8	6426	88.4	87.0, 89.9
Received information about HIV/AIDS from health worker in the prior 12 months	3003	69.1	66.1, 72.1	4927	66.9	64.5, 69.3
Received information about HIV/AIDS from any source in the prior 12 months	3842	92.6	91.4, 93.7	6676	92.4	91.4, 93.5

The above programmatic applications notwithstanding, the prevention cascade has unique challenges compared to the traditional HIV care and treatment cascade, and has received some criticism for its limitations [27]. Many of these limitations have been identified previously in other applications of the prevention cascade framework to real-world data [17-19,26,28]. For example estimating the percentages contained in each step of a prevention cascade requires collecting more information directly from participants than the traditional HIV care and treatment cascade. Because the CBIHS was not designed explicitly to produce an HIV prevention cascade, we did not capture all elements of the cascade for all prevention interventions, which limited our ability to describe the cascade for services like HIV testing and counselling and voluntary medical male circumcision. An additional challenge for applying prevention cascades is unpacking local or national influences on the availability and uptake of prevention services. For example the low effective use of condoms in our study population could have been driven by the approval of PrEP for use in East African countries; however, this is an unlikely explanation since PrEP availability was nascent at selected study sites during the time of the CBIHS.

We described small differences by sex in condom use at last vaginal sex, consistent with prior reports from the region of differences in effective condom use by sex [29]. These observations may be explained partly by structural barriers to condom use, such as economic and gender inequalities and intimate partner violence (IPV), which disproportionately affect women and can hinder women's ability to negotiate for consistent condom use. It has been shown that women who have experienced IPV are 1.5 times more likely to acquire HIV than women who have not experienced IPV [30-32]. A significant percentage of women visiting venues in cross-border areas experienced physical violence or violence during sex, which might explain the lower condom use observed. Other structural factors have been shown to impact condom use, including poverty, alcohol use before sex and policing practices [33,34]. To improve condom and other HIV prevention commodity uptake and efficacy at cross-border areas, HIV prevention programmes must carefully screen for structural barriers and offer one or more integrated mitigation services, such as IPV support services, peer navigation, substance use disorder treatment and income generating activities, among others [35].

HIV prevention programmes should deploy structural interventions in combination with evidence-informed biomedical and behavioural prevention interventions tailored to the needs of the community and the local context [2]. HIV prevention programmes may capitalize on opportunities to create synergies between combination interventions. For example receipt of HIV/AIDS education was high in our study population, and this can serve as an important starting point for promoting HIV testing services, condom adherence, or new prevention methods like PrEP. Similarly, existing HIV testing and peer educator services at venues can be leveraged to improve condom uptake through condoms provision, education on HIV risk during pre- and post-test counselling, and HIV behaviour change communication to promote condom use.

This study identified other opportunities for improving HIV prevention programmes. The preponderance of men found at

Table 4. Venue characteristics and HIV prevention services available at venues with high percentages (top tertile) of persons living with HIV and persons who are not virally suppressed in cross-border areas in the East Africa Cross-Border Integrated Health Study, 2016-2017

	Venues with high % of visitors living with HIV (n = 90)[a]		Venues with high % of virally unsuppressed visitors (n = 28)[a]		All Venues (n = 883)	
	Weighted %[b]	95% CI	Weighted %[b]	95% CI	Weighted %[b]	95% CI
Venue characteristic (%)						
Venue type						
Bar/pub/restaurant	49.1	38.0, 60.2	33.3	13.9, 52.6	45.3	41.7, 48.9
Commercial spot[c]	3.8	0.0, 7.6	9.3	0.0, 20.9	9.4	7.2, 11.7
Hotel/guest house/lodge	29.8	19.4, 40.1	25.9	10.2, 41.7	29.9	26.6, 33.1
Nightclub/disco/brothel	3.2	0.0, 6.9	-	-	2.4	1.3, 3.6
Outside areas[d]	10.0	3.4, 16.7	19.2	3.1, 35.4	4.5	3.0, 6.1
Transportation hub[e]	0.8	0.0, 2.4	2.8	0.0, 8.5	1.7	0.7, 2.6
Other	3.3	0.0, 6.6	9.5	0.0, 24.1	6.8	5.0, 8.6
Condoms available[f]	54.8	44.3, 65.2	58.3	36.1, 80.5	51.8	48.2, 55.3
Alcohol sold	71.0	60.6, 81.4	53.7	31.6, 75.9	63.8	60.3, 67.3
Sex takes place on-site	58.8	47.9, 69.8	59.9	39.8, 80.1	49.1	45.6, 52.6
Sex work at venue	75.9	65.9, 85.9	53.7	34.9, 72.6	55.0	51.4, 58.7
Female sex workers live at venue	25.0	15.5, 34.5	22.2	5.8, 38.7	17.9	15.0, 20.7
Mean number of prevention services						
Overall	2.15	1.58, 2.72	2.26	1.26, 3.25	1.79	1.63, 1.96
At venues where alcohol is available and/or sex takes place on-site	2.34	1.72, 2.96	2.54	1.32, 3.76	2.02	1.83, 2.20

[a]In the venues with high proportions of persons living with HIV, 8.3% to 40.7% of the persons visiting that venue live with HIV. In the venues with high proportions of persons living with unsuppressed HIV, 100% of the persons with HIV visiting that venue live with unsuppressed HIV; [b]Data weighted and standard errors adjusted to account for survey design; [c]Commercial spots included markets, hair salons, shops, cinemas, recreation and game centres and schools; [d]Outside areas include beaches, parks, sex worker streets and construction sites; [e]Transportation hubs included truck stops and lorry/railway stations; [f]Condoms available for free or for sale. CI, confidence interval.

Table 5. Average number of HIV prevention services available by venue type in cross-border areas in the East Africa Cross-Border Integrated Health Study, 2016-2017

	All Areas (n = 883)		
	Number of venues	Weighted mean	95% CI
Venue type			
Bar/pub/restaurant	407	1.65	1.41, 1.89
Commercial spot[a]	74	1.47	0.98, 1.95
Hotel/guest house/lodge	266	1.77	1.51, 2.04
Nightclub/disco/brothel	22	2.10	1.26, 2.94
Outside area[b]	39	3.03	1.84, 4.22
Transportation hub[c]	13	3.67	1.70, 5.64
Other	62	1.92	1.24, 2.60

[a]Commercial spots included markets, hair salons, shops, cinemas, recreation and game centres and schools; [b]Outdoor area included beaches, parks, construction sites and streets; [c]Transportation hubs included truck stops and lorry/railway stations. CI, confidence interval.

cross-border venues suggests possibilities to implement targeted HIV case-finding strategies that engage men with novel HIV testing modalities, such as index testing and HIV self-testing, and linkage to treatment or prevention as appropriate. Similarly, we described how bars, pubs and restaurants had a higher proportion of patrons living with HIV, but a lower average number of available HIV prevention services than other types of venues. This heterogeneity in availability of services across venue type suggests that current HIV prevention programming may not be sufficiently tailored to site-level differences in the epidemic at cross-border areas. Targeting HIV prevention interventions to the people and places that need them most can be a more efficient and impactful way to deliver HIV services [36].

This study has several limitations. First, the small sample size for some key and priority populations in our study, such as men who have sex with men and persons who inject drugs, limit inferences about the prevention needs and access to services of these groups in selected cross-border areas. Second, the analytic weights used do not account for bias introduced by informative refusals or participants leaving the venue when they learn that a survey is being conducted. Moreover, self-

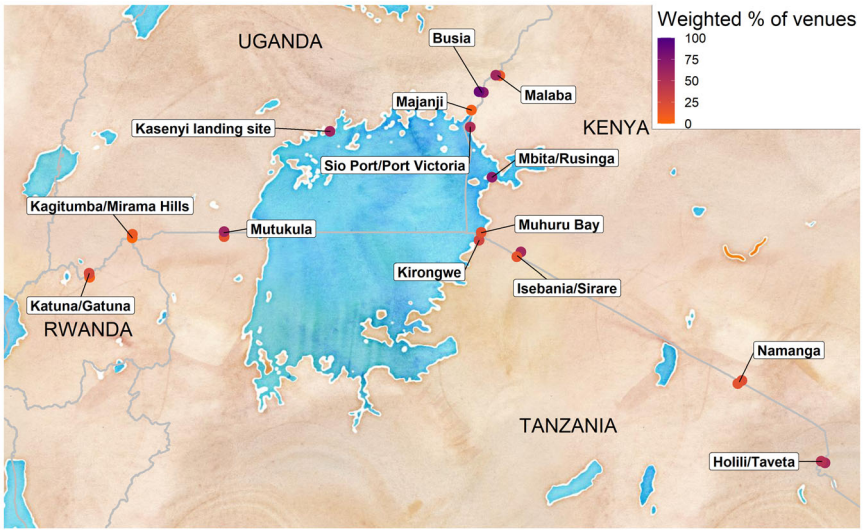

Figure 3. Map of cross-border areas in East Africa included in the East Africa Cross-Border Integrated Health Study (2016-2017) with weighted percentages of venues with free male/female condoms available in the prior six months among all venues visited by uninfected persons having difficulty accessing condoms.

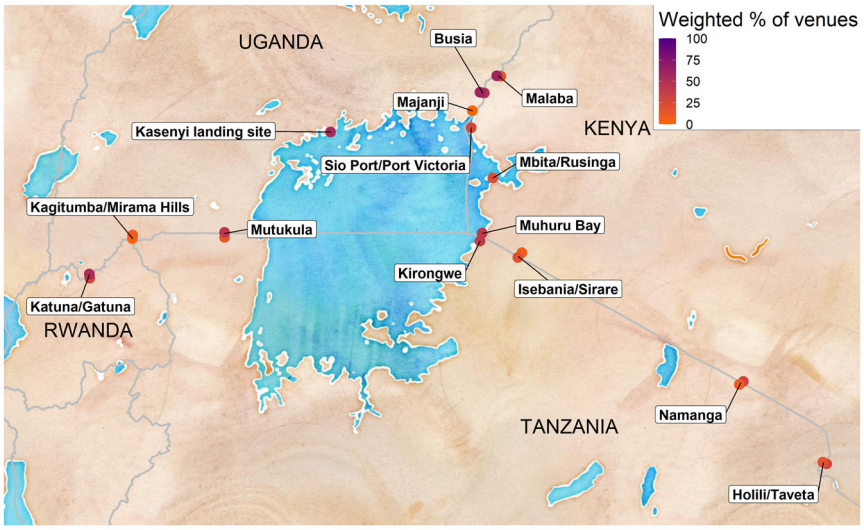

Figure 4. Map of cross-border areas in East Africa included in the East Africa Cross-Border Integrated Health Study (2016-2017) with weighted percentages of venues visited by education outreach among all venues visited by uninfected persons not using condoms.

reported responses to the bio-behavioural survey have potential to introduce recall bias and social desirability bias into respondent data. Finally, the CBIHS did not examine the effects of social gender norms, income inequality, human rights violations on access to and uptake of, HIV prevention services and future studies should collect data on these structural factors.

To improve HIV prevention programming in East African cross-border areas, future studies should examine whether recent investments in transnational coordination and service delivery since the time of the CBIHS have overcome the barriers to prevention uptake and adherence documented here [1-2,5,30]. Implementation science research, including empirically supported frameworks and measures, may clarify the extent to which evidence-informed HIV prevention interventions are being routinely deployed in combination to reach key and priority populations in cross-border areas, as well as the reach, adoption, sustainability and effectiveness of such efforts. Recently, several interventions have been proposed and/or implemented in cross-border areas, such as introducing cross-border health units, liberalizing access to health services across borders, and creating harmonized, cross-border HIV care and treatment protocols. Acquiring knowledge about the effectiveness, sustainability and scalability of these interventions will be vital to improving HIV prevention in these areas. Also, we need more data on the context and infrastructure required to successfully implement interventions to improve HIV knowledge and condom availability in cross-border areas and populations. New knowledge on effective

strategies to adapt existing behaviour change communication for cross-border populations is needed to better encourage effective use of condoms and other HIV prevention commodities. Finally, further research is needed to refine the prevention cascade framework to be maximally relevant to real-world HIV prevention settings, and to capture the dynamic nature of HIV risk behaviour and client preferences for various combinations of HIV prevention services, including PrEP [21,37].

5 | CONCLUSIONS

There remain critical opportunities to improve HIV prevention for key and mobile populations at venues in East African cross-border areas, specifically to increase availability and use of condoms and other primary HIV prevention interventions. Delivering effective HIV prevention in this setting requires adapting programming to fit the local HIV epidemic, including tailoring services to address granular differences in service availability and uptake by demographic and risk behaviour profile, venue type and geographical location. Applying the prevention cascade framework helps improve HIV prevention interventions by standardizing visualization of barriers to prevention delivery, quickly highlighting gaps, comparing efforts across different populations at risk and identifying priorities for future HIV prevention efforts. Harnessing this unique and important data source to examine access to and gaps in prevention services can be a useful and complementary public health tool to protect the populations in cross-border areas.

AUTHORS' AFFILIATIONS

[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]U.S. Agency for International Development, Kenya/East Africa Regional Mission, Nairobi, Kenya; [3]College of Health Sciences, School of Public Health, Makerere University, Kampala, Uganda; [4]Department of Medicine, Division of Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [5]MEASURE Evaluation, Carolina Population Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

COMPETING INTERESTS

One author (PA) is employed by the funding agency. The other authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

AV performed the analysis and wrote the manuscript. PA and FS were involved in designing and conducting the study and revised the manuscript. GEM and MM were involved in study design, overseeing data collection, analysis, and revision of the manuscript. MH was involved in the revision of the manuscript. SW was involved in study design and revised the manuscript. JKE designed the study, oversaw data collection, participated in data analysis and revised the manuscript.

ACKNOWLEDGEMENTS

MEASURE Evaluation is implemented by the Carolina Population Center, University of North Carolina at Chapel Hill in partnership with ICF International; John Snow, Inc.; Management Sciences for Health; Palladium; and Tulane University. Views expressed are not necessarily those of USAID or the United States Government.

FUNDING

This work supported by the United States Agency for International Development (USAID) under the terms of MEASURE Evaluation cooperative agreement AID-OAA-L-14-00004.

REFERENCES

1. Joint United Nations Programme on HIV/AIDS, UNAIDS (Joint United Nations Programme on HIV/AIDS). FAST-TRACK Ending the AIDS epidemic by 2030. UNAIDS; 2014.
2. UNAIDS. Combination HIV Prevention: Tailoring and Coordinating Biomedical, Behavioural and Structural Strategies to Reduce New HIV Infections. Unaids. 2010.
3. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: The ANRS 1265 trial. PLoS Med. 2005;2:e298.
4. Kurth AE, Celum C, Baeten JM, Vermund SH, Wasserheit JN. Combination HIV prevention: significance, challenges, and opportunities. Curr HIV/AIDS Rep. 2011;8(1):62–72.
5. UNAIDS. Prevention Gap Report [Internet]. 2016 [cited 2019 Jul 9]. Available from: https://www.unaids.org/sites/default/files/media_asset/2016-prevention-gap-report_en.pdf
6. Haacker M, Fraser-Hurt N, Gorgens M. Effectiveness of and financial returns to voluntary medical male circumcision for HIV Prevention in South Africa: an incremental cost-effectiveness analysis. Plos Med. 2016;13:e1002012.
7. Uganda AIDS Commission Republic of Uganda. National HIV and AIDS Strategic Plan 2015/2016- 2019/2020, An AIDS free Uganda, My responsibility! [Internet]. 2015 [cited 2019 May 28]. Available from: https://hivhealthclearinghouse.unesco.org/sites/default/files/resources/22280.pdf
8. Ministry of Health-Rwanda. Rwanda HIV and AIDS National Strategic Plan July 2013 - June 2018. Ministry of health; 2013.
9. National AIDS Control Programme. Consensus estimates on key population size and HIV prevalence in Tanzania [Internet]. 2014. Available from: www.nacp.go.tz/site/download/TanzaniaKPconsensusmtgreport8142014withlogos.pdf
10. Githuka G, Hladik W, Mwalili S, Cherutich P, Muthui M, Gitonga J, et al. Populations at increased risk for HIV infection in Kenya: Results from a national population-based household survey, 2012. J Acquir Immune Defic Syndr. 2014;66 Suppl 1:S46–56.
11. Opio A, Muyonga M, Mulumba N. HIV infection in fishing communities of lake victoria basin of Uganda - a cross-sectional sero-behavioral survey. PLoS ONE. 2013;8:e70770.
12. Kwena ZA, Njuguna SW, Ssetala A, Seeley J, Nielsen L, De Bont J, et al. HIV prevalence, spatial distribution and risk factors for HIV infection in the Kenyan fishing communities of Lake Victoria. PLoS ONE. 2019;14:e0214360.
13. National Aids Control Council. Kenya Aids Strategic Framework. Kenya: Ministry of Health; 2015.
14. Edwards JK, Arimi P, Ssengooba F, Mulholland G, Markiewicz M, Bukusi EA, et al. The HIV care continuum among resident and non-resident populations found in venues in East Africa cross-border areas. J Int AIDS Soc. 2019;21:e25226.
15. Measure Evaluation. East Africa Cross-Border Integrated Health Study [Internet]. Chapel Hill. 2017 [cited 2019 Jun 25]. Available from:https://www.measureevaluation.org/resources/publications/tr-17-188
16. Weir SS, Pailman C, Mahlalela X, Coetzee N, Meidany F, Boerma JT. From people to places: focusing AIDS prevention efforts where it matters most. AIDS. 2003;17(6):895–903.
17. Garnett GP, Hallett TB, Takaruza A, Hargreaves J, Rhead R, Warren M, et al. Providing a conceptual framework for HIV prevention cascades and assessing feasibility of empirical measurement with data from east Zimbabwe: a case study. Lancet HIV. 2016;3(7):e297–306.
18. Fearon E, Phillips A, Mtetwa S, Chabata ST, Mushati P, Cambiano V, et al. How can programs better support female sex workers to avoid HIV infection in Zimbabwe? a prevention cascade analysis. J Acquir Immune Defic Syndr. 2019;81(1):24–35.
19. Hargreaves JR, Delany-Moretlwe S, Hallett TB, Johnson S, Kapiga S, Bhattacharjee P, et al. The HIV prevention cascade: integrating theories of epidemiological, behavioural, and social science into programme design and monitoring. Lancet HIV. 2016;3(7):e318–e322.
20. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett TB, Hargreaves JR. HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades. Lancet HIV. 2019;6(1):e60–6.
21. Krishnaratne S, Hensen B, Cordes J, Enstone J, Hargreaves JR. Interventions to strengthen the HIV prevention cascade: a systematic review of reviews. Lancet HIV. 2016;3(7):e307–17.
22. Zalla LC, Herce ME, Edwards JK, Michel J, Weir SS. The burden of HIV among female sex workers, men who have sex with men and transgender women in Haiti: results from the 2016 Priorities for Local AIDS Control Efforts (PLACE) study. J Int AIDS Soc. 2019;22:e25281.
23. Herce ME, Miller WM, Bula A, Edwards JK, Sapalalo P, Lancaster KE, et al. Achieving the first 90 for key populations in sub-Saharan Africa through venue-

based outreach: challenges and opportunities for HIV prevention based on PLACE study findings from Malawi and Angola. J Int AIDS Soc. 2018;21 Suppl 5:e25132.
24. Weir SS, Merli MG, Li J, Gandhi AD, Neely WW, Edwards JK, et al. A comparison of respondent-driven and venue-based sampling of female sex workers in Liuzhou, China. Sex Transm Infect. 2012;88 Suppl 2:i95–101.
25. MEASURE Evaluation. Priorities for Local AIDS Control Efforts (PLACE) [Internet]. 2019 [cited 2019 Jun 25]. Available from: https://www.measureevaluation.org/resources/tools/hiv-aids/place
26. Moorhouse L, Schaefer R, Thomas R, Nyamukapa C, Skovdal M, Hallett TB, et al. Application of the HIV prevention cascade to identify, develop and evaluate interventions to improve use of prevention methods: examples from a study in east Zimbabwe. J Int AIDS Soc. 2019;22 Suppl 4:e25309.
27. Godfrey-Faussett P. The HIV prevention cascade: more smoke than thunder? Lancet HIV. 2016;3(7):e286–8.
28. Hensen B, Fearon E, Schaap A, Lewis JJ, Weiss HA, Tembo M, et al. Application of an HIV prevention cascade to identify gaps in increasing coverage of voluntary medical male circumcision services in 42 rural Zambian communities. AIDS Behav. 2019;23(5):1095–103.
29. Walusaga HA, Kyohangirwe R, Wagner GJ. Gender differences in determinants of condom use among HIV clients in Uganda. AIDS Patient Care STDS. 2012;26(11):694–9.
30. UNAIDS. When Women Lead Change Happens: Women advancing the end of AIDS [Internet]. 2017 [cited 2020 Feb 28]. Available from: https://www.unaids.org/sites/default/files/media_asset/when-women-lead-change-happens_en.pdf
31. Department of Reproductive Health Research London School of Hygiene and Tropical Medicine South African Medical Research Council. WHO | Global and regional estimates of violence against women. World Health Organization. 2013.
32. Black MC, Breiding MJ. Adverse health conditions and health risk behaviors associated with intimate partner violence - United States, 2005. Morb Mortal Wkly Rep. 2008;57(5):113–7.
33. Shields A, Thomas R, Hahn S, Weidmann J. Criminalizing condoms: how policing practices put sex workers and HIV services at risk [Internet]. Open Society Foundations. 2012 [cited 2020 Feb 28]. Available from: https://www.opensocietyfoundations.org/uploads/77d576b0-41b0-45d8-ba72-afae15438e50/criminalizing-condoms-20120717.pdf
34. Matovu JKB, Ssebadduka NB. Knowledge, attitudes & barriers to condom use among female sex workers and truck drivers in Uganda: a mixed-methods study. Afr Health Sci. 2013;13(4):1027–33.
35. Wagman JA, King EJ, Namatovu F, Kiwanuka D, Kairania R, Semanda JB, et al. Combined intimate partner violence and HIV/AIDS prevention in rural Uganda: design of the SHARE intervention strategy. Health Care Women Int. 2016;37(3):362–85.
36. Anderson SJ, Cherutich P, Kilonzo N, Cremin I, Fecht D, Kimanga D, et al. Maximising the effect of combination HIV prevention through prioritisation of the people and places in greatest need: A modelling study. Lancet. 2014;384(9939):249–56.
37. Haberera JE, Bangsberga DR, Baetenc JM, Currane K, Koechline F, Amicof KR, et al. Defining success with HIV pre-exposure prophylaxis: a prevention-effective adherence paradigm. AIDS. 2015;29(11):1277–85.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Data S1. Additional results and details on methodology and statistical analysis

Sibanda EL et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25524
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25524/full | https://doi.org/10.1002/jia2.25524

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Use of data from various sources to evaluate and improve the prevention of mother-to-child transmission of HIV programme in Zimbabwe: a data integration exercise

Euphemia L Sibanda[1,2,§*], Karen Webb[3,4*], Carolyn A Fahey[5], Mi-Suk Kang Dufour[5], Sandra I McCoy[5], Constancia Watadzaushe[1], Jeffrey Dirawo[1], Marsha Deda[3], Anesu Chimwaza[6], Isaac Taramusi[7], Angela Mushavi[6], Solomon Mukungunugwa[6], Nancy Padian[5] and Frances M Cowan[1,2]

[§]**Corresponding author:** Euphemia L Sibanda, CeSHHAR Zimbabwe, 4 Bath Rd Belgravia, Harare, Zimbabwe. Tel: 2634333393. (euphemia@ceshhar.co.zw)
*Joint first authors.

Abstract

Introduction: Despite improvements in prevention of mother-to-child transmission (PMTCT) of HIV outcomes, there remain unacceptably high numbers of mother-to-child transmissions (MTCT) of HIV. Programmes and research collect multiple sources of PMTCT data, yet this data is rarely integrated in a systematic way. We conducted a data integration exercise to evaluate the Zimbabwe national PMTCT programme and derive lessons for strengthening implementation and documentation.

Methods: We used data from four sources: research, Ministry of Health and Child Care (MOHCC) programme, Implementer – Organization for Public Health Interventions and Development, and modelling. Research data came from serial population representative cross-sectional surveys that evaluated the national PMTCT programme in 2012, 2014 and 2017/2018. MOHCC and Organization for Public Health Interventions and Development collected data with similar indicators for the period 2018 to 2019. Modelling data from 2017/18 UNAIDS Spectrum was used. We systematically integrated data from the different sources to explore PMTCT programme performance at each step of the cascade. We also conducted spatial analysis to identify hotspots of MTCT.

Results: We developed cascades for HIV-positive and negative-mothers, and HIV exposed and infected infants to 24 months post-partum. Most data were available on HIV positive mothers. Few data were available 6-8 weeks post-delivery for HIV exposed/infected infants and none were available post-delivery for HIV-negative mothers. The different data sources largely concurred. Antenatal care (ANC) registration was high, although women often presented late. There was variable implementation of PMTCT services, MTCT hotspots were identified. Factors positively associated with MTCT included delayed ANC registration and mobility (use of more than one health facility) during pregnancy/breastfeeding. There was reduced MTCT among women whose partners accompanied them to ANC, and infants receiving antiretroviral prophylaxis. Notably, the largest contribution to MTCT was from postnatal women who had previously tested negative (12/25 in survey data, 17.6% estimated by Spectrum modelling). Data integration enabled formulation of interventions to improve programmes.

Conclusions: Data integration was feasible and identified gaps in programme implementation/documentation leading to corrective interventions. Incident infections among mothers are the largest contributors to MTCT: there is need to strengthen the prevention cascade among HIV-negative women.

Keywords: PMTCT; PMTCT cascade; prevention cascade; data integration; data triangulation; data layering; HIV

Additional Supporting Information may be found online in the Supporting Information tab for this article.

Received 2 October 2019; **Accepted** 23 April 2020

1 | INTRODUCTION

Although significant gains have been made in reducing mother to child transmission (MTCT) of HIV globally, there still remains an unacceptably high number of transmissions estimated at 170,000 and 160,000 new infections in 2017 and 2018 respectively; with all infected infants requiring antiretroviral therapy (ART) for life [1,2] and facing an increased risk of significant morbidity and mortality that persists into adulthood [3]. To date very few countries have attained MTCT elimination status according to WHO validation criteria (≤50 new infections per 100,000 live births and a transmission rate of <5% in breastfeeding populations and <2% in non-breastfeeding populations) [1,4,5]. Success in delivery of prevention of mother-to-child transmission (PMTCT) programmes is typically evaluated according to the PMTCT cascade – a series of

sequential steps that need to be implemented to optimise care and prevention outcomes among HIV-positive women, HIV-negative women at risk of infection, and their babies [6]. Indicators to measure success have evolved over time in parallel with knowledge and WHO PMTCT guideline updates [6]. Although the importance of primary prevention among mothers has always been recognized (UNAIDS PMTCT prong 1) [7], to date cascade reporting has largely focused on MTCT outcomes (UNAIDS prongs 3 and 4). Given the growing proportion of MTCT occurring postnatally, with significant contribution from mothers who previously tested HIV negative [2], it is critical to pay attention to HIV prevention outcomes among pregnant or breastfeeding women in high prevalence settings. Both research studies and programme evaluations have documented losses to follow-up at different steps along the cascades [8-11]. The value of PMTCT cascade analysis for reporting PMTCT programme performance [12,13], and for identifying gaps and appropriate interventions to strengthen quality of facility-based PMTCT services [14,15] is well established [6] and has informed use of other prevention, care and treatment cascades in the HIV field [11,16-20].

The Global Plan to eliminate new HIV infections among children and keep their mothers alive (2010) [21] stimulated analyses of country PMTCT gaps and bottlenecks at each step of the cascade to strengthen programming. However, previous PMTCT cascade analyses have primarily utilised aggregate cross-sectional data from routine programme reporting with known limitations and importantly, not reported HIV status of either HIV-negative women in antenatal care (ANC) through delivery and postnatal period or exposed children at 18 to 24 months, or the proportion with HIV-free survival at 24 months [6].

Together with implementing and research partners, Ministry of Health and Child Care (MOHCC) in Zimbabwe is tracking the progress towards elimination of MTCT (EMTCT) using a range of platforms. Although these data are shared, there has been no formal process to systematically integrate these data and maximise the learning they can provide. Public health triangulation/data integration is a process for reviewing, synthesizing and interpreting secondary data from multiple sources that bear on the same question to make public health decisions [22,23].

In this study, we report on the process and results of a "data integration initiative" undertaken by MOHCC in partnership with implementing partners and researchers which aims to integrate data from different sources in order to give a fuller picture of performance of the national PMTCT programme. Results will be used to strengthen the impact of the PMTCT programme in Zimbabwe. Additionally, this process aims to identify data gaps required to inform programming and modelling across the region more broadly.

2 | METHODS

The data integration working group comprising individuals from MOHCC, National AIDS Council, research and implementing partner organisations met biweekly from May to September 2019 to: (i) identify relevant data (ii) develop a system for integration (iii) develop cascades using integrated data (iv) identify data gaps (v) identify areas for programme improvement, and (vi) identify geographies/facilities for specific intervention.

2.1 | Data sources

We triangulate data from four sources: MOHCC, research, programme and modelling (Figure 1). Each source includes multiple types of data, providing individual, facility and population level evidence, with different strengths and weaknesses. For example, the research is population-representative, used robust methods for data collection and cleaning, and, importantly, includes mother-baby (MB) pairs who are lost to follow-up from the health system. However, unlike programme data where health outcomes are verifiable on medical record, some survey outcomes are self-reported. See Table 1 for detailed description of the data sources.

The data collection process for each is given below.

2.1.1 | Research

Between 2012 and 2018, researchers partnered with MOHCC to conduct an external evaluation of Zimbabwe's PMTCT programme. Three representative, cross-sectional, population-based surveys were conducted in catchment areas surrounding the same 157 randomly selected health facilities in five of Zimbabwe's ten provinces. Multi-stage sampling was used to select facilities and MB pairs for inclusion. The study population consisted of infants born 9-18 months before the survey and their biological mothers or caregivers aged ≥16 years old. Infants 9-18 months old were selected to be able to detect HIV transmissions occurring during pregnancy, delivery and breastfeeding. Importantly, the survey aimed to include mothers or infants who had died since delivery, in which case verbal autopsy data were collected. All mother/caregiver participants completed an interviewer administered questionnaire and provided a dried blood spot sample for HIV testing. Details of survey methods have been published previously [24]. In 2017/2018, the survey was extended to include MB pairs where babies were 19-36 months old specifically to explore retention of mothers and babies in the later post-partum period. In depth data on PMTCT services offered at facilities were also collected.

2.1.2 | MOHCC

Through the National PMTCT Programme, MOHCC collects a wide range of programmatic data at 1560 health facilities across Zimbabwe into multiple paper registers that track engagement of mothers/infants at different cascade points including antenatal, delivery and postnatal service uptake and clinical outcomes. In 36 Districts, MOHCC has piloted the MB Pair register which tracks all MB (HIV positive and negative) from birth to 24 months. For each MTCT that is recorded, MOHCC recently introduced detailed case investigation and documentation of potential causes of transmission. This is recorded on paper then entered into a national database. At 624 high volume facilities, MOHCC enters data aggregated from Patient OI/ART Care Booklets into an Electronic Patient Monitoring System. Data entered onto monthly return forms are entered into the District Health Information System 2 (DHIS2) on a monthly basis with centralized data entry and retrieval at district level. MOHCC data are recorded by health workers who have a high workload and typically do not have time for routine quality assurance and data validation.

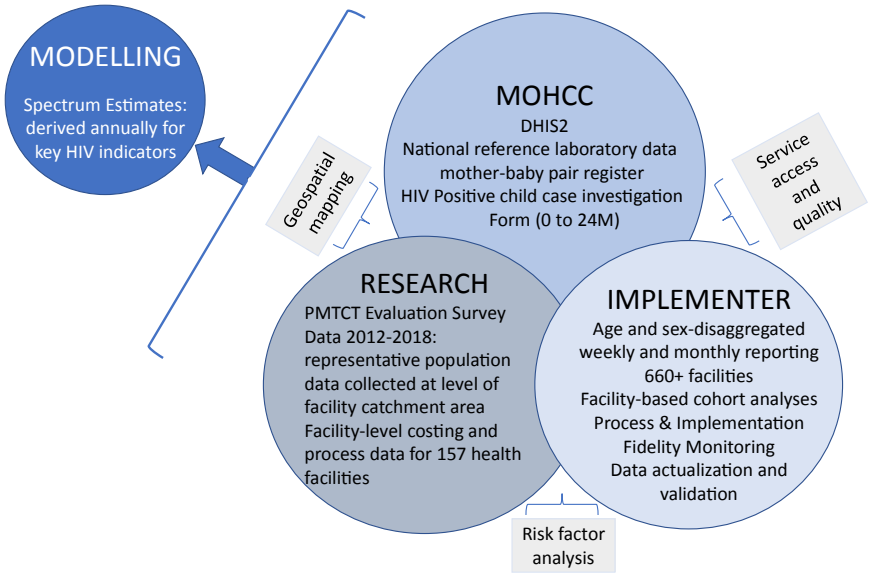

Figure 1. Data sources and domains.
DHIS2, District Health Information System 2; MOHCC, Ministry of Health and Child Care; PMTCT, prevention of mother-to-child transmission.

2.1.3 | *Implementing partner*

The local implementing partner, Organization for Public Health Interventions and Development (OPHID), has supported MOHCC with implementation of the National PMTCT Programme since 2001. Through President's Emergency Plan for AIDS Relief (PEPFAR)/USAID funding, OPHID currently provides support at multiple health system levels to strengthen HIV Care and Treatment at over 660 health facilities in six Provinces through the Families and Communities for Elimination (FACE HIV) Programme. This support includes weekly, monthly and quarterly data collection and analysis of PEPFAR Data Accountability Transparency and Impact Measurement (DATIM) indicators, age- and sex-disaggregated cross-sectional service indicators, and targeted process and cohort-based programme assessments. The data sources for OPHID's programme mirror MOHCC data sources, but the frequency and granularity of targeted analysis is more intense. In addition, OPHID actively engages in data strengthening and strategic utilisation at health facilities through monthly facility-level data consolidation and visualization activities, district level data triangulation meetings and annual data actualization.

2.1.4 | *Modelling*

United Nations Programme on HIV/AIDS (UNAIDS) supports national Programmes to make annual estimates of key HIV indicators. These estimates rely on national surveillance and survey data, national programme data as well as epidemic patterns derived from scientific studies. The Spectrum software is used to combine this information under specific assumptions to produce estimates of key indicators, including the number of people living with HIV by age and sex, new infections, AIDS deaths, AIDS orphans, the need for treatment and prevention, including PMTCT. In this study, we report Spectrum estimates on PMTCT outcomes.

2.2 | Data handling and analysis

Drawing on previous work in data triangulation and evidence-informed intervention design [22,25], we followed four stages in the data triangulation: (1) Evidence attribute mapping; (2) Data quality assessment; (3) PMTCT Cascade Data Layering Analysis; and, (4) Data-Driven Intervention Design. The cascade data layering analysis was conducted at geographic level rather than individual level because unique identifier data were not available for programme data.

2.2.1 | *Evidence attribute mapping*

We mapped the data to understand attributes of each source including defining the population, period covered, data collection methods, geographical coverage, and relative strength and weaknesses [23]. We then determined the availability of data for each step along an expanded PMTCT cascade that includes infant HIV status at 18-24 months and HIV-free survival [6].

2.2.2 | *Data quality assessment*

We assessed the relative strengths and weaknesses of each data source according to four major categories: conformance of data values to intended format and allowed values (e.g. for survey data we verified that numeric data, such as age, appeared as such, and we did additional checks if age of mother did not fall between 16 and 55 years. For programme data which were aggregate, examples of conformance checks included application of validation rules that numerators were smaller than denominators along the cascade and that historical trends in reporting were realistic with data verification for outliers). We also checked for completeness (extent of missingness), plausibility, for example verifying that dates of birth/delivery and early infant diagnosis made temporal sense, and

Table 1. Data sources and attributes for the integration exercise

	Research	Programme				Modelling
	PMTCT survey	DHIS2	PEPFAR DATIM	MB Pair register	Case investigation forms	Spectrum
Population	Representative, population level MB pairs 9-18 and 19-36 months	Attendees of health facilities	Attendees of health facilities	Attendees of health facilities	MB pairs where MTCT is recorded	
# Records (N)	2018: 7709 MB 9-18 months; 1221 MB 19-36 months 2012: 8800 2014: 10,404	448,475 women registered in ANC	177,706 women registered in ANC	Aggregate MB pair patient entries not documented	271 newly diagnosed infant-HIV positive MB pairs	
Period covered	2017-2018	2018-2019	2018-2019	2018-2019	January 2018-September 2019	
Data collection method	Population based survey in catchment areas of health facilities	Collation of data originally recorded on programme forms	Collation of data originally recorded on programme forms	Register completed longitudinally for each MB pair	Forms completed for each MTCT that is recorded	
Data type	Individual level	Aggregate at the facility level	Aggregate at the facility level	Individual level	Individual level	Population level
Geographical coverage	Catchment areas of 5 of 10 Zimbabwean provinces	National	669 health facilities in 24 districts	36 districts	669 health facilities in 6 Provinces	National estimate
Strengths	Robust data collection and cleaning Inclusion of MB pairs not currently in care (including if either M or B have died) Population-representative estimates	National-level data Objective data reporting using programme forms Monthly reporting for continuous performance monitoring Outcomes verifiable with source documents	Monthly reporting for continuous performance monitoring (support for rapid course correction) Outcomes verifiable with source documents	Longitudinal follow-up of MB pairs	Detailed investigation of each MTCT	Population level impacts and outcomes
Weaknesses	Some outcomes are self-reported Expensive Does not facilitate real-time quality improvement	Aggregate cross sectional data Limited resources to validate/clean the data	Aggregate data	Paper registers with incomplete abstraction to electronic format	Incomplete data and low coverage (completed and entered form for each laboratory diagnosis)	Informed by programme data which may not be accurate/complete
Summary of data quality assessment	Good	Fair	Fair	Poor	Good	Fair

ANC, antenatal care; DHIS2, District Health Information System 2; MB, mother-baby; MCTC, mother-to-child transmission; MOHCC, Ministry of Health and Child Care; PEPFAR/DATIM, President's Emergency Plan for AIDS Relief/Data Accountability Transparency and Impact Measurement; PMTCT. prevention of mother-to-child transmission.

Sibanda EL et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25524
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25524/full | https://doi.org/10.1002/jia2.25524

relevance of data values. See Appendix for the framework that was used [26].

2.2.3 | *PMTCT cascades data layering analysis*

We constructed mother and infant cascades according to a comprehensive cascade framework [6], indicating engagement of (i) HIV-positive women, (ii) HIV exposed infants and (iii) HIV-negative women according to each of the four data sources. For the research we used data from the 2017/2018 survey. For MOHCC and OPHID data, proportions were calculated for 2018. We used the latest modelling estimates that were based on 2017/2018 data.

For each data source, we examined risk factors for poor programme performance such as poor health service uptake, ART initiation and MB retention using different methods according to available data. We only performed univariable analysis to determine risk factors for MTCT from survey data because there were too few MTCTs (25 in total) to conduct multivariable analysis. For the survey, we conducted a spatial analysis of MTCT hotspots using MTCT data. We layered this with MOHCC data on new positives so as to identify geographic target areas for enhanced prevention interventions. Risk factors for MTCT were further explored through analysis of detailed case investigation of MTCT that was supported by OPHID, and also through analysis of modelling outcomes.

Using patterns determined from geographic regions where data from all sources were available, we determined the feasibility and utility of extrapolating to regions/facilities with missing data. Although each data source was analysed individually, for the integration exercise we evaluated concordance in cascade indicator data across available sources, and identified information gaps and areas of poor performance across the PMTCT cascade.

2.3 | Ethical considerations

The research (serial surveys) had ethical approval from Medical Research Council of Zimbabwe, reference numbers MRCZ/A/1655, MRCZ/A/ 1826, MRCZ/A/2162 for 2012, 2014 and 2017 surveys respectively. Approval was also obtained from the following ethics committees: University College London (2517/004), University of California Berkeley (2014-02-6038) and Liverpool School of Tropical Medicine (16-063). Written informed consent was obtained from survey participants before study procedures were done. MOHCC and OPHID data were collected programmatically with verbal consent; with all but PMTCT case investigation (where names were necessary for follow-up but was de-identified at data entry and in generated reports) using deidentified data.

3 | RESULTS

Table 1 shows a summary of the data that were available for triangulation. Data came from similar periods which made comparisons feasible, except for prior survey rounds which albeit provided important baseline and midline comparisons prior to HIV care and treatment guideline changes including Option B+ and Treat All. We recruited 8800; 10,404 and 7709 mother/caregiver infant dyads from the 2012, 2014 and 2018 surveys respectively. For women attending ANC, in DHIS2 and OPHID DATIM, 448,475 and 177,706, records were used respectively.

3.1 | Engagement at different steps of the cascade

We present separate cascades for HIV-positive women (Figure 2a), HIV-exposed infants (Figure 2b) and HIV negative women (Figure 2c) constructed using data from the four sources. Each cascade is constructed up to 24 months postnatal as median duration of breastfeeding, and consequent risk of MTCT in Zimbabwe (and elsewhere in the region) is 18 months. Overall, the different data sources showed similar trends, with data gaps later in all three cascades. The exception is for HIV testing in labour and delivery among eligible women. While available evidence on antenatal and perinatal cascade indicators is relatively complete, there are information gaps in all cascades during the postnatal period. For example, there are more data points from more sources for HIV infected women. There are few data on MTCT following early infant diagnosis (6-8 weeks postnatal) in the infant cascade. While MOHCC has introduced a MB pair register to track individual outcomes of MB pairs from birth to 24 months, there are no reported data available for HIV-negative mothers from any source in the post natal period resulting in poor understanding of coverage and outcomes of HIV re-testing intended to identify maternal incident infection in the postnatal period. At present, cascade data on primary prevention for pregnant and lactating women testing HIV negative (i.e. referral and linkage rates of HIV-negative women to HIV prevention services such as pre-exposure prophylaxis (PrEP)) is completely lacking. Importantly, no data are routinely reported on the final outcomes for: HIV positive mothers alive on ART at 24 months (Figure 2a), HIV-exposed infants at cessation of breastfeeding (Figure 2b) or among HIV negative women in the post-partum period (Figure 2c). There are gaps in reporting viral load monitoring cascades among HIV-positive pregnant and lactating mothers.

3.2 | MTCT of HIV

Survey data showed that MTCT by 9-18 months post-partum decreased from 9.5%, 5.1% and 3.4% in 2012, 2014 and 2018 respectively, while Spectrum showed estimates of 7.78% in 2018 by end of breastfeeding. Analysis of trends of MTCT by province showed heterogeneity across and within provinces (data not shown) [27]. Layering of survey and MOHCC data shows that similar geographical areas are hot spots for MTCT (Figure 3). MOHCC data includes data from all ten provinces, showing regions where it is most critical to intervene.

Risk factor analysis in the 2018 survey (which covered five of ten provinces) found that a higher prevalence of partner accompaniment for first ANC was associated with a decrease in MTCT, as was knowledge of an HIV-positive status before pregnancy and receipt of antiretroviral prophylaxis for the baby, Table 2. Women who travelled (received care at more than one facility) more than doubled the risk of MTCT. Of note, out of 25 MTCTs in the 2018 survey, 12 were among MB pairs where the mother had previously tested HIV negative. Programme data on HIV Positive Child Case Investigation found that the majority of mothers that transmitted HIV to their infants booked for ANC late, with a median of

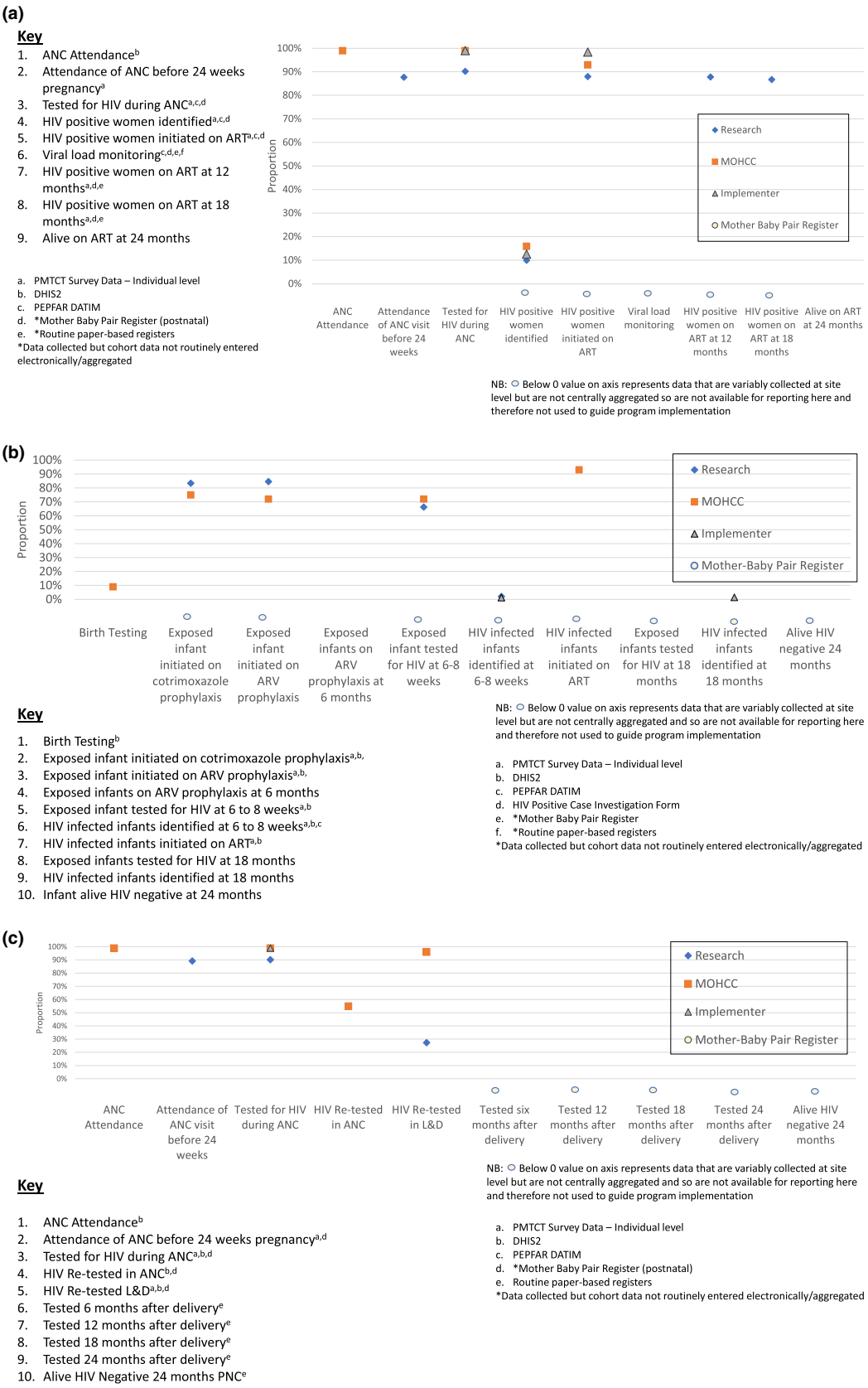

Figure 2. Cascade for (a) HIV-positive women; (b) HIV-exposed infants; (c) HIV-negative women.
ANC, antenatal care; ART, antiretroviral therapy; DHIS2, District Health Information System 2; MOHCC, Ministry of Health and Child Care; PEPFAR/DATIM, President's Emergency Plan for AIDS Relief/Data Accountability Transparency and Impact Measurement; PMTCT, prevention of mother to child transmission.

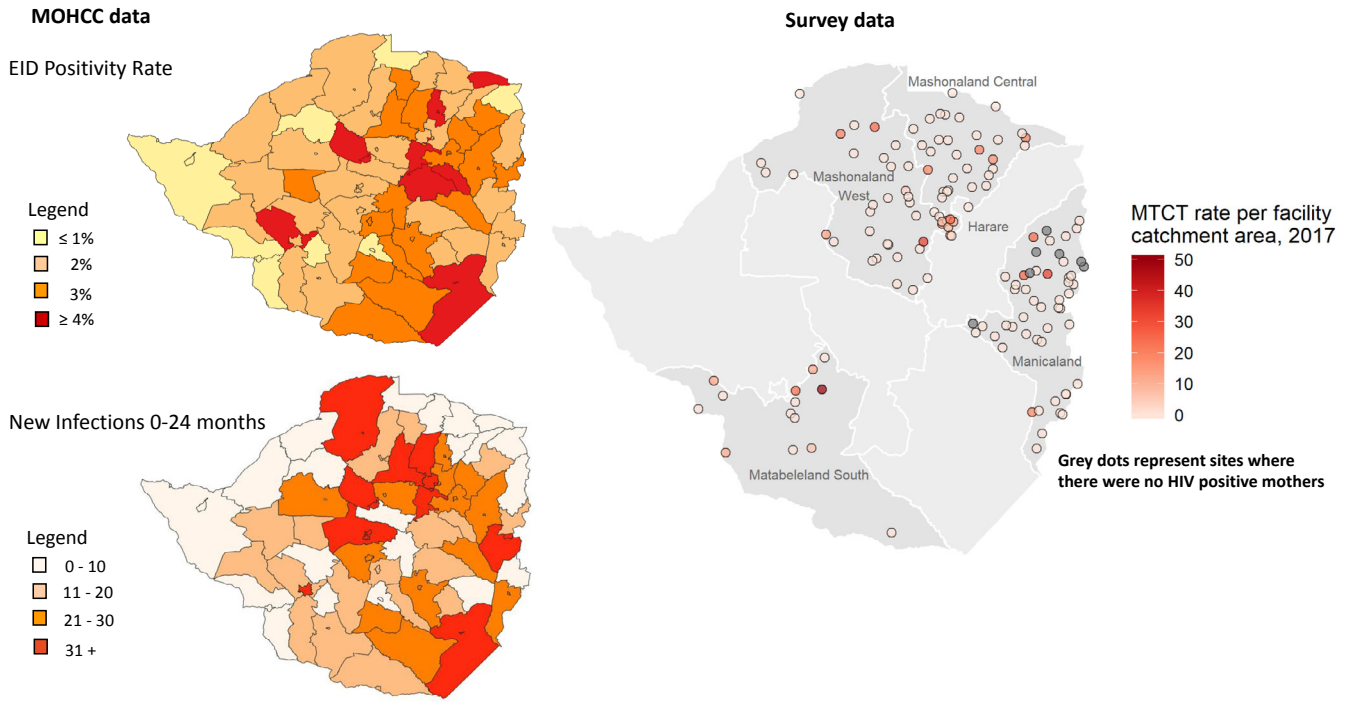

Figure 3. Spatial representation of MTCT across the country.
MOHCC, Ministry of Health and Child Care; MTCT, mother-to-child transmission.

Table 2. Univariable analysis of factors associated with MTCT in 2018 survey

Factor	Number (%) MTCT	Odds ratio (95% confidence interval)	*p*
Timing of ANC registration/month	–	1.20 (0.96-1.52)	0.11
Partner accompaniment to ANC			
No	14 (5.45)	1	0.01
Yes	3 (1.30)	0.23 (0.065-0.81)	
No partner	1 (25.00)	5.79 (0.56-59.25)	
HIV status before pregnancy			
Negative	14 (6.6)	1	0.01
Positive	7 (2.1)	0.32 (0.13-0.81)	
Baby received ARV prophylaxis			
No	14 (7.9)	1	0.003
Yes	11 (2.4)	0.29 (0.13-0.65)	
Received care at more than one facility			
No (one facility)	11 (2.6)	1	0.03
Yes	12 (6.5)	2.55 (1.10-5.89)	

ANC, antenatal care; ARV, antiretroviral; MTCT, mother-to-child transmission.

Table 3. Descriptive analysis among case investigation form respondents (N = 271 HIV-positive infants)

Factor	Number (%) or parameter
Timing of ANC registration/month	Median 23.5 weeks/5.4 months (N = 96)
Male partner HIV status	
Negative	20 (7.4)
Positive	104 (38.4)
Unknown	109 (40.2)
Not Documented	37 (13.7)
HIV status before pregnancy	
Negative	143 (52.7)
Positive	81 (29.9)
Not documented	47 (17.3)
Baby received ARV prophylaxis	
No	67 (24.7)
Yes	166 (61.2)
Not documented	38 (14.0)
Received care at more than one facility	48/219 (21.9) - maternal mobility noted in free text comments

ANC, antenatal care; ARV, antiretroviral.

23.5 months, and 40% were unaware of their partner's HIV status, Table 3. Additionally, 53% of infected babies were born to mothers who were reported to be negative before pregnancy. Case investigation data also demonstrate MTCT was explained by late HIV diagnosis and limited time on ART among mothers before delivery. In addition, as reported in all survey rounds, the case investigation process revealed that maternal mobility increased transmission risk.

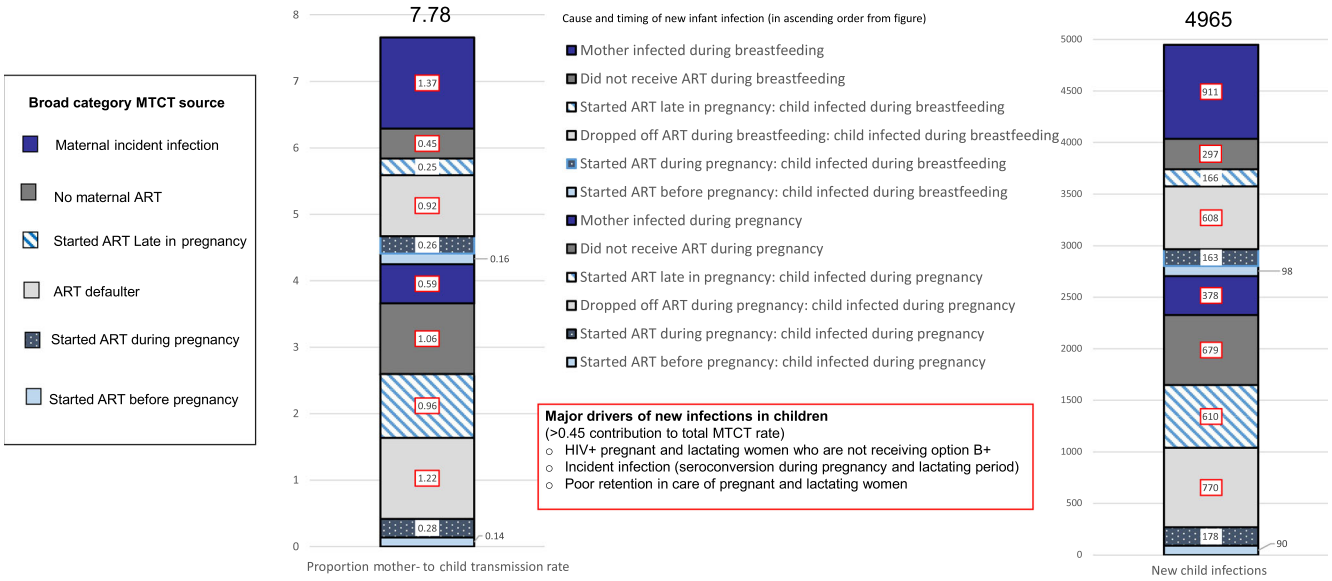

Figure 4. Modelling of MTCT rate by source.
ART, antiretroviral therapy; MTCT, mother to child transmission.

Box 1. Data integration leads to programme strengthening – maternal mobility during perinatal care and risk of postnatal transmission Preliminary analysis of the *2018 survey* data showed that MTCT was higher in the group who visited >1 facility (6.5% vs. 2.6%, odds ratio 2.55 (95% confidence interval 1.10-5.89), $p = 0.03$).

MOHCC HIV Positive Child Case Investigation Forms documenting maternal and infant characteristics of new paediatric diagnoses were submitted by 118/669 OPHID-supported sites from January 2018 to September 2019 and were electronically entered and analysed centrally. During form review, free text comments reported maternal travel during antenatal/postnatal HIV care among 21.9% (48/219) of HIV-positive women who transmitted to their infants 0-24 months.

Travel during infant exposure period has been recommended as a standardized indicator on a revised *MOHCC HIV Positive Child Case Investigation Form* for implementation at all health facilities in Zimbabwe.

Based on these findings, OPHID is working with MOHCC to implement the Strengthening of Information Systems for Elimination of MTCT (SISTEM) – to strengthen PMTCT Programme implementation fidelity and documentation in high MTCT incidence health facilities. SISTEM includes routinely asking and documenting travel plans during the antenatal and postnatal period and strengthened referral systems for women reporting an intention to travel. OPHID is also contributing to the development of a standardized MOHCC Differentiated ART Service Delivery model for mobile and migrant populations, with special considerations for pregnant and lactating mothers.

Of note, modelling indicated that the majority of MTCTs are attributable to mothers who become infected during breastfeeding (Figure 4), pointing to the need to strengthen HIV-retesting, risk screening, primary prevention and follow-up care of HIV-negative mothers postnatally (in addition to the care for HIV-positive mothers which has been more optimally given).

A key finding is the variable coverage and completeness of MTCT case investigation: some health facilities complete this comprehensively for all newly diagnosed infants, while in many facilities there were gaps which did not allow elucidation of the cause of transmission.

The data integration process led to decisions on how programmes/data systems could be improved. See Figure 5 and Boxes 1 and 2 for examples of such decisions/effects.

4 | DISCUSSION

We describe a process for integrating data from different sources to evaluate the PMTCT programme and formulate interventions for strengthening both the data and implementation processes. We found that across datasets, ANC coverage is high, although women generally present late. Uptake of HIV testing among women who present to health facilities is near universal. There are gaps in viral load monitoring of mothers, which may impact MTCT rates. There is variability in PMTCT programme success, with clear MTCT hot spots identified. Investigation of MTCT cases is a recently introduced intervention; we found that this intervention has not yet been adopted across all sites and those sites that implement do so with variable fidelity. Risk factor analysis of MTCT found that late

Box 2. Data integration leads to programme strengthening – postnatal MTCT is increasingly important *UNAIDS SPECTRUM modelling* in Zimbabwe (and globally) suggests that 40% of transmissions are occurring postnatally during breast feeding with a substantial proportion of infections among mothers who were HIV negative at the time of delivery (Figure 4). However, to date there has been limited empirical evidence to support this. In the *2018 PMTCT impact evaluation survey* 12 of the 25 transmissions (48% 95% CI 28.4-67.6) identified had occurred in mothers reporting that they were HIV negative in ANC.

Furthermore, analysis of *MOHCC HIV Positive Child Case Investigation Forms* in OPHID-supported facilities revealed that 23% (61/271) of mothers that transmitted HIV to their infants were only diagnosed in the postnatal period.

MOHCC has introduced a *post natal MB Pair register with electronic data entry into DHIS2* which tracks all mother infant pairs from 0 to 24 months postnatally to ensure timely retesting, retention in HIV prevention and care and final outcome ascertainment of both HIV-positive and HIV-negative MB pairs. Entry and analysis of MB service uptake and outcomes will be critical for informing PMTCT programme efforts as Zimbabwe approaches EMTCT.

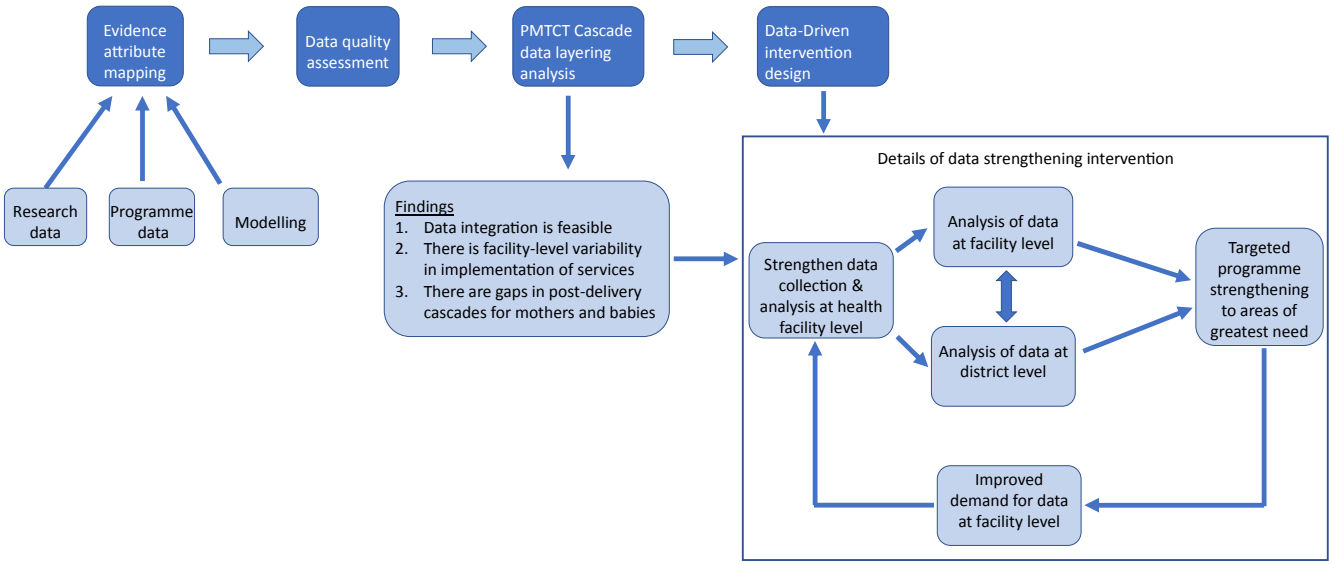

Figure 5. Process of data integration and summary of findings and resulting intervention.
PMTCT, prevention of mother-to-child transmission.

ANC registration with corresponding delay in initiation of ART was critical. Other factors associated with MTCT include mobility of mothers and accompaniment to HIV testing or ANC by partners. Of note, estimates of MTCT differ between Spectrum and survey data (7.78% and 3.8% in 2018), likely because the survey measured MTCT up to a median of 11.5 months postnatally whereas Spectrum estimates MTCT at cessation of breastfeeding. Both modelling and research data suggest that the largest source of MTCT is among women who have tested HIV negative during ANC but who seroconvert and transmit during breastfeeding, but there are currently no programme data showing follow-up of HIV-negative women postnatally.

Lack of follow-up data of HIV-negative women in the face of high HIV incidence in this group calls for strengthening of implementation and documentation of prevention interventions in this group: there is need to increase the demand, supply and optimal use of both retesting and prevention methods among HIV-negative women postnatally. Women need to receive information/education on existing prevention methods, with tailored messaging according to type of woman, for example, young women may be told about mentored mothers programmes [28] while other women may benefit from PrEP or circumcision of their partners. The PMTCT cascade would therefore need to be extended to capture engagement with prevention: (i) how many women know of prevention methods; (ii) how many took up prevention methods, and, (iii) how many optimally used the methods; see Figure 6. In pursuit of ensuring better follow-up of HIV-negative women MOHCC are currently rolling out guidelines to routinely support and document engagement of individual MB pairs to 24 months postpartum regardless of maternal HIV status. All

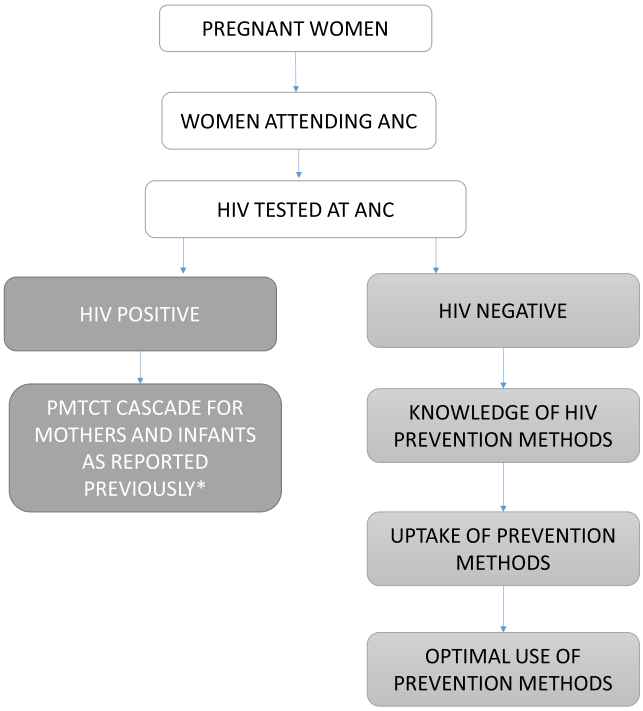

Figure 6. Expanded PMTCT Cascade to include the prevention cascade among HIV-Negative Women.
*Hamilton *et al*., JAIDS 2017. ANC, antenatal care; PMTCT, prevention of mother-to-child transmission.

MB pairs living in a facility catchment area are entered into a mother infant care register to facilitate tracking and early identification of loss to follow-up, with data entered electronically into DHIS2. This process could be strengthened through training and mentoring of health workers to implement with fidelity and regularly review and act on their programme data to optimize maternal retention in the primary prevention cascade of recommended services.

Similarly, facilities need to be supported to improve and act on results of their MTCT case investigation to provide learning on where gaps/bottlenecks are. Although MOHCC has introduced MTCT case investigation it has not yet been widely implemented. Health facilities need capacity building to strengthen their use of data to ensure timely improvements in implementation, which may include training and mentorship as well as providing feedback on performance. In addition, given the negative impact of mobility of women during pregnancy on MTCT, interventions to strengthen engagement and ensure between facility referral are being considered. Together with MOHCC, OPHID are planning to pilot a differentiated service delivery model for mobile and migrant pregnant and lactating women living with HIV, which includes data strengthening for documentation of referrals and confirmed uptake.

There is need to promote early registration for ANC. Previous qualitative research in Zimbabwe has shown that although demand for ANC among women is high, they may face personal/family barriers such as fear of HIV testing and lack of male partner support [29], and supply-side barriers such as reluctance to engage with unfriendly health workers. Many suggestions on how uptake of ANC can be improved have been made [29], including improvement of male partner support and removal/abolition of user fees [30], which MOHCC has adopted.

The strengths of this paper include the comprehensive data that comes from four sources, giving us deeper understanding of the PMTCT programme in Zimbabwe. Combining data from different sources potentially allows us to overcome the inherent limitations/weaknesses of each individual data source. For example, while survey data on timing of testing and engagement of services are limited by self-reporting, programme data are generally objectively (if incompletely) collected. Our survey data have robust numerators and denominators, while programme data have incomplete data on denominators. The systematic process by which we conducted the integration/triangulation exercise gives us confidence in the results. Also, the triangulation process has potential utility for extrapolating missing data, which may prove important when data are not immediately available.

Limitations of the data integration exercise include the use of different sampling and data collection methods, with sampling occurring at different time periods which limits the ability to compare with certainty. The quality and completeness of data varied by data source. Indicators were not always measured in the same way (for example some were measured through self-report during the survey but by clinic record from programm). Spectrum estimates of post-partum transmission relied on transmission rates pre-ART. Although there was overlap of geographic regions covered in many instances, in some cases there was poor or no overlap. Despite all these weaknesses, integration ensured that weaknesses in one data source were compensated for to a certain extent by the other sources, and we showed similar findings where data across sources were available.

5 | CONCLUSIONS

By systematically integrating data from multiple sources, a number of areas for PMTCT programme strengthening were identified. In addition, important data gaps became apparent. The data integration working group is developing a package of data strengthening interventions informed by this work for rollout and evaluation and proposes that the cascades be extended to fully capture PMTCT and maternal and infant survival.

AUTHORS' AFFILIATIONS

[1]Centre for Sexual Health and HIV AIDS Research, Harare, Zimbabwe; [2]Liverpool School of Tropical Medicine, Liverpool, UK; [3]Organization for Public Health Interventions and Development (OPHID), Harare, Zimbabwe; [4]London School of Hygiene and Tropical Medicine, London, UK; [5]University of California Berkeley, Berkeley, CA, USA; [6]Ministry of Health and Child Care, Zimbabwe, Harare, Zimbabwe; [7]National AIDS Council, Zimbabwe, Harare, Zimbabwe

COMPETING INTERESTS

No competing interests are declared.

AUTHORS' CONTRIBUTIONS

ELS, KW, FMC, SM, NP and AM formulated the research study and design. CW, JD, MD, IT, AC, KW, AM and SM collected data and informed design of data collection methods. IT, AC, MD, JD, MKD, CF and SIM analysed data or contributed to analysis. ELS and KW wrote the first draft of the manuscript. FMC, KW, ELS, NP, EG, SIM, CF, MKD, SM and AC substantial intellectual input to manuscript.

ACKNOWLEDGEMENTS

The data integration exercise described here was not funded. The research surveys reported in this publication were supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number R01HD080492. Support for OPHID FACE HIV Programme is from President's Emergency Plan for AIDS Relief (PEPFAR) through USAID for Families and Communities for Elimination of HIV in Zimbabwe (AID-613-A-12-00003). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

REFERENCES

1. UNAIDS. Global AIDS update: miles to go, closing the gaps, breaking barriers, righting injustices. In: UNAIDS, editor. Global AIDS update. Geneva, Switzerland: UNAIDS; 2018. p. 88-97.
2. UNAIDS. Start free stay free AIDS free 2019 report. In: UNAIDS, editor. Start free stay free AIDS free. Geneva, Switzerland: UNAIDS; 2019. p. 1-36.
3. Brennan AT, Bonawitz R, Gill CJ, Thea DM, Kleinman M, Useem J, et al. A meta-analysis assessing all-cause mortality in HIV-exposed uninfected compared with HIV-unexposed uninfected infants and children. AIDS. 2016;30(15):2351–60.
4. Taylor M, Newman L, Ishikawa N, Laverty M, Hayashi C, Ghidinelli M, et al. Elimination of mother-to-child transmission of HIV and syphilis (EMTCT): process, progress, and program integration. PLoS Med. 2017;14:e1002329.
5. World Health Organisation. Global guidance on criteria and processes for validation: elimination of mother-to-child transmission of HIV and syphylis. In: WHO, editor. WHO guidance. Geneva, Switzerland: WHO; 2014. p. 1-32
6. Hamilton E, Bossiky B, Ditekemena J, Esiru G, Fwamba F, Goga AE, et al. Using the PMTCT Cascade to Accelerate Achievement of the Global Plan Goals. J Acquir Immune Defic Syndr. 1999;2017 75 Suppl 1:S27–35.
7. UNAIDS. Count down to zero. Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. In: UNAIDS, editor. Count down to zero. Geneva, Switzerland: UNAIDS; 2011. p. 1-48.
8. Sibanda EL, Weller IV, Hakim JG, Cowan FM. The magnitude of loss to follow-up of HIV-exposed infants along the prevention of mother-to-child HIV transmission continuum of care: a systematic review and meta-analysis. AIDS. 2013;27(17):2787–97.
9. Rawizza HE, Chang CA, Chaplin B, Ahmed IA, Meloni ST, Oyebode T, et al. Loss to follow-up within the prevention of mother-to-child transmission care cascade in a large ART program in Nigeria. Curr HIV Res. 2015;13(3):201–9.
10. Cichowitz C, Mazuguni F, Minja L, Njau P, Antelman G, Ngocho J, et al. Vulnerable at each step in the PMTCT care cascade: high loss to follow up during pregnancy and the postpartum period in Tanzania. AIDS Behav. 2019;23(7):1824–32.
11. Chi BH, Tih PM, Zanolini A, Stinson K, Ekouevi DK, Coetzee D, et al. Implementation and operational research: reconstructing the PMTCT cascade using cross-sectional household survey data: the PEARL study. J Acquir Immune Defic Syndr. 2015;70(1):e5–9.
12. Zeng H, Chow EP, Zhao Y, Wang Y, Tang M, Li L, et al. Prevention of mother-to-child HIV transmission cascade in China: a systematic review and meta-analysis. Sex Transm Infect. 2016;92(2):116–23.
13. McCoy SI, Buzdugan R, Padian NS, Musarandega R, Engelsmann B, Martz TE, et al. Implementation and operational research: uptake of services and behaviors in the prevention of mother-to-child HIV transmission cascade in Zimbabwe. J Acquir Immune Defic Syndr. 2015;69(2):e74–81.
14. Gimbel S, Voss J, Mercer MA, Zierler B, Gloyd S, Coutinho Mde J, et al. The prevention of mother-to-child transmission of HIV cascade analysis tool: supporting health managers to improve facility-level service delivery. BMC Res Notes. 2014;7:743.
15. Sherr K, Asbjornsdottir K, Crocker J, Coutinho J, de Fatima Cuembelo M, Tavede E, et al. Scaling-up the Systems Analysis and Improvement Approach for prevention of mother-to-child HIV transmission in Mozambique (SAIA-SCALE): a stepped-wedge cluster randomized trial. Implement Sci. 2019;14(1):41.
16. Hargreaves JR, Delany-Moretlwe S, Hallett TB, Johnson S, Kapiga S, Bhattacharjee P, et al. The HIV prevention cascade: integrating theories of epidemiological, behavioural, and social science into programme design and monitoring. Lancet HIV. 2016;3(7):e318–22.
17. Cowan FM, Davey CB, Fearon E, Mushati P, Dirawo J, Cambiano V, et al. The HIV care cascade among female sex workers in Zimbabwe: results of a population-based survey from the sisters antiretroviral therapy programme for prevention of HIV, an integrated response (SAPPH-IRe) trial. J Acquir Immune Defic Syndr. 2017;74(4):375–82.
18. Fox MP, Rosen S. A new cascade of HIV care for the era of "treat all." PLoS Med. 2017;14:e1002268.
19. Church K, Machiyama K, Todd J, Njamwea B, Mwangome M, Hosegood V, et al. Identifying gaps in HIV service delivery across the diagnosis-to-treatment cascade: findings from health facility surveys in six sub-Saharan countries. J Int AIDS Soc. 2017;20(1):21188.
20. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett TB, Hargreaves JR. HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades. Lancet HIV. 2019;6(1):e60–6.
21. UNAIDS. Global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Geneva, Switzerland: UNAIDS; 2010.
22. Rutherford GW, McFarland W, Spindler H, White K, Patel SV, Aberle-Grasse J, et al. Public health triangulation: approach and application to synthesizing data to understand national and local HIV epidemics. BMC Public Health. 2010;10:447.
23. Fielding NG. Triangulation and mixed methods designs: data integration with new research technologies. J Mix Methods Res. 2012;6(2):124–36.
24. Buzdugan R, Kang Dufour MS, McCoy SI, Watadzaushe C, Dirawo J, Mushavi A, et al. Option A improved HIV-free infant survival and mother to child HIV transmission at 9–18 months in Zimbabwe. Aids. 2016;30(10):1655–62.
25. Wight D, Wimbush E, Jepson R, Doi L. Six steps in quality intervention development (6SQuID). J Epidemiol Community Health. 2016;70(5):520-5.
26. Kahn MG, Callahan TJ, Barnard J, Bauck AE, Brown J, Davidson BN, et al. A harmonized data quality assessment terminology and framework for the secondary use of electronic health record data. EGEMS. 2016;4(1):1244.
27. Fahey CA, McCoy SI, Koyuncu A, Kang Dufour M, Mushavi A, Mahomva A, et al. Spatial analysis to identify emerging hot spots on MTCT in Zimbabwe, 2012-2018. In: CROI, editor. Conference on retroviruses and opportunistic infections. Seattle (WA): IAS-USA; 2019.
28. Carbone NB, Njala J, Jackson DJ, Eliya MT, Chilangwa C, Tseka J, et al. "I would love if there was a young woman to encourage us, to ease our anxiety which we would have if we were alone": adapting the Mothers2Mothers Mentor Mother Model for adolescent mothers living with HIV in Malawi. PLoS ONE. 2019;14:e0217693.
29. d'Elbee M, Indravudh PP, Mwenge L, Kumwenda MM, Simwinga M, Choko AT, et al. Preferences for linkage to HIV care services following a reactive self-

test: discrete choice experiments in Malawi and Zambia. AIDS. 2018. https://doi.org/10.1097/QAD.0000000000001918.
30. Hercot D, Meessen B, Ridde V, Gilson L. Removing user fees for health services in low-income countries: a multi-country review framework for assessing the process of policy change. Health Policy Plan. 2011;26 Suppl 2:ii5-15.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Hill LM et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25502
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25502/full | https://doi.org/10.1002/jia2.25502

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

HIV risk, risk perception, and PrEP interest among adolescent girls and young women in Lilongwe, Malawi: operationalizing the PrEP cascade

Lauren M Hill[1,2,§], Bertha Maseko[3], Maganizo Chagomerana[3,4], Mina C Hosseinipour[3,4], Linda-Gail Bekker[5], Audrey Pettifor[6] and Nora E Rosenberg[1,3]

[§]**Corresponding author:** Lauren M Hill, 324 Rosenau Hall, CB #7440, Chapel Hill, NC, USA 27599. Tel: 919-966-3761. (hilllm@email.unc.edu)

Abstract

Introduction: As a user-controlled HIV prevention method, oral pre-exposure prophylaxis (PrEP) holds particular promise for adolescent girls and young women (AGYW). HIV prevention cascades, critical frameworks for the design and evaluation of PrEP programmes, outline the priorities of identifying individuals at greatest HIV risk and motivating them to initiate PrEP through perceived HIV risk. To inform future iterations of these cascades and PrEP delivery for AGYW, the objective of this study was to understand the level of interest in PrEP among AGYW at highest HIV risk, and the potential role of perceived risk in motivating PrEP interest.

Methods: Using data from a cohort study of HIV-negative AGYW in Lilongwe, Malawi (February 2016 to August 2017), we assessed the relationship between epidemiologic HIV risk (risk index developed in a previous analysis) and PrEP interest, and the extent to which perceived risk explains the relationship between HIV risk and PrEP interest. We further aimed to operationalize the pre-initiation steps of the HIV prevention cascade in the study population.

Results: In total, 825 AGYW were included in analyses, of which 43% met the criterion for high epidemiologic HIV risk. While epidemiologic risk scores were positively associated with PrEP interest, high numbers of AGYW both above and below the high-risk cutoff were very interested in PrEP (68% vs. 63%). Perceived risk partially explained the relationship between HIV risk and PrEP interest; greater epidemiologic HIV risk was associated with high perceived risk, which was in turn associated with PrEP interest. Many more high-risk AGYW were interested in PrEP (68%) than expressed a high level of perceived HIV risk (26%).

Conclusions: These results highlight key relationships between epidemiologic HIV risk, risk perception and interest in PrEP. While risk perception did partially explain the relationship between epidemiologic risk and PrEP interest, there may be other important motivational mechanisms that are not captured in many HIV prevention cascades. The high number of participants with risk scores below the high-risk cutoff who both expressed high perceived risk and interest in PrEP suggests that demand for PrEP among AGYW may not be well aligned with epidemiologic risk.

Keywords: adolescent girls and young women; PrEP; cascade; HIV risk; Africa

Received 30 September 2019; **Accepted** 6 April 2020

1 | INTRODUCTION

Adolescent girls and young women (AGYW) in sub-Saharan Africa are an important population for HIV prevention [1,2]. In Malawi, AGYW ages 15 to 24 have more than twice the risk of HIV infection as their male counterparts [3-5]. This disproportionate burden of HIV risk among AGYW can be explained by a number of biological, social and behavioural factors [6], including difficulty negotiating condom use [7,8]. To date, the predominant prevention technology available in Malawi has been the male condom, which is primarily male-controlled and affords women limited ability to protect their sexual health. In contrast, oral pre-exposure prophylaxis (PrEP) is an effective individually-controlled prevention method, a promising alternative or additional prevention tool for AGYW [9-11].

Following World Health Organization (WHO) guidelines recommending offering PrEP to at-risk populations, including AGYW in high burden settings [12], many countries including Malawi are beginning to make provisions to offer PrEP to AGYW. Despite the promise of PrEP and its impending rollout, we know little about the acceptability and potential uptake of PrEP among AGYW, including those in greatest need. With limited resources for PrEP [13], we need to understand if those AGYW at greatest HIV risk are the most likely to initiate PrEP. Furthermore, we need to understand *how* AGYW at greatest risk may become motivated to consider PrEP.

HIV prevention cascades provide valuable frameworks and metrics by which to evaluate the impact of prevention programmes, and to identify important intermediary endpoints to guide the development of effective prevention programmes [14]. The majority of these cascades begin by identifying the at-risk population [14-17], but the intermediary steps between identification of this population and initiation of a prevention method differ across cascades. That said, the thematic commonality between intermediary steps in many cascades are explicit or implicit mechanisms motivating initiation of a given prevention method. While Schaefer et al.'s 2019 unified cascade is the only to explicitly include a "motivation" step [14], and Hargreaves et al. similarly include "demand side" factors which may motivate or facilitate interest and access [18], the most commonly included motivational step is perceived HIV risk [15-16,18,19]. The inclusion of risk perception in the majority of cascades implies that HIV risk perception is a key process through which individuals at elevated risk may be motivated to consider PrEP or other HIV prevention methods. However, empirical data on this implicit assumption are lacking. Understanding whether or not this mechanism is evident in AGYW can inform whether risk perception is an important target in programmes to promote PrEP interest and eventual uptake among high-risk young women, and can be used to inform future iterations of the HIV prevention cascade to clarify priorities for motivational mechanisms to target.

To address this gap, using data from an observational cohort study with AGYW in Lilongwe, Malawi we aim to answer two primary questions: (1) Are those AGYW at highest HIV risk actually the most likely to (a) perceive themselves to be at risk and (b) express interest in PrEP use? and (2) To what extent does perceived risk explain the relationship between HIV risk and PrEP interest? We further aim to operationalize the pre-initiation stages of the prevention cascade in the study population. The answers to these questions will build understanding of likely outcomes for key precursors to PrEP interest and uptake in the early days of rollout to AGYW.

2 | METHODS

2.1 | Study context

The Girl Power-Malawi study was conducted at four health centres in Lilongwe, Malawi from February 2016 to August 2017 and assessed four service delivery models for AGYW [20,21]. All clinics were in urban and periurban areas and had antenatal HIV prevalence levels of at least 5%. None of the models of service delivery included PrEP information or PrEP services. At the one-year follow-up participants were asked about their hypothetical interest in PrEP. The data presented here are taken from behavioural surveys from this trial.

2.2 | Study participants and procedures

Two-hundred and fifty AGYW were recruited from the catchment areas surrounding each of the four study clinics (n = 1000 total) through community outreach, participant referral, and self-referral. AGYW were eligible to participate if they were 15 to 24 years old, from the catchment area, and willing to provide locator information (phone number and/or physical location). AGYW who were sexually active in the past six months were purposively recruited; study staff informally discussed romantic relationships and sexual activity with AGYW and invited those with current or past sexual activity for screening. Eligible and consenting participants were enrolled and followed for one year. All participants were asked to complete a behavioural survey at baseline, six months, and one year assessing socioeconomic, behavioural, biomedical and partnership characteristics; interest in using PrEP; and HIV risk perception. Surveys were administered in Chichewa by young female research officers using Open Data Kit software [22]. Phone and physical tracing were conducted for participants who missed research visits. Eight-hundred and sixty-seven AGYW participated in the one-year visit (87% retention). The present analysis excludes AGYW who reported an HIV-positive test result by the one-year follow-up visit (42 participants).

2.3 | Ethical review

Girl Power-Malawi received approval from the National Health Science Research Committee in Malawi and the University of North Carolina Institutional Review Board. Voluntary written informed consent was obtained from participants 18 to 24 years old. Assent and permission by a parent, guardian or authorized representative were obtained for adolescents 15 to 17 years old. In cases of limited literacy, an impartial witness was present.

2.4 | Measures

2.4.1 | Epidemiologic HIV risk

Indicators of HIV risk used were previously identified as those associated with HIV incidence in the Girl Power-Malawi cohort [23]. All nine identified risk factors were assessed at one year. Indicators included two sociodemographic factors (age 20 to 24; being separated/divorced/widowed), four sexual partnership characteristics in the past six months (≥2 partners; exchanging sex for money or gifts (transactional sex); having ≥1 partner ≥5 years older; and known/suspected partner concurrency), two sexually transmitted infections (STI) symptoms in the past six months (abnormal vaginal discharge; genital sores/ulcers) and having a previous pregnancy (measures previously described [24]). In our previous work to develop this risk index, AGYW with ≥3 risk factors were 15.2 times as likely to acquire HIV as those with <3 factors [23]. We summed the nine risk indicators by participant to create a risk score, and created a dichotomous of "high risk" indicator for some analyses (≥3 factors indicating "high risk"). This high-risk cutoff was determined in the previous analysis; those with ≥3 risk factors had an HIV incidence rate >3 per 100 person-years, the WHO high-risk threshold [25].

2.4.2 | Perceived HIV risk

AGYW rated their perceived lifetime chance of acquiring HIV as: "no chance," "small chance" or "high chance." In bivariate analyses, this was dichotomized as "high chance" (1) versus other responses (0).

2.4.3 | *PrEP interest*

AGYW were rated their potential interest in using PrEP after receiving this explanation: "PrEP is a medicine that can be used to prevent HIV for people who are HIV-negative. To be protected with PrEP, a pill is taken every day. These pills contain some of the same medicine used to treat people who already have HIV. PrEP is not currently available in Malawi." Participants rated their interest in trying PrEP if it were available at the study clinic ("not at all interested," "somewhat interested" or "very interested"). For multivariate analyses, this was dichotomized as "very interested" (1) versus other responses (0).

Control variables included highest level of education (grade level) and household economic status evaluated through an adapted Filmer Pritchett Wealth Index including 13 household assets [26]. A composite wealth score was created by weighting each asset by its factor loading on the first component in a principle components analysis, placing individuals on a continuous scale of relative wealth and categorizing scores into terciles [26].

2.5 | Analysis

All analyses were performed in SAS v 9.4. We tested the following hypotheses: (1) Women with greater HIV risk will be more likely to a) be very interested in PrEP and b) perceive high HIV risk; (2) Women with greater perceived risk will be more likely to be very interested in PrEP; (3) Perceived risk will mediate the relationship between HIV risk and PrEP interest per hypotheses 1&2. We described the frequencies and percentages of categorical variables, and the median and inter-quartile range of continuous variables (Table 1). We then estimated unadjusted and adjusted odds ratios of the association between each exposure and outcome of interest and corresponding 95% Wald chi-square confidence intervals (Table 2). As adjustment for the control variables above did not qualitatively alter the results, only adjusted odds ratios are presented. To assess the assumption of linear associations between epidemiologic HIV risk and the response variables, we compared the fit of the linear model with three alternatives: a quadratic, a cubic, and a categorical model. Likelihood ratio tests did not indicate improved fit with these alternative models [27].

We assessed the mediation hypothesis by estimating indirect and direct effects using the PROCESS macro v3.3 [28]. Statistical mediation was determined by assessing the statistical significance of the indirect effect (product of a*b; Figure 1) by the criterion of a non-zero bootstrapped 95% confidence interval (5000 resamples) [28,29]. Estimates for each path are adjusted for the control variables above; in this analysis we assume no unmeasured confounding for the causal effect of the mediator on the outcome. The proportion of the relationship between HIV risk and PrEP interest explained by the perceived risk mediator was calculated as 1-c'/c (Figure 1) [28]. Finally, to characterize the "cascade" of level of perceived HIV risk and PrEP interest among high HIV risk AGYW, we calculated conditional frequencies of high perceived risk and being very interested in PrEP in this group (Figure 2). All hypothesis tests were completed using an imputed dataset. Given low levels of missing information (6% or less per variable), we employed deterministic imputation as follows [30]: Deterministic regression imputation for variables missing for >2% of participants; median imputation for variables missing for <2% of participants. PrEP, pre-exposure prophylaxis; STI, sexually transmitted infections.

Table 1. Descriptive Statistics at one year (N = 825)

	n (%) or median [IQR]
Age	20 [18 to 22] (range: 15 to 27)
Highest education level completed	
Less than a primary school education	179 (21.8%)
Primary school completed (8 to 11)	417 (50.9%)
Secondary school completed	244 (27.3%)
Currently enrolled in school	351 (42.6%)
Household economic status	
Lowest	294 (35.6%)
Middle	239 (29.0%)
Highest	292 (35.4%)
Marital status	
Single	547 (66.3%)
Married	222 (26.9%)
Separated/Divorced/Widowed	55 (6.7%)
Sexually active in past six months	796 (96.5%)
PrEP interest	
Not all interested	99 (12.7%)
Somewhat interested	168 (21.5%)
Very interested	515 (65.9%)
Perceived lifetime HIV risk	
No chance	504 (61.1%)
Small chance	122 (14.8%)
High chance	149 (18.1%)
Do not know	49 (5.9%)
HIV risk	
Risk count score	
Risk factor count	2 [1 to 3] (range: 0 to 8)
High risk (≥3 risk factors of 9)	351 (42.6%)
Risk factors	
Age 20+	491 (56.6%)
Separated, divorced, or widowed	55 (6.7%)
≥2 partners in past year	178 (22.4%)
STI symptoms (past six months)	
Ulcerative symptoms	55 (6.7%)
Discharge symptoms	72 (8.8%)
Transactional sex	162 (18.8%)
≥1 partner suspected concurrent	390 (47.3%)
≥1 partner ≥5 years older than participant	227 (29.4%)
Ever pregnant	357 (43.3%)

3 | RESULTS

3.1 | Participant characteristics

In total, 825 AGYW completing the one-year assessment not reporting an HIV-positive test result were included. At one year, the median age of participants was 20 years old (Table 1). Half had completed primary school (51%) and a

Table 2. Associations between HIV risk factors, perceived HIV risk, and PrEP interest

	PrEP interest ("very")		Perceived "high" HIV risk	
Risk factors (ref = first)	**n (%)[a]**	**aOR (95% CI)**	**n (%)[a]**	**aOR (95% CI)**
Perceived HIV risk				
No chance	295 (61.8%)	–	–	–
Small chance	83 (69.2%)	1.46 (0.95, 2.24)	–	–
High chance	111 (78.2%)	2.60 (1.68, 4.04)**	–	–
Epidemiologic HIV risk				
Risk factor count	–	1.13 (1.03, 1.24)**	–	1.28 (1.15, 1.42)***
Low/moderate risk (<3 risk factors)	297 (63.1%)	1.24 (0.92, 1.68)	58 (12.3%)	2.33 (1.60, 3.38)***
High risk (≥3 risk factors)	238 (67.8%)		91 (25.7%)	
HIV risk indicators				
Age 15 to 19	246 (74.1%)	0.65 (0.48, 0.89)**	60 (17.8%)	1.37 (0.94, 2.00)
Age 20+	269 (59.8%)		89 (20.4%)	
Not separated, divorced, or widowed	497 (64.6%)	1.24 (0.68, 2.27)	135 (17.5%)	1.32 (0.70, 2.53)
Separated, divorced, or widowed	38 (69.1%)		14 (25.5%)	
<2 partners in past year	369 (62.7%)	1.87 (1.27, 2.75)**	104 (17.7%)	1.50 (1.00, 2.27)
≥2 partners in past year	127 (76.1%)		43 (26.5%)	
STI symptoms (past six months)				
No ulcerative symptoms	475 (65.0%)	1.46 (0.78, 2.75)	136 (18.8%)	1.39 (0.72, 2.70)
Ulcerative symptoms	40 (78.4%)		13 (25.5%)	
No discharge symptoms	462 (65.3%)	1.14 (0.67, 1.92)	126 (17.9%)	1.97 (1.13, 3.42)*
Discharge symptoms	49 (71.0%)		21 (31.3%)	
No transactional sex	397 (62.7%)	2.24 (1.46, 3.44)**	117 (18.6%)	1.15 (0.73, 1.80)
Transactional sex	115 (78.8%)		32 (22.5%)	
No partner suspected concurrent	266 (61.2%)	1.42 (1.06, 1.90)*	49 (11.3%)	2.72 (1.86, 3.98)***
≥1 partner suspected concurrent	269 (69.0%)		100 (25.6%)	
No partner ≥5 years older than participant	416 (64.0%)	1.58 (1.13, 2.21)**	122 (18.9%)	1.55 (1.06, 2.27)*
≥1 partner ≥5 years older than participant	94 (77.1%)		26 (21.7%)	
Never pregnant	292 (67.4%)	0.99 (0.73, 1.35)	62 (14.1%)	1.73 (1.18, 2.54)**
Ever pregnant	222 (63.8%)		86 (25.8%)	

aORs adjusted for household economic status and education; aOR reference group is the first value listed in each row.
[a]Row percent reflecting proportion of respondents for each response category reporting being "very" interest in pre-exposure prophylaxis (PrEP) (column 1), or a "high" perceived HIV risk (column 2).
*$p<0.05$;
**$p<0.01$;
***$p<0.0001$.

quarter (27%) had completed secondary school. The majority of participants (66%) were single. Nearly all participants reported being sexually active in the past six months (97%).

The median number of HIV risk factors reported was 2. 43% met the "high-risk" cutoff of ≥3 risk factors. Most participants (61%) perceived no lifetime risk of HIV infection, while 15% and 18% perceived a small or high risk respectively. The majority (66%) were very interested in PrEP while 22% were somewhat interested, and 13% reported no interest.

3.2 | Epidemiologic HIV risk and PrEP interest

The number of reported risk factors was associated with PrEP interest (Table 2); each additional risk factor was associated

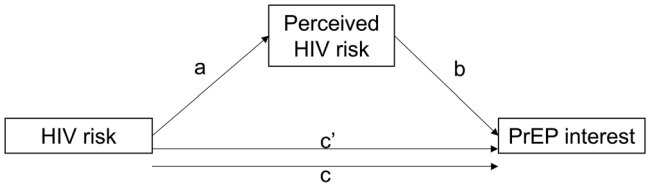

Figure 1. Mediation hypothesis and paths. PrEP, pre-exposure prophylaxis

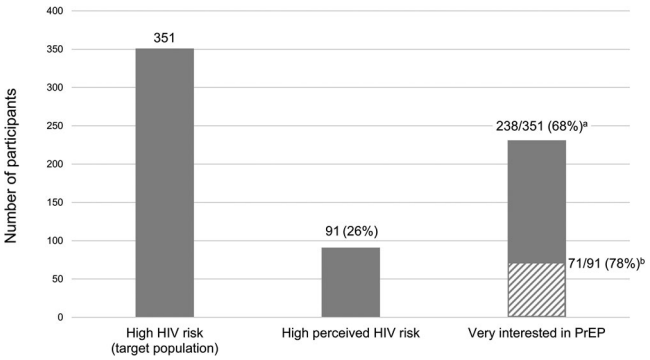

Figure 2. Operationalized pre-initiation PrEP cascade. [a]Proportion of high-risk participants (n = 351) reporting being very interested in PrEP. [b]Proportion of high-risk participants with high perceived HIV risk (n = 91) reporting being very interested in PrEP. PrEP, pre-exposure prophylaxis

with 13% higher odds of being "very" interested in PrEP (aOR = 1.13; 95% CI: 1.03, 1.24). Slightly more AGYW reporting ≥3 risk factors ("high risk") were very interested in PrEP, but this relationship was not statistically significant (Table 2). Four of the nine risk factors were associated with being very interested in PrEP in the expected direction: ≥2 partners, transactional sex, known/suspected partner concurrency, ≥1 partner ≥5 years older. Unexpectedly, women 20 years and older had *lower* odds of PrEP interest than those younger than 20 years. The other risk factors were not associated with PrEP interest.

3.3 | Perceived HIV risk and PrEP interest

Both level of perceived risk and reporting "high" perceived HIV risk were associated with PrEP interest (Table 2). AGYW reporting high perceived risk had over twice the odds of being very interested in PrEP (aOR = 2.60; 95% CI: 1.68, 4.04) as those reporting lower perceived risk. PrEP interest was high among all perceived risk levels: 62% among women reporting no perceived risk, 69% among those with low perceived risk, and 78% among those with high perceived risk.

3.4 | Mediation by perceived HIV risk: Indirect effect and direct effects

The indirect effect of epidemiologic HIV risk on PrEP interest through the mediator of perceived HIV risk was significant for both the binary indicator of high HIV risk and HIV risk score (Table 3; respective aORs: 1.14 95% CI: 1.05, 1.24; 1.04 95% CI: 1.01, 1.06). Perceived HIV risk explained 19% of the relationship between high epidemiologic risk and PrEP interest, and 25% of the relationship between HIV risk score and PrEP interest.

3.5 | Operationalized pre-initiation PrEP cascade

Many more high-risk AGYW were interested in PrEP than perceived themselves to be at high risk (Figure 2); of the 351 high-risk participants, only 26% perceived high HIV risk, while 68% were very interested in PrEP. Of the 91 high-risk participants who also had high perceived HIV risk, 78% were very interested in PrEP (striped bar).

4 | DISCUSSION

In summary, nearly half of AGYW reported risk factors placing them at high epidemiologic HIV risk. The majority expressed interest in PrEP, and epidemiologic risk was moderately associated with this interest. Only 26% of high-risk participants reported high perceived risk, but nevertheless were more likely to perceive high risk than their lower-risk counterparts. Perceived risk explained a quarter of the relationship between HIV risk and PrEP interest, suggesting that there may be other mechanisms motivating higher-risk AGYW's interest in PrEP.

4.1 | HIV risk and PrEP interest

The majority of AGYW were very interested in PrEP, and this interest was moderately associated with higher HIV risk scores. Risk indicators most closely associated with PrEP interest included behavioural and partner factors which AGYW might recognize from HIV-prevention education (e.g. partner concurrency, age disparate relationships). Approximately two-thirds of both high-risk and lower-risk women were very interested in PrEP. This generally high level of PrEP interest has been found in other populations of AGYW and older women in South Africa [31-33] and Kenya [34]. Although these findings represent hypothetical interest, they suggest that demand for PrEP among AGYW may not be well aligned with epidemiologic HIV risk. Because of currently limited resources for PrEP in many settings, demand for PrEP according to HIV risk should be monitored to assess the need to better target PrEP delivery to women at greatest risk [35].

4.2 | HIV risk and perceived risk

Although women with higher epidemiologic risk were more likely to report high perceived risk, 74% of those with high-risk scores did not have high perceived risk. These results echo

Table 3. Mediation results: indirect, direct and total effects of HIV risk on PrEP interest via perceived risk

	aOR (95% CI)	
	X = high HIV risk	X = HIV risk score
Indirect effect	1.14 (1.05, 1.24)	1.04 (1.01, 1.06)
Direct effect	1.19 (1.05, 1.24)	1.10 (1.00, 1.20)
Total effect	1.24 (0.92, 1.68)	1.13 (1.03, 1.23)
Proportion mediated	19.2%	25.2%

aORs adjusted for household economic status and education. PrEP, pre-exposure prophylaxis; CI, confidence interval.

findings from FEM-PrEP that half of women sero-converting while taking PrEP had reported no perceived chance of HIV acquisition. This was attributed by the investigators to overestimation of protective behaviours and protective reasoning (e.g. minimizing perceived risk, cognitive avoidance) [36].

4.3 | Perceived risk as a motivating mechanism

The mediation results indicated that perceived risk partially explained the relationship between epidemiologic risk and PrEP interest, thus there is reason to infer that perceived risk may be a motivating mechanism for PrEP interest in higher-risk women. Future randomized studies should seek to understand if interventions promoting accurate risk perception could promote PrEP initiation [23]. Yet, perceived risk explained only a quarter of the relationship between risk scores and PrEP interest, indicating that there may be other unobserved motivators. Qualitative studies should seek to understand additional factors motivating AGYW's PrEP interest beyond perceived risk. While some cascades include additional potential motivators, including attitudes towards the prevention method, social norms [18], and risk/benefit perceptions [19], more work is needed to understand the primary motivating mechanisms for PrEP initiation, to identify unified motivation indicators to inform and evaluate prevention programmes [14].

More research is needed to understand why many women who perceive no lifetime HIV risk would be very interested in PrEP. Previous evidence suggests that AGYW's PrEP decision-making can be driven by emotion and motivated reasoning about partner risk [37]. Our qualitative work with the study population suggests that fear of unplanned or uncontrollable risk factors including condom use errors, suspected/feared partner concurrency, and fear of rape were motivators for PrEP interest [38]. These factors could be seen as sources of HIV risk yet unlikely or hypothetical and therefore may not necessarily impute to a high perceived HIV risk while still serving to motivate interest in PrEP. Building a better understanding of these motivations will be important for the development and consolidation of PrEP-specific and other HIV prevention cascades [15-16,19]. Inclusion of cascade indicators reflecting a more robust understanding motivators for interest in PrEP and other HIV prevention technologies will encourage activities to target the most important precursors to PrEP uptake and prevention-effective use [14].

4.4 | The cascade framework and PrEP

Unlike HIV treatment cascades, our operationalized pre-initiation PrEP cascade (Figure 2) was non-linear: many more AGYW with high risk scores were interested in PrEP than perceived themselves to be at high risk. There have been similar findings in men who have sex with men [39,40]. This finding could be partially attributed to the fact that acknowledging interest in PrEP may present a lower "threshold" with regard to social desirability than acknowledging HIV risk behaviours or perceptions of HIV risk. This highlights a potential weakness of the cascade framework in defining progress towards PrEP initiation in high-risk individuals. While each bar in an HIV treatment cascade is generally a subset of the previous one, this may not be the case for PrEP. This potential characteristic could make setting 90-90-90 type targets for PrEP difficult, as the denominator for each step may be difficult to define.

Our results highlight one further question about the application of the cascade framework for PrEP. Over 60% of participants with low/moderate-risk scores were very interest in PrEP, and 12% of women with these scores reported high perceived risk. Should these women be excluded from the PrEP "target population" as defined by cascades? Women may be reticent to report risk behaviours [41,42], or may fear risks that could not be reported as current, known risk factors, as those assessed in most common risk indices (as in our qualitative work [38]). Future studies should seek to understand the potential implications of more expansive definitions of the target population and PrEP eligibility criteria based on perceived risk and expressed PrEP interest. This evidence is needed to inform policy discussions to determine the potential societal costs and benefits of offering PrEP to those who may be highly motivated to use it but are not at highest assessable risk. Future studies should also seek to understand the downstream effects of HIV risk perception and other potential motivators of PrEP use on retention in care and adherence, as qualitative evidence suggests that low perceived risk and insufficient motivation for PrEP use may be related to the low levels of adherence among women in PrEP demonstration trials [43-47].

5 | LIMITATIONS

The results of this study should be interpreted with key limitations in mind. First, participants' reports of PrEP interest, sexual behaviours and perceptions of risk were likely susceptible to social desirability bias. To mitigate this issue, participants were assured that their responses were confidential and that there were no right or wrong answers. We also used the highest threshold ("very") for PrEP interest to increase the theoretical specificity of this indicator. Second, few participants had previous knowledge of PrEP and PrEP was not available in the study setting at measurement, thus their reported interest in PrEP was hypothetical and based on limited consideration. Third, perceived HIV risk was measured with a single item, and thus may not capture all dimensions of perceived risk. Fourth, due to low cell counts for the associations between STI symptoms and PrEP interest, and between being separated/divorced/widowed and PrEP interest, tests may have been underpowered. Fifth, causal interpretations of all measures of association presented should be made with caution as they represent cross-sectional associations; qualitative studies are needed to better understand the causality of the relationships studied. Finally, sexually active AGYW were purposively recruited for participation from urban and periurban settings in Lilongwe. The findings of this study are primarily generalizeable to sexually active AGYW living in similar urban and periurban settings in the region.

6 | CONCLUSIONS

Our results bring to light relationships between epidemiologic risk, risk perception and PrEP interest and indicate directions for future research to inform effective HIV prevention programmes. A better understanding of mechanisms motivating

PrEP interest beyond perceived risk is needed to inform delivery of PrEP among AGYW in high burden settings. Our results suggest that early demand for PrEP may not be well aligned with epidemiologic risk in this population; more research is needed to understand the implications of expanding or retaining current target population and PrEP eligibility definitions which may exclude many interested and motivated potential users not meeting a cutoff for epidemiologic risk.

AUTHORS' AFFILIATIONS

[1]Department of Health Behavior, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [2]Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [3]UNC Project-Malawi, Lilongwe, Malawi; [4]Institute for Global Health and Infectious Diseases, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [5]Desmond Tutu HIV Centre, UCT, Faculty of Health Sciences, Cape Town, South Africa; [6]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

LH conducted the analysis and wrote the manuscript under the guidance of NR. NR conceptualized and led the Girl Power study. MH contributed to the overall study conceptualization and HIV-related analyses. LB and AP Contributed to the overall study conceptualization and design. BM contributed to study design and study implementation. MC contributed to data analysis. All authors contributed to the writing of the manuscript and approved the final manuscript for publication.

ACKNOWLEDGEMENTS

FUNDING

The study was funded by Evidence for HIV Prevention in Southern Africa (EHPSA), a DFID program managed by Mott MacDonald. Dr. Hill was funded by the National Institute of Mental Health (K01 MH121186) and the Agency for Healthcare Research and Quality (T32 HS000032). Dr. Rosenberg was funded by the National Institute of Mental Health (R00 MH104154) and the National Institute of Allergy and Infectious Diseases (P30 AI50410). Dr. Chagomerana was funded by the Fogarty International Center (D43 TW010060, P30 AI50410).

REFERENCES

1. Mathur S, Pilgrim N, Pulerwitz J. PrEP introduction for adolescent girls and young women. Lancet HIV. 2016;3(9):e406–8.
2. Idele P, Gillespie A, Porth T, Suzuki C, Mahy M, Kasedde S, et al. Epidemiology of HIV and AIDS among adolescents: current status, inequities, and data gaps. J Acquir Immune Defic Syndr. 2014;1 66 Suppl 2:S144–53.
3. Ministry of Health, Malawi. Malawi Population-based HIV Impact Assessment (MPHIA) 2015–16: first report. 2017. Available from: https://phia.icap.columbia.edu/wp-content/uploads/2017/11/Final-MPHIA-First-Report_11.15.17.pdf
4. UNAIDS. Country Factsheet: Malawi. Geneva: UNAIDS; 2018.
5. Malawi National Statistical Office. Malawi demographic and health survey. Maryland, USA: National Statistical Office; 2010.
6. Celum CL, Delany-Moretlwe S, McConnell M, van Rooyen H, Bekker L-G, Kurth A, et al. Rethinking HIV prevention to prepare for oral PrEP implementation for young African women. J Int AIDS Soc. 2015;18 4 Suppl 3:20227.
7. Sales JM, DiClemente RJ, Davis TP, Sullivan S. Exploring why young African American women do not change condom-use behavior following participation in an STI/HIV prevention intervention. Health Educ Res. 2012;27(6):1091–101.
8. Pettifor AE, Measham DM, Rees HV, Padian NS. Sexual power and HIV risk, South Africa. Emerg Infect Dis. 2004;10(11):1996–2004.
9. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399–410.
10. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423–34.
11. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587–99.
12. World Health Organization. WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection: module 12: adolescents and young adults. World Health Organization, Geneva. 2017.
13. UNAIDS. Invest in HIV prevention. Geneva: Joint United Nations Programme on HIV/AIDS. 2015.
14. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett TB, Hargreaves JR. HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades. Lancet HIV. 2019;6(1):e60–6.
15. Nunn AS, Brinkley-Rubinstein L, Oldenburg CE, Mayer KH, Mimiaga M, Patel R, et al. Defining the HIV pre-exposure prophylaxis care continuum. AIDS. 2017;31(5):731–4.
16. Garnett GP, Hallett TB, Takaruza A, Hargreaves J, Rhead R, Warren M, et al. Providing a conceptual framework for HIV prevention cascades and assessing feasibility of empirical measurement with data from east Zimbabwe: a case study. Lancet HIV. 2016;3(7):e297–306.
17. Dunbar MS, Kripke K, Haberer J, Castor D, Dalal S, Mukoma W, et al. Understanding and measuring uptake and coverage of oral pre-exposure prophylaxis delivery among adolescent girls and young women in sub-Saharan Africa. Sex Health. 2018;15(6):513–21.
18. Hargreaves JR, Delany-Moretlwe S, Hallett TB, Johnson S, Kapiga S, Bhattacharjee P, et al. The HIV prevention cascade: integrating theories of epidemiological, behavioural, and social science into programme design and monitoring. Lancet HIV. 2016;3(7):e318–22.
19. Kelley CF, Kahle E, Siegler A, Sanchez T, Del Rio C, Sullivan PS, et al. Applying a prep continuum of care for men who have sex with men in Atlanta, Georgia. Clin Infect Dis. 2015;61(10):1590–7.
20. Rosenberg NE, Pettifor AE, Myers L, Phanga T, Marcus R, Bhushan NL, et al. Comparing four service delivery models for adolescent girls and young women through the "Girl Power" study: protocol for a multisite quasi-experimental cohort study. BMJ Open. 2017;14:e018480.
21. Rosenberg NE, Bhushan NL, Vansia D, Phanga T, Maseko B, Nthani T, et al. Comparing youth-friendly health services to the standard of care through "Girl Power-Malawi": A quasi-experimental cohort study. J Acquir Immune Defic Syndr. 2018;79(4):458–466.
22. Brunette W, Sundt M, Dell N, Chaudhri R, Breit N, Borriello G. Open data kit 2.0: Expanding and refining information services for developing regions. Proceedings of the 14th Workshop on Mobile Computing Systems and Applications – HotMobile 13. New York, NY: ACM Press; 2013. p. 1.
23. Kudowa E, Chagomerana M, Phanga T, Maseko B, Price JT, Hosseinipour MC, et al. Incidence rate and predictors of HIV incidence among adolescent girls and young women in Lilongwe, Malawi. 10th IAS Conference on HIV Science; Mexico City, Mexico; 2019.
24. Price JT, Rosenberg NE, Vansia D, Phanga T, Bhushan NL, Maseko B, et al. Predictors of HIV, HIV risk perception, and HIV worry among adolescent girls and young women in Lilongwe, Malawi. J Acquir Immune Defic Syndr. 2018;77(1):53–63.
25. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2nd ed. Geneva: World Health Organization; 2016.
26. Filmer D, Pritchett LH. Estimating wealth effects without expenditure data—or tears: An application to educational enrollments in states of India. Demography. 2001;38(1):115–132.
27. Allison PD. Logistic regression using SAS: theory and application. Cary, NC: SAS Institute; 2012.
28. Hayes AF. Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. New York: Guilford Press; 2013.
29. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008;40(3):879–891.
30. Gelman A, Hill J. Missing-data imputation. Data Analysis Using Regression and Multilevel/Hierarchical Models. Cambridge: Cambridge University Press; 2006.
31. Govender EM, Mansoor LE, Abdool Karim Q. Influences of geo-spatial location on pre-exposure prophylaxis use in South Africa: positioning microbicides for better product uptake. AIDS Care. 2017;29(6):734–40.
32. Vazquez L, Moll AP, Kacin A, Ndlovu NE, Shenoi SV. Perceptions of HIV preexposure prophylaxis among young pregnant women from rural KwaZulu-Natal, South Africa. AIDS Patient Care STDS. 2019;33(5):214–9.

33. Joseph Davey D, Farley E, Towriss C, Gomba Y, Bekker L-G, Gorbach P, et al. Risk perception and sex behaviour in pregnancy and breastfeeding in high HIV prevalence settings: Programmatic implications for PrEP delivery. PLoS ONE. 2018;13:e0197143.
34. Pintye J, Beima-Sofie KM, Makabong'O PA, Njoroge A, Trinidad SB, Heffron RA, et al. HIV-uninfected Kenyan adolescent and young women share perspectives on using preexposure prophylaxis during pregnancy. AIDS Patient Care STDS. 2018;32:538-44.
35. Republic of South Africa Department of Health. MyPrEP [Internet] [cited 2019 Sep 16]. Available from: https://myprep.co.za/providers
36. Corneli AL, McKenna K, Headley J, Ahmed K, Odhiambo J, Skhosana J, et al. A descriptive analysis of perceptions of HIV risk and worry about acquiring HIV among FEM-PrEP participants who seroconverted in Bondo, Kenya, and Pretoria, South Africa. J Int AIDS Soc. 2014;17 3 Suppl 2:19152.
37. Hartmann M, McConnell M, Bekker L-G, Celum C, Bennie T, Zuma J, et al. Motivated reasoning and HIV risk? Views on relationships, trust, and risk from young women in Cape Town, South Africa, and implications for oral PrEP. AIDS Behav. 2018;22(11):3468–79.
38. Maseko B, Hill LM, Phanga T, Bhushan N, Vansia D, Kamtsendero L, et al. Perceptions of and interest in HIV pre-exposure prophylaxis use among adolescent girls and young women in Lilongwe, Malawi. PLoS ONE. 2020;15:e0226062.
39. Kesler MA, Kaul R, Myers T, Liu J, Loutfy M, Remis RS, et al. Perceived HIV risk, actual sexual HIV risk and willingness to take pre-exposure prophylaxis among men who have sex with men in Toronto, Canada. AIDS Care. 2016;28(11):1378–85.
40. Underhill K, Guthrie KM, Colleran C, Calabrese SK, Operario D, Mayer KH. Temporal fluctuations in behavior, perceived HIV risk, and willingness to use pre-exposure prophylaxis (PrEP). Arch Sex Behav. 2018;47(7):2109–21.
41. Glynn JR, Kayuni N, Banda E, Parrott F, Floyd S, Francis-Chizororo M, et al. Assessing the validity of sexual behaviour reports in a whole population survey in rural Malawi. PLoS ONE. 2011;6:e22840.
42. Poulin M. Reporting on first sexual experience: the importance of interviewer-respondent interaction. Demogr Res. 2010;22(11):237–88.
43. Corneli A, Perry B, McKenna K, Agot K, Ahmed K, Taylor J, et al. Participants' explanations for nonadherence in the FEM-PrEP clinical trial. J Acquir Immune Defic Syndr. 2016;71(4):452–61.
44. Amico KR, Wallace M, Bekker L-G, Roux S, Atujuna M, Sebastian E, et al. Experiences with HPTN 067/ADAPT study-provided open-label PrEP among women in Cape Town: facilitators and barriers within a mutuality framework. AIDS Behav. 2017;21(5):1361–75.
45. Ware NC, Wyatt MA, Haberer JE, Baeten JM, Kintu A, Psaros C, et al. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. J Acquir Immune Defic Syndr. 2012;59(5):463–8.
46. Roberts ST, Haberer J, Celum C, Mugo N, Ware NC, Cohen CR, et al. Intimate partner violence and adherence to HIV pre-exposure prophylaxis (PrEP) in African women in HIV serodiscordant relationships: a prospective cohort study. J Acquir Immune Defic Syndr. 2016;73(3):313–22.
47. Madrasi K, Chaturvedula A, Haberer JE, Sale M, Fossler MJ, Bangsberg D, et al. Markov mixed effects modeling using electronic adherence monitoring records identifies influential covariates to HIV preexposure prophylaxis. J Clin Pharmacol. 2017;57(5):606–15.

Ramautarsing RA et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25540
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25540/full | https://doi.org/10.1002/jia2.25540

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Evaluation of a pre-exposure prophylaxis programme for men who have sex with men and transgender women in Thailand: learning through the HIV prevention cascade lens

Reshmie A Ramautarsing[1], Ratchadaporn Meksena[1], Thanthip Sungsing[1], Tanat Chinbunchorn[1], Theeranat Sangprasert[2], Orawan Fungfoosri[2], Dusita Meekrua[3], Saman Sumalu[3], Thapana Pasansai[4], Witwasin Bunainso[4], Tashada Wongsri[5], Nuttakrit Mainoy[5], Donn Colby[6], Matthew Avery[7], Stephen Mills[7], Ravipa Vannakit[8], Praphan Phanuphak[1] and Nittaya Phanuphak[1,6,§]

[§]**Corresponding author:** Nittaya Phanuphak, Thai Red Cross AIDS Research Centre, PREVENTION, 104 Ratchadamri Road, Bangkok 10330, Thailand. Tel: +66 2 253 0996. (nittaya.p@prevention-trcarc.org)

Abstract

Introduction: Men who have sex with men (MSM) and transgender women (TGW) are two key populations (KPs) in Thailand at high risk for HIV. Uptake and scale-up of pre-exposure prophylaxis (PrEP) among them has been slow. We used data from Princess PrEP, Thailand's largest KP-led PrEP programme, to operationalize PrEP service cascades. We identified gaps and pointed out where additional data are needed to inform a larger HIV prevention cascade.

Methods: Numbers of people tested for HIV, tested HIV negative, eligible for PrEP (defined as any of the following in the past three months: condomless sex with partners of unknown/uncertain HIV status or antiretroviral treatment or viral load status, multiple partners, engaging in sex work, sexually transmitted infections, injecting drugs, using amphetamine-type stimulants, or repeated use of post-exposure prophylaxis), offered PrEP and accepted PrEP during January to November 2019 were retrieved from Princess PrEP database to inform PrEP service cascades for MSM and TGW. Reasons for not accepting PrEP were documented.

Results: Of 6287 MSM who received HIV testing in Princess PrEP, 92.3% were HIV negative and 70.2% of them were eligible for PrEP. PrEP was offered to 94.7% of those eligible and 48.0% of those offered accepted it. Among 900 TGW who had HIV testing, 95.3% tested HIV negative and 64.8% of them met PrEP eligibility criteria. Of these, 95.0% were offered PrEP and 43.9% of them accepted it. Among MSM and TGW who met PrEP eligibility criteria, no or low-HIV-risk perception was the most common reason provided (46.7% of 2007 MSM and 41.9% of 296 TGW) for not accepting PrEP.

Conclusions: PrEP service cascades from the Princess PrEP programme identified no or low-risk perception as key barrier to PrEP acceptance among MSM and TGW who met PrEP eligibility criteria. More implementation research studies are needed to explore PrEP motivation and access in larger communities outside of clinical services. This is to identify gaps and strategies to address them within motivation, access and effective use domains of the HIV prevention cascade.

Keywords: HIV prevention; pre-exposure prophylaxis; Thailand; men who have sex with men; transgender women; prevention cascade

Received 2 October 2019; **Accepted** 11 May 2020

1 | INTRODUCTION

Pre-exposure prophylaxis (PrEP) is extremely effective in reducing HIV acquisition and has resulted in dramatic decreases in new HIV infections when implemented as part of a combination prevention strategy [1,2]. However, PrEP can only be effective if it is used by those who can benefit from it, and if they use it correctly. For this, demand for PrEP needs to be generated, PrEP needs to be accessible by priority populations, and PrEP use needs to be effective. The HIV prevention cascade, proposed by Schaefer *et al*., is a framework that starts with identifying priority population that could benefit from using an HIV prevention method and consists of these three key domains: motivation for using this HIV prevention method, access to the method and effective use [3]. This cascade allows implementers to identify gaps in biomedical, behavioural and structural aspects of an HIV prevention method, plan interventions to close those gaps and monitor the interventions.

Key population (KPs) at high risk of HIV in Thailand include men who have sex with men (MSM), transgender women (TGW), people who inject drugs (PWID) and female sex workers (FSW). MSM and TGW account for more than half of new

HIV infections annually, with HIV prevalence ranging from 17.7% to 28.6% among MSM and 8.8% among TGW in different urban centres [4-6]. HIV prevention and treatment interventions targeting these KPs are imperative to ending AIDS in Thailand.

As Thailand has included PrEP as part of Universal Health Coverage since October 2019 [7,8], it has aimed to track the progress and guide the monitoring and evaluation of PrEP scale-up using the framework of the HIV prevention cascade. Here, we utilized data from the Princess PrEP programme – the largest PrEP programme in Thailand [9] – to operationalize PrEP service cascades for MSM and TGW. We explored gaps identified in these PrEP service cascades, including reasons for not accepting PrEP when offered, among MSM and TGW. We also pointed out where additional data is needed to inform a larger HIV prevention cascade [3]. We hypothesized that there would be gaps identified in PrEP service cascades for MSM and TGW, especially around PrEP uptake and retention. Understanding reasons why MSM and TGW did not accept PrEP when it was offered could guide how PrEP messaging should be reframed. In addition, innovative ways of data collection might be needed to gain more insight about PrEP retention and its effective use.

2 | METHODS

2.1 | Programme setting

The Princess PrEP programme is the largest PrEP programme in Thailand. It is part of the Key Populations-Led Health Services (KPLHS) model, through which trained lay providers, who themselves are members of the KPs they are serving, provide HIV services in community-based organizations (CBOs) [10]. HIV clinical services under KPLHS included point-of-care HIV and sexually transmitted infections (STIs) testing, PrEP and post-exposure prophylaxis (PEP) dispensing, antiretroviral treatment (ART) service linkages and ART dispensing for stable cases and case management support. A service package was designed by KP communities and co-delivered by KP lay providers, in close collaboration with public health sectors. For example TGW designed a service package which integrated gender affirming care with sexual health service to ensure that common health concerns prioritized by TGW were addressed.

The KPLHS model, including the Princess PrEP programme, is supported through the President's Emergency Plan for AIDS Relief (PEPFAR) under the US Agency for International Development (USAID) LINKAGES Project, whereas the PrEP medication itself is provided through the Thai Red Cross Princess Soamsawali HIV Prevention Fund. Through Princess PrEP, KP lay providers have been successfully dispensing free same-day PrEP since January 2016, contributing to 55% of Thai PrEP users [11]. The programme is currently implemented in six provinces, including Bangkok, Chonburi, Chiang Mai, Chiang Rai, Songkhla and Ubonratchathani, which have high HIV prevalence and incidence among KPs in Thailand [12]. This analysis focused on PrEP services delivered to MSM and TGW between January and November 2019. Routinely collected and de-identified service data were used. The programme was implemented under a protocol approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, which waived the need for informed consent from clients to ensure confidentiality and avoid unnecessary disclosure of self-identity [13].

2.2 | Data collection for PrEP service cascade

Although the programme started delivering PrEP services to KPs and collecting service data in 2016, data collection to inform PrEP service cascade started in January 2019. Data collection was adjusted at this point to be able to collect number of people tested for HIV, tested HIV negative, eligible for PrEP, offered PrEP and accepted PrEP. Counsellors during a counselling session recorded the data through an electronic case record form. All measures were self-reported by the client. Routine data quality assurance and improvement was conducted to ensure completeness of data.

Clients who tested HIV negative at any of the CBOs where Princess PrEP was implemented, were assessed for PrEP eligibility defining as any of the following in the previous three months: condomless sex with unknown HIV status partner(s), condomless sex with HIV-positive partner(s) not on ART or on ART with uncertain viral load status or unknown ART status, having multiple partners, engaging in sex work, symptoms or diagnosis of STIs, injecting drugs, using amphetamine-type stimulants (ATS), or repeated use of PEP. Eligible clients were offered PrEP by trained counsellors during the post-test counselling session. PrEP use, safety and efficacy were explained, and clients were asked if they were interested in taking PrEP. Acceptance of PrEP was documented. Those who did not accept PrEP were asked for their reasons by the counsellors. The counsellors then recorded the reasons by selecting them from the list of common reasons in the electronic case record form, which also provided free space to document reasons not included on the list.

Effective use at months 1 and 3 was defined as retention in care at months 1 and 3, as well as self-reported good adherence during those visits (i.e. at least 4 tablets per week or correct use of on-demand PrEP for MSM and 7 tablets per week for TGW due to indications that use of feminizing hormone therapy was associated with decreased tenofovir plasma and rectal tissue concentrations) [14,15].

2.3 | Statistical analyses

Statistical analyses were performed using Statistics and Data Science (STATA) version 15.1. Demographic data and cascade data were assessed using descriptive statistics as mean, standard deviation, median, interquartile range (IQR) and proportion. T-test and median test were used for comparison of continuous variables with normal and non-normal distribution respectively. Chi-squared test was used to compare categorical variables.

3 | RESULTS

3.1 | Men who have sex with men

3.1.1 | PrEP service cascade

Between 1 January and 30 November 2019, a total of 6287 MSM received HIV testing at one of the sites where Princess

PrEP was implemented. Of these, 5806 (92.3%) were HIV negative, of whom 4078 (70.2%) were eligible for PrEP based on the above mentioned criteria. Of these, 3863 (94.7%) were offered PrEP, of whom 1856 (48.0%) accepted PrEP (Figure 1). On-demand PrEP was chosen at initiation by 4% of MSM. Among those who retained in PrEP service at month 1 (822, 44.3%) and month 3 (457, 24.6%), 99.6% and 99.6% reported effective PrEP use respectively.

When disaggregated by age, MSM younger than 25 years old had lower acceptance of PrEP compared to MSM aged 25 years or older (36.0% vs. 56.7%), and showed lower retention at month 1 (31.5% vs. 50.2%) and month 3 (15.1% vs. 29.0%) (Figure 1).

3.1.2 | *Focusing on PrEP acceptance*

Among 1856 MSM who accepted PrEP, median (IQR) age was 28 (23-33) years (Table 1). Reported risks in the past three months included having multiple partners in 48.7%, condomless sex with unknown HIV status partner(s) in 48.6%, engaging in sex work in 3.6% and using ATS in 3.5%.

Among 2007 MSM not accepting PrEP, 938 (46.7%) perceived no or low risk, 385 (19.2%) did not want to take pills, 147 (7.3%) wanted to start at a later visit, 142 (7.1%) felt condom use was enough to prevent HIV, 102 (5.1%) could not come back for follow-up visit, 55 (2.7%) were not interested and 53 (2.6%) were afraid of side effects (Table 2).

3.2 | Transgender women

3.2.1 | *PrEP service cascade*

A total of 900 TGW received HIV testing between 1 January and 30 November 2019. Of these, 858 (95.3%) were HIV negative, of whom 556 (64.8%) met PrEP eligibility criteria. Of these, 528 (95.0%) were offered PrEP, of whom 232 (43.9%) accepted PrEP (Figure 2). Among those who retained in PrEP service at month 1 (80, 34.5%) and month 3 (43, 18.5%), 98.8% and 100% reported effective PrEP use respectively.

TGW younger than 25 years old had lower acceptance of PrEP compared to those aged 25 years or older (12.5% vs. 48.9%), but showed higher retention at month 1 (83.9% vs. 39.4%) and similar retention at month 3 (22.6% vs. 26.3%) (Figure 2).

3.2.2 | *Focusing on PrEP acceptance*

Of 232 TGW who accepted PrEP, median (IQR) age was 26 (23 – 30) years (Table 1). Reported risks in the past three months included having multiple partners in 45.7%, condomless sex with unknown HIV status partner(s) in 40.1% and engaging in sex work in 24.6%.

Among 296 TGW not accepting PrEP, 124 (41.9%) perceived no or low risk, 68 (23.0%) did not want to take pills, 15 (5.1%) wanted to start at a later visit, 24 (8.1%) felt condom use was enough for HIV prevention, 17 (5.7%) could not come back for follow-up visit, nine (3.0%) were afraid of side effects and two (0.7%) were not interested (Table 2).

4 | DISCUSSION

We used year 2019 data from the Princess PrEP programme, which is the largest PrEP programme in Thailand, to demonstrate and explore gaps in PrEP service cascades for MSM and TGW. Around two-thirds of MSM and TGW in our programme were eligible for PrEP based on risk eligibility criteria recommended in the National Guidelines [16]. An impressive 95% of both MSM and TGW who met PrEP eligibility criteria were offered PrEP, pointing to high level of PrEP service adoption among KP lay providers. However, just less than half of MSM and TGW who were offered PrEP accepted it.

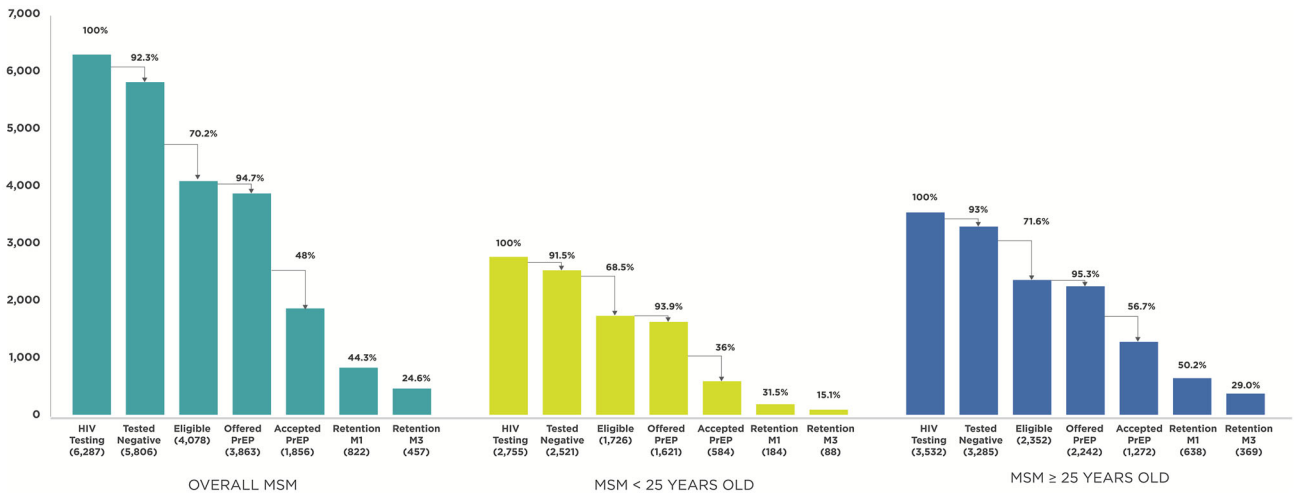

Figure 1. PrEP service cascade for men who have sex with men in the Princess PrEP programme, overall and by age group.
PrEP eligibility criteria: Any of the following in the previous three months: condomless sex with unknown HIV status partner(s), condomless sex with HIV-positive partner(s) not on antiretroviral treatment (ART) or on ART with uncertain viral load status or unknown ART status, having multiple partners, engaging in sex work, symptoms or diagnosis of STIs, injecting drugs, using amphetamine-type stimulants (ATS), or repeated use of post-exposure prophylaxis (PEP). PrEP, pre-exposure prophylaxis; MSM, men who have sex with men; M1, month 1 visit; M3, month 3 visit.

Table 1. Demographic and risk characteristics of men who have sex with men and transgender women who were offered PrEP in the Princess PrEP programme from 1 January to 30 November 2019

	Characteristics of Men who have sex with men (MSM)				Characteristics of Transgender women (TGW)			
Demographic and risk characteristics	**Offered PrEP (N = 3863)**	**Did not accept PrEP (N = 2007)**	**Accepted PrEP (N = 1856)**	***p*-value***	**Offered PrEP (N = 528)**	**Did not accept PrEP (N = 296)**	**Accepted PrEP (N = 232)**	***p*-value***
Age								
Median (IQR), years	26 (22, 32)	24 (21, 30)	28 (23, 33)	<0.001	25 (21, 30)	24 (20, 29)	26 (23, 30)	0.0180
<25 years old, n (%)	1621 (42%)[a]	1037 (51.7%)[a]	584 (31.6%)[a]	<0.001	248 (47%)	153 (51.7%)	95 (40.9%)	0.0140
Condomless sex with unknown HIV status partner(s), n (%)	1489 (38.5%)	587 (29.2%)	902 (48.6%)	<0.001	200 (37.9%)	107 (36.1%)	93 (40.1%)	0.305
Condomless sex with HIV-positive partner(s) not on ART or uncertain VL status or unknown ART status, n (%)	73 (1.9%)	10 (0.5%)	63 (3.4%)	<0.001	2 (0.4%)	1 (0.3%)	1 (0.4%)	0.99
Having multiple partners, n (%)	1338 (34.6%)	434 (21.6%)	904 (48.7%)	<0.001	167 (31.6%)	61 (20.6%)	106 (45.7%)	<0.001
Engaging in sex work, n (%)	100 (2.6%)	33 (1.6%)	67 (3.6%)	<0.001	79 (15%)	22 (7.4%)	57 (24.6%)	<0.001
Having STI symptom/diagnosis, n (%)	46 (1.2%)	17 (0.8%)	29 (1.6%)	<0.05	5 (0.9%)	2 (0.7%)	3 (1.3%)	0.658
Injecting substance(s), n (%)	15 (0.4%)	2 (0.1%)	13 (0.7%)	<0.05	0 (0%)	0 (0%)	0 (0%)	–
Using ATS, n (%)	74 (1.9%)	9 (0.4%)	65 (3.5%)	<0.001	3 (0.6%)	2 (0.7%)	1 (0.4%)	0.99
Repeated PEP use, n (%)	29 (0.8%)	2 (0.1%)	27 (1.5%)	<0.001	1 (0.2%)	0 (0%)	1 (0.4%)	0.439

PrEP, pre-exposure prophylaxis; IQR, interquartile range; THB, Thai Baht (32.5 THB equals 1 US dollar); ART, antiretroviral treatment; VL, viral load; STI, sexually transmitted infection; ATS, amphetamine-type stimulants; PEP, post-exposure prophylaxis.

[a]Missing data for age for 8 MSM who were offered PrEP: 3 who did not accept and 5 who did accept PrEP

**p*-values for comparisons made between individuals who did not accept PrEP vs. those who accepted PrEP.>

Table 2. Reasons for not accepting PrEP when offered among men who have sex with men and transgender women in the Princess PrEP programme

Primary reason given for not accepting PrEP	Men who have sex with men (n = 2007)	Transgender women (n = 296)
Perceived no or low risk		
No risk	864 (43.0%)	111 (37.5%)
Low risk	74 (3.7%)	13 (4.4%)
Did not want to take pills	385 (19.2%)	68 (23.0%)
Wanted to start PrEP at a later visit	147 (7.3%)	15 (5.1%)
Felt condom use was enough for HIV prevention	142 (7.1%)	24 (8.1%)
Could not come back for follow-up visit	102 (5.1%)	17 (5.7%)
Not interested	55 (2.7%)	2 (0.7%)
Afraid of side effects	53 (2.6%)	9 (3.0%)
Others	185 (9.2%)	37 (12.5%)

PrEP, pre-exposure prophylaxis.

Retention in PrEP service was low in both MSM and TGW although almost 100% of those who retained reported effective PrEP use.

We explored further the PrEP acceptance gap and found that almost half of MSM and TGW who met PrEP eligibility criteria perceived themselves as having no or low risk for HIV acquisition. Reframing of messaging around PrEP could significantly impact PrEP uptake. Whereas loss-framing messages (i.e. emphasizing risks) effectively reaches people who perceive themselves to be at risk, gain-framing messaging (i.e. emphasizing health) is more effective in reaching those who do not have this risk perception [17]. Focusing PrEP messaging around risk reduction rather than protection, pleasure or sexual health might miss or even distance those populations that would benefit most from PrEP [18]. In addition, we also found that PrEP acceptance among young MSM and TGW was lower than those among their older peers. PrEP messaging may need to be tailored to young KPs as they can often face particular HIV risks due to lower knowledge or lower ability to mitigate those risks [19].

By June 2019, Princess PrEP programme in six provinces accounted for 55% of PrEP users in Thailand, followed by 26% in the PrEP-15 programme which is a fee-based, KP-friendly, PrEP service at the largest HIV testing centre in Bangkok and 19% from the government-led PrEP service in 25 provinces [11,20]. PrEP is available for free through the Princess PrEP programme and the government-led service, using the same eligibility criteria. High PrEP uptake through KP-led CBOs led the Thai Government to announce the legal endorsement of the roles of KP lay providers in ending AIDS in June 2019. This legal endorsement has allowed HIV clinical services, including PrEP, to be provided by KP lay providers in close collaboration with healthcare providers [21].

We have previously shown that retention in the Princess PrEP programme was lower among TGW compared to MSM, among those younger than 25 years of age, and those with completed education less than bachelor's degree [9]. Alternative methods of adherence and retention support are needed to tailor interventions to the needs of the clients, including but not limited to mobile health technologies [22]. However, reasons for not retaining in PrEP service should be further explored to assess whether clients not returning for follow-up visits are still at risk while off PrEP, or if they are simply not at risk anymore. Use of PrEP can be flexible to match periods of different HIV risk, and while PrEP needs to be taken to be effective against HIV acquisition while someone is at risk, it does not need to be used when someone is not at risk [23].

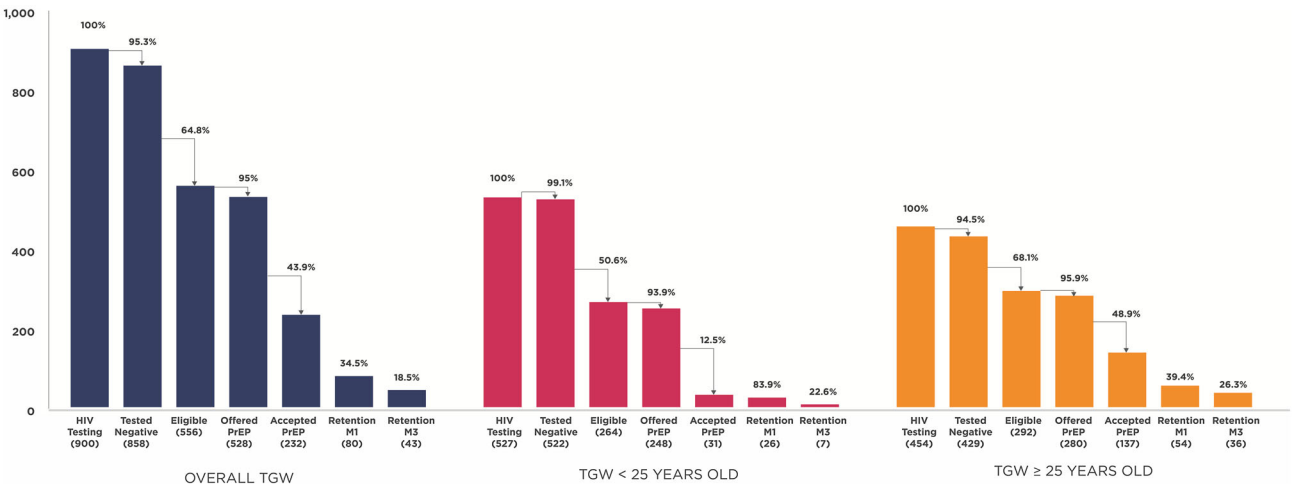

Figure 2. PrEP service cascade for transgender women in Princess PrEP programme, overall and by age group.
PrEP eligibility criteria: Any of the following in the previous three months: condomless sex with unknown HIV status partner(s), condomless sex with HIV-positive partner(s) not on antiretroviral treatment (ART) or on ART with uncertain viral load status or unknown ART status, having multiple partners, engaging in sex work, symptoms or diagnosis of STIs, injecting drugs, using amphetamine-type stimulants (ATS), or repeated use of post-exposure prophylaxis (PEP). PrEP, pre-exposure prophylaxis; TGW, transgender women; M1, month 1 visit; M3, month 3 visit.

This study has some limitations. Our data were limited to MSM and TGW in six provinces and might not be applicable to other KPs, such as FSW or PWID, or other geographical regions within Thailand. We used self-report of PrEP adherence which can overestimate the actual use of PrEP. Therefore, effective use of PrEP might be lower than what we reported here [24]. Other measures, including risk behaviours, were also self-reported which could be biased due to social desirability. We observed that 5% of eligible MSM and TGW were not offered PrEP. However, we did not systematically collect reasons to inform this service gap. In addition, our PrEP service cascades seemed to provide limited data to inform a larger HIV prevention cascade as we did not study PrEP motivation of MSM and TGW who did not access services at community-based clinics nor the level of access to services among these populations if motivated. According to the HIV prevention cascade, implementers are encouraged to identify gaps in the motivation, access and effective use of an HIV prevention method, plan interventions to close those gaps and monitor the interventions [3]. Ideally, after data on these aspects are applied to the cascade, the proportion of the priority population that is effectively covered by an HIV prevention method can be calculated, which can be used for the monitoring and evaluation of the programme.

Identifying individuals at risk that could benefit from using an HIV prevention method is the first step in operationalizing the HIV prevention cascade. A recent PrEP targets estimation exercise in Thailand revealed an estimated number of Thai people at substantial risk of HIV infection at 148,487 (73,058 – 239,152) in 2020 [25]. Current number of PrEP users in Thailand was reported to be 13,000 – 14,000 or just around 10% of the estimated target [26]. Demand for PrEP, which reflects motivation to use it, is one of the defining factors for the success of PrEP programmes. In the United Kingdom, demand for PrEP has resulted in increased availability of PrEP services, whereas in Australia, demand has secured commitment from policy makers [27,28]. This level of PrEP demand from potential users has not been evident in Thailand. Future implementation research should therefore be prioritized to study PrEP motivation and access in larger KP communities outside of clinical services.

5 | CONCLUSIONS

PrEP service cascades from the Princess PrEP programme identified no or low-risk perception as key barrier to PrEP acceptance among both MSM and TGW who met PrEP eligibility criteria. More implementation research studies are needed to explore PrEP motivation and service access in order to identify gaps and potential strategies to address them within a larger HIV prevention cascade. Definitions of retention and effective use of PrEP need to be further optimized as we gradually understand more the nature of PrEP use among various populations. As Thailand is rolling out and scaling up PrEP as part of its Universal Health Coverage, better data to be applied to the motivation, access and effective use domains of the HIV prevention cascade will allow us to efficiently plan and track progress of PrEP implementation.

AUTHORS' AFFILIATIONS

[1]Thai Red Cross AIDS Research Centre, PREVENTION, Bangkok, Thailand; [2]Rainbow Sky Association of Thailand, Bangkok, Thailand; [3]Service Workers in Group Foundation, Bangkok, Thailand; [4]Mplus Foundation, Chiang Mai, Thailand; [5]Caremat Foundation, Chiang Mai, Thailand; [6]Thai Red Cross AIDS Research Centre, SEARCH, Bangkok, Thailand; [7]FHI 360, Bangkok, Thailand; [8]Office of Public Health, United States Agency for International Development, Bangkok, Thailand

COMPETING INTERESTS

RAR received speakers fees and travel support from Gilead, and speakers fees from Alere. Other authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

RAR, PP and NP conceptualized the study. RAR, TS, TC, TS(2), OW, PM, SS, TP, WB, TW, DC, MA, SM, RV, PP and NP contributed significantly to the design of the programmes. TS, TC, TS(2), OW, PM, SS, TP, WB and TW contributed significantly to the collection of the data. RM analysed the data. RAR, MA, SM and NP drafted and revised the manuscript. All authors approved the manuscript before submission.

ACKNOWLEDGMENTS

FUNDING

The TDF/FTC used in the Princess PrEP programme was supported by the Thai Red Cross Princess Soamsawali HIV Prevention fund, with subsidized and/or donated TDF/FTC from the Thai Government Pharmaceutical Organisation and Atlanta Medicare. The implementation of the Princess PrEP programme was supported by US President's Emergency Plan for AIDS Relief and the US Agency for International Development through the Linkages Across the Continuum of HIV Services for Key Populations cooperative agreement (AID-OAA-A-14-0045) managed by FHI 360.

REFERENCES

1. Nwokolo N, Hill A, McOwan A, Pozniak A. Rapidly declining HIV infection in MSM in central London. Lancet HIV. 2017;4(11):e482–3.
2. Grulich AE, Guy R, Amin J, Jin F, Selvey C, Holden J, et al. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. Lancet HIV. 2018;5(11):e629–37.
3. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett TB, Hargreaves JR. HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades. Lancet HIV. 2019;6(1):e60–6.
4. Thailand Working Group on HIV/AIDS Projection. AIDS Epidemic Model Projection for HIV/AIDS in Thailand 2010-2030. Summary Report. 2010.
5. Joint United Nations. Program on HIV/AIDS (UNAIDS). Prevention GapReport. 2016.
6. Seekaew P, Pengnonyang S, Jantarapakde J, Sungsing T, Rodbumrung P, Trachunthong D, et al. Characteristics and HIV epidemiologic profiles of men who have sex with men and transgender women in key population-led test and treat cohorts in Thailand. PLoS One. 2018;13:e0203294.
7. Funding boost for healthcare: The Nation; 2019 [cited 2020 May 31]. Available from: http://www.nationmultimedia.com/Economy/30364003
8. NHSO board adds PrEP for high risk populations to fiscal year 2020 budget (Thai language). National Health Security Office; 2019 [cited 2020 May 31]. Available from: https://www.nhso.go.th/frontend/NewsInformationDetail.aspx?newsid=MjUzMg==
9. Phanuphak N, Sungsing T, Jantarapakde J, Pengnonyang S, Trachunthong D, Mingkwanrungruang P, et al. Princess PrEP program: the first key population-led model to deliver pre-exposure prophylaxis to key populations by key populations in Thailand. Sex Health. 2018;15(6):542–55.
10. Thai Red Cross AIDS Research Centre and FHI 360. Differentiated HIV Service Delivery along the cascade for men who have sex with men and transgender women in Thailand: lessons learned from the LINKGAGES project [cited 2020 May 31]. Available from: http://www.differentiatedcare.org/Portals/0/adam/Content/ZrutobOVxk-Fze9x6KfQTA/File/1%20Thailand%20-%20Thai%20Red%20Cross%20AIDS%20Research%20Centre.pdf.

11. Phanuphak N, Jantarapakde J, Himmad L, Sungsing T, Meksena R, Phomthong S, et al. Linkages to HIV confirmatory testing and antiretroviral therapy after online, supervised, HIV self-testing among Thai men who have sex with men and transgender women. J Int AIDS Soc. 2020;23:e25448.
12. Thailand National AIDS Committee. Thailand National Operational Plan Accelerating Ending AIDS 2015-2019. 2014.
13. International AIDS Society. IAS statement on U=U: Putting the science into action [cited 2020 May 31]. Available from: https://www.iasociety.org/The-latest/News/ArticleID/244/IAS-statement-on-U-U-Putting-the-science-into-action
14. Hiransuthikul A, Janamnuaysook R, Himmad K, et al. Drug-drug interactions between feminizing hormone therapy and pre-exposure prophylaxis among transgender women: the iFACT study. J Int AIDS Soc. 2019;22(7):e25338.
15. Cottrell ML, Prince HMA, Schauer AP, Sykes C, Maffuid K, Poliseno A, et al. Decreased tenofovir diphosphate concentrations in a transgender female cohort: Implications for HIV pre-exposure prophylaxis (PrEP). Clin Infect Dis. 2019;69 (12):2201-4.
16. Department of Disease Control, Thailand Ministry of Public Health. Thailand National Guidelines on Pre-Exposure Prophylaxis: HIV-PrEP. 2018 [cited 2020 April 19]. Available from: http://aidssti.ddc.moph.go.th/medias/view/126/549
17. Hull SJ. Perceived risk as a moderator of the effectiveness of framed HIV-test promotion messages among women: a randomized controlled trial. Health Psychol. 2012;31(1):114–21.
18. Rivet Amico K, Bekker LG. Global PrEP roll-out: recommendations for programmatic success. Lancet HIV. 2019;6(2):e137–40.
19. UNAIDS. Getting on the Fast-Track: The life-cycle approach to HIV, Finding solutions for everyone at every stage of life [cited 2020 Apr 19]. Available from: https://www.unaids.org/sites/default/files/media_asset/Get-on-the-Fast-Track_en.pdf
20. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Antiretroviral therapy for the prevention of HIV-1 transmission. N Engl J Med. 2016;375(9):830–9.
21. Regulation of the Ministry of Public Health on Persons Assigned by the Ministry, Department, Bureau, Bangkok Metropolitan Administration, Pattaya City Administration, Provincial Administration Organization, Municipality or Local Administration Organization Published in the Government Gazette or by The Thai Red Cross Society to work as Pharmaceutical Professionals under Supervision of the Officials Who Perform a Pharmaceutical Profession. B.E. 2562 2019 [cited 2020 May 31]. Available from: http://www.ratchakitcha.soc.go.th/DATA/PDF/2562/E/155/T_0001.PDF
22. Liu A, Stojanovski K, Lester R, Amico KR, McMahan V, Goicochea P, et al.Developing and implementing a mobile health (mHealth) adherence support system for HIV-uninfected men who have sex with men (MSM) taking pre-exposure prophylaxis (PrEP): the iText study. Abstract 165. 8th International Conference on HIV Treatment and Prevention Adherence; Miami, FL; 2014.
23. WHO. Implementation Tool for Pre-Exposure Prophylaxis of HIV Infection. Module 5: Monitoring and Evaluation. Geneva: World Health Organization (WHO/CDS/HIV/18.10). 2018.
24. Baker Z, Javanbakht M, Mierzwa S, Pavel C, Lally M, Zimet G, et al. Predictors of over-reporting hiv pre-exposure prophylaxis (PrEP) adherence among young men who have sex with men (YMSM) in self-reported versus biomarker data. AIDS Behav. 2018;22(4):1174–83.
25. Jacobson J, Siraprapasiri S. Estimation of PrEP targets for key and high-risk populations in Thailand, 2020-2022 [cited 2020 Apr 19]. Available from: http://www.boe.moph.go.th/aids/Downloads/book/2562/Final_Thailand_PrEP_targets_report.pdf
26. AVAC Global Advocacy for HIV Prevention. Global PrEP tracker [cited 2020 Apr 19]. Available from: https://www.prepwatch.org/resource/global-prep-tracker/
27. Aloysius I, Savage A, Zdravkov J, Korologou-Linden R, Hill A, Smith R, et al. Internet-based pre-exposure prophylaxis with generic tenofovir DF/emtricitabine in London: an analysis of outcomes in 641 patients. J Virus Erad. 2017;3 (4):218–22.
28. Zablotska IB, Selvey C, Guy R, Price K, Holden J, Schmidt HM, et al. Expanded HIV pre-exposure prophylaxis (PrEP) implementation in communities in New South Wales, Australia (EPIC-NSW): design of an open label, single arm implementation trial. BMC Public Health. 2018;18(1):210.

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Cost-effectiveness of couples' voluntary HIV counselling and testing in six African countries: a modelling study guided by an HIV prevention cascade framework

Kristin M Wall[1,2,§], Mubiana Inambao[1,3], William Kilembe[1], Etienne Karita[1], Elwyn Chomba[4], Bellington Vwalika[1,5], Joseph Mulenga[1], Rachel Parker[1], Tyronza Sharkey[1], Amanda Tichacek[1], Eric Hunter[1,6,7], Robert Yohnka[1], Gordon Streeb[8], Phaedra S Corso[9] and Susan Allen[1]

[§]**Corresponding author**: Kristin M Wall, 1518 Clifton Road NE, Atlanta, Georgia 30322, USA. Tel: +001 404-727-9088. (kmwall@emory.edu)

Abstract

Introduction: Couples' voluntary HIV counselling and testing (CVCT) is a high-impact HIV prevention intervention in Rwanda and Zambia. Our objective was to model the cost-per-HIV infection averted by CVCT in six African countries guided by an HIV prevention cascade framework. The HIV prevention cascade as yet to be applied to evaluating CVCT effectiveness or cost-effectiveness.

Methods: We defined a priority population for CVCT in Africa as heterosexual adults in stable couples. Based on our previous experience nationalizing CVCT in Rwanda and scaling-up CVCT in 73 clinics in Zambia, we estimated HIV prevention cascade domains of motivation for use, access and effectiveness of CVCT as model parameters. Costs-per-couple tested were also estimated based on our previous studies. We used these parameters as well as country-specific inputs to model the impact of CVCT over a five-year time horizon in a previously developed and tested deterministic compartmental model. We consider six countries across Africa with varied HIV epidemics (South Africa, Zimbabwe, Kenya, Tanzania, Ivory Coast and Sierra Leone). Outcomes of interest were the proportion of HIV infections averted by CVCT, nationwide CVCT implementation costs and costs-per-HIV infection averted by CVCT. We applied 3%/year discounting to costs and outcomes. Univariate and Monte Carlo multivariate sensitivity analyses were conducted.

Results: We estimated that CVCT could avert between 54% (Sierra Leone) and 62% (South Africa) of adult HIV infections. Average costs-per-HIV infection averted were lowest in Zimbabwe ($550) and highest in South Africa ($1272). Nationwide implementations would cost between 7% (Kenya) and 21% (Ivory Coast) of a country's President's Emergency Plan for AIDS Relief (PEPFAR) budget over five years. In sensitivity analyses, model outputs were most sensitive to estimates of cost-per-couple tested; the proportion of adults in heterosexual couples and HIV prevention cascade domains of CVCT motivation and access.

Conclusions: Our model indicates that nationalized CVCT could prevent over half of adult HIV infections for 7% to 21% of the modelled countries' five-year PEPFAR budgets. While other studies have indicated that CVCT motivation is high given locally relevant promotional and educational efforts, without required indicators, targets and dedicated budgets, access remains low.

Keywords: Africa; cost-effectiveness; costs and cost analysis; couples; HIV; HIV prevention cascade; prevention and control

Received 17 October 2019; **Accepted** 23 April 2020

1 | INTRODUCTION

Incident HIV infections in sub-Saharan Africa have fallen 13% over recent years due to global prevention efforts [1]. However, this decline in new infections is slowing, gaps in the scale-up of treatment and prevention services persist, and flatlined funds are not projected to meet 2030 Sustainable Development Goals [1,2]. Now more than ever, maximizing the value of limited funding is critical, and evaluating the cost-effectiveness of HIV prevention and treatment strategies is essential for improved resource allocation [1,3]. The HIV prevention cascade, which evaluates domains of intervention motivation for use, access and effectiveness among a priority population, provides a useful framework to evaluate and advocate for prevention interventions [4] and has been used to evaluate interventions such as pre-exposure prophylaxis (PrEP), voluntary medical male circumcision (VMMC) and prevention of mother-to-child transmission (PMTCT) [5-8].

The HIV prevention cascade has yet to be described or evaluated for couples' voluntary HIV counselling and testing

(CVCT), an evidence-based intervention in which couples receive joint pre-test counselling, testing and post-test counselling with counsellor-facilitated serostatus disclosure [9,10]. CVCT decreases sexual and perinatal HIV incidence [11-16] by educating and placing joint responsibility on the dyad to increase uptake of condoms, VMMC, family planning, antiretroviral therapy (ART) and PMTCT [13-15,17]. The priority population for CVCT is stable couples. With the exception of South Africa, most African adults are in cohabiting sexual unions [18], and the majority of HIV transmissions in sub-Saharan Africa occur in heterosexual HIV discordant or concordant HIV-negative couples [19]. Despite World Health Organization (WHO) [9] and the US Centers for Disease Control and Prevention (CDC) [10] CVCT recommendations, only a small percentage of African adults have been tested with partners.

Building on our technical support for the nationalization of CVCT in antenatal clinics (ANC) in Rwanda, where >80% of couples are now tested [20], we recently reported the cost-effectiveness of a CVCT demonstration project serving 207,428 Zambian couples in 73 government clinics [21]. Receiving CVCT was associated with a 79% reduction in seroincidence among discordant couples using ART, 63% among discordant couples not using ART and 47% among concordant-negative couples. The cost-per-HIV infection averted (CHIA) for CVCT was $659. We then built and validated a deterministic compartmental model which incorporated key domains from the HIV prevention cascade framework and reported the CHIA for nationalizing CVCT in Zambia ($394 CHIA) [21].

In the present analysis, we adapt this model to estimate the proportion of adult HIV infections averted, total costs and CHIA for nationalizing CVCT in six countries across sub-Saharan Africa.

2 | METHODS

2.1 | Ethics approval

This retrospective costing and modelling study used de-identified data from the publicly available sources cited. The Institutional Research Board at Emory University waived informed consent requirements.

2.2 | Deterministic compartmental model

Our CVCT CHIA model details are published [21]. In summary, a deterministic compartmental model with one-year time steps based on a series of differential equations was developed in Excel which allows heterosexual adult couples who are either concordant HIV-negative or discordant, and on ART or off ART, to transition between states of HIV status and/or ART use over time. Our previous model structure [21] has been adapted here to incorporate HIV prevention cascade domains of motivation and access, which the previous model did not include.

Our model uses HIV seroincidence rates in uncounselled ("pre-CVCT") serodiscordant and concordant-negative couples (which is assumed to be a function of all current prevention programmes taking place in country) and applies the estimated effectiveness of CVCT among couples depending on their joint HIV serostatus and ART use. These effectiveness estimates are applied each year, and couples move from concordant negative to discordant and from discordant to concordant positive accordingly. Estimated "pre-CVCT" ART use and ART initiation in the year following CVCT are also model parameters, with an additional proportion of HIV-positive individuals taking up ART each year. Estimated costs-per-couple tested are based on our programmatic experience. The model outputs HIV infections averted by CVCT (by subtracting the cumulative infections that are projected to occur post-CVCT from those occurring pre-CVCT), total incremental financial costs to implement CVCT and incremental CHIA by CVCT [21]. As evidence suggests that the HIV prevention impact of CVCT is sustainable for at least five years [22-25], we chose a five-year time horizon.

In the model, we conceptualize the expansion of CVCT in four phases: initiation, expansion, maturation and maintenance which are described in more detail below. These phases are defined by a changing set of estimated values for the HIV prevention cascade domains of motivation and access among the priority population for CVCT (Figure 1) and cost-per-couple tested.

Using this model, we previously estimated the cost-effectiveness of nationalizing CVCT in Zambia by applying the actual financial expenditures and CVCT effectiveness observed when scaling-up services in 73 government clinics in Lusaka, Copperbelt and Southern Provinces which reached 207,428 couples. We conducted sensitivity analyses to evaluate the effect of possible differential loss to follow-up, informative censoring using inverse probability of censoring weighting [26,27], and inverse probability of treatment weighting to evaluate the possibility of confounding when using observational data to estimate intervention effects. We found that our model was robust in these sensitivity analyses [21]. Additionally, to internally validate the model, we used logical testing by varying transition probabilities and setting costs and outcomes to 0 separately, which resulted in logical expected values.

2.3 | Base-case model parameters applied to all countries

Base-case estimates for CVCT HIV prevention impact were derived from our CVCT implementation in 73 Zambian government clinics [21] (Table 1). Briefly, from September 2010 to March 2016, CVCT services were implemented including joint pre-test counselling; rapid HIV testing; joint post-test counselling; provision of condoms and referrals as needed for ART, VMMC and family planning. History of prior HIV testing and self-reported ART use were documented. HIV antibody-negative individuals had repeat tests one month after CVCT. Discordant couples returned for quarterly retesting and counselling, and concordant HIV-negative couples returned for annual retesting and counselling [28]. Promotions utilized influential community health workers and mass media [28,29].

During the implementation, the impact of CVCT was assessed over longitudinal follow-up. HIV seroincidence rates for discordant and concordant HIV-negative couples were calculated as incident infections divided by HIV-negative person-years (PY) of follow-up, stratified by whether couples had ("post-CVCT") or had not ("pre-CVCT") received CVCT. As shown in Table 1, in concordant-negative couples, we

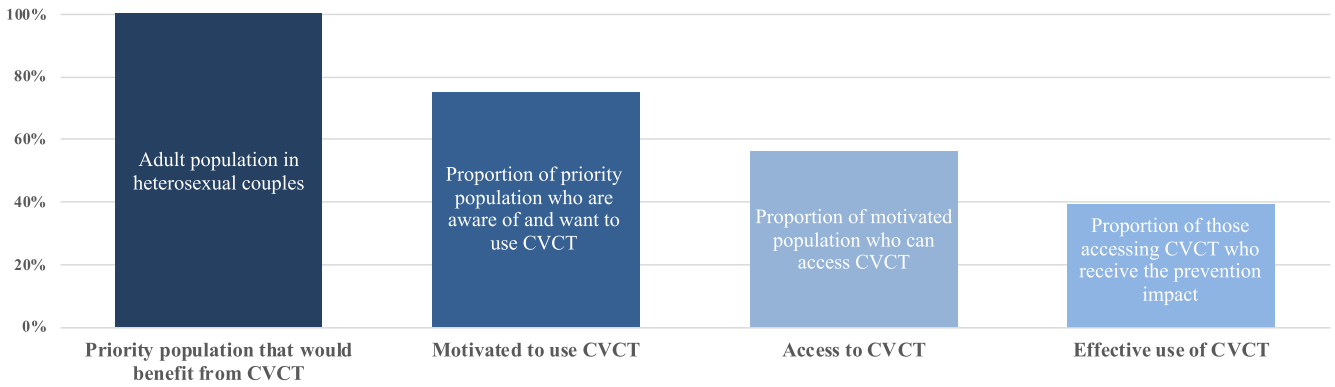

Figure 1. Generic HIV prevention cascade for CVCT. CVCT, couples' voluntary HIV counselling and testing.

Table 1. Base-case model parameters applied to all countries

	Value and source
CVCT effective use (HIV prevention impact)	
Among concordant HIV-negative couples	47% [21]
Among discordant couples not on ART	63% [21]
Among discordant couples on ART	79% [21]
ART use	
Immediate increase in uptake after CVCT	38% [21]
Additional uptake per year	5% [21]
CVCT motivation among the priority population	
Initiation phase	20% of couples [20,21]
Expansion phase	38% of couples [20,21]
Maturation phase	66% of couples [20,21]
Maintenance phase	15% of couples [20,21]
CVCT access among those motivated	
Initiation phase	50% of motivated couples [20,21]
Expansion Phase	56% of motivated couples [20,21]
Maturation phase	60% of motivated couples [20,21]
Maintenance phase	70% of motivated couples [20,21]

ART, antiretroviral treatment; CVCT, couples' voluntary HIV counselling and testing; USD, United States Dollar.

observed a 47% reduction in HIV seroincidence pre-CVCT (1.1/100PY) versus post-CVCT (0.6/100PY). In serodiscordant couples in which the HIV+ partner was not on ART, we observed a 63% reduction in incidence (13.0/100PY pre-CVCT versus 4.8/100PY post-CVCT). Finally, in serodiscordant couples in which the HIV+ partner was on ART, we observed a 79% reduction in incidence (8.5/100PY pre-CVCT versus 1.8/100PY post-CVCT) [21]. We also use the increase in ART uptake reported in the previously published manuscript (38% of non-users initiated ART after CVCT with 5%/year additional uptake thereafter) [21]. Self-reported ART initiation is not assumed to imply adherence/suppressive ART.

Base-case estimates for cost-per-couple tested, motivation for CVCT, and access to CVCT were derived from both the Zambian implementation study described and our years of experience supporting nationalization of CVCT in Rwanda [20,21]. We derived incremental financial costs from the donor's perspective from a primary costing study of actual expenditures to implement CVCT in government clinics following Global Heath Cost Consortium guidance [30]. Cost data were reported by activity were recorded by study staff during programme implementation and entered in AccPac (Sage Group). Based on our experiences in Rwanda and Zambia [20,21], motivation for CVCT, and access to CVCT varied over time and are used to define implementation phases as shown in Table 1: initiation phase (advocacy, training and promotions to motivate 20% of couples, 50% of whom have CVCT access); expansion phase (continued advocacy and training, increased community and politico-administrative involvement, CVCT certification for a majority of providers and active promotions to motivate 38% of couples, 56% of whom have CVCT access); maturation phase (an established programme with CVCT integrated into existing services including ANC, individual HIV counselling and testing, ART, VMMC and family planning services and 66% of couples are motivated, 60% of whom have CVCT access); and finally the maintenance phase (for hard-to-reach residual and new couples where only 15% are motivated, of whom 70% have CVCT access). Thus, 80% of couples are assumed to be reached with testing, as seen in Rwandan ANC [20].

2.4 | Country-specific parameters

South Africa, Zimbabwe, Kenya, Tanzania, Ivory Coast and Sierra Leone have diverse HIV epidemics and published data available for the model inputs (Table 2). Country-specific model parameters include: (1) proportion of adults in cohabiting heterosexual couples, (2) couple HIV serostatus distribution, (3) ART use, (4) HIV seroincidence in uncounselled (pre- CVCT) concordant-negative couples, (5) HIV seroincidence in uncounselled discordant couples not on ART, (6) HIV seroincidence in uncounselled discordant couples on ART and (7) estimated cost-per-couple tested. Published estimates of HIV seroincidence in uncounselled concordant-negative couples [31-34] and uncounselled discordant non-ART using couples [31-35] are limited to Eastern Africa. Given limited data for Southern African countries, model inputs 4, 5 and 6 (Table 2) were estimated from Zambia data [21]. As no published data are

Table 2. Country-specific base-case model parameters

	Southern Africa				Eastern Africa				Western Africa			
	South Africa		Zimbabwe		Kenya		Tanzania		Ivory Coast		Sierra Leone	
Model input	Value		Value		Value		Value		Value		Value	
1												
Adult population (ages 15 to 64)	37,904,001	[37]	7 892 000	[37]	2 974 500	[37]	3 001 700	[37]	1 383 900	[37]	428 200	[37]
Adult population in stable couples (%)	35%	[18]	58%	[18]	57%	[18]	57%	[18]	59%	[18]	62%	[18]
2												
Discordant couples among all stable couples (%)	16%	[18]	9%	[18]	6%	[18]	5%	[18]	5%	[18]	3%	[18]
Concordant-negative couples among all stable couples (%)	70%	[18]	80%	[18]	91%	[18]	91%	[18]	93%	[18]	97%	[18]
3												
Adults on ART of all estimated positive adults (%)	62%	[38]	89%	[38]	69%	[38]	72%	[38]	55%	[38]	43%	[38]
4												
Uncounselled seroincidence among concordant-negative couples (per 100 PY)	1/100 PY	[21]	1/100 PY	[21]	0.5/100 PY	[31-34]	0.5/100 PY	[31-34]	0.5/100 PY	[a]	0.5/100 PY	[a]
5												
Uncounselled seroincidence among non-ART using discordant couples (per 100 PY)	13/100 PY	[21]	13/100 PY	[21]	10/100 PY	[31-35,39]	10/100 PY	[31-35,39]	10/100 PY	[a]	10/100 PY	[a]
6												
Uncounselled seroincidence among ART using discordant couples (per 100 PY)	8/100 PY	[21]	8/100 PY	[21]	5/100 PY	[a]	5/100 PY	[a]	5/100 PY	[a]	5/100 PY	[a]
7												
Cost-per-couple tested (2015 USD)		[21,40]		[21,40]		[21,40]		[21,40]		[21,40]		[21,40]
Initiation phase	$229		$84		$59		$73		$103		$71	
Expansion phase	$153		$56		$39		$49		$69		$47	
Maturation phase	$76		$28		$20		$24		$34		$24	
Maintenance phase	$92		$34		$24		$29		$41		$28	

"Uncounselled" indicates pre-couples' voluntary HIV counselling and testing. Demographic Health Survey defines stable couples as partners consensually living together in a union within a household. Most recent Demographic Health Survey data used. ART, antiretroviral treatment; PY, person year.

[a]Estimated based on lower HIV incidence in Eastern and Western Africa versus Southern Africa [36].

Wall KM et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25522
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25522/full | https://doi.org/10.1002/jia2.25522

available for HIV seroincidence in uncounselled ART-using discordant couples in Eastern and Western Africa, we used 5/100PY reflecting the broadly lower incidence in Eastern/Western versus Southern Africa [36]. Finally, since the primary cost driver for CVCT is salaries for counselling, testing and promotions [20,21], we derived a conversion factor using country-specific nurse salaries (USD 2015) applied to cost-per-couple tested estimates calculated from our Zambian implementation ($75 initiation phase, $50 expansion phase, $25 maturation phase, $30 maintenance phase [21]) to generate cost-per-couple tested estimates for each country.

2.5 | Base-case analyses

The estimated proportion of adult HIV infections averted, total CVCT implementation costs, CHIA and proportion of President's Emergency Plan for AIDS Relief (PEPFAR) budgets required for nationwide implementation in each selected country are outcomes of interest. These are presented alongside per capita gross domestic products (GDPs) for context. All outcomes and costs were discounted at 3%/year as recommended by the US Public Health Service Task Force [41]. We adhered to Consolidated Health Economic Evaluation Reporting Standards [42] for cost-effectiveness analyses.

2.6 | One-way and probabilistic sensitivity analyses

We conducted one-way sensitivity analyses for all model inputs by varying each parameter ±20%. Inputs which most influenced model outputs are reported. Because key model parameters of cost-per-couple tested and CVCT effectiveness were derived from just two countries, we also conducted probabilistic Monte Carlo simulation multivariate sensitivity analyses for each parameter of interest (±50% of base-case estimates using a uniform distribution) with 1000 draws in Excel. Average outcomes and standard deviations from simulated results are reported. A uniform distribution was chosen to fix a functional form on the parameter estimates and to reflect a large degree of uncertainty around the selected parameters.

3 | RESULTS

The total cost for nationwide CVCT implementation and cumulative infections averted are also shown in Table 3. Estimated average CHIA ranged from $1272 in South Africa to $550 in Zimbabwe. Our model estimated that CVCT could prevent between 54% and 62% of HIV infections. The proportion of the 2018 PEPFAR budget required for CVCT nationalization over five years ranged from 7% in Kenya to 21% in Ivory Coast. For context, per capita GDP for each country is shown.

Figure 2 presents country-specific CHIA estimates by implementation phase. During the initiation phase, the CHIA ranged from $2503 in South Africa to $1080 in Zimbabwe. During the expansion phase, the CHIA ranged from $720 to $1672. During the maturation phase, the CHIA ranged from $360 to $831. Finally, during the maintenance phase, the CHIA ranged from $437 to $1005.

3.1 | Sensitivity analyses

One-way sensitivity (Table 4 presents representative findings from South Africa) analyses indicated our model was relatively robust to parameter assumptions, with resulting CHIA still relatively low compared to other HIV prevention interventions (discussed below). Our model was most sensitive to the costs-per-couple tested (varying input parameters by ±20% resulted in total CVCT costs which were ±20% different from base-case). Our model was also sensitive to varying the proportion of adults in heterosexual couples (a higher proportion of adults in heterosexual couples lead to a proportional increase in HIV infections averted and total CVCT costs). Similarly, our model was sensitive to the proportion of couples motivated for and with access to CVCT (with increasing

Table 3. Proportion of adult infections averted, overall CHIA and total cost for CVCT in six African countries (primary base-case analyses)

Southern Africa	Total cost of CVCT	Cumulative HIV infections averted	Average CHIA[a]	Proportion of infections averted, %	2018 PEPFAR Budget [43]	Cost of CVCT as % of PEPFAR budget for five years, %	Per capita GDP
South Africa	$532,704,861	418,855	$1272	62	$575,258,390	19	$13,054
Zimbabwe	$67,053,208	121,984	$550	58	$145,546,200	9	$2,224
East-Central Africa							
Kenya	$176,419,535	231,312	$763	57	$505,480,000	7	$3,384
Tanzania	$219,582,392	219,486	$1000	56	$512,422,250	9	$3,094
Western Africa							
Ivory Coast	$145,955,594	119,508	$1221	57	$140,508,601	21	$3,771
Sierra Leone	$33,113,126	34,803	$951	54	Unknown	–	$1,547

No PEPFAR budget reported for Sierra Leone. Per capita GDP (2017 estimates in 2015 USD): https://www.cia.gov/library/publications/the-world-factbook/rankorder/2004rank.html. CHIA, cost per HIV infection averted; CVCT, Couples' HIV voluntary counselling and testing; PEPFAR: President's Emergency Plan for AIDS Relief.
[a]Weighted average across all implementation phases.

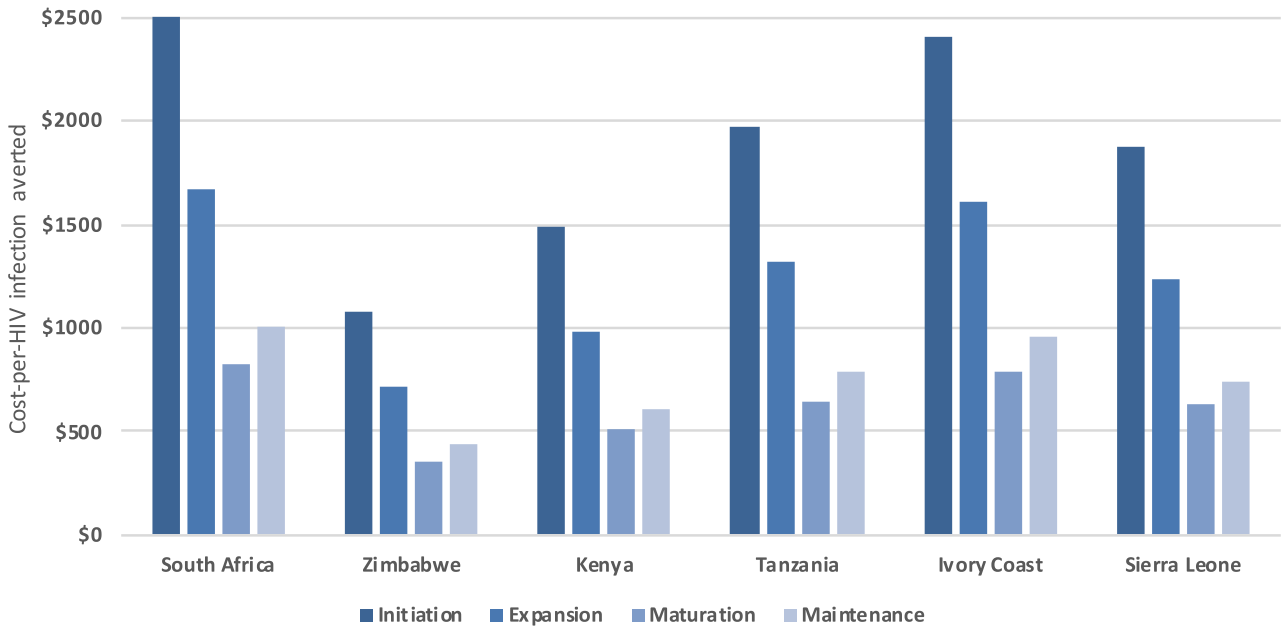

Figure 2. Modelled cost-per-HIV infection averted by phase of CVCT implementation in six sub-Saharan African countries. CVCT, couples' HIV voluntary counselling and testing.

motivation and access was associated with proportional changes in increased infections averted and costs).

Additionally, our model was relatively sensitive (with results varying roughly ±10% relative to base-case) to the proportion of concordant negative and discordant couples in the population (with higher proportions of at-risk couples leading to increased infections averted and therefore lower CHIAs).

A higher pre-CVCT seroincidence rate in concordant-negative couples and higher CVCT effectiveness in concordant-negative couples both increased HIV infections averted. Finally, increasing CVCT effectiveness in ART using discordant couples by ±20% varied total infections averted by roughly ±10% (with higher prevention impact leading to increased infections averted and improved cost-effectiveness).

Examining the country-specific parameters specifically, differences in model outcomes across countries are influenced by differences in seroincidence rates pre-CVCT (with higher uncounselled seroincidence rates being associated with higher numbers of infections averted and improved cost-effectiveness) and the proportion of couples who were discordant (with higher discordancy associated with higher numbers of infections averted and improved cost-effectiveness).

Probabilistic multivariate sensitivity analyses (Table 5) also highlighted that total CVCT costs were sensitive to cost-per-couple tested, with coefficients of variation of 15% to 16%. Our model was less susceptible to variation in CVCT impact, with coefficients of variation of 10% to 12%.

4 | DISCUSSION

Our model estimated that CVCT could prevent over half of adult HIV infections for 7% to 21% of selected countries' five-year PEPFAR budgets. Applying an HIV prevention cascade framework [5] is helpful to evaluate CVCT. In the countries under study, the priority population for CVCT, stable couples, comprises 35% to 62% of the adult population. Key barriers and solutions related to this priority population's motivation to use CVCT, CVCT access and effective use are summarized in Table 6 and discussed in detail below.

4.1 | Motivation

Sensitivity analyses indicated countries with a higher proportion of heterosexual couples motivated to uptake CVCT prevented more infections. Motivation for CVCT has been high across studies in diverse populations including heterosexual couples in Mozambique [44,45], Tanzania [46,47], South Africa [48,49], Uganda [50], Thailand [51], Iran [52] and men who have sex with men (MSM) in South Africa [53] and the US [54,55]. Although promising, these are relatively small-scale efforts: knowledge of CVCT remains low in many settings and education and demand creation are essential to increase broad motivation [28-29,56]. Key barriers to motivation include lack of community knowledge of HIV serodiscordance and HIV risk. For example we found that only 30% of couples seeking CVCT in Durban knew about serodiscordance [49]. Other barriers to motivation include opportunity costs, men's inability to attend regular clinic hours, limited knowledge that CVCT services exist, and concerns about consequences like relationship dissolution [28-29,56,57].

Reports highlight successful strategies to overcome these barriers and increase motivation including use transport reimbursement [57]; nonmonetary incentives in Zambia [58] and rural Zimbabwe [59]; invitations plus facilitated contact tracing to support partner attendance in Malawi [60]; male-focused interactive sessions with testimonies from 'expert couples'

Table 4. Parameters and results of one-way sensitivity analyses: Illustrative example of South Africa

Sensitivity analysis parameters	Infections averted % change[a]	Total cost of CVCT % change[a]	CHIA % change[a]
Discount rate			
2%	3%	5%	2%
4%	−3%	−5%	−2%
Cost/couple tested (by implementation phase)			
$183; $122; $61; $74	0%	−20%	−20%
$274; $184; $91; $110	0%	20%	20%
Proportion adults in heterosexual couples			
28%	−20%	−20%	0%
42%	20%	20%	0%
Proportion couples motivated for CVCT (by implementation phase)			
40%; 40%; 53%; 12%	−20%	−20%	0%
60%; 60%; 79%; 18%	20%	20%	0%
Proportion couples with access to CVCT (by implementation phase)			
16%; 32%; 48%; 56%	−20%	−20%	0%
24%; 48%; 72%; 84%	20%	20%	0%
Proportion concordant negative			
56%	−9%	0%	10%
84%	10%	0%	−9%
Proportion discordant			
13%	−9%	0%	10%
19%	11%	0%	−10%
HIV seroincidence rates before CVCT (per 100 PY)			
Among concordant HIV-negative couples			
0.80	−9%	0%	10%
1.20	9%	0%	−8%
Among ART using HIV discordant couples			
6.40	−6%	0%	6%
9.60	6%	0%	−6%
Among non- ART using HIV discordant couples			
10.40	−4%	0%	4%
15.60	4%	0%	−4%
CVCT prevention impact			
Among concordant HIV-negative couples			
38%	−7%	0%	8%
56%	7%	0%	−7%
Among ART using HIV discordant couples			
63%	−10%	0%	11%
95%	11%	0%	−10%
Among non-ART using HIV discordant couples			
50%	−2%	0%	2%
76%	2%	0%	−2%
ART use			
Among HIV-positive adults before CVCT			
50%	2%	0%	−2%
74%	−3%	0%	3%
Among HIV-positive adults after CVCT			
61%	−1%	0%	1%
92%	1%	0%	−1%
Proportion initiating ART each year after CVCT			
4%	0%	0%	0%
6%	0%	0%	0%

ART, antiretroviral treatment; CHIA, cost-per-HIV infection averted; CVCT, couples' voluntary HIV counselling and testing; PY, person-years.
[a]% Change relative to base-case primary analyses.

Table 5. Probabilistic sensitivity analysis results

Varying costs-per-couple tested by ±50% (uniform distribution) of the base-case estimates[a]						
Southern Africa	**Total cost of CVCT**	**SD**	**CV**	**Average CHIA**	**SD**	**CV**
South Africa	527,493,591	80,271,276	15%	$1280	$198	15%
Zimbabwe	67,478,299	9,792,498	15%	$466	$73	16%
East-Central Africa						
Kenya	175,560,051	28,074,065	16%	$765	$116	15%
Tanzania	219,184,615	33,759,017	15%	$997	$158	16%
Western Africa						
Ivory Coast	145,820,457	22,312,561	15%	$1217	$191	16%
Sierra Leone	33,384,147	4,850,786	15%	$953	$145	15%
Varying CVCT impacts by ±50% (uniform distribution) of the base-case estimates[b]						
Southern Africa	**Cumulative HIV infections averted**	**SD**	**CV**	**Average CHIA**	**SD**	**CV**
South Africa	420,653	45,818	11%	$1304	$146	11%
Zimbabwe	116,862	14,257	12%	$570	$68	12%
East-Central Africa						
Kenya	232,821	25,860	11%	$788	$86	11%
Tanzania	220,013	25,895	12%	$1043	$120	12%
Western Africa						
Ivory Coast	118,752	12,769	11%	$1269	$131	10%
Sierra Leone	34,876	4091	12%	$998	$120	12%

CHIA, cost per HIV infection averted; CV, coefficient of variation is the standard deviation divided by the mean estimate; CVCT, couples voluntary HIV counselling and testing; SD, standard deviation.
[a]No impact on cumulative HIV infections averted; [b]no impact on total cost of CVCT.

who received CVCT in rural Uganda [50]; and CVCT invitations and promotions delivered by influential community leaders and via mass media in Zambia and Rwanda [28-29,56]. Additionally, the desire to keep one's partners safe from transmission is a motivating factor for ART and PrEP use [61,62], and "undetectable = untransmittable" messaging may reduce stigma and motivate couples to uptake CVCT and ART to achieve viral suppression [63]. Finally, messaging should emphasize that outcomes of intimate partner violence (IPV), relationship dissolution or emotional distress are rare and CVCT typically *strengthens* relationships [16-17,54,60,64,65]. To broadly increase CVCT motivation, budgets for training, demand creation and incentives (all included in our modelled CVCT costs) will be required.

4.2 | Access

Sensitivity analyses indicated that countries with a higher proportion of heterosexual couples with CVCT access will prevent more infections at a higher cost. The PEPFAR 2020 Country Operation Plan [43] highlights family HIV testing and emphasizes that HIV prevention among pregnant, postpartum and breastfeeding women should include "couples-based services to promote scaled-up testing and treatment of male partners." However, as CVCT is not broadly offered as standard of care in the selected countries, nor it is a required indicator for reporting [66], access remains low across Africa. As with most interventions, a main barrier to access is the cost of wide-spread implementation. As expected, higher costs-per-couple tested increase total CVCT costs. Economies of scale are incorporated into estimated cost-per-couple tested (over time, costs to test couples decrease, with the exception of the final "hard-to-reach" couples).

Our experience in Zambia reflected the initiation and expansion phases [21]. Government clinic staff were paid during their off-duty hours. Unfortunately, the amount of funding available was insufficient to maintain momentum. In contrast, Rwanda succeeded in increasing access and nationalizing CVCT in ANC between 2008 and 2013 (after which CVCT become a social norm and demand creation was no longer needed) [20]. Based on the estimated impact of CVCT in Rwanda from observational epidemiological studies [11,23,24], the Rwandan government health insurance and performance-based financing plans now reimburse the costs of CVCT, and additional funding for off-duty staff is no longer required. Reaching Rwanda's success will require investment. As many demonstration projects correspond to the more expensive initiation phase, implementers may fail to see that continuous investment is necessary to achieve social diffusion, incorporate CVCT into daily clinical practice and adapt data recording and reporting tools to achieve sustained access [57].

In addition to clinic-based CVCT, mobile testing in Rwanda [29]; home-based couples' testing in Tanzania [67], Kenya [68] and Malawi [69]; and self-testing to increase CVCT in Kenya

Table 6. CVCT HIV prevention cascade domains with key barriers and solutions

Motivation	Access	Effective use
Reasons for gap		
Lack of knowledge and low risk perception	Lack of availability or easy access in government facilities	Inconsistent condom use, continued outside partner risk
Lack of men's ability to attend regular clinic hours, opportunity costs	Lack of trained government providers	Lack of ART uptake
Concerns about CVCT consequences	Perceived cost/affordability	Non-linkage to ART programmes
Evidence-based ways to close the gap		
Interventions		
Incentives/transport reimbursement	Convenient service delivery hours and platforms	Ongoing condom and behavioural counselling, targeted safe conception and alcohol counselling
Partner tracing, male-focused sessions, 'expert couple' and influential community leader promotions	Provider training and reimbursement (possibly during off-hours)	Integration with ART (for treatment and prevention) programmes
Informational messaging highlighting partner safety, U = U, and addressing common concerns		
Platforms to deliver interventions		
Clinics, community health workers, influential peers and mass media	Clinic-based services, mobile testing, home-based testing, self-testing	Clinic-based services, mobile testing, home-based testing, self-testing
Policies to support interventions		
Budgets for training messaging, demand creation and incentives	Budgets, required reporting indicators and targets for CVCT	Budgets for integrated services, ongoing M&E
	Training and reimbursement of providers	

ART, antiretroviral treatment; CVCT, couples voluntary HIV counselling and testing; M&E, monitoring and evaluation.

[70] have been studied. An improved understanding of differences in CVCT access and costs (as well as motivation) for different modalities is warranted.

4.3 | Effective use

CVCT decreases sexual and perinatal HIV incidence [11-16] by educating and placing joint responsibility on the dyad to increase uptake of condoms, VMMC, family planning, ART and PMTCT [13-15,17]. CVCT effectiveness must be monitored to understand facilitators and barriers to achieving reductions in HIV incidence. Our previous analyses found factors associated with inconsistent condom use, non-ART initiation or continued outside partner risk in discordant couples post-CVCT included alcohol use and fertility intentions [71]. To improve effective use of CVCT for all couples, targeted safe conception or alcohol counselling may be warranted. Importantly, as seen in sensitivity analyses, a higher prevention impact in concordant-negative couples increased CVCT cost-effectiveness. It has been argued that CVCT may have a sizable impact on the epidemic through HIV prevention in concordant-negative couples (via reduction in outside relationship risk) since they comprise the majority of the population [72,73].

For the smaller though higher-risk population of discordant couples, "Test-and-Treat" will continue to expand. Unfortunately, many country's HIV incidence rates have not decreased as substantially as predicted in the test-and-treat era, and several large cluster-randomized trials have failed to clearly demonstrate the population-level prevention impact of universal test-and-treat policies [74]. Where CVCT increases ART uptake and adherence in serodiscordant couples, it may bolster the effectiveness of test-and-treat. Additionally, to achieve the PEPFAR 2020 priority of PrEP for discordant couples [43], CVCT can effectively identify discordant couple candidates. Although PrEP is not currently available in most countries outside of relatively small demonstration and research projects, CVCT counselling can be updated to include PrEP as it becomes available.

Finally, an improved understanding of the effectiveness of CVCT in home-based settings, mobile-testing and via self-testing is needed with regular monitoring and evaluation of these delivery platforms. With self-testing in particular, how well couples disclose, understand their respective results and adopt appropriate risk reduction without facilitated joint post-test counselling merits further investigation [75-78].

4.4 | Comparative cost-effectiveness

We found CVCT CHIA estimates to be similar to interventions largely considered cost-effective including individual voluntary HIV counselling and testing (estimated in a previous systematic review of studies in sub-Saharan Africa at $1315 [79] and $483

for an individual and couples testing intervention in Kenya [79,80]) and family planning for PMTCT via prevention of unintended pregnancy ($663) [79]. A recent systematic review of 60 studies from African countries reported median CHIA estimates for VMMC ($2965), ART for PMTCT ($1144), treatment-as-prevention interventions ($7903) and PrEP ($13,267) [81].

4.5 | Limitations

As in all models, we attempt to simplify a complex reality, and outputs are dependent on assumptions. Extensive sensitivity analyses quantify the impact of these assumptions. Our model seeks to isolate the impact of CVCT on HIV infections averted given constant pre-CVCT and post-CVCT HIV incidence. We do not attempt to predict the course of the epidemic in the selected countries over time by considering myriad other prevention or treatment interventions. More detailed models isolating the prevention impact of CVCT attributable to condom use, VMMC uptake, improved ART uptake and adherence, and/or reductions in concurrent relationships are warranted. While deterministic compartmental models are well-suited to examine average characteristics in a population and are thus appropriate for our goal, they do not evaluate individual-level effects as do agent-based models. Finally, while some studies of HIV prevention interventions translate infections averted into disability-adjusted life-years averted or quality-adjusted life-years gained, a recent systematic review did not find standard conversions applicable across country settings [81]. While such cost-utility estimates are often applied to determine if an intervention is cost-effective [82], this threshold is often questioned by experts since it does not consider intervention affordability [83,84]. While cost-utility analyses are useful for comparing interventions with different natural units, given dedicated HIV prevention budgets and the common use of CHIA estimates in other studies [81], we feel that CHIA is a more useful comparative measure.

5 | CONCLUSIONS

Our model indicated that nationalized CVCT could prevent over half of adult HIV infections for 7% to 21% of the modelled countries' five-year PEPFAR budgets. Unfortunately, WHO CVCT guidelines have yet to be broadly implemented. While studies indicate that CVCT motivation is high given locally relevant promotional and educational efforts, access remains low without dedicated budgets or required indicators.

AUTHORS' AFFILIATIONS

[1]Rwanda Zambia HIV Research Group, Department of Pathology & Laboratory Medicine, School of Medicine and Hubert Department of Global Health, Rollins School of Public Health, Laney Graduate School, Emory University, Atlanta, GA, USA; [2]Department of Epidemiology, Rollins School of Public Health, Laney Graduate School, Emory University, Atlanta, GA, USA; [3]Department of Obstetrics and Gynecology, Ndola Central Hospital, Ndola, Zambia; [4]Ministry of Health, Lusaka, Zambia; [5]Department of Obstetrics and Gynecology, School of Medicine, University of Zambia, Lusaka, Zambia; [6]Department of Pathology & Laboratory Medicine, School of Medicine, Emory University, Atlanta, GA, USA; [7]Emory Vaccine Center, Yerkes National Primate Research Center, Emory University, Atlanta, GA, USA; [8]Departments of Economics and Political Science, Emory University, Atlanta, GA, USA; [9]Office of Research, Kennesaw State University, Kennesaw, GA, USA

COMPETING INTEREST

The authors have no conflicts of interest.

AUTHORS' CONTRIBUTIONS

KMW contributed to the analysis and interpretation of data; drafted the article and revised it critically for important intellectual content; and gave final approval of the version to be published. MI contributed to the conception and design of the study, revised the article critically for important intellectual content and gave final approval of the version to be published. WK contributed to the conception and design of the study, revised the article critically for important intellectual content and gave final approval of the version to be published. EK contributed to the conception and design of the study, revised the article critically for important intellectual content and gave final approval of the version to be published. EC contributed to the conception and design of the study, revised the article critically for important intellectual content and gave final approval of the version to be published. BV contributed to the conception and design of the study, revised the article critically for important intellectual content and gave final approval of the version to be published. JM contributed to the conception and design of the study, revised the article critically for important intellectual content and gave final approval of the version to be published. RP contributed to the analysis and interpretation of data; revised the article critically for important intellectual content and gave final approval of the version to be published. TS contributed to the analysis and interpretation of data; revised the article critically for important intellectual content and gave final approval of the version to be published. AT contributed to the study conception and design, revised the article critically for important intellectual content and gave final approval of the version to be published. EH contributed to the analysis and interpretation of data; revised the article critically for important intellectual content and gave final approval of the version to be published. RY contributed to the analysis and interpretation of data; revised the article critically for important intellectual content and gave final approval of the version to be published. GS contributed to the analysis and interpretation of data; revised the article critically for important intellectual content and gave final approval of the version to be published. PC contributed to the analysis and interpretation of data; revised the article critically for important intellectual content and gave final approval of the version to be published. SA contributed to the study design and conception, contributed to the analysis and interpretation of data; revised the article critically for important intellectual content and gave final approval of the version to be published.

ACKNOWLEDGEMENTS

FUNDING

This work was supported by Arise—Enhancing HIV Prevention Programs for At-Risk Populations, through financial support provided by the Canadian Government through Foreign Affairs, Trade and Development Canada (DFATD, formerly CIDA, http://www.international.gc.ca/international/index.aspx?lang=eng) with technical support from PATH [CID.1450-08863-SUB to SA]. Arise implements innovative HIV prevention initiatives for vulnerable communities, with a focus on determining cost-effectiveness through rigorous evaluations. This study was also supported by the United Kingdom Department for International Development (DFID, https://www.gov.uk/government/organisations/department-for-international-development) [UK202340-102 to SA]; the International AIDS Vaccine Initiative (https://www.iavi.org/) with the generous support of the American people through the United States Agency for International Development (USAID, https://www.usaid.gov/); National Institutes of Health (https://www.nih.gov/) grants [R01 MH66767 to SA, R01 HD40125 to SA and R01 MH95503 to SA, K01 MH107320 to KMW, R01 AI051231 to SA]; the AIDS International Training and Research Program Fogarty International Center [D43 TW001042 to SA] and the Emory Center for AIDS Research [P30 AI050409]. The contents are the responsibility of the authors and do not necessarily reflect the views of sponsors, who had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

REFERENCES

1. UNAIDS. Global AIDS Update 2019. 2019 [cited 2020 Feb 25]. Available from: https://www.unaids.org/en/resources/documents/2019/2019-global-AIDS-update
2. Global Burden of Disease Health Financing Collaborator Network. Spending on health and HIV/AIDS: domestic health spending and development assistance in 188 countries, 1995–2015. Lancet. 2018;391(10132):1799–829.
3. Granich R, Gupta S, Montaner J, Williams B, Zuniga JM. Pattern, determinants, and impact of HIV spending on care and treatment in 38 high-burden low- and middle-income countries. J Int Assoc Provid AIDS Care. 2016;15(2):91–100.
4. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett TB, Hargreaves JR. HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades. Lancet HIV. 2019;6(1):e60–6.
5. Moorhouse L, Schaefer R, Thomas R, Nyamukapa C, Skovdal M, Hallett TB, et al. Application of the HIV prevention cascade to identify, develop and evaluate interventions to improve use of prevention methods: examples from a study in east Zimbabwe. J Int AIDS Soc. 2019;22:e25309.
6. Hensen B, Fearon E, Schaap AB, Lewis JJ, Weiss HA, Tembo M, et al. Application of an HIV prevention cascade to identify gaps in increasing coverage of voluntary medical male circumcision services in 42 rural Zambian communities. AIDS Behav. 2019;23(5):1095–103.
7. Bhattacharjee P, Musyoki HK, Becker M, Musimbi J, Kaosa S, Kioko J, et al. HIV prevention programme cascades: insights from HIV programme monitoring for female sex workers in Kenya. J Int AIDS Soc. 2019;22:e25311.
8. Garnett GP, Krishnaratne S, Harris KL, Hallett TB, Santos M, Enstone JE, et al. Cost-effectiveness of interventions to prevent HIV acquisition. In: Holmes KK, Bertozzi S, Bloom BR, Jha P, editors. Major infectious diseases. 3rd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2017 Nov.
9. WHO. Guidance on couples HIV testing and counselling including antiretroviral therapy for treatment and prevention in serodiscordant couples: recommendations for a public health approach. 2012 [cited 2020 March 5]. Available from: http://apps.who.int/iris/bitstream/10665/44646/1/9789241501972_eng.pdf
10. CDC. Testing together. 2020 [cited 2020 March 5]. Available from: https://www.cdc.gov/hiv/effective-interventions/diagnose/testing-together/index.html
11. Allen S. Confidential HIV testing and condom promotion in Africa. Impact on HIV and gonorrhea rates. JAMA. 1992;268(23):3338–43.
12. Fideli US, Allen SA, Musonda R, Trask S, Hahn BH, Weiss H, et al. Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa. AIDS Res Hum Retroviruses. 2001;17(10):901–10.
13. Painter TM. Voluntary counseling and testing for couples: a high-leverage intervention for HIV/AIDS prevention in sub-Saharan Africa. Soc Sci Med. 2001;53(11):1397–411.
14. McKenna SL, Muyinda GK, Roth D, Mwali M, Ng'andu N, Myrick A, et al. Rapid HIV testing and counseling for voluntary testing centers in Africa. AIDS. 1997;11 Suppl 1:S103–10.
15. Were WA, Mermin JH, Wamai N, Awor AC, Bechange S, Moss S, et al. Undiagnosed HIV infection and couple HIV discordance among household members of HIV-infected people receiving antiretroviral therapy in Uganda. J Acquir Immune Defic Syndr. 2006;43(1):91–5.
16. Roth DL, Stewart KE, Clay OJ, van der Straten A, Karita E, Allen S. Sexual practices of HIV discordant and concordant couples in Rwanda: effects of a testing and counselling programme for men. Int J STD AIDS. 2001;12(3):181–8.
17. Becker S, Mlay R, Schwandt HM, Lyamuya E. Comparing couples' and individual voluntary counseling and testing for HIV at antenatal clinics in Tanzania: a randomized trial. AIDS Behav. 2010;14(3):558–66.
18. Demographic and Health Surveys. 2020 [cited 2020 Feb 25]. Available from: http://www.measuredhs.com/
19. Chemaitelly H, Awad SF, Shelton JD, Abu-Raddad LJ. Sources of HIV incidence among stable couples in sub-Saharan Africa. J Int AIDS Soc. 2014;17:18765.
20. Karita E, Nsanzimana S, Ndagije F, Wall KM, Mukamuyango J, Mugwaneza P, et al. Implementation and operational research: evolution of couples' voluntary counseling and testing for HIV in Rwanda: from research to public health practice. J Acquir Immune Defic Syndr. 2016;73(3):e51–8.
21. Wall KM, Inambao M, Kilembe W, Karita E, Vwalika B, Mulenga J, et al. HIV testing and counselling couples together for affordable HIV prevention in Africa. Int J Epidemiol. 2019;48(1):217–27.
22. Dunkle KL, Greenberg L, Lanterman A, Stephenson R, Allen S. Source of new infections in generalised HIV epidemics – Authors' reply. Lancet. 2008;372(9646):1300–1.
23. Allen S, Meinzen-Derr J, Kautzman M, Zulu I, Trask S, Fideli U, et al. Sexual behavior of HIV discordant couples after HIV counseling and testing. AIDS. 2003;17(5):733–40.
24. Allen S, Tice J, Van de Perre P, Serufilira A, Hudes E, Nsengumuremyi F, et al. Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. BMJ. 1992;304(6842):1605–9.
25. Wall KM, Kilembe W, Vwalika B, Haddad LB, Lakhi S, Onwubiko U, et al. Sustained effect of couples' HIV counselling and testing on risk reduction among Zambian HIV serodiscordant couples. Sex Transmit Infect. 2017;93(4):259–66.
26. Jiménez-Moro JL, Gómez J.Inverse probability of censoring weighting for selective crossover in oncology clinical trials. Paper SP02 2014 [cited 2018 April 26]. Available from: https://www.lexjansen.com/phuse/2014/sp/SP02.pdf
27. Howe CJ, Cole SR, Lau B, Napravnik S, Eron JJ. Selection bias due to loss to follow up in cohort studies. Epidemiology. 2016;27(1):91–7.
28. Wall KM, Kilembe W, Nizam A, Vwalika C, Kautzman M, Chomba E, et al. Promotion of couples' voluntary HIV counselling and testing in Lusaka, Zambia by influence network leaders and agents. BMJ Open. 2012;2:e001171.
29. Wall K, Karita E, Nizam A, Bekan B, Sardar G, Casanova D, et al. Influence network effectiveness in promoting couples' HIV voluntary counseling and testing in Kigali, Rwanda. AIDS. 2012;26(2):217–27.
30. Global Health Cost Consortium. Analyzing and presenting results: Principles 15–17. 2020 [cited 2020 February 11]. Available from: https://ghcosting.org/pages/standards/principles/analysing_and_presenting_results
31. Carpenter LM, Kamali A, Ruberantwari A, Malamba SS, Whitworth JAG. Rates of HIV-1 transmission within marriage in rural Uganda in relation to the HIV sero-status of the partners. AIDS. 1999;13(9):1083–9.
32. Hugonnet S, Mosha F, Todd J, Mugeye K, Klokke A, Ndeki L, et al. Incidence of HIV infection in stable sexual partnerships: a retrospective cohort study of 1802 couples in Mwanza Region, Tanzania. J Acquir Immune Defic Syndr. 2002;30(1):73–80.
33. Serwadda D, Gray RH, Wawer MJ, Stallings RY, Sewankambo NK, Konde-Lule Bongs Lainjo JK, et al. The social dynamics of HIV transmission as reflected through discordant couples in rural Uganda. AIDS. 1995;9(7):745–50.
34. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study. Group. N Engl J Med. 2000;342(13):921–9.
35. Chemaitelly H, Awad SF, Abu-Raddad LJ. The risk of HIV transmission within HIV-1 sero-discordant couples appears to vary across sub-Saharan Africa. Epidemics. 2014;6:1–9.
36. Kamali A, Price MA, Lakhi S, Karita E, Inambao M, Sanders EJ, et al. Creating an African HIV clinical research and prevention trials network: HIV prevalence, incidence and transmission. PLoS ONE. 2015;10:e0116100.
37. The World Bank. Indicators. 2019 [cited 2020 Feb 25]. Available from: https://data.worldbank.org/indicator/SP.POP.1564.TO?view=chart
38. UNAIDS. AIDSInfo: people living with HIV receiving ART. 2018 [cited 2020 Feb 25]. Available from: http://www.unaids.org/en/dataanalysis/datatools/aidsinfo/
39. Awad SF, Chemaitelly H, Abu-Raddad LJ. Estimating the annual risk of HIV transmission within HIV sero-discordant couples in sub-Saharan Africa. Int J Infect Dis. 2018;66:131–34.
40. PayScale. 2020 [cited 2020 Apr 9]. Available from: https://www.payscale.com/
41. Weinstein MC. Recommendations of the panel on cost-effectiveness in health and medicine. JAMA. 1996;276(15):1253–8.
42. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. Int J Technol Assess Health Care. 2013;29(2):117–22.
43. PEPFAR. PEPFAR 2020 Country Operational Plan Guidance for all PEPFAR Countries. 2019 [cited 2020 Mar 1]. Available from: https://www.state.gov/wp-content/uploads/2019/11/2019-11-25-COP20-Guidance-Full-Consolidated_Public-2-1.pdf
44. Audet CM, Blevins M, Chire YM, Aliyu MH, Vaz LME, Antonio E, et al. Engagement of men in antenatal care services: increased HIV testing and treatment uptake in a community participatory action program in mozambique. AIDS Behav. 2016;20(9):2090–100.
45. Audet CM, Graves E, Barreto E, De Schacht C, Gong W, Shepherd BE, et al. Partners-based HIV treatment for seroconcordant couples attending antenatal and postnatal care in rural Mozambique: a cluster randomized trial protocol. Contemp Clin Trials. 2018;71:63–9.
46. Becker S, Mlay R, Schwandt HM, Lyamuya E. Comparing couples' and individual voluntary counseling and testing for HIV at antenatal clinics in Tanzania: a randomized trial. AIDS Behav. 2010;14(3):558–66.

47. Theuring S, Mbezi P, Luvanda H, Jordan-Harder B, Kunz A, Harms G. Male involvement in PMTCT services in Mbeya Region, Tanzania. AIDS Behav. 2009;13 Suppl 1:92–102.
48. Kilembe W, Wall KM, Mokgoro M, Mwaanga A, Dissen E, Kamusoko M, et al. Implementation of couples' voluntary HIV counseling and testing services in Durban, South Africa. BMC Public Health. 2015;15:601.
49. Kilembe W, Wall KM, Mokgoro M, Mwaanga A, Dissen E, Kamusoko M, et al. Knowledge of HIV serodiscordance, transmission, and prevention among couples in Durban, South Africa. PLoS ONE. 2015;10:e0124548.
50. Matovu JKB, Todd J, Wanyenze RK, Kairania R, Serwadda D, Wabwire-Mangen F. Evaluation of a demand-creation intervention for couples' HIV testing services among married or cohabiting individuals in Rakai, Uganda: a cluster-randomized intervention trial. BMC Infect Dis. 2016;16(1):379.
51. Lolekha R, Kullerk N, Wolfe MI, Klumthanom K, Singhagowin T, Pattanasin S, et al. Assessment of a couples HIV counseling and testing program for pregnant women and their partners in antenatal care (ANC) in 7 provinces, Thailand. BMC Int Health Human Rights. 2014;14:39.
52. Ayatollahi J, Ayatollahi J, Nasab Sarab MA, Sharifi M. Acceptability of HIV/AIDS testing among pre-marital couples in Iran (2012). Niger Med J. 2014;55(4):294–8.
53. Stephenson R,Rentsch C, Sullivan P, McAdams-Mahmoud A, Jobson G, Struthers H, et al. Attitudes toward couples-based HIV counseling and testing among MSM in Cape Town, South Africa. AIDS Behav. 2013;17 Suppl 1:S43–50.
54. Sullivan PS, White D, Rosenberg ES, Barnes J, Jones J, Dasgupta S, et al. Safety and acceptability of couples HIV testing and counseling for US men who have sex with men: a randomized prevention study. J Int Assoc Provid AIDS Care. 2014;13(2):135–44.
55. Wall KM, Canary L, Workowski K, Lockard A, Jones J, Sullivan P, et al. Acceptability of couples' voluntary HIV testing among HIV-infected patients in care and their HIV-negative partners in the United States. Open AIDS J. 2016;10:1–13.
56. Kelley AL, Hagaman AK, Wall KM, Karita E, Kilembe W, Bayingana R, et al. Promotion of couples' voluntary HIV counseling and testing: a comparison of influence networks in Rwanda and Zambia. BMC Public Health. 2016;16:744.
57. Inambao M, Kilembe W, Canary LA, Czaicki NL, Kakungu-Simpungwe M, Chavuma R, et al. Transitioning couple's voluntary HIV counseling and testing (CVCT) from stand-alone weekend services into routine antenatal and VCT services in government clinics in Zambia's two largest cities. PLoS ONE. 2017;12:e0185142.
58. Czaicki NL, Davitte J, Siangonya B, Kastner R, Ahmed N, Khu NH, et al. Predictors of first follow-up HIV testing for couples' voluntary HIV counseling and testing in Ndola, Zambia. J Acquir Immune Defic Syndr. 2014;66(1):e1–7.
59. Sibanda EL, Tumushime M, Mufuka J, Mavedzenge SN, Gudukeya S, Bautista-Arredondo S, et al. Effect of non-monetary incentives on uptake of couples' counselling and testing among clients attending mobile HIV services in rural Zimbabwe: a cluster-randomised trial. Lancet Glob Health. 2017;5(9):e907–15.
60. Rosenberg NE, Mtande TK, Saidi F, Stanley C, Jere E, Paile L, et al. Recruiting male partners for couple HIV testing and counselling in Malawi's option B+ programme: an unblinded randomised controlled trial. Lancet HIV. 2015;2(11):e483–91.
61. Patel RC, Stanford-Moore G, Odoyo J, Pyra M, Wakhungu I, Anand K, et al. "Since both of us are using antiretrovirals, we have been supportive to each other": facilitators and barriers of pre-exposure prophylaxis use in heterosexual HIV serodiscordant couples in Kisumu, Kenya. J Int AIDS Soc. 2016;19(1):21134.
62. Patel RC, Leddy AM, Odoyo J, Anand K, Stanford-Moore G, Wakhungu I, et al. What motivates serodiscordant couples to prevent HIV transmission within their relationships: findings from a PrEP implementation study in Kenya. Cult Health Sex. 2018;20(6):625–39.
63. UNAIDS. Undetectable = Untransmittable. 2018 [cited 2020 March 5]. Available from: https://www.unaids.org/sites/default/files/media_asset/undetectable-untransmittable_en.pdf
64. Semrau K, Kuhn L, Vwalika C, Kasonde P, Sinkala M, Kankasa C, et al. Women in couples antenatal HIV counseling and testing are not more likely to report adverse social events. AIDS (London, England). 2005;19(6):603–9.
65. Desgrees-du-Lou A, Orne-Gliemann J. Couple-centred testing and counselling for HIV serodiscordant heterosexual couples in sub-Saharan Africa. Reprod Health Matters. 2008;16(32):151–61.
66. PEPFAR. Monitoring, evaluation, and reporting indicator reference guide. 2019 [cited 2020 Mar 5]. Available from: https://www.state.gov/wp-content/uploads/2019/10/PEPFAR-MER-Indicator-Reference-Guide-Version-2.4-FY20.pdf
67. Njau B, Watt MH, Ostermann J, Manongi R, Sikkema KJ. Perceived acceptability of home-based couples voluntary HIV counseling and testing in Northern Tanzania. AIDS care. 2012;24(4):413–9.
68. Krakowiak D, Kinuthia J, Osoti AO, Asila V, Gone MA, Mark J, et al. Home-based HIV testing among pregnant couples increases partner testing and identification of serodiscordant partnerships. J Acquir Immune Defic Syndr. 2016;72:S167–73.
69. Becker S, Taulo FO, Hindin MJ, Chipeta EK, Loll D, Tsui A. Pilot study of home-based delivery of HIV testing and counseling and contraceptive services to couples in Malawi. BMC Public Health. 2014;14:1309.
70. Masters SH, Agot K, Obonyo B, Napierala Mavedzenge S, Maman S, Thirumurthy H. Promoting partner testing and couples testing through secondary distribution of HIV self-tests: a randomized clinical trial. PLoS Med. 2016;13:e1002166.
71. Joseph Davey DL, Wall KM, Kilembe W, Naw HK, Brill I, Vwalika B, et al. HIV incidence and predictors of HIV acquisition from an outside partner in serodiscordant couples in Lusaka, Zambia. J Acquir Immune Defic Syndr. 2017;76(2):123–31.
72. Over M.Opportunities for presidential leadership on AIDS: from an "Emergency Plan" to a sustainable policy. 2009 [cited 2020 March 5]. Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.178.8723&rep=rep1&type=pdf
73. Chemaitelly H, Awad SF, Shelton JD, Abu-Raddad LJ. Sources of HIV incidence among stable couples in sub-Saharan Africa. J Int AIDS Soc. 2014;17(1):18765.
74. Abdool Karim SS. HIV-1 Epidemic control - insights from test-and-treat trials. N Engl J Med. 2019;381(3):286–8.
75. Anglewicz P, Chintsanya J. Disclosure of HIV status between spouses in rural Malawi. AIDS Care. 2011;23(8):998–1005.
76. Nyandat J, van Rensburg G. Non-disclosure of HIV-positive status to a partner and mother-to-child transmission of HIV: evidence from a case-control study conducted in a rural county in Kenya. South Afr J HIV Med. 2017;18(1):691.
77. Maeri I, El Ayadi A, Getahun M, Charlebois E, Akatukwasa C, Tumwebaze D, et al. "How can I tell?" Consequences of HIV status disclosure among couples in eastern African communities in the context of an ongoing HIV "test-and-treat" trial. AIDS Care. 2016;28 Sup3:59–66.
78. King R, Wamai N, Khana K, Johansson E, Lindkvist P, Bunnell R. "Maybe his blood is still strong": a qualitative study among HIV-sero-discordant couples on ART in rural Uganda. BMC Public Health. 2012;12(1):801.
79. Galarraga O, Colchero MA, Wamai RG, Bertozzi SM. HIV prevention cost-effectiveness: a systematic review. BMC Public Health. 2009;9 Suppl 1:S5.
80. John FN, Farquhar C, Kiarie JN, Kabura MN, John-Stewart GC. Cost effectiveness of couple counselling to enhance infant HIV-1 prevention. Int J STD AIDS. 2008;19(6):406–9.
81. Sarkar S, Corso P, Ebrahim-Zadeh S, Kim P, Charania S, Wall K. Cost-effectiveness of HIV prevention interventions in Sub-Saharan Africa: a systematic review. EClinicalMedicine. 2019;10:10–31.
82. WHO. Cost effectiveness and strategic planning (WHO-CHOICE). 2013. Available from: https://www.who.int/choice/cost-effectiveness/en/.
83. Bertram MY, Lauer JA, De Joncheere K, Edejer T, Hutubessy R, Kieny M-P, et al. Cost-effectiveness thresholds: pros and cons. Bull World Health Organ. 2016;94(12):925–30. Accessed May 1, 2020.
84. Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. Value Health. 2016;19(8):929–35.

Were D et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25537
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25537/full | https://doi.org/10.1002/jia2.25537

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Using a HIV prevention cascade for identifying missed opportunities in PrEP delivery in Kenya: results from a programmatic surveillance study

Daniel Were[1,§], Abednego Musau[1], Jane Mutegi[1], Patricia Ongwen[1], Griffins Manguro[2], Mercy Kamau[1], Tom Marwa[1], Hellen Gwaro[1], Irene Mukui[3], Marya Plotkin[4] and Jason Reed[4]

[§]**Corresponding author**: Daniel Were, 14 Riverside Drive, off Riverside Drive, P.O Box 66119, 00800, Nairobi, Kenya. Tel: +254708000322. (daniel.were@jhpiego.org)

Abstract

Introduction: HIV prevention cascades have been systematically evaluated in high-income countries, but steps in the pre-exposure prophylaxis (PrEP) service delivery cascade have not been systematically quantified in sub-Saharan Africa. We analysed missed opportunities in the PrEP cascade in a large-scale project serving female sex workers (FSW), men who have sex with men (MSM) and adolescent girls and young women (AGYW) in Kenya.

Methods: Programmatic surveillance was conducted using routine programme data from 89 project-supported sites from February 2017 to December 2019, and complemented by qualitative data. Healthcare providers used nationally approved tools to document service statistics. The analyses examined proportions of people moving onto the next step in the PrEP continuum, and identified missed opportunities. Missed opportunities were defined as implementation gaps exemplified by the proportion of individuals who could have potentially accessed each step of the PrEP cascade and did not. We also assessed trends in the cascade indicators at monthly intervals. Qualitative data were collected through 28 focus group discussions with 241 FSW, MSM, AGYW and healthcare providers, and analysed thematically to identify reasons underpinning the missed opportunities.

Results: During the study period, 299,798 individuals tested HIV negative (211,927 FSW, 47,533 MSM and 40,338 AGYW). Missed opportunities in screening for PrEP eligibility was 58% for FSW, 45% for MSM and 78% for AGYW. Of those screened, 28% FSW, 25% MSM and 65% AGYW were ineligible. Missed opportunities for PrEP initiation were lower among AGYW (8%) compared to FSW (72%) and MSM (75%). Continuation rates were low across all populations at Month-1 (ranging from 29% to 32%) and Month-3 (6% to 8%). Improvements in average annual Month-1 (from 26% to 41%) and Month-3 (from 4% to 15%) continuation rates were observed between 2017 and 2019. While initiation rates were better among younger FSW, MSM and AGYW (<30 years), the reverse was true for continuation.

Conclusions: The application of a PrEP cascade framework facilitated this large-scale oral PrEP programme to conduct granular programmatic analysis, detecting "leaks" in the cascade. These informed programme adjustments to mitigate identified gaps resulting in improvement of selected programmatic outcomes. PrEP programmes are encouraged to introduce the cascade analysis framework into new and existing programming to optimize HIV prevention outcomes.

Keywords: PrEP; cascades; HIV prevention; key; missed opportunities; sub-Saharan Africa

Received 7 October 2019; **Accepted** 7 May 2020

1 | INTRODUCTION

Despite the strides made in fighting the HIV epidemic, globally an estimated 1.7 million people still acquire HIV infection annually [1]. Kenya has the fifth largest HIV epidemic in the world. By 2018, an estimated 1.3 million adults were living with HIV, with an estimated 36,000 new adult HIV infections annually [2]. In the last decade, HIV incidence in the general population in Kenya has stabilized or fallen, but key populations, including female sex workers (FSW), men who have sex with men (MSM) and persons who inject drugs (PWID) continue to experience a high burden of HIV and influence the HIV transmission dynamics. FSW, MSM and PWID accounted for 15% of new HIV infections in East and Southern Africa (ESA) in 2018 [1]. Similarly, a third of all new HIV infections in Kenya are attributed to FSW, MSM and PWID [3].

Globally, adolescent girls and young women (AGYW) aged 15 to 24 years are disproportionately affected by the HIV epidemic and accounted for 60% of the estimated 510,000 new HIV infections within that age group in 2018 [1,4]. AGYW experience a higher vulnerability compared to their male counterparts due to biological and socio-cultural factors,

gender and power dynamics and economic disadvantage [4]. In sub-Saharan Africa (SSA), AGYW represent 10% of the population, but contribute one in every five new HIV infections [5]. Furthermore, AGYW accounted for 26% of all new HIV infections in Eastern and Southern Africa in 2018 [1]. AGYW in Kenya were estimated to account for 28% of new HIV infections among individuals 15 years and older in 2017 [6]. Kenya's epidemic is geographically heterogeneous hence majority of these new infections were concentrated in a few counties with high HIV incidence in the general population [6].

Oral pre-exposure prophylaxis (PrEP) is being rolled out in many SSA countries [7] following WHO's 2015 recommendation [8]. Kenya issued guidelines in 2016 promoting oral PrEP as part of a comprehensive package of HIV prevention services, including condoms, voluntary medical male circumcision (VMMC), treatment as prevention, stigma and violence prevention, post-exposure prophylaxis, among others [9], and subsequently launched national scale-up in 2017 [10]. To reach FSW and MSM, Kenya's national HIV programme provides services mainly through community-led drop in centres (standalone clinics that primarily provide HIV prevention, care and treatment services to FSW and MSM) and peer outreach [11-13]. Additionally, AGYW are served through public and private health facilities that integrate sexual and reproductive health (SRH) services. Since its adoption, PrEP is delivered for FSW, MSM and AGYW through these integrated platforms [10,14].

Cascades have been used extensively to quantify steps [15,16] and identify gaps in service delivery, including for HIV care and treatment services [17,18] as well as tuberculosis [19]. HIV prevention cascades are now being proposed to strengthen HIV prevention programmes, and a number of cascades have been developed [20-23]. Available cascades have been developed using routinely collected programme data [22], population-based survey data [24], or a blend of the two data sources [11].

In a PrEP cascade, quantifiable benchmarks are measured as clients move through the process of receiving services, from initial HIV testing, risk and clinical eligibility screening, to PrEP initiation and continuation [25]. Measurement in a PrEP cascade and interpretation of gaps is complicated by challenges related to the temporality and typology of individuals' risk behaviours, that is despite being in a high HIV risk category, not all people taking PrEP are continuously at substantial risk and so may or may not fully progress through the cascade, even if using PrEP effectively [26]. Furthermore, individuals may switch to alternative HIV prevention interventions hence a holistic cascade that incorporates complementary prevention interventions is desirable [24]. Although PrEP cascades have been operationalized in developed countries [27-29], it is only recently that PrEP cascades are increasingly emerging in SSA [24,30,31]. Furthermore, the majority are derived using research data. To the best of our knowledge, there are no published examples of PrEP cascades using routine programmatic data from the region.

This paper presents an analysis of programmatic surveillance data from a large PrEP scale-up project for FSW, MSM and AGYW in Kenya. The objectives of the study were as follows: to describe the programmatic application of an oral PrEP cascade; to quantify progression across each step of the cascade for FSW, MSM and AGYW beneficiaries of the project, looking at differences between populations; and, to identify missed opportunities and programme implications from trends in each step.

2 | METHODS

This analysis was conducted using data collected from February 2017 to December 2019 in three geographical clusters (Lake, Nairobi and Coast) in Kenya (Figure 1), in the context of a large-scale routine service delivery project providing PrEP to FSW, MSM and AGYW. The study design was a programmatic surveillance approach [32] using routine service delivery and qualitative data.

2.1 | Project description

Jilinde (Bridge to Scale) is a five-year project, which began in July 2016, implemented in collaboration with the Ministry of Health (MOH) of Kenya. Jilinde is scaling up oral PrEP through integration into routine health services in drop-in centres (DICEs), public and private health facilities. The project, implemented in 10 out of the 47 counties in Kenya, aimed to enrol 15,500 FSW, 3300 MSM and 2000 AGYW on PrEP (Figure 1). Project targets were set with the goal of enrolling 15% of all FSW and 33% of all MSM in nine out of the ten counties of Kenya on PrEP based on national size estimates [33], whereas AGYW targets were exploratory to establish interest in PrEP uptake among AGYW, and only in one county (Migori).

Individuals enter the PrEP pathway illustrated in Figure 2 through community mobilization mainly conducted by peer educators trained by the project. Individuals who express interest in PrEP are referred to the different facilities providing PrEP, where they undergo HIV testing services (HTS) following the national guidelines [34]. Upon confirmation of negative HIV status, clients undergo a behavioural risk screening. Those who screen positive for substantial behavioural risk, or who request PrEP, are referred to an onsite clinician who conducts a clinical assessment and provides PrEP to clients who are eligible and opt-in [10]. Typically, HTS, eligibility screening and clinical assessment occur on the same day. Clients enrolled on PrEP are scheduled for a follow-up visit at the same facility one month following initiation and monthly thereafter, and are provided with the option to access adherence support interventions including: short message service (SMS) reminders; phone call reminders; PrEP support groups and adherence buddies.

2.2 | Data sources and analysis

We used two main data sources; routine programmatic data to operationalize the PrEP cascade, and qualitative data to identify underlying reasons for the implementation gaps.

2.2.1 | Routine programmatic data

Data were collected from 89 sites (34 DICEs, 42 public health facilities and 13 private health facilities) in the 10 counties where the Jilinde project operates. The data were collected in the context of routine service delivery, with standardized tools

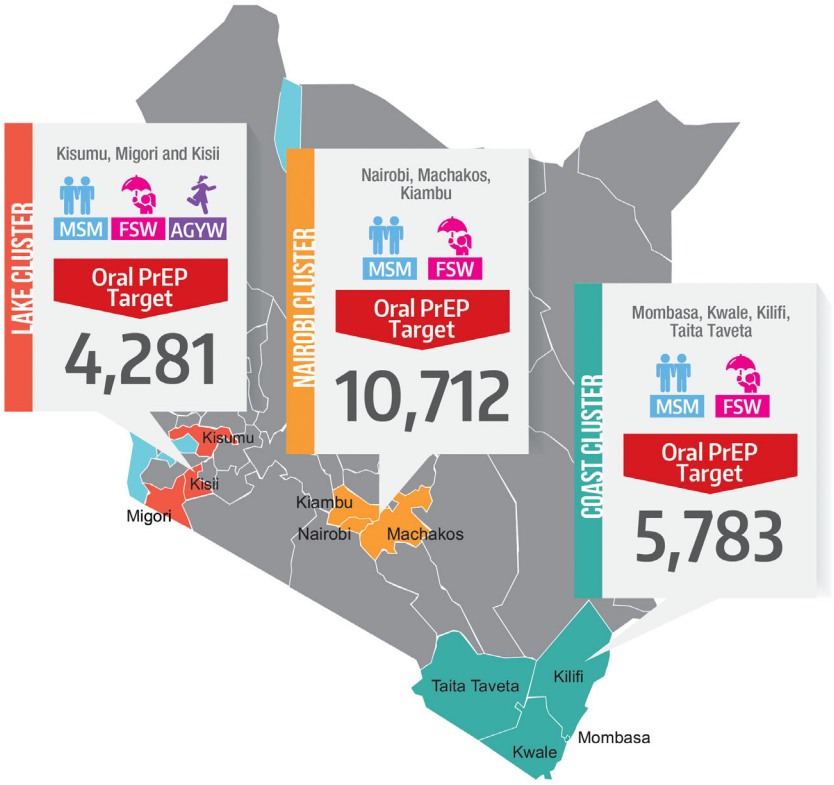

Figure 1. Geographical coverage and oral PrEP targets of the Jilinde Project in Kenya.
Source: Jilinde Project. PrEP, pre-exposure prophylaxis.

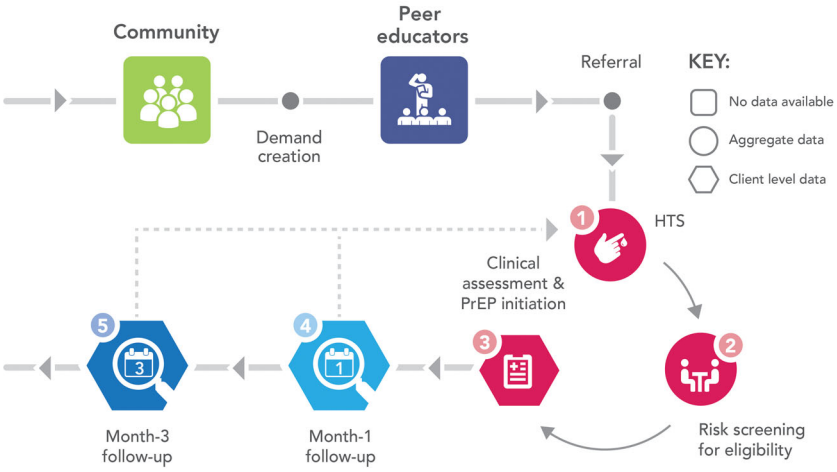

Figure 2. PrEP service delivery pathway in the Jilinde project – PrEP cascade incorporates steps 1 to 5.
Source: Jilinde Project. PrEP, pre-exposure prophylaxis.

approved by the MOH. These include the national HTS registers (for first three steps of the cascade: tested for HIV, tested HIV negative and screened for PrEP eligibility) and client encounter forms (for last three steps of the cascade: initiation on PrEP, attendance at Month-1 and Month-3 follow-up) as summarized in Figure 2. Healthcare providers (HTS providers, clinical officers and nurses) provided HTS and PrEP and recorded information in the HTS registers, which are aggregated into a site-level monthly report. PrEP initiation and follow-up data from the client encounter forms was monitored longitudinally at the client level. Monthly data verification and quarterly data quality audits were conducted to ensure data quality.

The analyses for the cascade examines simple proportions of people moving onto the next step in the PrEP continuum. The starting point is the cumulative number of individuals

who underwent HIV testing. The first three steps of the cascade are computed using aggregate data generated from national HIV testing tools, which summarize the counts of individuals who progressed through the steps. The subsequent steps (initiated PrEP, Month-1 and Month-3 follow-up) are computed using client-level data that accounts for unique individuals. A PrEP refill within 37 and 97 days of scheduled return at successful follow-up visit at one and three-month post-start served as a proxy for continued PrEP use at Month-1 and Month-3 respectively. The proportions for each step of the cascade are computed using the number of individuals reaching that step as the numerator, and the number who reached the previous step in the cascade as a denominator.

The cascade indicators are defined as follows: Tested HIV negative is the aggregate number of individuals whose HIV test results were negative as a proportion of the cumulative number of individuals who underwent an HIV test. Screened is the proportion of individuals who underwent behavioural risk screening among individuals whose HIV test results were negative, whereas eligible is the proportion of individuals who met eligibility criteria for PrEP among individuals screened. Initiated PrEP is the number of individuals who were prescribed and dispensed a 30 days' supply of PrEP as a proportion of the cumulative number of individuals who were eligible for PrEP. Month-1 follow-up is the number of individuals who had returned for a PrEP refill as a proportion of the number of individuals who had completed 37 days' post-PrEP initiation. Month-3 follow-up is the number of individuals who had returned for a PrEP refill as a proportion of the number of individuals who had completed 97 days' post-PrEP initiation.

"Missed opportunities," were proportions of individuals who could have potentially accessed each step in the PrEP continuum who did not. Missed opportunities include individuals who tested HIV negative and could have been screened, but were not; those who were eligible for PrEP, but did not initiate and those who initiated PrEP, but did not return on time for their Month-1 and Month-3 follow-up visit. The identification of missed opportunities and institution of programme adjustments was implemented continuously throughout the surveillance period. To detect changes in the indicators at various points during the surveillance period, we compared the proportions of the cascade indicators across different months from February 2017 to December 2019.

2.2.2 | Qualitative data

Data were collected between October 2017 and May 2019 through 28 focus group discussions (FGDs). Participants included 44 FSW, 59 MSM, 91 AGYW and 47 healthcare providers, who were purposively selected from project-supported sites. FGDs were moderated by trained sex-matched qualitative researchers in English, Kiswahili or local language (Dholuo) and conducted in privacy. FGDs were audio-recorded and handwritten notes taken. The handwritten notes were typed and audio files transcribed verbatim. The transcripts for FGDs conducted in Kiswahili and Dholuo were translated to English. Thematic analysis was conducted using Nvivo 11. Emergent themes are summarized in Table 2.

2.3 | Ethical considerations

Ethical oversight was provided by the Kenya Medical Research Institute (KEMRI) institutional review board (IRB) and a non-research determination was obtained from the Johns Hopkins Bloomberg School of Public Health IRB.

3 | RESULTS

3.1 | Overall PrEP cascade

Between February 2017 and December 2019, 316,928 HIV tests were performed, of which 299,798 (95%) were HIV negative, though an unquantified level of repeat testing occurred. From these testing activities, 123,480 HIV-negative individuals were screened for PrEP, representing at least 41%, the exact estimate dependent upon the extent of repeat testing, and 86,550 (70%) were eligible for PrEP (Figure 3A). Among PrEP-eligible individuals, 25,542 (30%) consisting 17,794 (70%) FSW, 4,848 (19%) MSM and 2,900 (11%) AGYW, were initiated on PrEP, exceeding the project targets for FSW and MSM in Figure 1. Of these clients, 61% of FSW and 42% of MSM were above 24 years, whereas 55% of AGYW were between 20 and 24 years. Majority (81%) of clients initiated PrEP through DICEs, whereas 14% and 5% were initiated through public and private facilities respectively. Among initiates 7,796 (31%) returned for their Month-1 follow-up, and 1,908 (8%) for their Month-3 follow-up visits (Figure 3A). Cascades for the three population types are summarized in Figure 3B,C,D.

3.2 | Missed opportunities in the FSW, MSM and AGYW PrEP cascades

AGYW had higher missed opportunities for screening (78%) compared to FSW and MSM (Figure 4). There was a greater proportion of FSW who were not screened compared to MSM, 58% versus 45%. Among those screened, a substantially higher proportion of AGYW (65%) were ineligible for PrEP compared to 28% of FSW and 25% of MSM. Missed opportunities for PrEP initiation were higher for FSW (72%) and MSM (75%) compared to AGYW (8%). Majority of clients did not persist on PrEP use at Month-1 (69% of FSW, 71% of MSM and 68% of AGYW) and Month-3 (92% of FSW, 93% of MSM and 94% of AGYW) follow-ups.

3.3 | Cascades for FSW, MSM and AGYW disaggregated by age

When disaggregated by age, there were mixed variations in the proportion of individuals screened for PrEP and those found eligible for PrEP across the age groups for the three population types as summarized in Table 1. The proportion of individuals initiated on PrEP was highest among FSW and MSM below 20 years and lowest among individuals older than 30 years. Month-1 and Month-3 follow-up rates were slightly higher among older FSW and minimal variation was observed for AGYW.

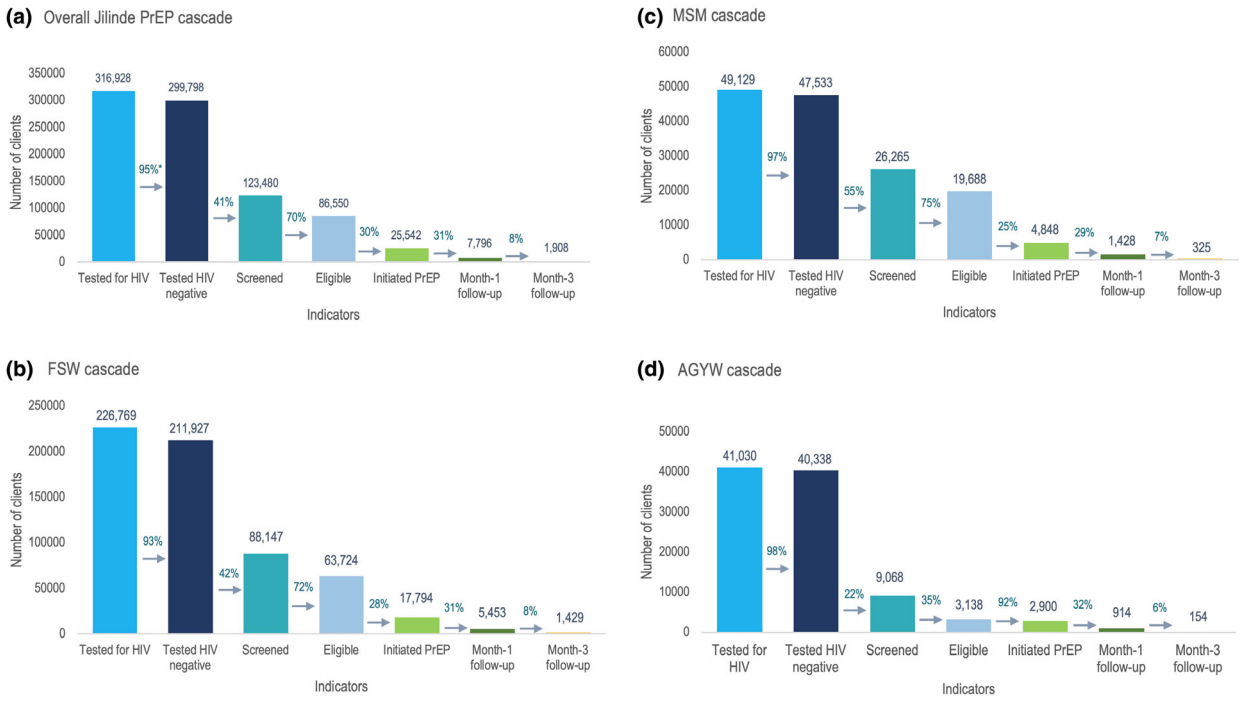

Figure 3. Overall Jilinde project (A) and population-specific (B, FSW; C, MSM; D, AGYW) PrEP cascades from February 2017 to December 2019.
*% denotes proportion of clients proceeding to the next step in the cascade. PrEP, pre-exposure prophylaxis.

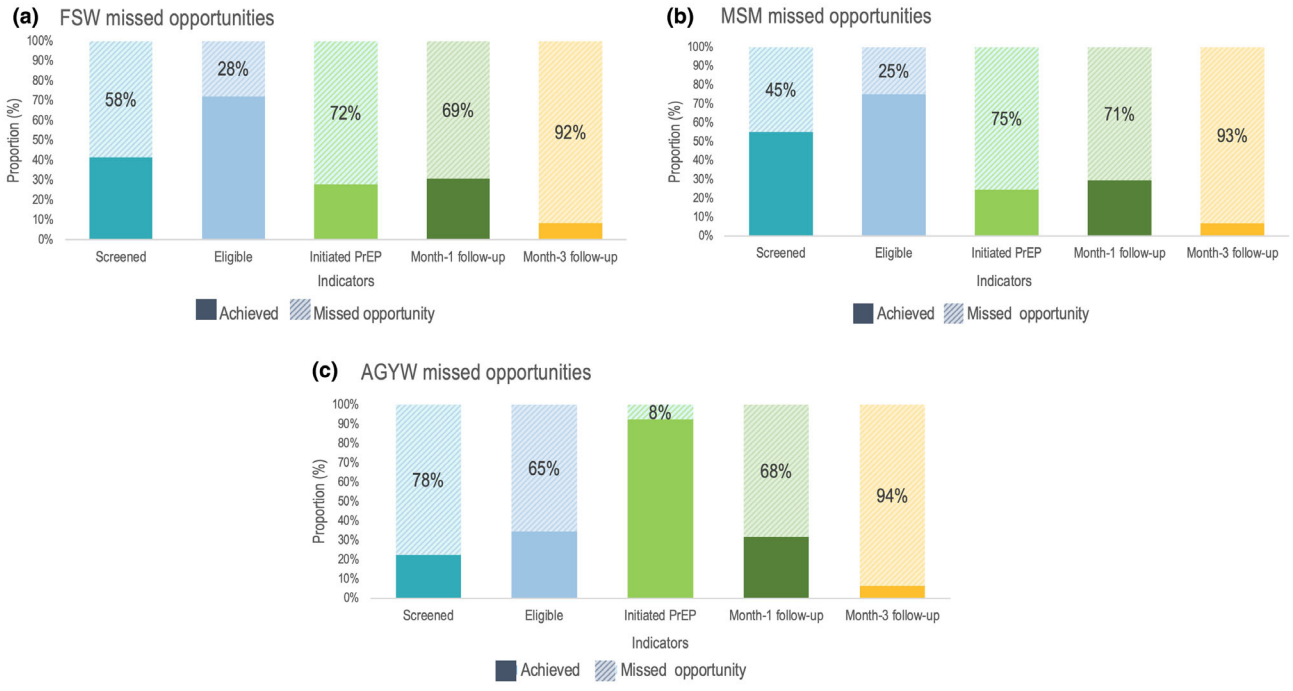

Figure 4. Missed opportunities in the FSW (A), MSM (B) and AGYW (C) PrEP cascades, July 2017 to December 2019.
AGYW, adolescent girls and young women; FSW, female sex workers; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis.

3.4 | Trends in the PrEP cascade

There were month-by-month variations across all the cascade indicators as summarized in Figure 5. The proportion of individuals reported to have tested HIV negative was lowest in March to June 2017. Thereafter, the annual average proportion of those testing HIV negative was 95% in 2017 and remained at 98% in 2018 and 2019. However, an annual decline in the proportion of individuals who were screened for PrEP eligibility (from 67% in 2017, 44% in 2018 to 37% in

Table 1. Cascade indicators for FSW, MSM and AGYW disaggregated by age groups (years)

	FSW				MSM				AGYW	
	15 to 19	20 to 24	25 to 30	>30	15 to 19	20 to 24	25 to 30	>30	15 to 19	20 to 24
Tested HIV Negative, %	99	99	98	86	98	97	98	92	99	98
Screened, %	37	39	44	42	58	56	58	51	22	23
Eligible, %	74	75	73	70	75	76	74	75	36	34
Initiation, %	37	35	29	21	36	28	22	18	95	91
Month-1 follow-up, %	25	29	32	33	31	28	30	33	31	32
Month-3 follow-up, %	6	7	8	10	8	6	7	8	5	5

AGYW, adolescent girls and young women; FSW, female sex workers; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis.

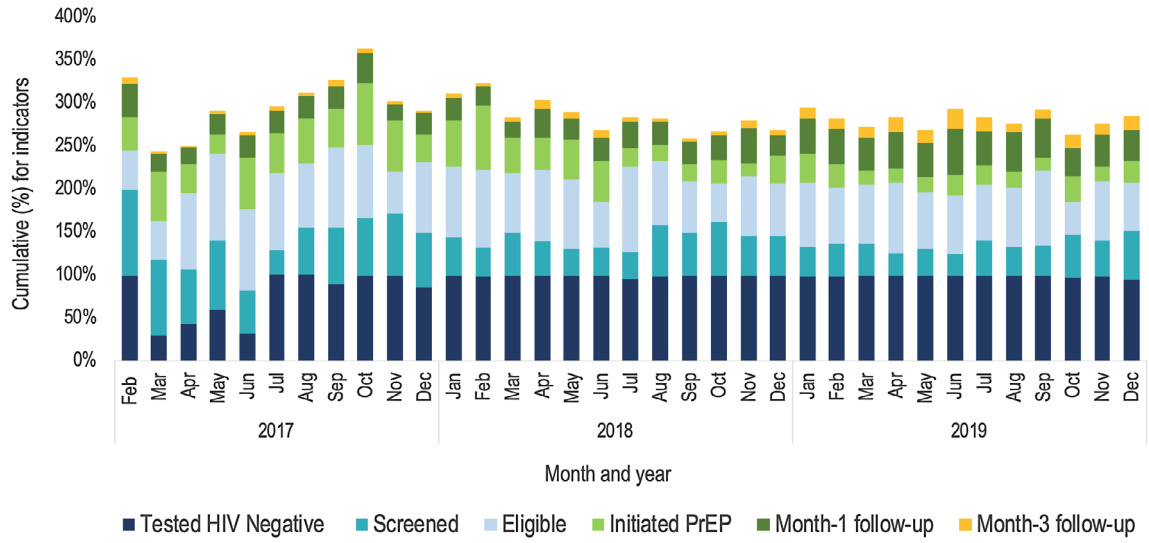

Figure 5. Trends in the Jilinde PrEP cascade indicators from February 2017 to December 2019.

2019) was observed. The proportion of individuals eligible for PrEP declined from an annual average of 77% in 2017, to 73% in 2018 and 68% in 2019. Additionally, those initiated on PrEP declined from 47% in 2017, to 36% in 2018 and 22% in 2019. The annual average Month-1 follow-up rate increased from 26% in 2017, to 27% in 2018 and 41% in 2019. Month-3 follow-up rates increased from 4% in 2017, to 6% in 2018 and 15% in 2019.

3.5 | Contextual findings on missed opportunities and programmatic adjustments

In addition to the population-specific missed opportunities presented in Figure 4, contextual factors underpinning the missed opportunities derived through qualitative research, and specific programmatic adjustments made by Jilinde or by the MOH are presented in Table 2.

4 | DISCUSSION

In this paper, we describe how the Jilinde project used PrEP cascade analysis to describe coverage and identify missed opportunities for oral PrEP among FSW, MSM and AGYW clients in routine settings where PrEP is integrated with other HIV prevention services. The study affirms the feasibility of constructing cascades using programmatic data complemented by qualitative enquiry to understand where and why implementation gaps exist, which can guide programming changes. From this study, the three main missed opportunities identified were screening for PrEP eligibility, PrEP initiation and follow-up. These varied across the different steps in the cascades, by age group, population type and during different time periods.

PrEP is nascent in SSA and many countries are in the formative stages of designing effective implementation approaches [7]. In the absence of implementation evidence on PrEP delivery at scale in SSA, HIV prevention programmes integrating PrEP can use programmatic and implementation research data to adapt and optimize implementation [35]. Countries can employ the cascade framework to facilitate critical programmatic analysis and institute necessary changes. Furthermore, complementary data sources have potential to generate in-depth explanations of the gaps, and suggest interventions needed to optimize implementation. The cascade approach employed in this analysis is comparable to studies

Table 2. Missed opportunities and contextual findings for Jilinde project

Missed opportunity in the PrEP cascade	Key themes from qualitative research	Sample quotes from FGDs	Continuous programmatic adjustments by Jilinde project
Screening for PrEP	Routine risk screening is low priority for HIV testing services (HTS) providers	*"…… we have a lot of work when a patient comes all you want to do is treat the patient. Focus on whatever brought the patient and you do not want to explore" (41-year-old female clinician from Migori)*	Advocacy to county health management teams through technical working groups and review meetings to enhance accountability for PrEP indicators
	PrEP screening conducted, but not recorded due to frequent changes in the documentation tools	*"… .. you screen yet you fail to indicate that you have screened. It is a challenge. …… if you don't document someone can easily say you did not screen." (27-year-old male HTS Provider from Migori)*	Jilinde advocated and the MOH revised the national HIV Testing Services Register (MOH 362) to capture eligibility screening
Eligibility for PrEP	Poor rapport between AGYW and providers inhibits disclosure of risk behaviours	*"… if we create a positive environment during the time we are with the client, then the client will not feel uncomfortable but if our starting point was not structured well, then this is where we get a client who will never be ready to disclose or to be open" (27-year-old male HTS Provider from Migori)*	Trained healthcare providers on delivery of youth-friendly services to make them more sensitive to AGYW
	Peer mobilization and referral of low risk individuals coupled with inadequate client education on PrEP	*"As for the youth peer providers (YPPs) try to link them (AGYW)…… even if they have the knowledge it is not that powerful to help us in terms of getting the right clients for PrEP." (36 year old male HTS provider from Migori)*	Trained mobilizers on communication skills, introduced "stages of change" tool
Initiation of PrEP	Myths and misconceptions about PrEP and low risk perception among FSW, MSM and AGYW	*"In MSM circles they say those who take PrEP are people who love sex a lot, they are addicted to it" (23-year-old MSM from Nairobi)*	Implementation of user-centered demand creation strategies utilizing social networks; recruitment and training of trusted peer educators to mobilize and refer their peers for PrEP
	Co-location of both PrEP and HIV services in comprehensive care centers (HIV clinics) resulted in PrEP clients feeling stigmatized as HIV positive	*"In our facility we've come to realize that most patients who are on PrEP don't like being mixed with HIV positive, so they don't like accessing PrEP at the comprehensive care centre (CCC), at times they prefer they access from the outpatient" (25-year-old female nurse from Machakos)*	Integrated PrEP with SRH services for AGYW; piloted DICE for AGYW; diversified service provision through community safe spaces, hotspots, outpatient departments, maternal child health and family planning clinics
	Stigma-related discouragement from peers, family and friends for eligible users	*"…parents discourage people not to take PrEP; they can say that this drug will increase immorality in the community" (21-year-old AGYW from Migori)*	Mass media, social media and promotional events to create a supportive environment for PrEP uptake
	Providers reluctance to prescribe PrEP associated with reluctance to increase provider workload; provider belief that client will not adhere to PrEP	*"… in our case is work load, we have one clinician who is supposed to do the outpatient, clear the queue outside there, at the same time is the person who is supposed to operate in the CCC. At times he gets tired and tells them - you come tomorrow for PrEP" (29-year-old male clinician from Machakos)*	Testimonies from champion providers and satisfied users to champion for PrEP delivery during facility review meetings
	Insensitive referral and access pathways in public and private health facilities	*"The testing place is different from the place I was asked questions and the place for collecting the medicine is also different. We took long because we were walking from one place to another" (22-year-old AGYW from Migori)*	Instituted continuous quality improvement to identify and address gaps in the PrEP delivery pathway; site level supervision, mentorship and coaching

Table 2. (*Continued*)

Missed opportunity in the PrEP cascade	Key themes from qualitative research	Sample quotes from FGDs	Continuous programmatic adjustments by Jilinde project
Continuation	Clients experiencing side effects, ambivalence and low intrinsic motivation to use prevention interventions	*"I was getting tired. I felt that the body could not make it. I wanted to go to work but I was unable. I just wanted to sleep and that made me angry and I stopped using them" (35-year-old FSW from Mombasa)*	Implemented persistence support interventions: pre-initiation counselling and readiness assessment, follow-up calls, SMS reminders, peer educators tracked clients lost-to-follow up and assisted clients to identify adherence buddies
	Myths and misconceptions about PrEP, stigma and negative peer influence	*"What made me to stop taking PrEP was my two friends who said that I was HIV positive. . ." (22-year-old, FSW from Kisii)*	Developed and disseminated frequently asked questions (FAQs) about PrEP brochures, established PrEP support groups and sharing testimonials from satisfied PrEP users
	Operational and access barriers (Long waiting time, arduous referral pathways)	*"It takes a lot of time because you find many people in a line. Sometimes people are busy there's no one to attend to you; you move from one place to another..." (22-year-old AGYW from Migori)*	System-level adjustments to improve the efficiency of PrEP services (PrEP refill days, community-based refills, integrated services, multi-month scripting)
	Provider perceptions (negative attitudes, stereotypes and discrimination)	*"Experienced nurses and clinicians at the facility I work are elderly and when they hear about giving someone the drugs, they will tell you "Change young man. Go and change." They can't give you the drug." (29-year-old male clinician from Nairobi)*	Trained healthcare providers on gender, sexual diversity and value clarification
	Unappealing branding (Similar to ARVs for treatment), and packaging (rattling pill bottle)	*". . .the way PrEP is; its branding is like ARVs. Someone can think I am positive because I have drugs . . .. So it is a problem and it is interfering with adherence. You take and stop because people are talking a lot, insults," (22-year-old MSM PrEP client from Nairobi)*	Piloted use of alternative and client-friendly pill carriers developed through human-centred design

AGYW, adolescent girls and young women; DICE, drop-in centre; FGDs, focus group discussions; FSW, female sex workers; HTS, HIV testing services; MOH, Ministry of Health; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; SMS, short message service; SRH, sexual and reproductive health.

that have developed cascades for various HIV prevention interventions such as PrEP, condoms and VMMC [21,23,31].

This study has established gaps in screening HIV-negative individuals for PrEP eligibility, similar to other programmes delivering PrEP [35,36]. Plausible explanations for the screening gaps for all populations, and especially AGYW, include prioritization of HIV case finding and huge workload occasioned by shortage of healthcare workers, which is consistent with previous studies in Kenya and elsewhere [36-41]. Furthermore, the rapid scale-up of PrEP in Kenya may have contributed to increased volume of HIV testing [14] reducing the propensity for HTS providers to offer eligibility screening to every HIV-negative client. Additionally, poor documentation attributed to shifting MOH guidance on behavioural risk screening tools and procedures may have contributed to the screening gaps identified.

PrEP initiation among eligible individuals was consistently low except for AGYW. The latter contrasts previous studies which have reported low PrEP uptake among AGYW [42-44]. The high PrEP uptake among AGYW could be attributed to targeted mobilization of potentially eligible AGYW through peer educators, integration of PrEP with sexual and reproductive services and implementation of community delivery models. This is congruent with existing literature which recommends that PrEP should be integrated into comprehensive programmes and delivery simplified to make it attractive to AGYW [44,45]. The consistently low PrEP uptake among FSW and MSM over the three-year period is consistent with studies globally, which report a high interest in PrEP, but low uptake [46-48]. Similar to the findings from the qualitative inquiry, studies have elucidated client-level and health system barriers, and perceived negative experiences when accessing or using PrEP as disincentives for PrEP uptake in numerous settings [49-52]. Furthermore, FSW and MSM were likely to be accessing alternative HIV prevention interventions, which they might have preferred over PrEP. This is corroborated by a study in Zimbabwe which elucidated that preference for condoms impeded PrEP uptake [53], whereas FSW in Kenya have reported high rates of condom use [11]. These findings suggest that intensive demand creation is essential to normalize PrEP and improve uptake as witnessed in the United States [47].

Overall continuation rates in the Jilinde cascade were low, compared to research studies and demonstration projects [47,50,52,54]. There is a paucity of evidence on continuation rates for FSW, MSM and AGYW from HIV prevention programmes that have scaled-up PrEP in SSA, and our findings may provide a more accurate illustration of continuation rates within a real-world scale-up context. Given that continuation is a proxy indicator for effective PrEP use, these continuation rates could be considered suboptimal given the risk profile of FSW, MSM and AGYW from geographies with high HIV incidence in the general population. It is plausible that missed opportunities for continuation may be over-estimated because the cascade did not document individuals who self-discontinued PrEP because their risk profile changed, or substituted PrEP with alternative prevention methods, given that PrEP was delivered in the context of a broader prevention programme. Findings from the qualitative research revealed that lack of motivation and commitment, stigma, product-related and health system challenges were explanations for the low PrEP continuation. These findings are consistent with studies which have documented similar barriers to PrEP continuation [44,49,52]. The programmatic interventions to improve continuation summarized in Table 2 showed promise in pivoting continuation rates in the project and similar observations have been replicated in studies in SSA [55] although this area warrants comprehensive investigation.

4.1 | Limitations

First, using aggregate data to populate the cascade does not facilitate in-depth longitudinal analysis of individual-level characteristics, which might contribute to a much deeper understanding of the missed opportunities for PrEP, yet this is highly relevant to the rollout of PrEP in SSA. Second, the cascade begins with HIV testing and omits useful information on the proportion of individuals from the target population reached with PrEP information and those referred for PrEP services due to lack of reliable community data. Expanded cascades including these data points can estimate coverage rates of the target populations and identify gaps in demand creation. Third, the current analysis only presents Month-1 and Month-3 continuation rates. Continuation rates beyond these periods are of utmost relevance in order to document optimal PrEP use among FSW, MSM and AGYW. Finally, this paper presents a PrEP-specific cascade although PrEP is delivered in combination with other HIV prevention interventions. Despite these limitations, this study presents worthwhile evidence about how cascades can be constructed using routinely collected and easily available data from national health systems.

5 | CONCLUSIONS

The PrEP cascade has provided a useful framework to guide planning, implementation and monitoring performance of the Jilinde project. Jilinde has used the cascade to identify missed opportunities in implementation and course corrected to increase effective delivery of PrEP services. The Jilinde PrEP cascade provides field experiences in using a cascade framework for programme monitoring and decision-making. By generating regular cascades, programmes can continue to monitor implementation adaptations and employ evidence-based interventions to respond to emerging gaps. Opportunities exist for developing cascades that incorporate the holistic package of HIV combination prevention interventions.

AUTHORS' AFFILIATIONS

[1]Jhpiego, Nairobi, Kenya; [2]International Center for Reproductive Health, Mombasa, Kenya; [3]National AIDS and STI Control Program, Nairobi, Kenya; [4]Jhpiego, Baltimore, MD, USA

COMPETING INTEREST

The authors have no conflict of interest to declare.

AUTHORS' CONTRIBUTIONS

DW and AM conceptualized the study. JM analysed the data. DW, AM, JM, PO, GM, MK, TM and HG wrote the initial draft, MP, JR and IM contributed and revised the draft. All authors read and approved this draft.

ACKNOWLEDGEMENTS

The Jilinde project is funded by the Bill & Melinda Gates Foundation under award number OPP1146198. In addition, the project received a donation of PrEP commodities (TDF/FTC) from Gilead Health Sciences. The views expressed in this manuscript are those of the authors and do not necessarily represent the opinions of the project donors. We acknowledge Gideon Mureithi and Jonesmus Wambua for graphic design and statistical analysis, the Ministry of Health, county governments and local implementing partners in Kenya.

REFERENCES

1. UNAIDS. UNAIDS DATA 2019. Geneva: UNAIDS; 2019.
2. National AIDS and STI Control Programme (NASCOP). Preliminary KENPHIA 2018 report. Nairobi: NASCOP;2020. p. 1–27.
3. National AIDS Control Council.Kenya: HIV prevention response and modes of transmission analysis. Kenya National AIDS Control Council. 2009;83.
4. UNAIDS. We've got the power: Women, adolescent girls and the HIV response. Geneva: UNAIDS; 2020. p. 1-51
5. UNAIDS. Women and HIV: A spotlight on adolescent girls and young. women.. 2019;1–20.
6. Ministry of Health, National AIDS Control Council. Kenya AIDS Progress Report 2018. Nairobi: NACC; 2018. p. 1–81.
7. Cowan FM, Delany-Moretlwe S, Sanders EJ, Mugo NR, Guedou FA, Alary M, et al. PrEP implementation research in Africa: what is new? J Int AIDS Soc. 2016;19:21101.
8. WHO. WHO expands recommendation on oral pre-exposure prophylaxis of HIV infection (PrEP). World Health Organ [Internet]. 2015;2 [cited 2019 Sep 14]. Available from: apps.who.int/iris/bitstream/10665/197906/1/WHO_HIV_2015.48_eng.pdf?ua=1
9. Ministry of Health, National AIDS & STI Control Programme. Guidelines on use of antiretroviral drugs for treating and preventing HIV infection in Kenya. Nairobi: NASCOP; 2016. p. 1–174.
10. National AIDS & STI Control Programme (NASCOP), Ministry of Health. Framework for the Implementation of Pre-Exposure Prophylaxis of HIV In Kenya. Nairobi: NASCOP; 2017. p. 1–84.
11. Bhattacharjee P, Musyoki HK, Becker M, Musimbi J, Kaosa S, Kioko J, et al. HIV prevention programme cascades: insights from HIV programme monitoring for female sex workers in Kenya. J Int AIDS Soc. 2019;22(S4):78–85.
12. Bhattacharjee P, Musyoki H, Prakash R, Malaba S, Dallabetta G, Wheeler T, et al. Micro-planning at scale with key populations in Kenya: Optimising peer educator ratios for programme outreach and HIV/STI service utilisation. PLoS One. 2018;13:e0205056.
13. NASCOP. National Guidelines for HIV/STI Programming with Key Population. 2014;1–174 [cited 2020 Mar 2]. Available from: http://www.icop.or.ke/wp-content/uploads/2016/10/KP-National-Guidelines-2014-NASCOP.pdf
14. Masyuko S, Mukui I, Njathi O, Kimani M, Oluoch P, Wamicwe J, et al. Pre-exposure prophylaxis rollout in a national public sector program: the Kenyan case study. Sex Health. 2018;15(6):578–86.
15. Godfrey-Faussett P. The HIV prevention cascade: more smoke than thunder? Lancet HIV [Internet]. 2016;3(7):e286–8 [cited 2019 Sep 20]. Available from: http://dx.doi.org/10.1016/S2352-3018(16)30062-5
16. Isbell Michael T, Kilonzo Nduku, Mugurungi O, Bekker L-G. We neglect primary HIV prevention at our peril. Lancet HIV. 2016;3(7):e284–5.
17. Gardner EM, Mclees MP, Steiner JF, Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clin Infect Dis. 2011;52(6):793–800.
18. Kilmarx PH, Mutasa-apollo T. Patching a leaky pipe. Curr Opin HIV AIDS. 2015;59–64.
19. Subbaraman R, Nathavitharana RR, Mayer KH, Satyanarayana S, Chadha VK, Arinaminpathy N, et al. Constructing care cascades for active tuberculosis: a strategy for program monitoring and identifying gaps in quality of care. PLoS Med. 2019;16(2):e1002754.
20. Garnett GP, Hallett TB, Takaruza A, Hargreaves J, Rhead R, Warren M, et al. Providing a conceptual framework for HIV prevention cascades and assessing feasibility of empirical measurement with data from east Zimbabwe: a case study. Lancet HIV. 2016;3(7):e297–306.
21. Weiner R, Fineberg M, Dube B, Goswami P, Mathew S, Dallabetta G, et al. Using a cascade approach to assess condom uptake in female sex workers in India: a review of the Avahan data. BMC Public Health. 2018;18(897):1–10.
22. Francis Caroline, Mills S. HIV cascade framework for key populations. Arlington: LINKAGES project; FHI360. 2015. p. 1–50.
23. Hensen B, Fearon E, Schaap A, Lewis JJ, Weiss HA, Tembo M, et al. Application of an HIV prevention cascade to identify gaps in increasing coverage of voluntary medical male circumcision services in 42 rural Zambian communities. AIDS Behav. 2019;23(5):1095–103.
24. Fearon E, Phillips A, Mtetwa S, Chabata ST, Mushati P, Cambiano V, et al. How can programs better support female sex workers to avoid hiv infection in Zimbabwe? A prevention cascade analysis. J Acquir Immune Defic Syndr. 2019;81(1):24–35.
25. Nunn AS, Brinkley-rubinstein L, Oldenburg CE, Mayer KH, Mimiaga M, Patel R, et al. Defining the HIV pre-exposure prophylaxis care continuum. AIDS. 2017;31(5):731–4.
26. Rosenberg ES, Marcus JL. Progress and pitfalls in measuring HIV preexposure prophylaxis coverage in the United States. Ann Epidemiol. 2018;28(12):830–2.
27. Chan PA, Glynn TR, Oldenburg CE, Montgomery MC, Robinette AE, Almonte A, et al. Implementation of preexposure prophylaxis for human immunodeficiency virus prevention among men who have sex with men at a New England sexually transmitted diseases clinic. Sex Transm Dis. 2016;43(11):717–23.
28. Kelley CF, Kahle E, Siegler A, Sanchez T, Del Rio C, Sullivan PS, et al. Applying a PrEP continuum of care for men who have sex with men in Atlanta, Georgia. Clin Infect Dis. 2015;61(10):1590–7.
29. Parsons JT, Rendina HJ, Lassiter JM, Whitfield THF, Starks TJ, Grov C, et al. Uptake of HIV pre-exposure prophylaxis (PrEP) in a national cohort of gay and bisexual men in the United States: the Motivational PrEP Cascade HHS Public Access. J Acquir Immune Defic Syndr. 2017;74(3):285–92.
30. Dunbar MS, Kripke K, Haberer J, Castor D, Dalal S, Mukoma W, et al. Understanding and measuring uptake and coverage of oral pre-exposure prophylaxis delivery among adolescent girls and young women in sub-Saharan Africa. Sex Health. 2018;15(6):513.
31. Koss CA, Charlebois ED, Ayieko J, Kwarisiima D, Kabami J, Balzer LB, et al. Uptake, engagement, and adherence to pre-exposure prophylaxis offered after population HIV testing in rural Kenya and Uganda: 72-week interim analysis of observational data from the SEARCH study. Lancet HIV. 2020;7(4):e249–61.
32. Schulz KF, Grimes DA. Epidemiology series Descriptive studies: what they can and cannot do. Lancet. 1954;2002(359):145–9.
33. National AIDS and STI Control Programme, Ministry of Health, Kenya. Geographic Mapping of Most at Risk Populations for HIV (MARPs) in Kenya. Nairobi: NASCOP; 2013. p. 1–111.
34. NASCOP. The Kenya HIV testing services guidelines. Nairobi: NASCOP; 2015. p. 1–78.
35. O'Malley G, Barnabee G, Mugwanya K. Scaling-up PrEP delivery in sub-Saharan Africa: what can we learn from the scale-up of ART? Curr HIV/AIDS Rep. 2019;16(2):141–50.
36. Kundu I, Martinez-Donate A, Karkada N, Roth A, Felsher M, Sandling M, et al. Attitudes and referral practices for preexposure prophylaxis (PrEP) among HIV rapid testers and case managers in Philadelphia: A mixed methods study. PLoS One. 2019;14(10):1–15.
37. Castel AD, Feaster DJ, Tang W, Willis S, Jordan H, Villamizar K, et al. Understanding HIV care provider attitudes regarding intentions to prescribe PrEP. J Acquir Immune Defic Syndr. 2016;70(5):520–8.
38. Eakle R, Weatherburn P, Bourne A. Understanding user perspectives of and preferences for oral PrEP for HIV prevention in the context of intervention scale-up: a synthesis of evidence from sub-Saharan Africa. J Int AIDS Soc [Internet]. 2019;22(S4):30–9 [cited 2019 Sep 20]. Available from https://onlinelibrary.wiley.com/doi/abs/10.1002/jia2.25306
39. Krakower DS, Oldenburg CE, Mitty JA, Wilson IB, Kurth AE, Maloney KM, et al. Knowledge, beliefs and practices regarding antiretroviral medications for HIV prevention: Results from a survey of healthcare providers in New England. PLoS One. 2015;10(7):1–15.
40. Karris MY, Beekmann SE, Mehta SR, Anderson CM, Polgreen PM. Are we prepped for preexposure prophylaxis (PrEP)? Provider opinions on the real-world use of PrEP in the United States and Canada. Clin Infect Dis. 2014;58(5):704–12.
41. Mack N, Odhiambo J, Wong CM, Agot K. Barriers and facilitators to pre-exposure prophylaxis (PrEP) eligibility screening and ongoing HIV testing among target populations in Bondo and Rarieda, Kenya: Results of a consultation with community stakeholders. BMC Health Serv Res. 2014;14(1):1–12.
42. Mugwanya KK, Pintye J, Kinuthia J, Abuna F, Lagat H, Begnel ER, et al. Integrating preexposure prophylaxis delivery in routine family planning clinics: a feasibility programmatic evaluation in Kenya. PLoS Medicine. 2019;16(9):22–9.
43. Oluoch LM, Mugo NR, Roxby AC, Wald A, Selke S, Magaret A, et al. Low uptake of preexposure prophylaxis among Kenyan adolescent girls at risk of HIV. 2019 Conference on retroviruses and opportunistic infections; March 4-7, 2019. Seattle, Washington; 2019 [cited 2019 Sep 20]. Available from https://www.croiconference.org/abstract/low-uptake-preexposure-prophylaxis-amongkenyan-adolescent-girls-risk-hiv/

44. Celum CL, Delany-Moretlwe S, Baeten JM, van der Straten A, Hosek S, Bukusi EA, et al. HIV pre-exposure prophylaxis for adolescent girls and young women in Africa: from efficacy trials to delivery. J Int AIDS Soc. 2019;22 (S4):23–9.
45. Haberer JE, Mugo N, Baeten JM, Pyra M, Bukusi E, Bekker LG. PrEP as a lifestyle and investment for adolescent girls and young women in sub-Saharan Africa. J Int Assoc Provid AIDS Care. 2019;18:1–5.
46. Eakle R, Bourne A, Mbogua J, Mutanha N, Rees H. Exploring acceptability of oral PrEP prior to implementation among female sex workers in South Africa. J Int AIDS Soc. 2018;21(2).
47. Finlayson T, Cha S, Denson D, Trujillo L, Xia M, Prejean J, et al.Changes in HIV PrEP Awareness and Use among Men who have Sex with Men, 2014 VS 2017. CROI Conference. 2017. Available from: http://www.croiconference.org/sessions/changes-hiv-prep-awareness-and-use-among-men-who-have-sex-men-2014-vs-2017
48. Snowden JM, Chen Y, Mcfarland W, Raymond HF. Prevalence and characteristics of users of pre-exposure prophylaxis (PrEP) amongst men who have sex with men, San Francisco, 2014 in a cross-sectional survey: Implications for disparities. Sex Transm Infect. 2017;93(1):52–5.
49. Emmanuel G, Folayan M, Undelikwe G, Ochonye B, Jayeoba T, Yusuf A, et al. Community perspectives on barriers and challenges to HIV pre-exposure prophylaxis access by men who have sex with men and female sex workers access in Nigeria. BMC Public Health. 2020;20(1):1–10.
50. Kyongo JK, Kiragu M, Karuga R, Ochieng C, Ngunjiri A, Wachihi C, et al. How long will they take it? Oral pre-exposure prophylaxis (PrEP) retention for female sex workers, men who have sex with men and young women in a demonstration project in Kenya. Journal of the International AIDS Society. 2018;20:54–55.
51. Kimani M, van der Elst EM, Chiro O, Oduor C, Wahome E, Kazungu W, et al. PrEP interest and HIV-1 incidence among MSM and transgender women in coastal Kenya. J Int AIDS Soc. 2019;22(6):1–8.
52. Kinuthia J, Pintye J, Abuna F, Mugwanya KK, Lagat H, Onyango D, et al. Pre-exposure prophylaxis uptake and early continuation among pregnant and post-partum women within maternal and child health clinics in Kenya: results from an implementation programme. Lancet HIV. 2020;7(1):e38–48.
53. Gombe MM, Cakouros BE, Ncube G, Zwangobani N, Mareke P, Mkwamba A, et al. Key barriers and enablers associated with uptake and continuation of oral pre-exposure prophylaxis (PrEP) in the public sector in Zimbabwe: Qualitative perspectives of general population clients at high risk for HIV. PLoS One. 2020;15(1):1–18.
54. Eakle R, Gomez GB, Naicker N, Bothma R, Mbogua J, Cabrera Escobar MA, et al. HIV pre-exposure prophylaxis and early antiretroviral treatment among female sex workers in South Africa: Results from a prospective observational demonstration project. PLoS Medicine. 2017;14(11):1–17.
55. Pintye J, Rogers Z, Kinuthia J, Mugwanya KK, Abuna F, Lagat H, et al. Two-way short message service (SMS) communication may increase pre-exposure prophylaxis continuation and adherence among pregnant and postpartum women in Kenya. Glob Heal Sci Pract. 2020;8(1):55–67.

Chabata ST et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25512
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25512/full | https://doi.org/10.1002/jia2.25512

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Condom use among young women who sell sex in Zimbabwe: a prevention cascade analysis to identify gaps in HIV prevention programming

Sungai T Chabata[1,§], Bernadette Hensen[2], Tarisai Chiyaka[1], Phillis Mushati[1], Joanna Busza[3], Sian Floyd[4], Isolde Birdthistle[4], James R Hargreaves[3] and Frances M Cowan[1,5]

[§]**Corresponding author**: Sungai T Chabata, Centre for Sexual Health and HIV/AIDS Research (CeSHHAR), 4 Bath Road, Belgravia, Harare, Zimbabwe. Tel: +263 77 3577686. (sungai@ceshhar.co.zw; sungaichabata@gmail.com)

Abstract

Introduction: Adolescent girls and young women (AGYW), including those who sell sex in sub-Saharan Africa, are especially vulnerable to HIV. Reaching them with effective prevention is a programmatic priority. The HIV prevention cascade can be used to track intervention coverage, and identify gaps and opportunities for programme strengthening. The aim of this study was to characterise gaps in condom use and identify reasons underlying these gaps among young women who sell sex (YWSS) in Zimbabwe using data from enrolment into an impact evaluation of the DREAMS programme. DREAMS provided a package of biomedical, social and economic interventions to AGYW aged 10 to 24 with the aim of reducing HIV incidence.

Methods: In 2017, we recruited YWSS aged 18 to 24 using respondent-driven sampling in six sites across Zimbabwe. We measured knowledge about efficacy of, access to, and effective (consistent) use of condoms with the most recent three sexual partners, separately by whether YWSS self-identified as female sex workers (FSW) or not. Among YWSS without knowledge about efficacy of, not having access to, and not effectively using condoms, we described the potential reasons underlying the gaps in the condom cascade. To identify socio-demographic characteristics associated with effective condom use, we used logistic regression modelling. All analyses were RDS-II weighted and restricted to YWSS testing HIV-negative at enrolment.

Results: We enrolled 2431 YWSS. Among 1842 (76%) YWSS testing HIV-negative, 66% (n = 1221) self-identified as FSW. 89% of HIV-negative YWSS demonstrated knowledge about efficacy of condoms, 80% reported access to condoms and 58% reported using condoms consistently with the three most recent sexual partners. Knowledge about efficacy of and effective use of condoms was similar regardless of whether or not YWSS self-identified as FSW, but YWSS self-identifying as FSW reported better access to condoms compared to those who did not (87% vs 68%; age- and site-adjusted (adjOR) = 2.69; 95% CI: 2.01 to 3.60; $p < 0.001$). Women who reported experiencing sexual violence in the past year and common mental disorder in the past week were less likely to use condoms consistently (43% vs. 60%; adjOR = 0.49; 95% CI: 0.35 to 0.68; $p < 0.001$) and (51% vs. 61%; adjOR = 0.76; 95% CI: 0.60 to 0.97; $p = 0.029$), respectively.

Conclusions: Despite high knowledge about efficacy of and access to condoms, there remain large gaps in self-reported consistent condom use among YWSS. Addressing the structural determinants of YWSS' inconsistent condom use, including violence, could reduce this gap. YWSS who do not self-identify as FSW have less access to condoms and may require additional programmatic intervention.

Keywords: HIV prevention cascade; condom cascade; female sex worker; young women who sell sex; HIV prevention; Zimbabwe; sub-Saharan Africa

Received 30 September 2019; **Accepted** 22 April 2020

1 | INTRODUCTION

Although HIV incidence is decreasing in sub-Saharan Africa, it remains high among adolescent girls and young women (AGYW) aged 15 to 24 [1]. Among AGYW, young women who sell sex (YWSS) are at particularly high HIV risk [2], less likely to access health services, more likely to experience violence from sexual partners, and less likely to use condoms consistently due to a lower ability to negotiate condom use [3]. Reducing HIV incidence among AGYW requires increased coverage of efficacious prevention methods, including condoms and oral pre-exposure prophylaxis (PrEP)[4-6].

The DREAMS Partnership was launched in ten African countries, including Zimbabwe, aiming to reduce HIV risk among AGYW through the delivery of comprehensive combination HIV prevention programming [7,8]. In Zimbabwe, where

YWSS, including young FSW, were among the target population, the core package included condom promotion and provision, and an offer of oral PrEP, supported by a range of behavioural and structural interventions [9].

HIV prevention cascades can highlight gaps in motivation for, access to and effective use of prevention tools [10,11]. Criticisms of the framework emphasise that HIV prevention is non-linear and complex, there are several prevention options, the prevention needs of individuals differ and change over time, and that measuring complex domains such as motivation, is challenging and not conducive to simplified models [12]. We operationalised a prevention cascade analysis for YWSS in Zimbabwe using data from enrolment into an impact evaluation of DREAMS. Overall, our goal was to explore whether application of prevention cascades at enrolment could be used to inform prevention programming by identifying priority interventions [13].

2 | METHODS

2.1 | Study setting and population

Between April and July 2017, we used respondent-driven sampling (RDS) in six sites across Zimbabwe to identify and recruit YWSS to a cohort study to evaluate the impact of DREAMS on HIV incidence [14,15]. Women were recruited from two large cities where DREAMS was implemented and a comparison group of women were recruited from four small towns selected based on their similarity with the DREAMS sites. In all six sites the national HIV prevention and treatment programme for FSW, "Sisters with a Voice", provides support and services to FSW, including HIV testing, community mobilisation, and condoms.

Women were eligible to participate if they were 18 to 24 years of age and explicitly exchanged sex for money, goods or services in the past month. Our aim was to recruit any young women engaged in selling sex, even if these women did not see themselves as FSW. Based on the sample size required for the impact evaluation [14], we aimed to recruit ~600 YWSS in each large city, and ~300 in each small urban site.

2.2 | Data collection

Data collection methods have been described elsewhere [14]. As reported [16], we conducted geographic and social mapping at each site to identify 6-10 'seed' participants, women who were purposefully selected to be representative of the social typology of YWSS, which is mainly street based, and geographic location of selling sex. Each 'seed' was interviewed and given two recruitment coupons to pass on to YWSS in her social network [14]. When YWSS receiving a coupon attended the survey site, they were given two coupons to pass on to two YWSS they knew, who sold sex in that location and who had not previously been recruited to the survey. Each participant was given an incentive of US$3 for participating in the survey, and an additional US$2 for each YWSS recruited. In all six sites, a maximum of six iterations of recruitment were performed [14].

YWSS consenting to participate completed a questionnaire on socio-demographics, sexual behaviours, including a partner loop that asked about condom use at last sex and condom-less sex in the past month with three most recent sexual partners, self-identification as FSW, and uptake of HIV services, including testing. Participants were offered rapid HIV testing services according to national HIV testing guidelines and were told the result of their HIV test.

2.3 | Measures

We operationalised the HIV prevention cascade measuring three core steps: knowledge about condom efficacy, access to and effective use of condoms [10,11]. We used knowledge about condom efficacy as a proxy for motivation to use condoms because we had insufficient data to measure motivation to align the condom cascade with the Schaefer et al framework [10]. We hypothesised that cascades may differ by whether or not women self-identified as FSW and constructed cascades for women who did and did not identify as such. All measures were self-reported.

Knowledge about efficacy of condoms was defined as agreeing that using condoms every time you have sex can prevent an HIV negative person from acquiring HIV infection. Access to condoms was defined as reporting that condoms are always available at places where women choose to obtain them. Effective use of condoms was defined as having used condoms during all sexual acts with three most recent partners in the past month. Three recent partners were a smaller proportion of the average number of partners reported by YWSS self-identified as FSW (20%) compared to those not self-identified as FSW (60%). Effective condom use was a derived variable that combined data from two variables: condom use at last sex and condom-less sex in the past month, with three most recent partners. The variable was coded 1 if women reported any condom-less sex with any partner, and coded 0 only if they reported no condom-less sex at last sex and in the last month with all three partners.

After constructing the cascade, we described perceived norms and perceptions about condom use among women without knowledge of condom efficacy, hypothesising that these might help better understand the gaps in their knowledge [13]. We described perceived use of condoms with (1) regular partners and (2) casual partners/clients by other young women, (3) perceived importance of using condoms with all sexual partners, and (4) whether using a condom every time they have sex is a good thing to do. Among women defined as not having access to condoms, we described whether women reported that: (1) it is easy for women like themselves to access free condoms, (2) it is expensive to travel to places where they get condoms, and (3) they are always able to get condoms for free at the places where they get condoms. Among women defined as not using condoms effectively, we described whether YWSS reported an ability to use condoms correctly, to negotiate condom use with any sexual partner, and confidence in their ability to ask a new sexual partner to use a condom. These measures related to self-efficacy and skills were based on those developed and used in other settings in sub-Saharan Africa [17-20].

In a risk factor analysis, we included variables known to be associated with effective condom use in the literature [21] and that could be amenable to identifying women at risk of not using condoms and strategies to improve condom use, including: age, educational attainment, marital status, self-identification as FSW, whether women ever experienced physical and sexual violence from a sexual partner or police, women's

relationship with other YWSS, number of close female friends, consumption of more than six alcoholic drinks in one night during last 12 months, and symptoms of common mental health disorders (CMD). Risk of CMD was assessed using the locally validated Shona Symptom Questionnaire (SSQ-14) [22], a set of fourteen questions about symptoms of depression and anxiety in the previous one week (cut off for risk of CMD is ≥ 9/14) [22-24].

2.4 | Statistical analysis

All analyses were restricted to women who tested HIV negative on the rapid HIV test offered during the survey. Data were RDS-II weighted, with women's responses weighted by the inverse of the reported number of YWSS that they knew i.e. the number of other women that she could have recruited to the survey [25], based on well established rationale for RDS-II weighting [26,27]. We pooled data from the six survey sites and normalised the RDS-II weights by site. Participant socio-demographic and sexual behaviour characteristics, as well as variables related to the cascade were described, and stratified by self-identification as FSW.

We constructed the condom cascade for all YWSS as well as by whether or not they self-identified as FSW, and compared each step by self-identification as FSW adjusting for age at the time of the survey and site of recruitment.

Subsequently, we used logistic regression to identify socio-demographic and sexual behaviour characteristics associated with effective condom use. For logistic regression analyses, we dropped seed participants and included a fixed term for site. Factors associated with effective condom use at $p \leq 0.10$-level in univariable analysis were included in the multivariable regression model, adjusting for all factors associated with effective condom use in the univariable analysis. We also explored whether the associations between the variables of interest and effective condom use were modified by whether or not women self-identified as FSW. Evidence of effect modification in unadjusted analyses ($p \leq 0.10$) resulted in further exploration in adjusted analyses.

Finally, we described potential reasons underlying gaps in the condom cascade among women defined as not having knowledge about condom efficacy, not having access to condoms, and not using condoms effectively. This analysis was also stratified by whether women self-identified as FSW or not. Analyses were conducted using STATA version 14.2.

2.5 | Ethics

The DREAMS impact evaluation was reviewed and approved by the Medical Research Council of Zimbabwe (Ref MRCZ/A/2085) and the London School of Hygiene and Tropical Medicine (Ref 11835). All participants were given information about the study and asked for written informed consent for participation.

3 | RESULTS

3.1 | Characteristics of women recruited to the study

We recruited 2431 YWSS, 1204 in two large cities and 1227 in the four small towns, 1842 (76%) tested HIV negative. The majority of HIV negative YWSS were aged 20 to 24 years (58%), had some but incomplete secondary school education, were never married, and reported having insufficient food in the past month (Table 1). Sixty-six percent (66%) self-identified as FSW. YWSS self-identifying as FSW were older, more likely to be divorced/separated, more likely to consume alcohol and to report good relationships with other YWSS (Table 1). YWSS identifying as FSW reported having more sexual partners and sex work clients in the past month compared to YWSS not identifying as FSW. YWSS self-identifying as FSW were also more likely to be at risk of CMD within the last week (37% vs. 27%), to have experienced physical and sexual violence from a sexual partner, and violence from police (6% vs. 2%) compared to non-identifying YWSS.

3.2 | The condom cascade

Overall, 89% of YWSS agreed that using condoms every time during sex can prevent an HIV negative person from acquiring HIV infection (efficacy knowledge), 80% reported that condoms were always available at places from which they chose to obtain them (access), and 58% reported having used condoms during all sexual acts with three most recent partners in the past month (effective use) (Figure 1).

A higher proportion of YWSS self-identifying as FSW reported access to condoms compared to YWSS not identifying as FSW (87% vs. 67%; age- and site-adjusted OR = 2.69; 95% CI: 2.01 to 3.60; $p < 0.001$). Knowledge about efficacy of condoms and effective use of condoms were similar between both groups of YWSS (90% vs. 89%; OR = 1.00; 95% CI: 0.68 to 1.47; $p = 0.997$), and (57% vs. 60%; OR = 0.94; 95% CI: 0.61 to 1.28; $p = 0.123$), respectively.

Adjusting for factors associated with effective condom use in univariable analysis, there was evidence that effective condom use was lower among YWSS at risk of CMD (51% vs. not at risk 61%; adjOR = 0.76; 95% CI: 0.60 to 0.97; $p = 0.029$) and women who ever experienced physical violence from a sexual partner (51% vs. women not experiencing physical violence 62%; adjOR = 0.74; 95% CI: 0.58 to 0.96; $p = 0.021$) (Table 2). There was strong evidence that effective condom use was lower among women who had experienced sexual violence in past 12 months compared to women reporting no sexual violence (43% vs. 60%; adjOR = 0.49; 95% CI: 0.35 to 0.67; $p < 0.001$). YWSS who reported neither a good nor bad relationship with other YWSS were less likely to use condoms effectively compared to YWSS with good relationship with other YWSS (50% vs. 60%; adjOR = 0.49; 95% CI: 0.35 to 0.68; $p = 0.030$). There was little evidence of an association with other factors explored and no statistical evidence for any effect modification by self-identification as FSW.

3.3 | Potential reasons underlying lack of knowledge about efficacy of, access to and effective use of condoms

Among YWSS who did not perceive condoms to be effective at preventing HIV, the majority reported that other YWSS use condoms with their casual partners/clients (80%) and regular partners (58%). Most women perceived the use of condoms with all sexual partners as important (97%) and considered using condoms every sex act as a good thing to do (84%). A

Table 1. Socio-demographic and sexual behavioural characteristics of YWSS testing HIV negative at enrolment into an RDS survey, by self-identification as FSW, RDS-II weighted (N = 1842)

	YWSS not identifying as FSW (N = 621)		YWSS identifying as FSW (N = 1221)		All YWSS (N = 1842)[a]		
	n	%	n	%	n	%	Comparison *p*-value[c]
Age							<0.001
18 to 19	316	52.4	409	35.4	725	41.6	
20 to 24	305	47.6	812	64.6	1117	58.4	
Highest level of education							<0.001
None/ incomplete primary	18	2.7	87	7.7	105	5.9	
Complete primary	44	7.6	108	9.5	152	8.8	
Incomplete secondary	518	82.9	990	80.0	1508	81.1	
Complete secondary or higher	41	6.7	36	2.9	77	4.2	
Marital status							<0.001
Never been married	465	75.2	685	56.9	1150	63.6	
Married/ living together as if married	21	3.4	16	1.7	37	2.3	
Divorced/ separated	135	21.4	512	40.8	647	33.9	
Widowed	0	0.0	8	0.6	8	0.4	
Insufficient food in past month							0.002
No	308	50.5	517	41.7	825	44.9	
Yes	313	49.5	704	58.3	1017	55.1	
Age at start of selling sex							0.001
≤15	60	9.1	142	11.8	202	10.8	
16 to 17	246	41.5	392	31.7	638	35.3	
18 to 24	311	49.4	687	56.5	998	53.9	
Duration since first started selling sex (years)							<0.001
0 to 2	403	67.8	633	52.5	1036	58.0	
3 to 4	162	25.0	372	30.9	534	28.8	
≥5	52	7.2	216	16.7	268	13.2	
Number of sexual partners in the past month							<0.001
0 to 4	474	80.0	432	37.3	906	52.8	
5 to 9	82	10.9	303	25.9	385	20.5	
≥10	64	9.1	481	36.8	545	26.7	
Number of clients in the past month							<0.001
0 to 4	501	84.1	485	42.1	986	57.4	
5 to 9	62	7.8	276	23.6	338	17.9	
≥10	57	8.1	454	34.3	511	24.8	
Relationship with other YWSS							<0.001
Good	385	63.6	869	71.6	1254	68.7	
Neither good nor bad	125	21.2	229	18.6	353	19.5	
Bad	60	10.3	97	8.2	157	9.0	
No relationship	48	4.9	26	1.5	74	2.7	
No. of close female friends							0.231
0	127	22.0	219	19.7	346	20.5	
1	356	56.8	667	55.0	1023	55.7	
≥2	138	21.2	335	25.3	473	23.8	
Alcohol consumption in the past 12 months							<0.001
Never	354	60.1	480	41.7	834	48.4	
Once a month or less	103	17.6	159	13.4	262	15.0	
2 to 4 times per month	67	9.7	183	14.5	250	12.7	
2 to 3 times per week	60	8.3	212	16.5	272	13.5	
4 or more times per week	37	4.3	187	13.9	224	10.4	

Table 1. (*Continued*)

	YWSS not identifying as FSW (N = 621)		YWSS identifying as FSW (N = 1221)		All YWSS (N = 1842)[a]		
	n	%	n	%	n	%	Comparison *p*-value[c]
Had more than six alcoholic drinks in one night during last 12 months							<0.001
Have not had alcohol in last 12 months	354	60.1	480	41.7	834	48.4	
Drank alcohol but no occasions of more than six drinks	160	25.3	386	32.2	546	29.7	
Yes, at least one occasion	107	14.6	355	26.1	462	21.9	
Risk of CMD[b]							<0.001
No	443	72.7	768	62.9	1211	66.4	
Yes	178	27.3	453	37.1	631	33.6	
Ever experienced physical violence from sexual partner							<0.001
No	437	70.5	707	60.3	1144	64.0	
Yes	184	29.5	514	39.7	698	36.0	
Experienced sexual violence from a sexual partner in the past 12 months							0.010
No	541	88.3	1005	82.9	1546	84.9	
Yes	79	11.7	216	17.1	295	15.1	
Experienced any form of violence from police in the past 12 months							<0.001
No	606	98.3	1150	94.4	1756	95.8	
Yes	13	1.7	69	5.6	82	4.2	

p-value is from Wald test. YWSS, young women who sell sex; FSW, female sex worker; RDS, respondent-driven sampling.
[a]17 women missing data on whether or not they self-identify as FSW; [b]Cut-off of ≥9; [c]Adjusted for age and site. CMD, common mental health disorders.

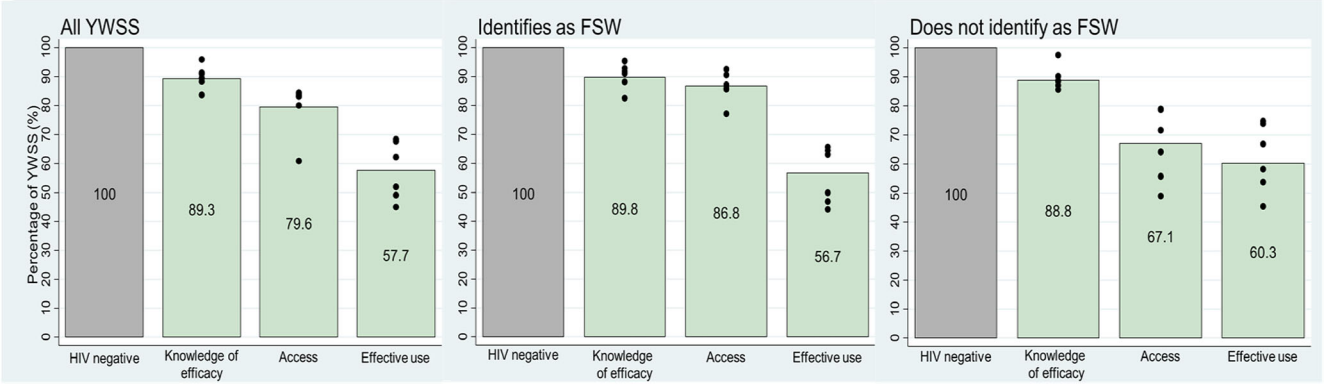

Figure 1. Condom cascades among YWSS overall, YWSS self-identifying as FSW and YWSS not self-identifying as FSW. Black spots indicate site-specific estimates.
YWSS, young women who sell sex; FSW, female sex worker.

high proportion (68%) of women reported that they cannot rely on condoms because they break easily (Figure 2A). There was little evidence that these factors differed by self-identification as FSW.

Among YWSS who lacked access to condoms, the majority (64%) reported that it is easy for young women like them to access free condoms and that they are always able to get condoms for free (58%). Access to free condoms was similar regardless of whether women self-identified as FSW or not (70% vs 61% respectively; age- and site-adjusted (adjOR) =1.43; 95% CI: 0.82 to 2.47; $p = 0.204$) (Figure 2B). Few women (31%) reported that places to get condoms are far

Table 2. Factors associated with effective condom use among YWSS testing HIV negative at enrolment into an RDS survey, RDS-II weighted (N = 1810)

Characteristic	N (%)	# of YWSS who had effective condom use in the past month (N = 1058) n (%)	Crude OR (95% CI)	*p*-value	Adjusted OR[a] (95%CI)	*p*-value
Age at enrolment				0.039		0.965
18 to 19	712 (41.5)	432 (59.9)	1		1	
20 to 24	1098 (58.5)	626 (56.1)	0.78 (0.62 to 0.99)		0.99 (0.76 to 1.30)	
Highest level of education				0.584		
Primary or less	253 (14.6)	141 (55.4)	1			
Incomplete secondary	776 (42.9)	476 (58.5)	1.20 (0.85 to 1.69)			
Complete secondary or higher	781 (42.5)	441 (57.6)	1.16 (0.82 to 1.65)			
Marital status				0.003		0.062
Never married	1130 (63.7)	667 (59.4)	1		1	
Ever married	680 (36.3)	391 (54.7)	0.69 (0.54 to 0.89)		0.77 (0.59 to 1.01)	
Insufficient food in past month				0.506		
No	807 (44.8)	466 (55.5)	1			
Yes	1003 (55.2)	592 (59.4)	1.08 (0.86 to 1.36)			
Self-identified as FSW				0.023		0.386
No	598 (35.8)	356 (60.3)	1		1	
Yes	1195 (64.2)	696 (56.7)	0.75 (0.59 to 0.96)		0.89 (0.69 to 1.16)	
Age at start of selling sex				0.166		
≤15	196 (10.8)	103 (50.2)	1			
16 to 17	637 (35.7)	363 (54.9)	1.15 (0.79 to 1.69)			
18 to 24	974 (53.5)	590 (60.9)	1.36 (0.95 to 1.96)			
Duration since first started selling sex (years)				0.003		0.054
0 to 2	1015 (57.7)	631 (61.1)	1		1	
3 to 4	530 (29.0)	293 (54.9)	0.81 (0.63 to 1.04)		0.86 (0.66 to 1.12)	
≥5	262 (13.3)	132 (48.3)	0.58 (0.42 to 0.80)		0.64 (0.45 to 0.91)	
Relationship with other YWSS				0.025		0.030
Good	1238 (69.1)	746 (60.2)	1		1	
Neither good nor bad	345 (19.5)	182 (49.7)	0.67 (0.51 to 0.90)		0.67 (0.50 to 0.90)	
Bad or no relationship	223 (11.4)	127 (56.1)	0.88 (0.62 to 1.24)		0.88 (0.63 to 1.25)	
No. of close female friends				0.578		
0	342 (20.7)	198 (57.8)	1			
1	1008 (55.6)	584 (57.1)	0.99 (0.75 to 1.34)			
≥2	460 (23.7)	276 (58.8)	1.15 (0.82 to 1.62)			
Had more than six alcoholic drinks in one night during last 12 months				0.032		0.450
Have not had alcohol in last 12 months	816 (48.1)	506 (61.7)	1		1	
Drank alcohol but no occasions of more than six drinks	542 (29.9)	319 (55.4)	0.74 (0.56 to 0.96)		0.85 (0.64 to 1.11)	
Yes, at least one occasion	452 (22.0)	233 (51.9)	0.72 (0.54 to 0.97)		0.99 (0.72 to 1.35)	

Table 2. (*Continued*)

Characteristic	N (%)	# of YWSS who had effective condom use in the past month (N = 1058) n (%)	Crude OR (95% CI)	*p*-value	Adjusted OR[a] (95%CI)	*p*-value
Risk of CMD in the past week				<0.001		0.029
No	1182 (66.1)	737 (61.0)	1		1	
Yes	628 (33.9)	321 (51.1)	0.66 (0.52 to 0.83)		0.76 (0.60 to 0.97)	
Ever experienced physical violence from sexual partner				<0.001		0.021
No	1122 (64.1)	697 (61.5)	1		1	
Yes	688 (35.9)	361 (50.8)	0.60 (0.48 to 0.76)		0.74 (0.58 to 0.96)	
Experienced sexual violence from a sexual partner in the past 12 months				<0.001		<0.001
No	1518 (84.7)	930 (60.3)	1		1	
Yes	291 (15.3)	127 (42.6)	0.43 (0.31 to 0.58)		0.49 (0.35 to 0.67)	
Experienced any form of violence from police in the past 12 months				0.003		0.239
No	1726 (95.9)	1016 (58.4)	1		1	
Yes	80 (4.1)	40 (40.4)	0.45 (0.27 to 0.77)		0.71 (0.41 to 1.25)	

p-value is from Wald test. YWSS, young women who sell sex; FSW, female sex worker; RDS, respondent-driven sampling; OR, odds ratio.
[a]Adjusted for all factors associated with effective condom use in crude analysis.

from their homes or that it is expensive to travel to get condoms (16%), with no evidence for difference by how YWSS self-identified. Forty-percent (40%) reported that staff at places where they get condoms talk badly about them because they sell sex, with no evidence for a difference by self-identification as FSW.

Among YWSS not using condoms effectively, YWSS self-identifying as FSW were more likely to report that they were confident to get condoms when they needed them (92% vs. 79%; adjOR = 2.61; 95% CI: 1.41 to 4.84; $p = 0.002$) and were able to use condoms correctly (87% vs. 75%; adjOR = 1.95; 95% CI: 1.15 to 3.31; $p = 0.013$) compared to YWSS not identifying as FSW. Ability to negotiate condom use with any sexual partner and confidence in one's ability to ask a new sexual partner to use a condom was high and similar between both groups of YWSS (Figure 2C).

4 | DISCUSSION

We operationalised a condom cascade using data collected from HIV-negative YWSS in six sites in Zimbabwe in 2017. Knowledge about the efficacy of condoms was high. However, reported effective use with their three most recent partners was low and access to condoms differed between YWSS who self-identified as FSW and those who did not. YWSS perceived that their peers used condoms and considered condoms important. Yet condoms were not considered reliable, YWSS not identifying as FSW had less access to free condoms and lower condom use self-efficacy. Effective condom use was lower among those experiencing violence and being at risk of CMD, suggesting that these factors affect women's capability to use condoms.

Our analysis revealed gaps in access to condoms and in confidence in condom use, particularly among YWSS not identifying as FSW, who were younger and started selling sex more recently. These gaps point to the need for tailored programming depending on how YWSS self-identify [21,28]. Demand creation for condoms may have been neglected in recent years. Re-enforcing the message that condoms are effective when used correctly, coupled with promotion of how to use condoms properly and that they should be used consistently, is critical. At the time of our study, PrEP was not widely available; few women had heard of PrEP. Currently, there is little literature on motivation to use PrEP and factors affecting ability to adhere to PrEP [29]. Prevention cascades may inform our thinking about how to support PrEP use and adherence, highlighting that alongside access and knowledge of PrEP efficacy, programmes need to consider self-efficacy and confidence, and how violence and CMD are likely to affect longer-term PrEP use. Further, our study suggests the need to promote PrEP as an option for women who feel they cannot negotiate condom use because they are at risk of violence, or who may struggle to negotiate condom use with partners who insist on condom-less sex [30].

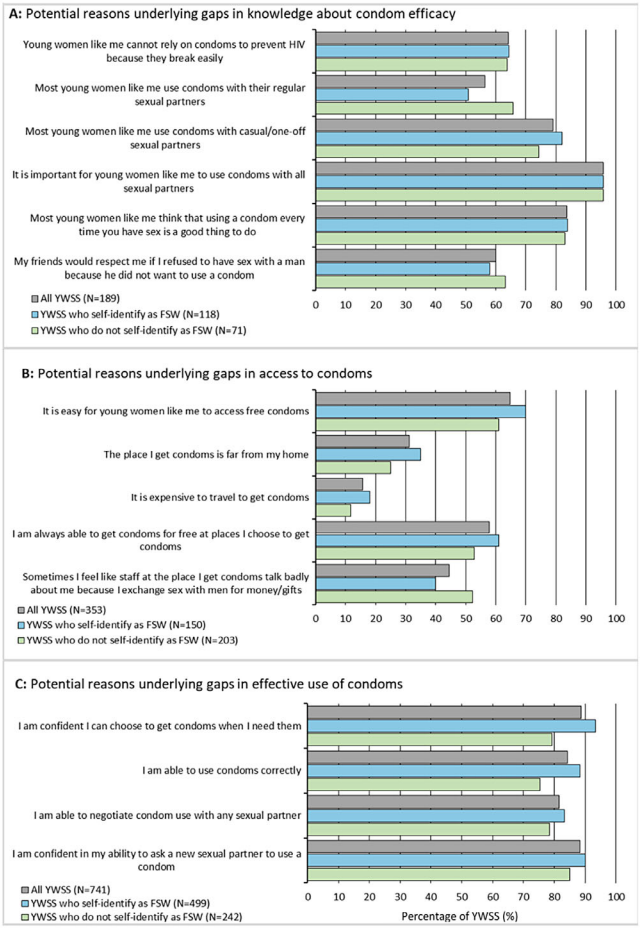

Figure 2. Potential reasons underlying gaps in knowledge about efficacy of, access to and effective use of condoms among YWSS without knowledge about efficacy of, not having access to, and not effectively using condoms, respectively.
YWSS, young women who sell sex; FSW, female sex workers.

Self-efficacy to use condoms is likely compromised by physical and sexual violence from sexual partners. HIV prevention programmes need to provide access to violence prevention services, including violence mitigation packages [31,32]. Women participating in the survey reported high levels of violence, and our analysis of the final cascade step revealed that experiencing violence was associated with reported ineffective use of condoms with their three most recent partners. These findings are similar to other studies [33,34], which have shown that intimate partner violence is associated with poorer condom use self-efficacy and condom use [32,35]. By measuring structural factors that may influence steps along a cascade, programmes would be better placed to understand factors influencing service use and to support YWSS to access a holistic package of services. Included in the DREAMS package of interventions was post-violence care, school-based HIV and violence prevention, social protection interventions and community mobilisation [8]. Greater investments in strategies to reduce violence experienced by YWSS in particular [3] alongside interventions targeting the male partners of YWSS are needed. Access to such interventions could be included in monitoring targets for DREAMS among key populations, alongside HIV testing, condoms and PrEP.

This study has several strengths. We recruited a large number YWSS from multiple sites using a similar RDS method, and included YWSS who do and do not self-identify as FSW who are often missed by research and HIV prevention programmes [36]. Our RDS diagnostics (reported elsewhere [21,37]) suggest that our sample is likely to be representative of the network of YWSS recruited. These analyses gave us a unique opportunity to operationalise a prevention cascade within a large group of HIV-negative YWSS, recruited for an impact evaluation of DREAMS, among whom data on condom use is limited in sub-Saharan Africa [38].

A limitation of the data we report is our reliance on self-reports of subjects prone to social desirability bias. Approaches to strengthen valid reporting, including ACASI, are available but were not possible to use in these surveys. We were not able to include detailed questions about partner's influence in determining condom use. However, understanding women's agency in condom negotiation with individual partners may be better placed for qualitative inquiry, particularly among those women who reported experiencing violence and for whom violence was strongly associated with effective condom use [14,15].

The cascades we present have limitations. In the absence of a standard measure for motivation [10], we used knowledge about the efficacy of condoms as the first step in our cascade. Knowledge that condoms can prevent HIV is necessary but not sufficient for motivation. We described norms and perceptions regarding condom use, which revealed that many women consider condoms unreliable. Our measure of access is also limited. Condoms always being available may not mean women have access if the places where condoms are available are not acceptable [10]. Discrimination by staff may deter YWSS from accessing condoms [39]. Among YWSS defined as lacking access to condoms, some reported that staff at the place they get condoms talk badly about them because they sell sex. Our measure of effective condom use may also over-report consistent condom use. Women's behaviours with their three most recent partners may not be reflective of behaviours with all partners. Also, YWSS could be having condom-less sex due to pregnancy intentions, particularly with a non-paying partner. We estimate that our approach focusing on the three most recent partners covered at least 50% of partners in the last month. As such, and despite limitations, our measure is similar to those reported in other studies [40]. The questions to quantify reasons for any gaps in knowledge about efficacy, access and effective use were related to domains considered of importance in the cascade presented by Schaefer et al [10] and Hargreaves et al [11], and combine behavioural theories [41]. There may, however, be reasons underlying gaps in access to condoms among YWSS who do not self-identify as FSW and in effective use among all women that we failed to measure, including whether women disclosed their sex work to friends, family and partners.

A further limitation is that the prevention cascade is intended to be a simple and practical framework to strengthen prevention programming [10,42]. Although the cascades we present are in themselves simple, the collection of data through RDS surveys is complex and such data is not routinely available to programmes. However, questions included in the survey or related to motivation and access could be collected by peer educators or through micro-planning methods, with qualitative data collection methods used to complement

quantitative findings. Data routinely collected by FSW programmes in Kenya and in Zimbabwe [43,44] provided powerful information to strengthen programming, revealing gaps in reaching younger FSW [42]. Combining survey data, when available, with data collection by peer educators, including micro-planning, could prove a powerful tool to identify gaps and strengthen programming for YWSS in Zimbabwe and other settings [42,45].

5 | CONCLUSIONS

We used the HIV prevention cascade to determine effective condom use among YWSS at high risk of HIV and identify programme gaps and possible strategies to increase condom use. This approach was very useful in identifying gaps but needs to be complemented by qualitative enquiry to better understand why gaps exist.

AUTHORS' AFFILIATIONS

[1]Centre for Sexual Health and HIV/AIDS Research (CeSHHAR) Zimbabwe, Harare, Zimbabwe; [2]Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom; [4]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom; [5]Faculty of Clinical Sciences and International Public Health, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

COMPETING INTERESTS

No competing interests to declare.

AUTHORS' CONTRIBUTIONS

SC planned and conducted the analysis, and wrote the first draft; BH was involved in planning the analysis and contributed to writing; TC and PM led the data collection; JB provided critical review of the article, particularly the introduction; SF, IB, JH, and FC were involved in the conception of the study, and BH, FC and JH critically revised the article. All authors contributed to the writing and have read and approved the final version.

ACKNOWLEDGEMENTS

We would like to thank the survey team and the women who participated in the study.

FUNDING

The DREAMS impact evaluation in Zimbabwe was funded by the Bill & Melinda Gates Foundation (OPP1136774, http://www.gatesfoundation.org). Foundation staff advised the study team, but did not substantively affect the study design, instruments, interpretation of data or decision to publish.

REFERENCES

1. Dellar RC, Dlamini S, Karim QA. Adolescent girls and young women: key populations for HIV epidemic control. J Int AIDS Soc. 2015;18 2 Suppl 1:19408. https://doi.org/10.7448/ias.18.2.19408
2. UNAIDS. HIV and young people who sell sex: a technical brief. Geneva, Switzerland; 2014.
3. Busza J, Mtetwa S, Mapfumo R, Wong-Gruenwald R, Hanisch D, Cowan F. Underage and underserved: reaching young women who sell sex in Zimbabwe. AIDS Care. 2016;28 Sup2:14–20
4. Skovdal M. Facilitating engagement with PrEP and other HIV prevention technologies through practice-based combination prevention. J Int AIDS Soc. 2019;22(S4):e25294. https://doi.org/10.1002/jia2.25294.
5. Petroni S, Ngo TD. Stemming HIV in adolescents: gender and modes of transmission. Lancet. 2018;392(10162):2335–6. https://doi.org/10.1016/s0140-6736(18)32150-0
6. Cornell M, Dovel K. Reaching key adolescent populations. Current Opinion in HIV and AIDS. 2018;13(3):274-280. https://doi.org/10.1097/COH.0000000000000457
7. Abdool Karim Q, Baxter C, Birx D. Prevention of HIV in Adolescent Girls and Young Women: Key to an AIDS-Free Generation. J Acquir Immune Defic Syndr. 2017;75 Suppl 1:S17–s26. https://doi.org/10.1097/qai.0000000000001316.
8. Saul J, Bachman G, Allen S, Toiv NF, Cooney C, Beamon TA. The DREAMS core package of interventions: a comprehensive approach to preventing HIV among adolescent girls and young women. PLoS ONE. 2018;13:e0208167. https://doi.org/10.1371/journal.pone.0208167.
9. Chimbindi N, Birdthistle I, Shahmanesh M, Osindo J, Mushati P, Ondeng'e K, et al. Translating DREAMS into practice: early lessons from implementation in six settings. PLoS ONE. 2018;13:e0208243. https://doi.org/10.1371/journal.pone.0208243
10. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett TB, Hargreaves JR. HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades. Lancet HIV. 2019;6(1):e60–e6. https://doi.org/10.1016/S2352-3018(18)30327-8.
11. Hargreaves JR, Delany-Moretlwe S, Hallett TB, Johnson S, Kapiga S, Bhattacharjee P, et al. The HIV prevention cascade: integrating theories of epidemiological, behavioural, and social science into programme design and monitoring. Lancet HIV. 2016;3(7):e318–22. https://doi.org/10.1016/s2352-3018(16)30063-7.
12. Godfrey-Faussett P. The HIV prevention cascade: more smoke than thunder? The Lancet HIV. 2016;3(7):e286–e8. https://doi.org/10.1016/S2352-3018(16)30062-5.
13. Moorhouse L, Schaefer R, Thomas R, Nyamukapa C, Skovdal M, Hallett TB, et al. Application of the HIV prevention cascade to identify, develop and evaluate interventions to improve use of prevention methods: examples from a study in east Zimbabwe. J Int AIDS Soc. 2019;22(S4):e25309. https://doi.org/10.1002/jia2.25309.
14. Hensen B, Hargreaves JR, Chiyaka T, Chabata S, Mushati P, Floyd S, et al. Evaluating the impact of DREAMS on HIV incidence among young women who sell sex: protocol for a non-randomised study in Zimbabwe. BMC Public Health. 2018;18(1):203. https://doi.org/10.1186/s12889-018-5085-6.
15. Birdthistle I, Schaffnit SB, Kwaro D, Shahmanesh M, Ziraba A, Kabiru CW, et al. Evaluating the impact of the DREAMS partnership to reduce HIV incidence among adolescent girls and young women in four settings: a study protocol. BMC Public Health. 2018;18(1):912. https://doi.org/10.1186/s12889-018-5789-7.
16. Chiyaka T, Mushati P, Hensen B, Chabata S, Hargreaves JR, Floyd S, et al. Reaching young women who sell sex: Methods and results of social mapping to describe and identify young women for DREAMS impact evaluation in Zimbabwe. Plos One. 2018;13:e0194301. https://doi.org/10.1371/journal.pone.0194301.
17. Oppong Asante K, Osafo J, Doku PN. The role of condom use self-efficacy on intended and actual condom use among university students in Ghana. J Community Health. 2016;41(1):97–104. https://doi.org/10.1007/s10900-015-0073-6.
18. Closson K, Dietrich JJ, Lachowsky NJ, Nkala B, Palmer A, Cui Z, et al. Sexual self-efficacy and gender: a review of condom use and sexual negotiation among young men and women in Sub-Saharan Africa. J Sex Res. 2018;55(4–5):522–39. https://doi.org/10.1080/00224499.2017.1421607.
19. Leddy A, Chakravarty D, Dladla S, de Bruyn G, Darbes L. Sexual communication self-efficacy, hegemonic masculine norms and condom use among heterosexual couples in South Africa. AIDS Care. 2016;28(2):228–33. https://doi.org/10.1080/09540121.2015.1080792.
20. Ajayi AI, Olamijuwon EO. What predicts self-efficacy? Understanding the role of sociodemographic, behavioural and parental factors on condom use self-efficacy among university students in Nigeria. PLoS ONE. 2019;14:e0221804. https://doi.org/10.1371/journal.pone.0221804.
21. Hensen B, Chabata ST, Floyd S, Chiyaka T, Mushati P, Busza J, et al. HIV risk among young women who sell sex by whether they identify as sex workers: analysis of respondent-driven sampling surveys, Zimbabwe, 2017. J Int AIDS Soc. 2019;22:e25410. https://doi.org/10.1002/jia2.25410.
22. Chingono R, Chibanda D, Chabata ST, Maringwa G, Mupambireyi Z, Simms V., et al., Validation of the 8-item Shona Symptom Questionnaire, as a measure of common mental disorders in a population with high HIV prevalence in Zimbabwe. 13th International AIDSImpact Conference; 2017; Cape Town, South Africa.
23. Patel V, Simunyu E, Gwanzura F, Lewis G, Mann A. The Shona Symptom Questionnaire: the development of an indigenous measure of common mental disorders in Harare. Acta Psychiatrica Scandinavia. 1997;95:469–75.

24. Chibanda D, Verhey R, Gibson LJ, Munetsi E, Machando D, Rusakaniko S, et al. Validation of screening tools for depression and anxiety disorders in a primary care population with high HIV prevalence in Zimbabwe. J Affect Disord. 2016;198:50–5. https://doi.org/10.1016/j.jad.2016.03.006.
25. Volz E, Heckathorn DD. Probability based estimation theory for respondent driven sampling. J Off Stat. 2008;24(1):79–97.
26. Heckathorn DD. Extensions of respondent-driven sampling: analyzing continuous variables and controlling for differential recruitment. Sociol Methodol. 2007;37(1):151–207.
27. Cowan FM, Mtetwa S, Davey C, Fearon E, Dirawo J, Wong-Gruenwald R, et al. Engagement with HIV prevention treatment and care among female sex workers in Zimbabwe: a respondent driven sampling survey. PLoS ONE. 2013;8:e77080. https://doi.org/10.1371/journal.pone.0077080.
28. Prakash R, Bhattacharjee P, Blanchard A, Musyoki H, Anthony J, Kimani J, et al. Effects of exposure to an intensive HIV-prevention programme on behavioural changes among female sex workers in Nairobi, Kenya. Afr J AIDS Res. 2018;17(2):99–108. https://doi.org/10.2989/16085906.2017.1377268.
29. Ahmed N, Pike C, Bekker L-G. Scaling up pre-exposure prophylaxis in sub-Saharan Africa. Curr Opin Infect Dis. 2019;32(1):24–30. https://doi.org/10.1097/qco.0000000000000511.
30. Cáceres CF, O'Reilly KR, Mayer KH, Baggaley R. PrEP implementation: moving from trials to policy and practice. J Int AIDS Society. 2015;18 4 Suppl 3:20222. https://doi.org/10.7448/IAS.18.4.20222.
31. Parkhurst JO. Structural approaches for prevention of sexually transmitted HIV in general populations: definitions and an operational approach. J Int AIDS Soc. 2014;17(1):19052. https://doi.org/10.7448/IAS.17.1.19052
32. Twahirwa Rwema JO, Lyons CE, Ketende S, Bowring AL, Rao A, Comins C, et al. Characterizing the influence of structural determinants of HIV risk on consistent condom use among female sex workers in Senegal. J Acquir Immune Defic Syndr. 2019;81(1):63–71. https://doi.org/10.1097/qai.0000000000001991.
33. Swan H, O'Connell DJ. The impact of intimate partner violence on women's condom negotiation efficacy. J Interpers Violence. 2012;27(4):775–92. https://doi.org/10.1177/0886260511423240.
34. Onyango MA, Adu-Sarkodie Y, Agyarko-Poku T, Asafo MK, Sylvester J, Wondergem P, et al. "It's All About Making a Life": Poverty, HIV, Violence, and other vulnerabilities faced by young female sex workers in Kumasi, Ghana. J Acquir Immune Defic Syndr. 2015;68:S131–S7. https://doi.org/10.1097/qai.0000000000000455.
35. Bandyopadhyay K, Banerjee S, Goswami DN, Dasgupta A, Jana S. Predictors of inconsistent condom use among female sex workers: a community-based study in a red-light area of Kolkata, India. Indian J Community Med. 2018;43(4):274–8. https://doi.org/10.4103/ijcm.IJCM_84_18.
36. Busza J, Mtetwa S, Chirawu P, Cowan F. Triple jeopardy: adolescent experiences of sex work and migration in Zimbabwe. Health Place. 2014;28:85–91. https://doi.org/10.1016/j.healthplace.2014.04.002.
37. Chabata ST, Hensen B, Chiyaka T, Mushati P, Mtetwa S, Hanisch D, et al. Changes over time in HIV prevalence and sexual behaviour among young female sex-workers in 14 sites in Zimbabwe, 2013–2016. AIDS Behav. 2019;23(6):1494–507. https://doi.org/10.1007/s10461-019-02410-1.
38. Weiner R, Sisimayi C. Development and institutionalising HIV Prevention Cascades in the National Monitoring System in Zimbabwe; 2019.
39. Wanyenze RK, Musinguzi G, Kiguli J, Nuwaha F, Mujisha G, Musinguzi J, et al. "When they know that you are a sex worker, you will be the last person to be treated": perceptions and experiences of female sex workers in accessing HIV services in Uganda. BMC Int Health Hum Rights. 2017;17(1):11. https://doi.org/10.1186/s12914-017-0119-1.
40. Fearon E, Phillips A, Mtetwa S, Chabata ST, Mushati P, Cambiano V, et al. How can programs better support female sex workers to avoid HIV Infection in Zimbabwe? A prevention cascade analysis. J Acquir Immune Defic Syndr. 2019;81(1):24–35. https://doi.org/10.1097/qai.0000000000001980.
41. Michie S, van Stralen MM, West R. The behaviour change wheel: A new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6(1):42. https://doi.org/10.1186/1748-5908-6-42.
42. Bhattacharjee P, Musyoki HK, Becker M, Musimbi J, Kaosa S, Kioko J, et al. HIV prevention programme cascades: insights from HIV programme monitoring for female sex workers in Kenya. J Int AIDS Soc. 2019;22 Suppl 4:e25311. https://doi.org/10.1002/jia2.25311.
43. Cowan FM, Chabata ST, Musemburi S, Fearon E, Davey C, Ndori-Mharadze T, et al. Strengthening the scale-up and uptake of effective interventions for sex workers for population impact in Zimbabwe. J Int AIDS Soc. 2019;22 Suppl 4:e25320. https://doi.org/10.1002/jia2.25320.
44. Busza J, Chiyaka T, Musemburi S, Fearon E, Davey C, Chabata S, et al. Enhancing national prevention and treatment services for sex workers in Zimbabwe: a process evaluation of the SAPPH-IRe trial. Health Policy Plan. 2019;34(5):337–45. https://doi.org/10.1093/heapol/czz037.
45. Bhattacharjee P, Musyoki H, Prakash R, Malaba S, Dallabetta G, Wheeler T, et al. Micro-planning at scale with key populations in Kenya: Optimising peer educator ratios for programme outreach and HIV/STI service utilisation. PLoS ONE. 2018;13:e0205056. https://doi.org/10.1371/journal.pone.0205056.

Holmes LE et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25521
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25521/full | https://doi.org/10.1002/jia2.25521

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Qualitative characterizations of relationships among South African adolescent girls and young women and male partners: implications for engagement across HIV self-testing and pre-exposure prophylaxis prevention cascades

Leah E Holmes[1,§], Michelle R Kaufman[2], Albert Casella[2], Mutsa Mudavanhu[3], Lillian Mutunga[3], Tara Polzer[4], Jean Bassett[3], Annelies Van Rie[5] and Sheree Schwartz[1]

[§]**Corresponding author:** Leah E Holmes, 435 Hanover Street Apt 4B, Boston, MA 02114, USA. Tel: +1(774) 278-1028. (lholmes@lastmilehealth.org)

Abstract

Introduction: Adolescent girls and young women (AGYW) in sub-Saharan Africa have emerged as a priority population in need of HIV prevention interventions. Secondary distribution of home-based HIV self-test kits by AGYW to male partners (MP) is a novel prevention strategy that complements pre-exposure prophylaxis (PrEP), a female-controlled prevention intervention. The objective of this analysis was to qualitatively operationalize two HIV prevention cascades through the lens of relationship dynamics for secondary distribution of HIV self-tests to MP and PrEP for AGYW.

Methods: From April 2018 to December 2018, 2200 HIV-negative AGYW aged 16-24 years were enrolled into an HIV prevention intervention which involved secondary distribution of self-tests to MP and PrEP for AGYW; of these women, 91 participants or MP were sampled for in-depth interviews based on their degree of completion of the two HIV prevention cascades. A grounded theory approach was used to characterize participants' relationship profiles, which were mapped to participants' engagement with the interventions.

Results: In cases where AGYW had a MP with multiple partners, AGYW perceived both interventions as inviting distrust into the relationship and insinuating non-monogamy. Many chose not to accept either intervention, while others accepted and attempted to deliver the self-test kit but received a negative reaction from their MP. In the few cases where AGYW held multiple partnerships, both interventions were viewed as mechanisms for protecting one's health, and these AGYW exhibited confidence in accepting and delivering the self-test kits and initiating PrEP. Women who indicated intimate partner violence experiences chose not to accept either intervention because they feared it would elicit a violent reaction from their MP. For AGYW in relationships described as committed and emotionally open, self-test kit delivery was completed with ease, but PrEP was viewed as unnecessary. MP experience with the cascade corroborated AGYW perspectives and demonstrated how men can perceive female-initiated HIV prevention options as beneficial for AGYW and a threat to MP masculinity.

Conclusions: Screening to identify AGYW relationship dynamics can support tailoring prevention services to relationship-driven barriers and facilitators. HIV prevention counseling for AGYW should address relationship goals or partner's influence, and engage with MP around female-controlled prevention interventions.

Keywords: HIV prevention cascade; pre-exposure prophylaxis; HIV self-testing; South Africa; adolescent girls and young women; relationships

Received 30 September 2019; **Accepted** 23 April 2020

1 | INTRODUCTION

Adolescent girls and young women (AGYW) aged 15-24 years have emerged as a priority population in need of urgent intervention due to high HIV incidence rates in sub-Saharan Africa and disproportionate gender differences in HIV risk [1-3]. Within South Africa, the interplay of relationship dynamics, schemas of masculine dominance and high prevalence of intimate partner violence (IPV) have strong implications for HIV prevention behaviours among young women and men [4-9]. Despite recent increases in HIV testing among South Africans, many AGYW remain unaware of their own and their partners' status, which presents barriers to successful HIV prevention [10-14]. Furthermore, men lag in engagement in HIV treatment and prevention cascades [10-14].

HIV self-testing is increasing and offers opportunities for reaching populations less traditionally served by clinic-based services, including men [10-14]. The use of secondary distribution of self-test kits by AGYW to increase testing and status

disclosure among male partners (MP) is a novel HIV prevention strategy [10-14]. One study recently demonstrated the effectiveness of this approach in antenatal care (ANC) and postnatal care settings [10] but may produce different results outside of the ANC context [10].

Pre-exposure prophylaxis (PrEP), when taken consistently, is currently the female-controlled prevention intervention with the greatest efficacy, and it has the potential to empower AGYW who are in relationships characterized by power imbalances [15]. Overall reductions in HIV acquisition in men and women have been demonstrated through randomized control trials of PrEP across multiple settings [15-22]. However, PrEP effectiveness has not been consistently achieved across studies, particularly among young women outside of serodiscordant relationships, due to limited product adherence [15]. Still, the promise of PrEP for AGYW is great, should interventions succeed in generating demand, motivating uptake and supporting adherence [23].

There is limited evidence around how relationship-level barriers and facilitators influence secondary distribution of HIV self-tests and PrEP uptake and adherence among AGYW. Thus, this study applied a qualitative approach that operationalizes and evaluates how relationship landscapes influence two HIV prevention cascades: (1) secondary distribution of self-test kits by AGYW to MPs; and (2) PrEP for AGYW. By sampling AGYW who did/did not complete each step of the HIV prevention cascades, we hope to generate a nuanced understanding of the interpersonal circumstances that empower or hinder women to take control of their sexual health. Based on our findings, we propose recommendations for implementation of relationship-centred HIV interventions for AGYW in South Africa.

2 | METHODS

2.1 | Study population and intervention

In the parent study, the interventions offered were part of a DREAMS Innovations Challenge package designed to keep HIV-negative AGYW in South Africa HIV-free [24]. Between April 2018 and December 2019, 2200 AGYW in northern Johannesburg were screened for enrollment into the parent study. The intervention package contained two oral HIV self-test kits (one for the AGYW and one for her MP to facilitate couples' testing when preferred or for multiple MP as appropriate), an instructional pamphlet, a video explaining the self-testing process, condoms and lubricant. Formative research was conducted beforehand to inform the intervention content and video messaging (Tembo, unpublished work).

AGYW were eligible for enrollment into the parent study if they were aged 16-24 years, tested HIV negative, had a current male sexual partner for ≥3 months at enrollment, reported they were unaware of their partner's HIV status, and did not report relationship violence or fear of violence. Participants were recruited at a primary health clinic or within their community through a mobile team. Study team members administered baseline surveys to AGYW, counselled AGYW on test kit delivery to MP, and offered PrEP as an additional prevention option. Following enrollment and receipt of the self-tests, AGYW were contacted two weeks later to ascertain the self-testing results and were reminded of PrEP as an additional prevention option. Follow-up calls or clinic meetings continued for three months to monitor final outcomes.

Using predominantly follow-up data, study staff selected AGYW to participate in a qualitative sub-study assessing barriers and facilitators to completion of the MP testing and PrEP prevention cascades; AGYW who were eligible for the parent study but refused participation were also enrolled. AGYW were evenly recruited across each of the cascade steps, and MPs were invited to participate if their AGYW had provided consent for the study team to contact him. Participants were not recruited to be representative of parent study outcomes, but to inform future intervention adaptations.

Of note, DREAMS programming in the area focused exclusively on clinic and community-based HIV testing and linkage to care for HIV-positive cases. The DREAMS Innovations team accompanied the program at times to recruit AGYW testing HIV negative for the parent study.

2.2 | Data collection and analysis

Qualitative, semi-structured in-depth interviews (IDIs) were conducted from May 2018 to February 2019. IDI participants (n = 50 AGYW parent study participants, 32 MPs, and 9 AGYW who declined the intervention), were purposively sampled based on the degree to which they completed the HIV prevention cascades (Figure 1). AGYW aged 18-24 provided written informed consent, and AGYW <18 years provided assent and written parental consent. Qualitative study participants were compensated R100 ($7USD) for IDI transport. Permission to recruit MP refusing testing was not granted, so this perspective was only captured among AGYW. IDIs were completed with either the AGYW or MP in a relationship, but not both.

IDIs were conducted by four South African qualitative interviewers, exploring facilitators and barriers to completing the HIV prevention cascades. IDIs lasted approximately 35-50 minutes and were conducted in English and/or local languages. IDIs were audio-recorded, transcribed verbatim and translated into English. Weekly team meetings were held to debrief and modify probing to explore emerging themes. IDIs were conducted until saturation of themes was achieved.

Investigators employed an inductive, grounded theory approach to iteratively develop a codebook. Double coding of 30 randomly selected transcripts was performed with an *a priori* agreement level of 85% (below which full double coding would have been applied). Post-coding analyses employed a deductive approach that mapped participants' engagement with the self-testing and PrEP cascades to the relationship profiles that emerged.

Ethical approval was granted by the Human Research Ethics Committee at the University of Witwatersrand in Johannesburg, South Africa, and oversight seconded by the Johns Hopkins Bloomberg School of Public Health to the South African Committee.

2.3 | Context from the parent study

In the parent study, acceptability of HIV self-testing was high, with over 95% of AGYW accepting and delivering self-test kits to their partners, and over 80% of MP who were offered the

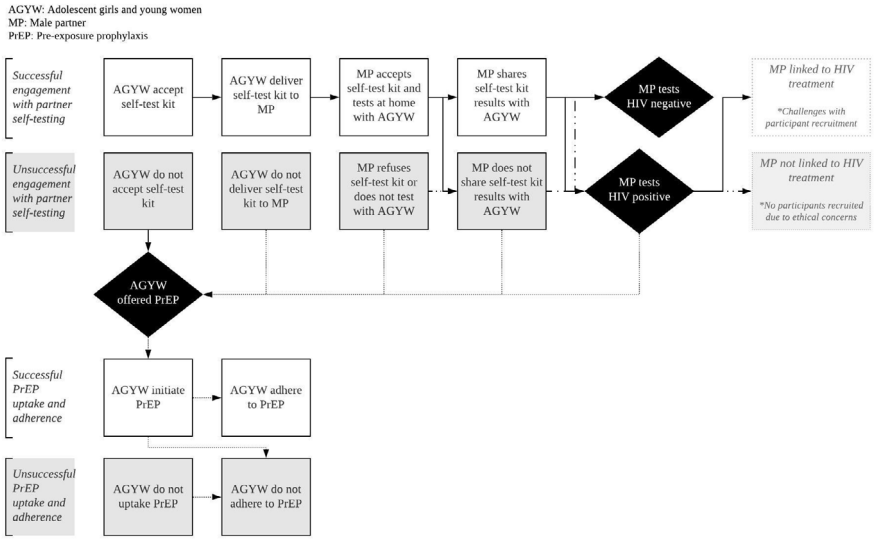

Figure 1. HIV prevention cascade for self-testing and PrEP interventions.

test accepting and showing the results to their female partners. Over a third of AGYW were interested in PrEP, but only 3% initiated and even fewer adhered to PrEP.

3 | RESULTS

Demographic and relationship characteristics of the 91 IDI participants are detailed in Table 1. Over half of the participants were in steady (non-casual) relationships, but not living with their partner. Over 30% of AGYW believed their MP had other sexual partners.

3.1 | Relationship typologies

Four relationship typologies emerged that influenced completion of the two HIV prevention cascades for AGYW and MPs. The two most common relationships were characterized by high turnover and/or multiple partnerships, mainly AGYW with MPs who held multiple partnerships, though also multiple partnerships held by an AGYW. Less common was a third type of relationship characterized by IPV. Despite screening for IPV prior to intervention enrollment, approximately 25% of the interviewed AGYW indicated they had a violent MP. The fourth and common relationship type was characterized by stability and/or the MP's openness. Detailed relationship profile descriptions and their general impact on cascade completions are detailed below and summarized collectively in Figure 2.

3.1.1 | Relationship turnover and multiple partnerships

Many AGYW indicated their primary partner had relationships with other women. In these cases, AGYW were often the secondary partner of a man who was married or had a female partner living in another province. Despite the high acceptability of self-testing demonstrated in the parent study, in almost all cases where AGYW had a MP with multiple partners, self-test kit delivery was a challenge. AGYW did not perceive the intervention as a mechanism to facilitate discussions around HIV, but rather, thought it would invite distrust into the relationship and insinuate non-monogamy from either the AGYW or MP.

> *I think he has a 'makhwapheni' [side chick] . . . When I take this kit with me, we are going to fight. He was going to take it personally: 'you should have told me that you suspect me of something'. – AGYW who did not accept self-test kit*

In most cases when the MP was believed to have multiple partners, AGYW did not accept the intervention or accepted the self-test kit but did not deliver it. Other AGYW in this category viewed self-testing as an opportunity to learn their partner's status, but when attempting to deliver the self-test kit met resistance and/or were unsuccessful at convincing their partner to test in their presence, or never received the results. In some cases, the MP's response to self-testing altered AGYW perceptions of the relationship, with AGYW indicating that they trusted their partner less or feared that he might be HIV positive.

> *He took the test privately. When I asked him about the results, he said he tested negative. I asked him where the proof is, then he told me that there is no proof. I thought maybe he is positive. – AGYW whose MP did not share results*

Despite AGYW perceiving their MP's response to self-testing as a sign of an HIV-positive status, this was rarely identified as influencing her motivations to uptake PrEP. Most AGYW in this typology acknowledged PrEP as a risk reduction strategy, but few initiated it. Reasons paralleled concerns around self-testing, with many AGYW indicating it would signal to MPs that she or the MP were non-monogamous.

Another prominent concern was fear that MPs might misinterpret an AGYW's intentions to take PrEP as an accusation

Table 1. Characteristics of qualitative study participants and relationships (n = 80)[a]

Participant characteristics	AGYW (n = 49) Mean (sd)	Male partner (n = 31) Mean (sd)
Age (years)	21.1 (2.1)	26.4 (4.9)
	n (%)	**n (%)**
Education completed		
Some primary	1 (2)	2 (6)
Some secondary	12 (24)	5 (16)
Completed secondary	20 (41)	16 (52)
Any tertiary	16 (33)	8 (26)
South African	45 (92)	20 (65)
Relationship status		
Casual	9 (18)	4 (13)
Steady, not living together	31 (64)	14 (45)
Steady, living together	9 (18)	11 (36)
Married	0 (0)	2 (6)
Characteristics of the AGYW in the relationship[b]	**n (%)**	**n (%)**
Age category of AGYW		
Adolescent girl (16-19 years)	13 (27)	11 (35)
Young woman (20-24 years)	73 (73)	20 (65)
AGYW is pregnant	3 (6)	11 (35)
AGYW is a mother	21 (43)	11 (35)
AGYW had more than one sexual partner in past six months	11 (22)	2 (6)
AGYW has steady income	13 (27)	8 (26)
AGYW perceives male partner to have multiple partners	15 (31)	7 (23)
AGYW perceives male partner to have more power in the relationship	28 (57)	18 (58)

AGYW, adolescent girls and young women.
[a]Overall, 91 individuals participated in the qualitative study. Quantitative information missing for n = 9 AGYW not enrolled in the parent study (refused to take the HIV self-test kit, but agreed to the qualitative interview), 1 AGYW unlinked to her quantitative results, and 1 male partner, thus n = 80 for this table; [b]As reported by the female partner.

that he is HIV positive. Similarly, for those who initiated PrEP but did not adhere, challenges around relationship trust emerged and negatively impacted adherence. For instance, most AGYW indicated they would not tell their partners they were using PrEP out of fear it would elicit an angry reaction or lead to relationship tension. Interviews with MP's demonstrated these AGYW concerns were valid.

> *I would ask why does she want to take such a thing? It will definitely mean she wants to sleep around. – MP, accepted test and shared results*

Furthermore, within this relationship characterization, issues of transient and long-distance relationships emerged, notably with MP from outside Johannesburg having primary partners at home. Depending on the type of relationship in which an AGYW was involved, engagement in self-testing fluctuated, with some AGYW unable to engage their partner in testing or results sharing despite successfully delivering the test-kit. In most cases, AGYW indicated intention to deliver the kit but did not because they had not been with their partner since receiving the test. In other cases, AGYW would deliver the self-test kit to their MP, but he shared his results with his primary partner, but not secondary partners. Regarding PrEP, all AGYW in relationships with transient men held the perception that their MPs likely had multiple partners but expressed little urgency around initiating PrEP.

3.1.2 | *AGYW with multiple partners*

There were a few cases where AGYW indicated they were engaging with multiple men until they were ready to be in a more serious relationship. These AGYW viewed self-testing and PrEP as mechanisms for protecting one's health and demonstrated confidence in accepting or delivering the self-test kit. Almost all AGYW with multiple partners initiated PrEP because they understood the risks associated with their behaviour or the behaviours of their partners. However, AGYW did not want to disclose PrEP use to their partners due to concerns of how MP might react. For AGYW who did initiate PrEP, adherence varied – many stopped taking PrEP due to side effects.

> *He does not know I am on PrEP . . . It would come as if I do not trust him. He might think that I think that he is sleeping around with many girls. - AGYW, initiated PrEP*

Interviews with the MPs supported AGYW's concerns around PrEP and self-testing and most MPs disclosed they had multiple partners. MPs reported mixed perceptions around PrEP – some approved of PrEP as a protective intervention for AGYW but would not support it if their sexual partner used it. Others demonstrated concern that offering AGYW PrEP would increase non-monogamy by providing AGYW with the protection and thus freedom to have sex with multiple men.

> *PrEP is good because it will protect her, but I have concerns about it . . . There are sexually active women out there having multiple partners without protection. In that situation . . . she might end up being a [HIV] carrier. – MP, accepted test and shared results*

3.1.3 | *IPV and male partner temperament*

While AGYW in violent relationships were not the target recipient of this intervention, some AGYW indicated experiences of IPV or indicated they had a temperamental, angry partner. These AGYW were largely concentrated in the group

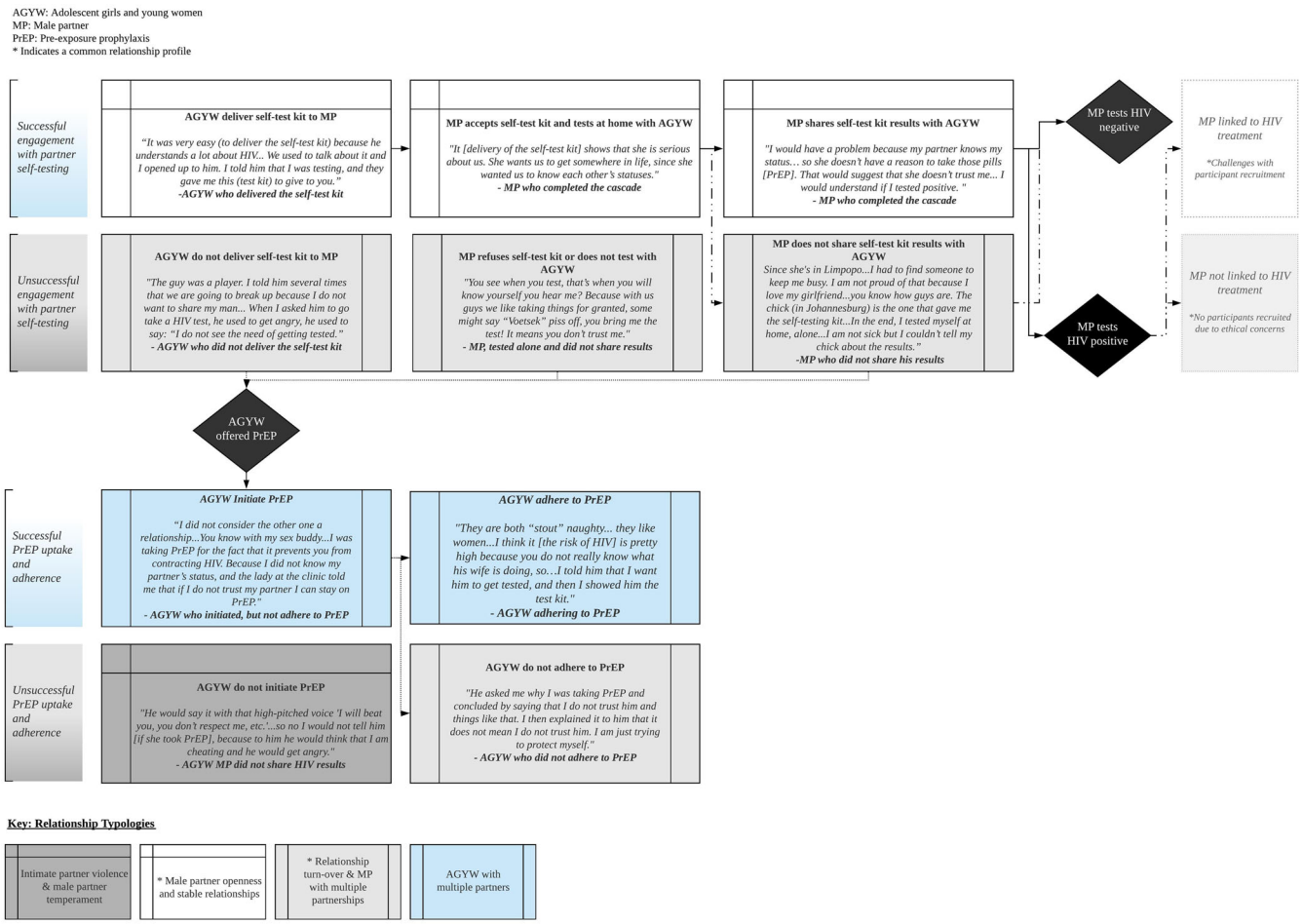

Figure 2. Relationship typologies and engagement in the HIV prevention cascade for self-testing and PrEP interventions.

of women who did not accept or did not deliver the self-test kit or take PrEP. AGYW in this group universally acknowledged that PrEP and partner self-testing would be beneficial but chose not to accept either intervention because they believed it would elicit violence.

Many AGYW explained that when they historically tried to discuss HIV or testing with their partner, he would react violently. Furthermore, a subset of AGYW who lived with their partners and were interested in PrEP expressed fear that their partner would react violently if he found the pills.

> *I did not deliver the self-test kit. This guy is very crazy, and I fear him … When I asked him about the test, he became angry. People say he is abusing his wife, and I am afraid he will beat me. – AGYW who did not deliver the self-test kit*

Violent MPs were not recruited for qualitative interviews, prioritizing safety of the AGYW. However, many MP IDI participants on their own accord mentioned that neither partner self-testing nor PrEP would be plausible interventions for women with violent partners, reinforcing AGYW concerns.

3.1.4 | Male partner openness and stable relationships

The self-testing intervention was successful among AGYW who were in stable relationships, which include AGYW who described their relationships as "committed" or "serious," who claimed they "trusted" their partner, who were in a relationship for many years, and who were only dating each other. This relationship type was the second most common substudy profile. The intervention was also successful for AGYW who described their partner's temperament as "open-minded," "accepting" and "understanding," and whose partners were willing to discuss HIV-related subjects. In many of these cases, AGYW had previously discussed HIV with their partner or had previously tested together. In other cases, AGYW were confident offering the self-test kit because they believed their MPs would be receptive to HIV discussions.

> *It was not disappointing because he did not make a big deal out of it. He understood that testing for HIV was a necessity and he was really open to it. – AGYW delivered self-test kit*

AGYW engaged in a serious relationship completed the cascade steps with ease. Specifically, AGYW and MPs who successfully tested together reported increased trust and openness resulting from the self-testing intervention.

Most AGYW in stable relationships reported no need to initiate PrEP because they trusted their partner, felt confident they could communicate about testing in the future, or could convince him to use alternative prevention methods such as condoms.

> *I am not interested in taking PrEP because I am dating one partner and he is only dating me. – AGYW did not take PrEP*

Overall, MPs in stable, serious relationships (as defined above) perceived self-testing as a gesture that their AGYW was committed to the relationship and to protecting his health. MPs in this subgroup also held the perception that PrEP was a beneficial intervention for many women but felt that their own sexual partner should have no reason to initiate PrEP, especially if he was HIV negative.

> *She wasn't forcing me but was asking me and that made me happy. My partner loves me so much that she brought me an HIV self-test kit so that I can know where I stand. – MP, accepted test and shared HIV results*

4 | DISCUSSION

While there is extensive literature examining adolescent and young adult relationship dynamics in South Africa [4-9], less is known about how relationship profiles impact engagement across the HIV prevention cascades for female-initiated prevention methods. Applying the prevention cascade framework through qualitative sampling and analysis generated insights regarding relationship heterogeneity and completion of HIV prevention cascades that might not have been observed in a random sample. This may be particularly important as sensitive information not reported in the parent study, such as violence and multiple partnerships, would have gone unidentified. Use of qualitative methods in the sub-study allowed for more nuanced insight into the challenges AGYW face completing the prevention cascades of self-testing and PrEP interventions.

A critical insight gleaned from this analysis is that AGYW in high-risk relationships had lower success navigating the HIV prevention cascades, even for female-led interventions. For situations in which the MP was perceived to have multiple partners or was violent, AGYW had limited success engaging with both PrEP and secondary distribution of self-testing interventions. Consistent with other studies highlighting the non-monogamous and transient nature of relationships for South African AGYW, these results demonstrate that the adoption of PrEP and delivery of self-test kits from AGYW to MPs is often impeded by the same gender norms that disadvantage AGYW in engaging with other HIV prevention options, such as negotiating male condom use [4-9,22,25,26]. Furthermore, recent studies on female PrEP use in Johannesburg have shown that a woman's ability and willingness to use PrEP is strongly influenced by her MP and that perceived or actual MP resistance makes adherence difficult [27]. Purposive sampling of AGYW and MP across completion of the two prevention cascades illuminated several of these barriers that were unelicited through the quantitative parent study and reinforce evidence that AGYW face similar perceived or actual relationship-related barriers to HIV prevention. This further suggests that increased emphasis should be placed on screening for relationship characteristics during implementation to gauge whether MPs will support or oppose an AGYW's involvement in HIV prevention [26,28]. Depending on the type of relationship, implementers can encourage AGYW to disclose PrEP use to MPs, or suggest other strategies that minimize potential adverse reactions while still engaging in prevention methods where possible [28].

While the primary recipients of the intervention were not AGYW experiencing IPV or AGYW living physically distant from their partners, the cascade sampling approach revealed the pervasiveness and under-reporting of violence in South African youth and the nuances behind long-distance partnerships. These various relationship manifestations can hinder AGYW's engagement in interventions they perceive as protective and beneficial [4-9,22]. For young women whose partners have multiple partners, recognizing her barriers to HIV prevention uptake and fully considering the relationship dynamics may be critical to support her navigation through prevention options.

Despite challenges, the interventions were successful for many AGYW who were in partnerships with MP characterized as supportive or open in their communication patterns. These AGYW viewed self-testing and PrEP as mechanisms for empowerment and protecting one's health, and demonstrated confidence in accepting, delivering and seeing the results of the HIV self-test kit and initiating PrEP. This finding reinforces that test kit delivery is highly acceptable and desirable outside the ANC context [10]. Furthermore, developing positive patterns of engagement with MPs at a young age may carry forward to support AGYW's navigation of continued HIV testing and prevention practices within relationships as she ages. While non-adherence and discontinuation of PrEP among AGYW in sub-Saharan Africa is well documented and inhibits PrEP effectiveness [23,25-29], these results reinforce that young women's decisions not to use PrEP are frequently rational and represent the delicate balance of weighing relationship risks and benefits [23]. Furthermore, understanding the delineation between AGYW engaged with a man who has multiple partners or AGYW engaged with multiple partners herself could help to identify whether an AGYW will perceive an intervention as an empowerment mechanism for addressing her own risk versus an intervention that threatens stability and trust within her relationship [25,28].

Together, these findings suggest that the starting place for tailoring counselling and delivery of HIV prevention interventions for young women is not just a review of her sexual behaviour and vulnerabilities, but an assessment of her relationship environment. Strengthening relationship dynamics within intimate partnerships to prevent HIV has been previously suggested [25,27-29], and future work should identify how unmarried AGYW select into relationships with men who

exhibit positive relationship qualities or how they develop relationships in which they can practice open communication. As an increasing number of HIV prevention programs begin to engage young men [10-13], both young women and men should be counselled on basic healthy communication patterns, with online digital health and/or mentorship targeting adolescents in this space promoted [25]. Furthermore, to tailor interventions to effectively address the complexity behind HIV prevention implementation, these results emphasize the need for strategies that address violent behaviour or support young women in the removal from her violent situation [23,25].

This study has limitations. Given that this was a qualitative study, we cannot generalize to the entire population of AGYW. Additionally, due to the parent study design, AGYW in identifiably violent relationships were not enrolled in the intervention, thus, results may not be generalizable to AGYW in more violent relationships. Furthermore, the study relied on self-reported data from the AGYW, potentiating misreporting by AGYW about intervention completion either in the parent or qualitative studies. For instance, IPV was disclosed in the qualitative study. Additionally, AGYW and MPs agreeing to interviews may be different from those not represented, suggesting that other intervention challenges and facilitators might exist but were not captured. However, the study was able to successfully recruit AGYW from each step of the prevention cascades, apart from HIV-positive MPs, reflecting a diverse set of participants. Finally, participants were strategically selected for qualitative interviews based on their placement in the cascades and were not representative of HIV prevention cascade completion, but rather highlight typologies of AGYW relationships that succeeded or struggled with cascade engagements.

5 | CONCLUSIONS

Overall, applying the prevention cascade approach to qualitative sampling of AGYW enrolled in PrEP and secondary distribution self-testing interventions reinforced the nuance behind relationship factors and HIV prevention, and suggested that screening around relationship types and differentiating HIV prevention services and counselling according to the specific relationship situations could improve intervention uptake and outcomes. To date, interventions targeting AGYW in isolation have often produced disappointing findings, as they rarely account for the context in which individuals live. Identifying and tailoring interventions to AGYW's environments, specifically factoring in long-distance relationships, living situations, sexual networks, and partnership dynamics may hold promise for achieving greater HIV prevention success. Furthermore, incorporation of communication skills-building strategies within larger HIV prevention interventions for adolescents may offer benefits for HIV prevention and general well-being.

AUTHORS' AFFILIATIONS

[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [2]Department of Health. Behavior & Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [3]Witkoppen Health and Welfare Clinic, Johannesburg, South Africa; [4]Social Surveys Africa, Johannesburg, South Africa; [5]Department of Epidemiology and Social Medicine, University of Antwerp, Antwerp, Belgium

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

JB, LM, AVR, SS, MK and TP designed the study. MM, LM, JB, TP, LH and SS oversaw data collection. MM, LM, LH, MK, AC, SS and TP reviewed the content of the transcripts as they came in and engaged in regular debriefing and analysis calls with the data collection team. LH and AC coded the transcripts. All authors contributed to the writing of the manuscript and have read and approved the final version.

ACKNOWLEDGEMENTS

The authors thank the young women and men participating in this study, as well as the data collection teams at Witkoppen Health and Welfare Centre and Social Surveys Africa.

FUNDING

The research reported in this publication was supported by the Fogarty International Center of the National Institutes of Health under Award Number R21-TW010897. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Funding for the parent award within which this study was based came from the United States Department of State as part of the DREAMS Innovation Challenge, managed by JSI Research & Training Institute, Inc. (JSI). The opinions, findings, and conclusions stated herein are those of the authors and do not necessarily reflect those of the United States Department of State or JSI.

REFERENCES

1. Dellar RC, Dlamini S, Karim QA. Adolescent girls and young women: key populations for HIV epidemic control. J Int AIDS Soc. 2015;18 2 Suppl 2: 19408.
2. Celum CL, Delany-Moretlwe S, Mcconnell M, van Rooyen H, Bekker L-G, Kurth A, et al. Rethinking HIV prevention to prepare for oral PrEP implementation for young African women. J Int AIDS Soc. 2015;18 4 Suppl 3:20227.
3. Dellar R, Karim QA. Understanding and responding to HIV risk in young South African women: clinical perspectives. S Afr Med J. 2015;105(11):952.
4. Pettifor A, MacPhail C, Anderson AD, Maman S. "If I buy the Kellogg's then he should [buy] the milk": young women's perspectives on relationship dynamics, gender power and HIV risk in Johannesburg, South Africa. Cult Health Sex. 2012;14(5):477–90.
5. Rosenthal L, Levy SR. Understanding women's risk for HIV infection using social dominance theory and the four bases of gendered power. Psychol. Women Q. 2010;34(1):21–35.
6. Jewkes RK, Dunkle K, Nduna M, Shai N. Intimate partner violence, relationship power inequity, and incidence of HIV infection in young women in South Africa: a cohort study. Lancet. 2010;376(9734):41–8.
7. Dunkle KL, Jewkes RK, Brown HC, Gray GE, McIntryre JA, Harlow SD. Gender-based violence, relationship power, and risk of HIV infection in women attending antenatal clinics in South Africa. Lancet. 2004;363(9419):1415–21.
8. Pettifor AE, Measham DM, Rees HV, Padian NS. Sexual power and HIV risk, South Africa. Emerging Infect Dis. 2004;10(11):1996–2004.
9. Thirumurthy H, Masters SH, Mavedzenge SN, Maman S, Omanga E, Agot K. Promoting male partner HIV testing and safer sexual decision making through secondary distribution of self-tests by HIV-negative female sex workers and women receiving antenatal and post-partum care in Kenya: a cohort study. Lancet HIV. 2016;3(6):e266–74.
10. Hlongwa M, Mashamba-Thompson T, Makhunga S, Hlongwana K. Mapping evidence of intervention strategies to improving men's uptake to HIV testing services in sub-Saharan Africa: a systematic scoping review. BMC Infect Dis. 201919(1):e496.
11. De Allegri M, Agier I, Tiendrebeogo J, Louis VR, Ye M, Mueller O, et al. Factors affecting the uptake of HIV testing among men: a mixed-methods study in rural Burkina Faso. PLoS ONE. 2015;10:e0130216.

12. Shand T, Thompson-de Boor H, van den Berg W, Peacock D, Pascoe L. The HIV blind spot: men and HIV testing, treatment and Care in in Sub-Saharan Africa. IDS Bull. 2014;45(1):53–60.
13. Orne-Gliemann J, Balestre E, Tchendjou P, Miric M, Darak S, Butsashvili M, et al. Increasing HIV testing among male partners. AIDS. 2013;27(7):1167–77.
14. Cowan FM, Delany-Moretlwe S, Sanders EJ, Mugo NR, Guedou FA, Alary M, et al. PrEP implementation research in Africa: what is new? J Int AIDS Soc. 2016;19 7 Suppl 6:21101.
15. Braksmajer A, Senn T, McMahon J. The potential of pre-exposure prophylaxis for women in violent relationships. AIDS Patient Care STDs. 2016;30(6):274–81.
16. Baeten J, Heffron R, Kidoguchi L, Mugo N, Katabira E, Bukusi E, et al. Near elimination of HIV transmission in a demonstration project of PrEP and ART. Conference on Retroviruses and Opportunistic Infections; 23-26 Feb 2016; Seattle, WA. 2015.
17. Matthews L, Baeten J, Celum C, Bangsberg D. Periconception pre-exposure prophylaxis to prevent HIV transmission: benefits, risks, and challenges to implementation. AIDS. 2010;24:1975–82.
18. Bekker L, Grant R, Hughes J, Seattle RS.2015. HPTN 067/ADAPT Cape Town: a comparison of daily and nondaily PrEP dosing in African women. Conference on Retroviruses and Opportunistic Infections; 2016 Feb 23–26; Seattle, WA. 2015.
19. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015;372(6):509–18.
20. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367(5):411–22.
21. Bekker L-G, Johnson L, Cowan F, Overs C, Besada D, Hillier S. Combination HIV prevention for female sex workers: what is the evidence? Lancet. 2015;385 (9962):72–87.
22. Celum CL, Delany-Moreltwe S, Baeten JM, van der Straten A, Hosek S, et al. HIV pre-exposure prophylaxis for adolescent girls and young women in Africa: from efficacy trials to delivery. J Int AIDS Soc. 2019;22 Suppl 4. https://doi.org/10.1002/jia2.25298.
23. Gourlay A, Birdthistle I, Mthiyane NT, Orindi BO, Muuo S, Kwaro D, et al. Awareness and uptake of layered HIV prevention programming for young women: analysis of population-based surveys in three DREAMS settings in Kenya and South Africa. BMC Public Health. 2019;19:1417. https://doi.org/10.1186/s12889-019-7766-1.
24. Schwartz S, Mutunga L, Mudavanhu M, Van Loo M, Ngwako L, Bassett J, Van Rie A. Empowering adolescent girls and young women to remain HIV-free: Outcomes of a DREAMS HIV self-testing and PrEP combination prevention intervention targeting AGYW and male partners. Poster presentation (WEPEC515) at the 10th International AIDS Society Conference on HIV Science (IAS 2019), Mexico City, Mexico, July 24, 2019.
25. Sayles J, Pettifor A, Wong M,MacPhail C, Lee S-J, Hendriksen E, et al. Factors associated with self-efficacy for condom use and sexual negotiation among south African youth. J Acquir Immune Defic Syndr. 2006;43(2):226–33.
26. Corneli A, Perry B, Agot K, Ahmed K, Malamatsho F, van Damme L. Facilitators of adherence to the study pill in the FEM-PrEP clinical trial. PLoS ONE. 2015;10(4):1–18. https://doi.org/10.1371/journal.pone.0125458.
27. Hartmann M, McConnell M, Bekker L, Celum C, Bennie T, Zuma J, et al. Motivated reasoning and HIV risk? Views on relationships, trust, and risk from young women in Cape Town, South Africa, and implications for oral PrEP. AIDS Behav. 2018;22(11):3468–79. https://doi.org/10.1007/s10461-018-2044-2.
28. Amico K, Wallace M, Bekker L,Roux S, Atujuna M, Sebastian E, et al. Experiences with HPTN 067/ADAPT study-provided open-label PrEP among women in Cape Town: facilitators and barriers within a mutuality framework. AIDS Behav. 2017;21(5):1361–75.
29. Van der Elst EM, Mbogua J, Operario D, Mutua G, Kuo C, Mugo P, et al. High acceptability of HIV pre-exposure prophylaxis but challenges in adherence and use: qualitative insights from a phase I trial of intermittent and daily PrEP in at-risk populations in Kenya. AIDS Behav. 2013;17(6):2162–72.

Bershteyn A et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25527
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25527/full | https://doi.org/10.1002/jia2.25527

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Impact along the HIV pre-exposure prophylaxis "cascade of prevention" in western Kenya: a mathematical modelling study

Anna Bershteyn[1,2,§], Monisha Sharma[2,3], Adam N Akullian[2,3], Kathryn Peebles[5], Supriya Sarkar[4], R Scott Braithwaite[1] and Edinah Mudimu[6]

[§]**Corresponding author**: Anna Bershteyn, 227 East 30th Street, Sixth Floor, New York City, New York 10016. USA. Tel: +1-646-501-2565. (anna.bershteyn@nyulangone.org)

Abstract

Introduction: Over one hundred implementation studies of HIV pre-exposure prophylaxis (PrEP) are completed, underway or planned. We synthesized evidence from these studies to inform mathematical modelling of the prevention cascade for oral and long-acting PrEP in the setting of western Kenya, one of the world's most heavily HIV-affected regions.

Methods: We incorporated steps of the PrEP prevention cascade – uptake, adherence, retention and re-engagement after discontinuation – into EMOD-HIV, an open-source transmission model calibrated to the demography and HIV epidemic patterns of western Kenya. Early PrEP implementation research from East Africa was used to parameterize prevention cascades for oral PrEP as currently implemented, delivery innovations for oral PrEP, and future long-acting PrEP. We compared infections averted by PrEP at the population level for different cascade assumptions and sub-populations on PrEP. Analyses were conducted over the 2020 to 2040 time horizon, with additional sensitivity analyses for the time horizon of analysis and the time when long-acting PrEP becomes available.

Results: The maximum impact of oral PrEP diminished by over 98% across all prevention cascades, with the exception of long-acting PrEP under optimistic assumptions about uptake and re-engagement after discontinuation. Long-acting PrEP had the highest population-level impact, even after accounting for possible delays in product availability, primarily because its effectiveness does not depend on drug adherence. Retention was the most significant cascade step reducing the potential impact of long-acting PrEP. These results were robust to assumptions about the sub-populations receiving PrEP, but were highly influenced by assumptions about re-initiation of PrEP after discontinuation, about which evidence was sparse.

Conclusions: Implementation challenges along the prevention cascade compound to diminish the population-level impact of oral PrEP. Long-acting PrEP is expected to be less impacted by user uptake and adherence, but it is instead dependent on product availability in the short term and retention in the long term. To maximize the impact of long-acting PrEP, ensuring timely product approval and rollout is critical. Research is needed on strategies to improve retention and patterns of PrEP re-initiation.

Keywords: HIV prevention; pre-exposure prophylaxis; cascade; mathematical modelling; Kenya; sub-Saharan Africa

Additional Supporting Information may be found online in the Supporting Information tab for this article.

Received 30 September 2019; **Accepted** 27 April 2020

1 | INTRODUCTION

HIV is a leading cause of death in sub-Saharan Africa [1], particularly in Eastern and Southern Africa, which contain a majority of the world's HIV burden and incidence [2]. Western Kenya contains some of the world's hardest-hit communities, with approximately one in four adults living with HIV in the counties of Homa Bay and Siaya [3]. Over the past decade, rates of new HIV infections have declined in western Kenya, concurrently with scale-up of HIV treatment and preventative interventions such as male circumcision, but remain among the highest rates observed globally [4].

Oral pre-exposure prophylaxis (PrEP) reduces the risk of HIV acquisition [5,6], but implementation has been slow to expand in Eastern and Southern Africa [7] due to numerous social, political, cultural and logistical barriers [8]. Some of these barriers have a multiplicative effect, compounding to make population-level impact more challenging.

A "prevention cascade" framework has been proposed for HIV [9] and for PrEP in particular [10,11] to organize the

components of PrEP implementation that have an effect on HIV prevention. This is analogous to the HIV "treatment cascade," or care continuum framework, widely adopted for treatment of people living with HIV (PLHIV), which helped to inform the UNAIDS 90-90-90 targets for HIV diagnosis, treatment and viral load suppression [12]. Here we adapt a previously developed agent-based HIV network transmission model, which includes a detailed model of HIV care and prevention, to simulate the cascades of prevention affecting the population-level impact of PrEP. Our analysis provides quantitative insights into a relatively new and increasingly critical concept in HIV prevention research.

2 | METHODS

2.1 | Model of HIV in western Kenya

We developed a cascade of prevention model for PrEP within the health care component of EMOD-HIV, part of the EMOD transmission modelling software tool [13,14]. EMOD-HIV is an HIV epidemiological model that integrates population demography, HIV disease progression; and network-based HIV transmission configured to match age- and sex-specific propensities to form different sexual partnership types [15]. Interventions such as antiretroviral therapy (ART), voluntary medical male circumcision (VMMC), and PrEP are added to EMOD through a highly configurable health care module in which different steps of health seeking and outreach can be targeted to sub-populations and can be made to vary over time [16].

Prior to the current analysis, EMOD had been calibrated to fit the HIV epidemic in six counties in western Kenya: Siaya, Kisumu, Homa Bay, Migori, Kisii and Nyamira [17]. Model calibration methods, parameter values and their distributions, and quality of fit to HIV survey and routine data, have been published in detail elsewhere [17] and are summarized below, with emphasis on those model components most closely related to HIV prevention. Because PrEP rollout did not begin until 2017 – whereas the most recently available HIV prevalence survey was conducted in 2012 – the pre-existing model was not re-calibrated. As a model validation exercise, EMOD-HIV was calibrated to demographic, HIV prevalence, and viral suppression data from 32 high-incidence communities in Eastern Africa, including 16 communities in western Kenya, that were enrolled in a community-randomized trial of ART scale-up [18]. The model successfully predicted HIV incidence in these communities while still blinded to measured incidence, the trial's primary outcome [19].

Both traditional male circumcision and scale-up of VMMC were included using age- and county-specific circumcision coverage estimates from the Demographic and Health Surveys (DHS) [20]. Importantly, the model incorporated county-specific estimates of the population sizes of commercial sex workers based on an enumeration conducted in 2012, the same year as the most recently available HIV prevalence estimate [21].

The calibration target data, model parameters and fitted modelled trajectories for the six-county western Kenya model have been described in detail [17]. Briefly, the agent-based model represented the western Kenyan population, with an *in silico* model population equal to one-25th the population of western Kenya. The population structure was fit to match the Kenya Population and Housing Census, and with age-specific fertility rates and age- and sex-specific non-HIV mortality rates published by the UN Population Division [22,23]. The model was fit to age-, sex- and county-stratified HIV prevalence estimates from 2003 and 2008 to 2009 DHS Surveys, 2007 and 2012 AIDS Indicator Surveys, numbers of PLHIV on ART reported annually by the Kenya Ministry of Health, and population statistics from the Kenya Population and Housing Census [24,25].

Modelling fitting to data was performed using parallel simultaneous perturbation optimization, an algorithm that maximizes the posterior probability of the model's fit to data [26,27]. The cost function being minimized in the calibration process was the log-likelihood of the model's fit to population age/sex structure, number on ART, and age-, sex- and country-stratified HIV prevalence after accounting for the uncertainty of each estimate based on the survey design and sample size. After model fitting, 250 trajectories were obtained by resampling parameter sets among all those run during the fitting process in proportion to the likelihood score of each simulation. To estimate the impact of only historical levels of PrEP, for which the total number of averted infections is still small, the number of replicates was increased to 2000 model runs.

2.2 | Baseline levels of PrEP usage

County-specific estimates of PrEP use since the start of rollout were obtained from the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) [28], and national-level estimates were obtained from PrEPWatch [29]. PrEPWatch estimated the total number of PrEP users in Kenya in 2019 to be 44,000. Among the 14,258 PrEP users included in the PEPFAR dataset, 7866 resided in six counties comprising the former Nyanza province of western Kenya. We used the proportion of users in each county relative to the total to allocate the PrEPWatch estimates across the six counties of the Nyanza region, yielding a total of 24,274 users within Nyanza. The baseline scenario allocations by county were: 8,243 (34%) in Siaya, 5120 (21%) in Kisumu, 4820 (20%) in Homa Bay; 4663 (19%) in Migori; 1102 (5%) in Kisii; and 327 (1%) in Nyamira. To model continuation of 2019 levels of PrEP use, we simulated 25,000 users annually with the same proportions by county: 8489 in Siaya; 5273 in Kisumu; 4964 in Homa Bay; 4802 in Migori; 1135 in Kisii; and 337 in Nyamira.

2.3 | Target populations for PrEP scale-up

Scenarios of PrEP rollout were modelled by increasing the numbers of individuals on PrEP in four target populations: (1) adolescents and adults ages 15 to 29 living in areas with HIV prevalence exceeding 10%, which for western Kenya were Homa Bay, Siaya, Kisumu and Migori Counties; (2) adolescent girls and young women (AGYW) ages 15 to 24 living in counties with HIV prevalence exceeding 10%; (3) higher-risk AGYW, defined as female sex workers and women likely to have multiple sex partners in all counties, (4) and higher-risk males, defined as males in the high-incidence age group of 20 to 29 years who are clients of sex workers or likely to have multiple sex partners in all counties. Risk of multiple sex partners was modelled as a propensity to acquire multiple

simultaneous sex partners within the sexual network – with partner acquisition rates varying by age according to the matrix of age-dependent assortativity – as well as a three-fold higher risk of co-infection with a sexually transmitted infection.

2.4 | PrEP cascade steps

Previously published conceptual frameworks of the prevention cascade [9-11] have considered numerous potential steps of the HIV prevention cascade. To simplify the analysis given the paucity of data on individual steps, our analysis consolidates the proposed frameworks into four steps that they share in common: uptake, adherence, retention, and re-engagement (Figure 1). To parameterize each step, we reviewed current and ongoing PrEP implementation and demonstration projects referenced in review articles [8,30-32] and tabulated by the AIDS Vaccine Advocacy Coalition [33]. Of the 108 PrEP studies globally, 43 had at least one site in sub-Saharan Africa and 15 were completed as of April 2019. Published results from these studies were used to inform composite model assumptions of three potential prevention cascades: (1) currently available oral PrEP implementation ("oral conventional"), (2) future innovation in PrEP implementation strategies ("oral innovative"), and (3) new long-acting PrEP products ("long-acting").

2.5 | PrEP cascade parameterization

Assumptions regarding each step of the three PrEP cascades are summarized in Table 1. To represent the PrEP cascade achievable with currently available methods of oral PrEP delivery ("oral conventional"), we drew on existing data and coverage targets. For uptake, we used the World Health Organization (WHO) target of 10% coverage by 2020 of high-risk populations, defined as young people in high-prevalence settings and key populations in all settings [34]. This target is consistent with the achieved coverage in PrEP scale-up projects in sub-Saharan Africa [35,36]. Uptake in the model is defined as the proportion of individuals initiating PrEP annually.

To represent how ongoing oral implementation research can improve the PrEP cascade ("oral innovative"), we used results from a study conducted in Uganda which found that both uptake and retention on PrEP were three-fold higher among users who resided within two kilometres of a PrEP-dispensing clinic, after adjusting for other factors [38]. We assumed that innovations to overcome barriers to PrEP uptake and continuation could raise uptake three-fold to 30%. Our optimistic assumptions about long-acting PrEP assumed even higher uptake of 50% based on user preference research in western Kenya [40], while pessimistic assumptions assumed an uptake of 10%, the same as the WHO target for conventional oral PrEP.

Adherence patterns for daily oral PrEP are highly variable and have a strong correlation with PrEP efficacy. A meta-analysis of five clinical trials of oral PrEP in women in estimated an efficacy of 36% across all study participants, and 61% for participants with high adherence (defined as having detectable levels of PrEP drugs in 75% of blood samples) [37]. In the western Kenya setting, a study estimated far higher PrEP efficacy of 75% [5]. Therefore, we examined as pessimistic assumptions an adherence-driven efficacy of 36% for conventional PrEP and 61% for PrEP with innovative implementation, and an optimistic assumption of 75% efficacy for both conventional and innovative PrEP implementation. Since long-acting PrEP is independent of user adherence to daily pills (but rather reliant on continued clinical care) we assumed efficacy for long-acting PrEP was 95%, the same level as the upper limit scenario.

Retention has been a significant challenge in PrEP implementation. Among AGYW ages 15 to 29 initiating PrEP in Kenya, only 5% remained on PrEP after ten months [39]. In a large prevention project in Kenya and Uganda, the average duration of PrEP use was three months [35,38]. Therefore, we assumed a three-month retention period on PrEP. Drawing on the study of PrEP users living close to PrEP-dispensing clinics,

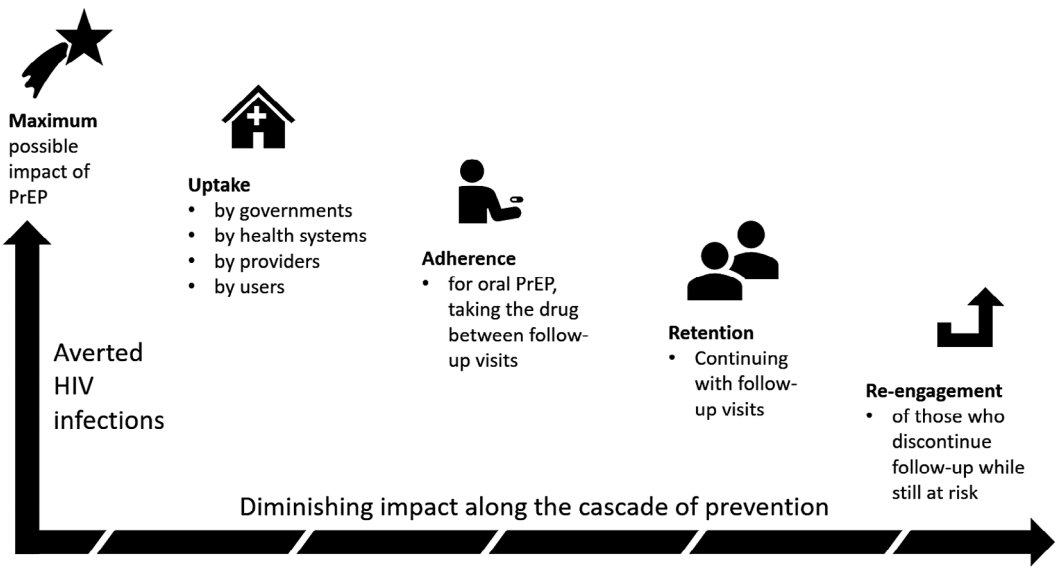

Figure 1. Diagram of the prevention cascade added to the EMOD-HIV model. PrEP, pre-exposure prophylaxis

Table 1. Prevention cascade model scenarios, assumptions and ranges used in sensitivity analysis

Cascade	Step	Assumption	Sources
Conventional oral PrEP	Uptake	10%	[34–36]
	Adherence	36% to 75%	[5,37]
	Retention	3 months	[35,38,39]
	Reengagement	0% to 100%	No available data
Innovative delivery of oral PrEP	Uptake	30%	[38]
	Adherence	61% to 75%	[5,37]
	Retention	9 months	[35,38,39]
	Reengagement	0% to 100%	No available data
Long-acting PrEP	Uptake	10% to 50%	[40]
	Adherence	95%	[40]
	Retention	9 months	[35,38,39]
	Reengagement	0% to 100%	No available data

PrEP, pre-exposure prophylaxis.

we assumed that the mean duration on PrEP could be tripled, from three months to nine months, through innovative implementation [38].

We did not find evidence to inform the fourth step of the prevention cascade: re-engagement of clients who have discontinued PrEP. Therefore, two model scenarios were compared: one in which users who discontinued PrEP would not re-initiate PrEP, and one in which PrEP re-initiation after discontinuation occurs at the same rate as for other PrEP-eligible individuals.

For each cascade step, the attenuation in PrEP impact was estimated as number of infections averted at the population level – including among those not on PrEP – relative to a baseline scenario in which PrEP usage increased at a steady rate based on 2019 levels. In lieu of annual discounting of impact, which is commonly performed in cost-effectiveness analyses, we instead used more interpretable undiscounted time horizons of 5, 10, 20 and 30 years ending in 2025, 2030, 2040 and 2050 respectively with all analyses beginning in 2020.

2.6 | Timelines for PrEP rollout

For oral innovative PrEP, we assumed that optimized strategies for PrEP delivery would be identified by 2021, based on projected completion dates of ongoing implementation studies. To account for the time required to implement new evidence-based strategies, we assumed innovative PrEP rollout ramped up in a linear fashion from 2021 to 2023. For long-acting PrEP, an ongoing clinical trial to measure efficacy among women in sub-Saharan Africa has an estimated completion date of May 2022 [41]. We assumed the most optimistic rollout would begin in 2023 with a two-year ramp up until 2025. This rapid timeline for long-acting PrEP was taken as an upper limit, and we compared how impact might diminish if long-acting PrEP availability were delayed until 2025, 2027 or 2029.

3 | RESULTS

The early PrEP rollout in western Kenya has already averted approximately 100 HIV infections annually, as shown in Figure 2. In a conservative projection that assumes no further expansion of PrEP beyond 2019 levels (approximately 25,000 users annually, each using PrEP for an average of three months), maintaining *status quo* PrEP availability could avert 2000 HIV infections in western Kenya by 2050.

Impact along the cascades diminished greatly due to compounding declines along each cascade step, under both pessimistic and optimistic assumptions about uptake and adherence (Figure 3). Although the model captured knock-on effects of PrEP averting infections in the community, the overall prevention cascades were approximately proportional to the assumed reduction in uptake, adherence and annual retention, and dropped off considerably if those who previously disengaged from PrEP were unwilling to re-initiate PrEP in the future.

Assuming those who discontinue PrEP could re-initiate as often as annually, the end-to-end prevention cascades for conventional oral PrEP, innovative delivery of oral PrEP, and long-acting PrEP had a drop-off in infections averted of 98.5%, 90.4% and 95.9% respectively under pessimistic assumptions, and 96.5%, 89.8% and 78.6% respectively under optimistic assumptions. Assuming those who discontinue PrEP are unwilling to re-initiate PrEP, the drop-off in impact was >98% all cascades except for the long-acting PrEP cascade under optimistic assumptions, where it was 96.6%.

The decline in impact along PrEP cascades was not sensitive to the target population receiving PrEP Figure S1 among the four populations tested: youth ages 15 to 29 in counties with >10% HIV prevalence, adolescent and young women ages 15 to 24 in counties with >10% HIV prevalence; sex workers and high-risk women in all counties; or sex worker clients and higher-risk men in all counties.

The time horizon of analysis substantially influenced the relative impact among the three prevention cascades Figure 4. In particular, optimism about the possible uptake of long-acting PrEP was offset by the delay in its availability and time required to ramp up coverage, so that an optimistic long-acting PrEP cascade was only distinguished itself from oral PrEP cascades over time horizons of ten or more years.

The timeline for rollout of long-acting PrEP in sub-Saharan Africa is uncertain. We examined how delayed rollout, relative to the optimistic timeline of a 2023 launch with a linear ramp-up through 2025, would diminish the impact of long-acting PrEP under optimistic assumptions (Figure 5). As expected, a product launch later than 2025 provides no opportunity for impact over the 2020 to 2025 period and would greatly diminish impact over a 10-year time horizon. However, examined over longer time horizons of 20 or 30 years, long-acting PrEP would out-perform oral PrEP under optimistic assumptions.

4 | DISCUSSION

Analogous to the care cascade for HIV treatment, we examined the use of an HIV prevention cascade to evaluate how different steps compound to influence population-level impact of PrEP in terms of HIV infections averted. We found that the population-level impact of PrEP diminishes considerably across the cascade of prevention. For oral PrEP, the largest drop-off in PrEP impact occurred from limited uptake. Even with

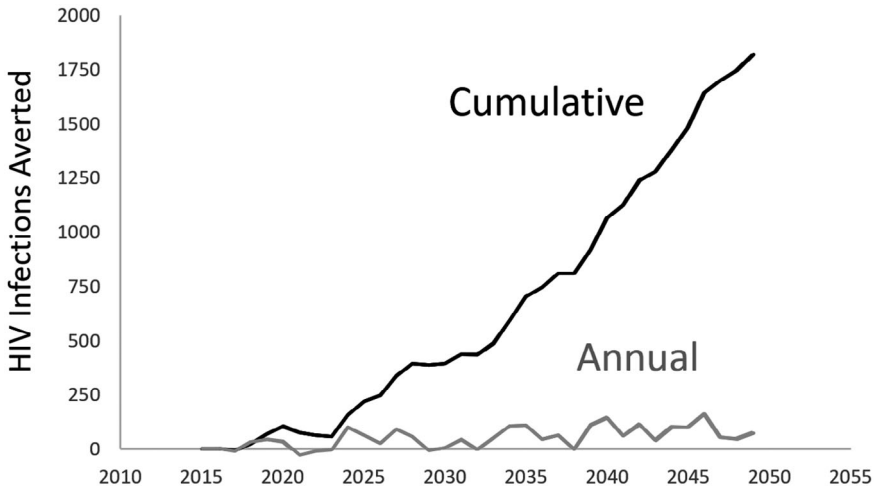

Figure 2. Infections averted by oral PrEP used at current levels in western Kenya. PrEP use was simulated for the six counties of Nyanza using estimates from PrEPWatch, and stratified at the county level using data from PEPFAR. As a conservative assumption, this analysis assumed a continued rate of 25,000 annual PrEP users in Nyanza, just above the 24,274 users estimated for 2019. Impact is estimated at the population, so that estimates include averted infections in PrEP users as well as averted infections among individuals in the sexual network of PrEP users. Impact is modest because western Kenya is still early in the process of PrEP roll-out. PrEP, pre-exposure prophylaxis; PEPFAR: president's emergency plan for AIDS relief

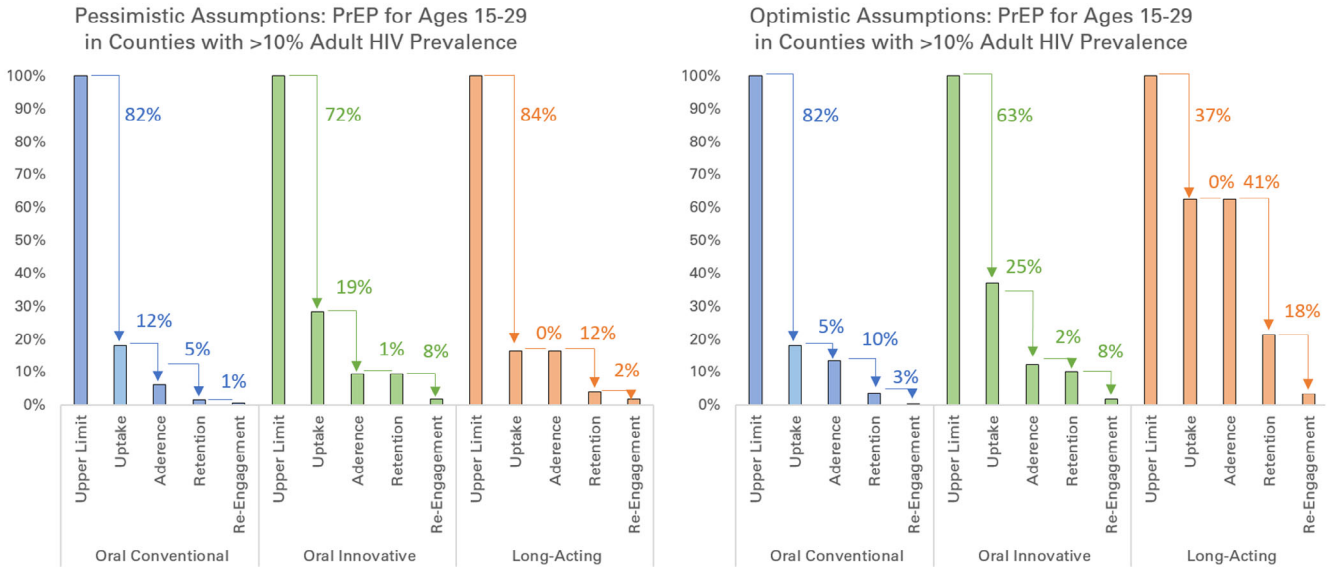

Figure 3. Percentage of infections averted along prevention cascades with pessimistic and optimistic assumptions. Arrows show absolute percentage decrease relative to the previous step of the cascade. Prevention cascades are shown for conventional implementation of oral PrEP (blue), innovative implementation of oral PrEP (green), and long-acting PrEP (orange) in western Kenya, under assumptions described in Table 1. The population receiving PrEP is men and women ages 15 to 29 in counties with HIV prevalence exceeding 10% (Homa Bay, Siaya, Kisumu, and Migori). Infections averted are calculated for the entire population, including those not on PrEP. PrEP, pre-exposure prophylaxis

optimistic assumptions about the impact of implementation innovations, uptake remained the greatest drop-off in the oral PrEP cascade. For long-acting PrEP, it is not known whether uptake will be limited to levels similar to that of oral PrEP as the main limiting factor. Under optimistic assumptions about uptake, the main limiting factor for long-acting PrEP would be retention.

With the exception of long-acting PrEP under optimistic assumptions about uptake, all other cascades caused a diminishing of >98% of impact after aggregating the compounding effects of each step of the cascades. Long-acting PrEP, under optimistic assumptions about uptake and re-engagement, still lost a substantial 78.6% of its impact long the cascade, highlighting the formidable challenge of compounding steps in prevention cascades even in the best of circumstances.

Introduction of long-acting PrEP could enable a shift of resources from adherence-focused interventions to ones that maximize retention and re-engagement. Such interventions might address support from intimate partners, perception of HIV risk, reducing and coping with stigma, and prioritization

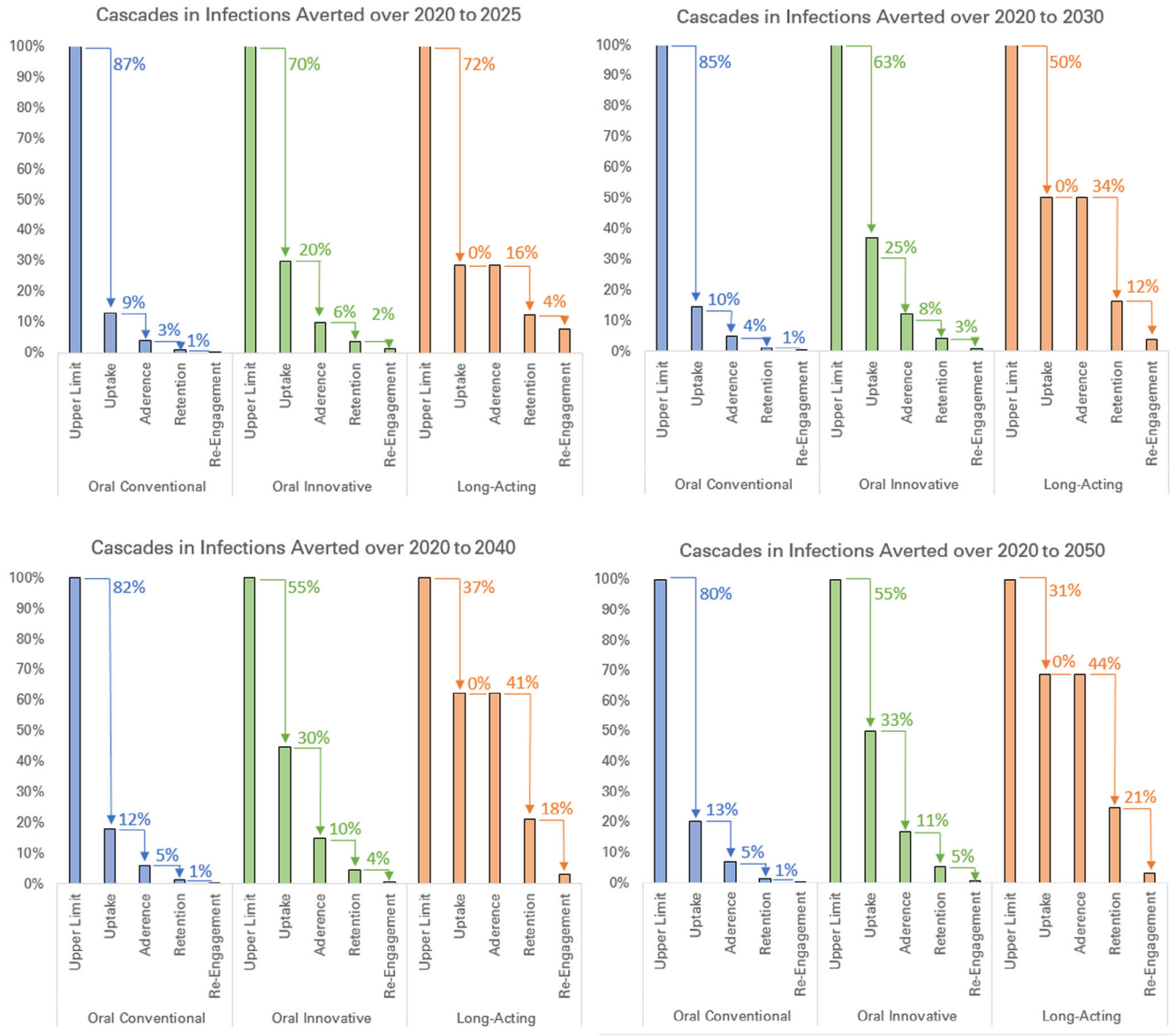

Figure 4. Percentage of infections averted along prevention cascades over different time horizons of analysis. Arrows show absolute percentage decrease relative to the previous step of the cascade. Prevention cascades for conventional implementation of oral PrEP (blue), innovative implementation of oral PrEP (green), and long-acting PrEP (orange) in western Kenya were organized into the uptake, adherence, retention and re-initiation of those at risk who have discontinued PrEP. The population receiving PrEP is men and women ages 15 to 29 in counties with HIV prevalence exceeding 10%. Infections averted is calculated for the entire population, including those not on PrEP. Infections averted are cumulative over time horizons of 2020 to 2025 (top left), 2020 to 2030 (top right), 2020 to 2040 (bottom left) and 2020 to 2050 (bottom right). PrEP, pre-exposure prophylaxis

of PrEP among competing priorities of providers and users [42,43]. In addition, the impact of long-acting PrEP was highly sensitive to assumptions about re-engagement after PrEP interruption. The current evidence gap about willingness to re-engage in PrEP will be especially critical to address for long-acting PrEP.

Our study has several important limitations. Evidence about the cascades of prevention, especially the "oral innovative" and "long-acting" PrEP cascades that have not yet been implemented, is limited to extrapolation from studies of oral conventional PrEP. We encountered the greatest evidence gaps for the final step of re-engagement of those who have discontinued PrEP. In light of uncertainty, we modelled several possible long-acting PrEP launch dates (2023, 2025, 2027 and 2029). Although 2029 is likely pessimistic since oral PrEP has improved readiness to adopt long-acting PrEP, it is possible that unexpected challenges could arise from trial results, regulatory approval, supply or other prerequisites to the launch of long-acting PrEP in Africa. Our analysis should be revisited as new information becomes available regarding the likely timeline of long-acting PrEP rollout.

Owing to the paucity of data on prevention cascades, our analysis consolidated more detailed frameworks for prevention cascades into just a small number of cascade steps that

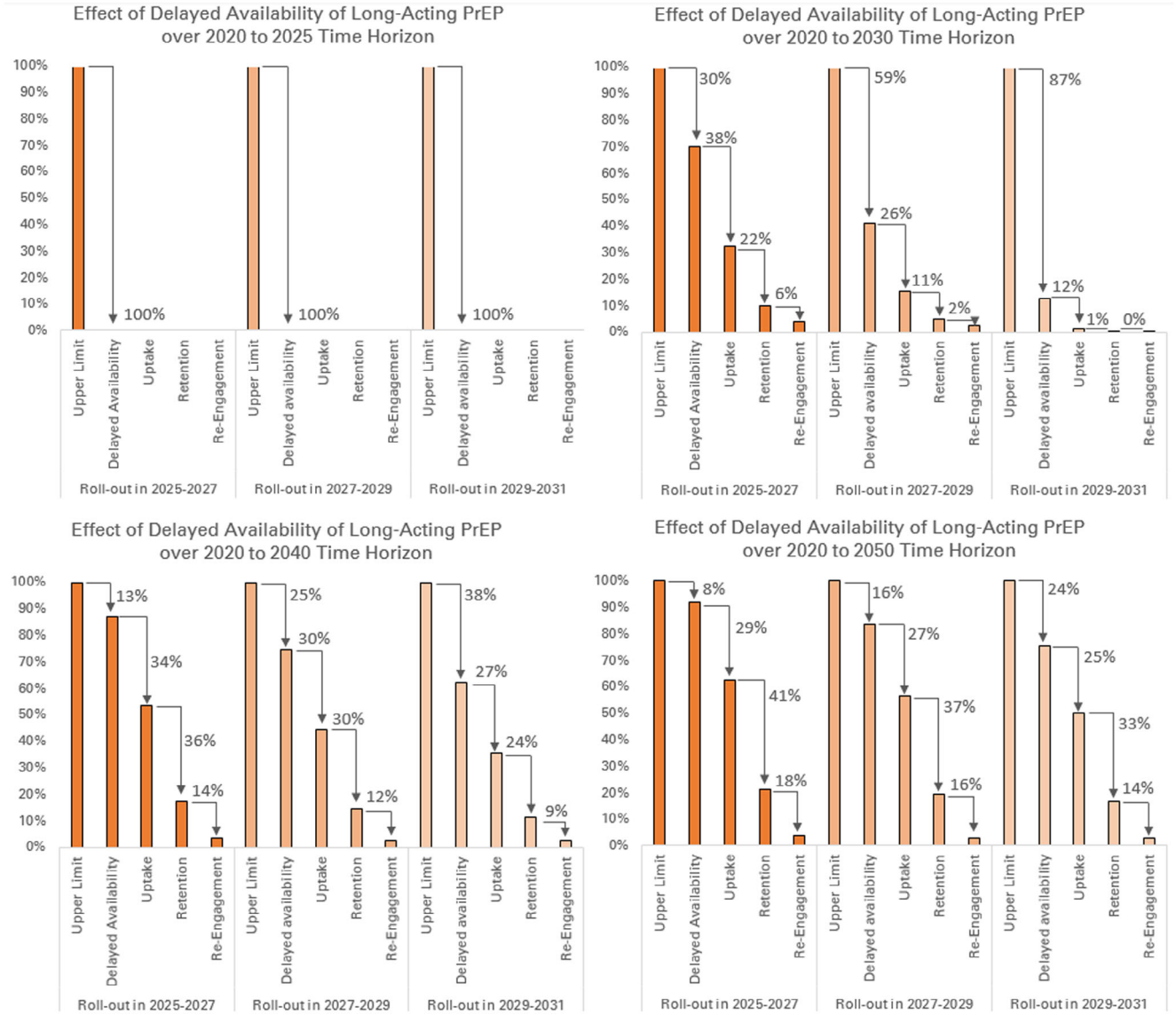

Figure 5. Percentage of infections averted along prevention cascades for long-acting PrEP for different timelines of product rollout and different time horizons of analysis. Adherence is not included in the depicted cascades; return for injections is subsumed into the retention step of the cascade. The target group is adults 15 to 29 in counties with prevalence above 10%. Infections averted are cumulative over time horizons of 2020 to 2025 (top left), 2020 to 2030 (top right), 2020 to 2040 (bottom left) and 2020 to 2050 (bottom right). PrEP, pre-exposure prophylaxis

those frameworks share in common. Expanding evidence about HIV prevention cascades may allow future analyses to disaggregate steps of the cascade that have been consolidated in this analysis. Future analyses could also leverage findings about integration of PrEP into existing HIV and non-HIV services, for example, whether PrEP availability influences rates of HIV testing, thus conferring additional benefits by supporting prompt HIV diagnosis.

There is a lack of empiric data on the overlap between HIV risk and the cascade of prevention, especially in terms of risk-driven patterns of discontinuation and re-engagement. Given evidence of logistical barriers to oral conventional PrEP retention and adherence, we conservatively assumed that adherence, retention, and re-engagement occurred independently of time periods of risky behaviour. Qualitative research suggests that users have intentions to discontinue PrEP when HIV risk is lower, and re-engage when risk is higher [44]. There is a negative association between PrEP use and psychosocial factors such as stigma and depression, which may increase HIV risk and reduce protective behaviours other than PrEP use [45]. To the extent that PrEP engagement may have a net positive correlation with HIV risk, our conservative assumptions overestimate the fall-off in impact across the prevention cascade.

Although our analysis attempts to leverage early results from PrEP implementation studies, a majority of global PrEP implementation studies are still ongoing. In addition, current users of PrEP may be biased toward "early adopters" and may not be representative of the population targeted to receive PrEP. Our analysis may necessitate revisiting if new future

implementation science exposes different PrEP cascade parameters compared to early evidence.

Finally, our model used simple demographic criteria (age, sex and geographic location) along with general stratification of HIV risk (sex work, multiple sex partners and STI co-infection rates) to determine the populations targeted for PrEP. Future, more detailed modelling should be coupled with emerging evidence on the characteristics of those to whom PrEP is offered at scale. Such characteristics could include having a recent sexually transmitted infection; beliefs about a partner's HIV status or viral suppression status; or other behavioural, biological or demographic indicators of HIV risk. Because the cascade analysis exhibited little sensitivity to the target group, we expect that additional details on the target group are unlikely to substantially change the proportional fall-off of impact along the cascade of prevention, but the characteristics would be important for estimating the absolute magnitude of impact. Additionally, fall-off along the prevention cascade could depend on the specific sub-population or reason for PrEP initiation – an interdependence that our analysis did not capture.

Our analysis provides insight into the most important steps in the cascade of prevention, as well as the overall attenuation of impact when the steps of the cascade are combined. Guided by conceptual frameworks for prevention cascades, such modelling can integrate emerging evidence in order to help guide priorities for implementation science and product development.

5 | CONCLUSIONS

Implementation challenges along the prevention cascade compound to diminish the population-level impact of PrEP. Even after accounting for the delay in long-acting PrEP availability in terms of HIV infections that will occur prior to rollout, long-acting PrEP nonetheless exhibited the best-performing prevention cascade over a 20- or 30-year time horizon. Our analysis projects that uptake will constitute the largest step-down in impact along the "oral conventional" and "oral innovative" PrEP cascades. For long-acting PrEP, our analysis suggests that the greatest limitations on impact will be caused by product availability timelines in the short term, and retention in the long term. To maximize the impact of long-acting PrEP, ensuring timely product approval and rollout is essential in the short term. In the long term, implementation research should focus on retention and re-engagement of users.

AUTHORS' AFFILIATIONS

[1]Department of Population Health, NYU Grossman School of Medicine, New York, NY, USA; [2]Institute for Disease Modeling, Bellevue, WA, USA; [3]Department of Global Health, University of Washington, Seattle, WA, USA; [4]Department of Epidemiology, Emory University, Atlanta, GA, USA; [5]Department of Epidemiology, University of Washington, Seattle, WA, USA; [6]Department of Decision Sciences, University of South Africa, Pretoria, South Africa

COMPETING INTEREST

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

EM, KP and AB conceived of the study. All authors reviewed the literature and other data sources. AB coded the model, ran the simulations, performed the analyses and drafted the manuscript. All authors edited the manuscript and have read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors thank the developers of the EMOD disease modelling framework and its associated scripts and calibration capabilities, especially Dan Bridenbecker, Daniel J. Klein, Christopher Lorton and Clark Kirkman.

FUNDING

AB and ANA received funding from the Global Good Fund. MS received funding from NIMH K01MH115789. The funders had no role in the study design, analysis, interpretation of data, or the decision to submit the paper for publication.

REFERENCES

1. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736–88.
2. Dwyer-Lindgren L, Cork MA, Sligar A, Steuben KM, Wilson KF, Provost NR, et al. Mapping HIV prevalence in sub-Saharan Africa between 2000 and 2017. Nature. 2019;570(7760):189.
3. De Cock KM, Rutherford GW, Akhwale W. Kenya AIDS indicator survey 2012. J Acquir Immune Defic Syndr. 2014;66:S1–S2.
4. Borgdorff MW, Kwaro D, Obor D, Otieno G, Kamire V, Odongo F, et al. HIV incidence in western Kenya during scale-up of antiretroviral therapy and voluntary medical male circumcision: a population-based cohort analysis. Lancet HIV. 2018;5(5):e241–49.
5. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399–410.
6. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423–34.
7. Hodges-Mameletzis I, Dalal S, Msimanga-Radebe B, Rodolph M, Baggaley R. Going global: the adoption of the World Health Organization's enabling recommendation on oral pre-exposure prophylaxis for HIV. Sex Health. 2018;15(6):489–500.
8. Cáceres CF, Mayer KH, Baggaley R, O'Reilly KR. PrEP implementation science: state-of-the-art and research agenda. J Int AIDS Soc. 2015;18:20527.
9. Garnett GP, Hallett TB, Takaruza A, Hargreaves J, Rhead R, Warren M, et al. Providing a conceptual framework for HIV prevention cascades and assessing feasibility of empirical measurement with data from east Zimbabwe: a case study. Lancet HIV. 2016;3(7):e297–306.
10. Nunn AS, Brinkley-Rubinstein L, Oldenburg CE, Mayer KH, Mimiaga M, et al. Defining the HIV pre-exposure prophylaxis care continuum. AIDS. 2017;31(5):731–4.
11. Dunbar MS, Kripke K, Haberer J, Castor D, Dalal S, Mukoma W, et al. Understanding and measuring uptake and coverage of oral pre-exposure prophylaxis delivery among adolescent girls and young women in sub-Saharan Africa. Sex Health. 2018;15(6):513–21.
12. Sidibé M, Loures L, Samb B. The UNAIDS 90–90–90 target: a clear choice for ending AIDS and for sustainable health and development. J Int AIDS Soc. 2016;19(1):21133.
13. Bershteyn A, Gerardin J, Bridenbecker D, Lorton CW, Bloedow J, Baker RS. Implementation and applications of EMOD, an individual-based multi-disease modeling platform. Pathog Dis. 2018;76(5):fty059. https://doi.org/10.1093/femspd/fty059.
14. Kerr CC. Is epidemiology ready for Big Software? Pathog Dis. 2019;77(1):ftz006. https://doi.org/10.1093/femspd/ftz006.
15. Bershteyn A, Klein DJ, Eckhoff PA. Age-dependent partnering and the HIV transmission chain: a microsimulation analysis. J R Soc Interface. 2013;10(88):20130613.
16. Klein DJ, Bershteyn A, Eckhoff PA. Dropout and re-enrollment: implications for epidemiological projections of treatment programs. AIDS. 2014;28:S47–59.
17. Bershteyn A, Mutai KK, Akullian AN, Klein DJ, Jewell BL, Mwalili SM. The influence of mobility among high-risk populations on HIV transmission in Western Kenya. Infect Dis Model. 2018;3:97–106.
18. Jewell B, Akullian A, Camlin CS, Kaur M, Clark T, Charlebois E. Understanding epidemic contexts within the cluster-randomized SEARCH trial: a

clustering approach to grouping rural communities in East Africa according to epidemic characteristics. 9th IAS Conference on HIV Science; 2017. http://programme.ias2017.org/Abstract/Abstract/3031.
19. Jewell BL, Bershteyn A. Predicting HIV Incidence in the SEARCH Trial: A Mathematical Modelling Study. bioRxiv. 2018;376244. https://doi.org/10.1101/376244.
20. Akullian A, Onyango M, Klein D, Odhiambo J, Bershteyn A. Geographic coverage of male circumcision in western Kenya. Medicine. 2017;96:e5885.
21. Odek WO, Githuka GN, Avery L, et al. Estimating the size of the female sex worker population in Kenya to inform HIV prevention programming. PLoS ONE. 2014;9:e89180.
22. Kenya National Bureau of Statistics, USAID, United Nations Population Fund. United States Census Bureau. Kenya Population and Housing Census 2009.
23. United Nations Population Division. World population prospects [cited 2017 Sep 15]. Available from: https://esa.un.org/unpd/wpp/DataQuery/
24. Central Bureau of Statistics - CBS/Kenya, Ministry of Health - MOH/Kenya, ORC Macro. Kenya Demographic and Health Survey 2003. Calverton, MD: CBS, MOH, and ORC Macro; 2004 [cited 2019 Sep 15]. Available from: http://dhsprogram.com/pubs/pdf/FR151/FR151.pdf
25. Kenya National Bureau of Statistics - KNBS, National AIDS Control Council/Kenya, National AIDS/STD Control Programme/Kenya, Ministry of Public Health and Sanitation/Kenya, Kenya Medical Research Institute. Kenya Demographic and Health Survey 2008-09. Calverton, MD: KNBS and ICF Macro; 2010. Available from: http://dhsprogram.com/pubs/pdf/FR229/FR229.pdf
26. Alaeddini A, Klein DJ.Parallel simultaneous perturbation optimization. arXiv:170400223 [math]. April 2017 [cited 2018 Dec 1]. Available from: http://arxiv.org/abs/1704.00223
27. Alaeddini A, Klein DJ. Application of a second-order stochastic optimization algorithm for fitting stochastic epidemiological models. In: 2017 Winter Simulation Conference 2017:2194-2206.
28. PEPFAR dashboard [cited 2019 Jul 14] Available from: https://data.pepfar.gov/dashboards
29. AVAC. A snapshot of PrEP scale-up, registration and resources for Kenya. PrEPWatch [2019 Jul 14]. Available from: https://www.prepwatch.org/country/kenya/
30. Desai M, Field N, Grant R, McCormack S. State of the art review: recent advances in PrEP for HIV. BMJ. 2017;359:j5011.
31. Zablotska IB, Baeten JM, Phanuphak N, McCormack S, Ong J. Getting pre-exposure prophylaxis (PrEP) to the people: opportunities, challenges and examples of successful health service models of PrEP implementation. Sex Health. 2018;15(6):481–4.
32. Heffron R, Ngure K, Odoyo J, et al. Pre-exposure prophylaxis for HIV-negative persons with partners living with HIV: uptake, use, and effectiveness in an open-label demonstration project in East Africa. Gates Open Res. 2017;1:3–10.
33. AVAC. Ongoing and planned PrEP demonstration and implementation studies. 2019 [cited 2019 Jul 15]. Available from: https://www.avac.org/resource/ongoing-and-planned-prep-demonstration-and-implementation-studies
34. Coleman R. Setting the scene, setting the targets. The Joint United Nations Programme on HIV/AIDS prevention targets of 2016 and estimating global pre-exposure prophylaxis targets. Sex Health. 2018;15(6):485.
35. Koss CA, Ayieko J, Mwangwa F, et al. Early adopters of human immunodeficiency virus preexposure prophylaxis in a population-based combination prevention study in rural Kenya and Uganda. Clin Infect Dis. 2018;67(12):1853–60.
36. Mugo NR, Ngure K, Kiragu M, Irungu E, Kilonzo N. The preexposure prophylaxis revolution; from clinical trials to programmatic implementation. Curr Opin HIV AIDS. 2016;11(1):80–6.
37. Hanscom B, Janes HE, Guarino PD, Huang Y, Brown ER, Chen YQ, et al. Preventing HIV-1 Infection in women using oral pre-exposure prophylaxis: a meta-analysis of current evidence. J Acquir Immune Defic Syndr. 2016;73(5):606–8.
38. Mayer CM, Owaraganise A, Kabami J, Kabami J, Kwarisiima D, Koss CA, et al. Distance to clinic is a barrier to PrEP uptake and visit attendance in a community in rural Uganda. J Int AIDS Soc. 2019;22:e25276.
39. Hosek S, Pettifor A. HIV prevention interventions for adolescents. Curr HIV/AIDS Rep. 2019;16(1):120–8.
40. Minnis AM, Browne EN, Boeri M, et al. Young women's stated preferences for biomedical HIV prevention: results of a discrete choice experiment in Kenya and South Africa. J Acquir Immune Defic Syndr. 2019;80(4):394–403.
41. Alwin DF. Integrating varieties of life course concepts. J Gerontol B Psychol Sci Soc Sci. 2012;67B(2):206–20.
42. Ahmed N, Pike C, Bekker L-G. Scaling up pre-exposure prophylaxis in sub-Saharan Africa. Curr Opin Infect Dis. 2019;32(1):24–30.
43. Eakle R, Weatherburn P, Bourne A. Understanding user perspectives of and preferences for oral PrEP for HIV prevention in the context of intervention scale-up: a synthesis of evidence from sub-Saharan Africa. J Int AIDS Soc. 2019;22 Suppl 4:e25306.
44. Haberer JE, Kidoguchi L, Heffron R, Mugo N, Bukusi E, Katabira E, et al. Alignment of adherence and risk for HIV acquisition in a demonstration project of pre-exposure prophylaxis among HIV serodiscordant couples in Kenya and Uganda: a prospective analysis of prevention-effective adherence. J Int AIDS Soc. 2017;20(1):21842.
45. Velloza J, Baeten JM, Haberer J, Ngure K, Irungu E, Mugo NR, et al. Effect of depression on adherence to oral PrEP among men and women in East Africa. J Acquir Immune Defic Syndr. 2018;79(3):330–8.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Percentage of infections averted along prevention cascades for different target groups receiving PrEP in western Kenya. Arrows show absolute percentage decrease relative to the previous step of the cascade. Cascades are shown for the target group of adults age 15 to 29 in the four counties with HIV prevalence exceeding 10% (top left), AGYW ages 15 to 24 in the four counties with HIV prevalence exceeding 10% (top right), higher-risk men in all counties, including clients of sex workers and those at risk of having multiple sex partners or participation in transactional sex (bottom left), and higher-risk women in all counties, including sex workers and those at risk of multiple sex partners or participation in transactional sex (bottom right). All scenarios use a 20-year time horizon over 2020 to 2040.

Wilson EC et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25539
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25539/full | https://doi.org/10.1002/jia2.25539

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Disparities in the PrEP continuum for trans women compared to MSM in San Francisco, California: results from population-based cross-sectional behavioural surveillance studies

Erin C Wilson[1,§], Caitlin M Turner[1], Sean Arayasirikul[1], Marguerita Lightfoot[2], Susan Scheer[3], Henry F Raymond[4] and Albert Liu[5]

[§]**Corresponding author**: Erin C Wilson, Center for Public Health Research, San Francisco Department of Public Health, 25 Van Ness Ave., San Francisco, California 94102 USA. Tel: +1-415-554-9021. (erincwilson@gmail.com)

Abstract

Introduction: Although transgender women (trans women) often are conflated with men who have sex with men (MSM) in HIV research and services, there are distinct population differences that are important for implementing effective HIV prevention. Our objective was to examine pre-exposure prophylaxis (PrEP) disparities between the two populations and compare individual, social and structural factors that influence differences between MSM and trans women along the PrEP continuum.

Methods: We analysed data from two population-based studies, one with trans women (Trans*National Study, 2016 - 18) and the other with MSM (National HIV Behavioral Surveillance, 2017). Trans women were recruited via respondent-driven sampling and MSM using time location sampling. Key indicators of the PrEP continuum were evaluated, including awareness, health insurance, provider discussions, recent use and adherence. Associations were also examined for PrEP continuum indicators and structural barriers (e.g. employment, homelessness).

Results: Transwomen were more likely than MSM to be Latino/a (30.4% vs. 25.8%; prevalence ratio (PR)=1.08, 95% CI 1.02 to 1.14) or African American (7.1% vs. 4.5%; PR = 1.12, 1.02 to 1.24), live at or below the poverty limit (70.7% vs. 15.8%; PR = 1.47; 1.41 to 1.53), be unemployed (50.1% vs. 26.3%; PR = 1.18, 1.13 to 1.24), be homeless (8.4% vs. 3.5%; PR = 1.15, 1.06 to 1.25) and to have less than a college degree (39.6% vs. 10.5%, PR = 1.41, 1.34 to 1.48). Trans women were more likely than MSM to have health insurance (95.7% vs. 89.7%, PR = 1.17, 1.06 to 1.28), but less likely than MSM to have heard of PrEP (79.1% vs. 96.7%; PR = 0.77, 0.73 to 0.81), talked with a provider about PrEP (35.5% vs. 54.9%; PR = 0.87, 0.83 to 0.91) and less likely than MSM to have used PrEP in the past six months (14.6% vs. 39.8%; PR = 0.80, 0.76 to 0.84). Among PrEP users, trans women were less likely to report being adherent to PrEP than MSM (70.4% vs. 87.4%; PR = 0.80, 0.70 to 0.91).

Conclusions: We found PrEP disparities for trans women compared to MSM and the need for differentiated implementation strategies to meet the specific PrEP barriers trans women face. Inclusion of trans women's HIV risks is needed in CDC guidance for PrEP. Interventions to increase trans women's awareness of PrEP including at the provider and community level are also needed. Finally, programming that addresses trans women's barriers to housing and income is also needed to reduce PrEP disparities.

Keywords: transgender women; HIV; pre-exposure prophylaxis; PrEP; disparities

Received 27 September 2019; **Accepted** 8 May 2020

1 | INTRODUCTION

In San Francisco, men who have sex with men (MSM) and transgender women (trans women) comprised 84% of new HIV diagnoses in 2015. There has been a significant decline in new HIV infections among MSM, but new infections among trans women remain persistently high [1,2]. Data from population-based behavioural surveillance studies found that almost half (39%) of trans women may be living with HIV in San Francisco compared to a quarter of cisgender MSM (26.3%) [3,4]. Meanwhile, pre-exposure prophylaxis (PrEP) awareness and use are increasing among MSM in the United States (US) [5,6] and in San Francisco [7]. Yet data from San Francisco showed that only 14% of 233 trans women were aware of PrEP one year after FDA approval, and little data points to improvements.

Although trans women often are conflated with MSM in HIV research and services [8], there are distinct differences between these two populations that are important for effective HIV prevention. For example, trans women face a number of unique barriers that can impact PrEP engagement, including concerns about side effects and the effect of PrEP and

gender-affirming hormones [9], substance use and mental health issues [10,11], incarceration [12], lack of social support [10], trauma/violence [11,13], family rejection [14], HIV stigma [15], anti-trans stigma [16,17], economic vulnerability [18] and housing instability [19,20]. Distrust of medical institutions and lack of access to trans-friendly providers are also significant barriers to engaging trans people in prevention services [21]. San Francisco is unique in that it has numerous trans-specific health clinics and providers; yet trans women still face barriers to health care, including prior anti-trans discriminatory experiences in healthcare settings, limitations in protocols to meet their healthcare needs and difficulties with sexual and drug use disclosure tied to their immigration status and/or sex work engagement [22-24]. Also, some trans women may be concerned about the impact of PrEP on hormone therapy or be worried that hormones reduces the efficacy of PrEP [25].

Data-driven approaches to HIV prevention can identify gaps in the PrEP continuum and highlight intervention targets. We compared the PrEP continuum between MSM and trans women in San Francisco to determine if there are disparities in PrEP awareness, provider discussions, use and adherence. We also explored the individual, social and structural factors that influenced differences between MSM and trans women along the PrEP continuum using two population-based studies. Both studies were conducted in San Francisco in overlapping periods of time with the similar recruitment and PrEP indicators. Poisson binomial regression was used to compare prevalence of PrEP continuum outcomes between populations in general and based on PrEP eligibility per CDC guidelines. Findings from this analysis will inform data-driven efforts to address disparities in PrEP and differentiate PrEP delivery for trans women in San Francisco.

2 | METHODS

We conducted a secondary analysis of data from population-based studies of HIV-uninfected trans women enrolled in the Trans*National Study (June 2016 to March 2018) and HIV-uninfected MSM enrolled in the local National HIV Behavioral Surveillance (NHBS) MSM cycle (August to December 2017). Study recruitment and enrolment methods for both studies are described elsewhere [18,26]. Briefly, Trans*National is a population-based cohort study of HIV incidence among trans women in the San Francisco Bay Area. Trans women were recruited using respondent-driven sampling. Participants age 18 years old and older who identified as a gender other than man who were male sex assigned at birth were eligible to participate. NHBS was a population-based, cross-sectional study of MSM in San Francisco recruited using time location sampling. Participants who were age 18 years or older and ever had sex with another man were eligible to participate. Data for NHBS were collected between August and December of 2017. Both studies included English and Spanish-speaking participants. All participants provided written informed consent for the survey and HIV testing. Ethical approval for human subjects was obtained by the Human Research Protection Program (HRPP) at the University of California San Francisco.

2.1 | Measures

Baseline participant demographics were assessed and compared for Trans*National and NHBS participants. Age was a continuous variable, defined as participants' year of age at the time of taking the baseline survey. Race/ethnicity was an indicator variable of participants' self-reported racial/ethnic identities. Categories were defined according to Office of Management and Budget standards [27] and further collapsed into the following categories: Black or African American (non-Hispanic or Latino/a), Latino/a or Hispanic, Other (non-Hispanic or Latino/a Asian, American Indian/Alaska Native, Native Hawaiian or other Pacific Islander, Other or multiracial) and White (non-Hispanic or Latino/a). Education level was categorized as possession of a high school degree, general education diploma or GED (i.e. a high school equivalency diploma for people who did not finish secondary education) or less versus having some college versus having a college degree or more. Participants provided their annual income. We re-coded income as below the poverty line (US $25,000), at or above the poverty line, or unknown based on the extremely low-income limit for affordable housing programmes in San Francisco [28]. Employment was dichotomized as either employed or unemployed. We also described and compared the prevalence of homelessness (i.e. living on the street or in a shelter, including living in a single room occupancy for the NHBS MSM cycle) and history of incarceration. We also examined healthcare access among participants in Trans*National and NHBS. We assessed whether participants saw a healthcare provider in the last 12 months, whether they currently had health insurance, and the type of insurance they possessed (public, private or a combination of public and private insurances). Sexual behaviours were also compared for trans women and MSM. Specifically, we examined number of condomless anal intercourse partners in the last six months, and the percent of participants' HIV-uninfected sexual partners who were on PrEP.

PrEP awareness was measured by asking participants, "Have you heard of PrEP before today?" Having talked to a provider about PrEP was asked as, "Have you discussed PrEP with your primary healthcare provider in the last 12 months?" PrEP use was considered having taken PrEP within the last six months. PrEP adherence was measured differently in each study. For Trans*National, we asked, "In the last seven days, how many days did you miss a dose of PrEP?," and in NHBS we used, "In the last 30 days, have you taken PrEP every day, almost every day, or less often?" Being adherent to PrEP was defined as having taken PrEP at least four times in the past week (Trans*National) or every day or almost every day (NHBS), a level of pill-taking associated with high levels of protection from HIV in prior studies [29,30]. In Trans*National, PrEP awareness and ever having used PrEP was assessed at baseline, whereas data on having ever talked to a provider about PrEP and PrEP adherence were assessed at the six-month follow-up assessment; for NHBS, these questions were asked at the one-time survey visit. PrEP candidacy also measured based on CDC guidelines for MSM because there are no trans-specific guidelines [31].

2.2 | Data analysis

The present analysis was restricted to trans women and MSM who were not living with HIV. Our Trans*National data set is a combination of socio-demographics and structural factors assessed at baseline, and PrEP indicators assessed at baseline and six months. Only trans women not living with HIV who completed every item measured for this analysis in their baseline and six-month follow-up assessment were included. Out of 428 HIV-negative participants at baseline, we retained 369 (86%) trans women who had completed their six-month assessments. Of the 497 MSM in NHBS who provided self-report of their HIV status, 399 MSM were included once we restricted to HIV-negative participants. We concatenated the MSM and trans women data sets, and adjusted for MSM versus trans women as an exposure variable in the comparison of outcomes.

First, we characterized the study samples by comparing socio-demographics and health care access among trans women and MSM using prevalence ratios (PRs) estimated from bivariable Poisson binomial regression models. Then, key steps of the PrEP continuum were evaluated using all data available within the restricted Trans*National (n = 369) and NHBS (n = 399) databases. These steps included PrEP awareness, discussing PrEP with a provider, PrEP use in the past six months and taking PrEP daily/almost daily (NHBS) or ≥4 times in the past week (Trans*National). Differences in PrEP continuum steps for trans women compared to MSM were also estimated with bivariable Poisson binomial regression models adjusting for race/ethnicity and homelessness, given the a priori differences hypothesized in study selection and PrEP outcomes by these factors for trans women compared to MSM. Controlling for race/ethnicity and homelessness was done to allow for an unbiased comparison between these two groups (i.e. MSM and trans women) given the differences in race/ethnicity diversity and homelessness and the importance of these factors on risk, especially for trans women [18,32].

Key steps in the PrEP continuum were also calculated among MSM and trans women considered candidates for PrEP based on CDC criteria [31], including: (1) being 18 years of age or older, (2) being HIV-negative, (3) having any male sex partners in the last six months and (4) having a non-monogamous HIV-negative male partner and having condomless anal intercourse or having an STD or having an HIV-positive primary partner. Prevalence ratios from Poisson binomial regression were used to compare prevalence of PrEP continuum outcomes for PrEP candidates who were trans women versus MSM.

3 | RESULTS

3.1 | Differences in socio-demographics and health care access between trans women and MSM

Trans women were significantly more likely than MSM to be Latino/a (30.4% vs. 25.8%; prevalence ratio [PR] = 1.08, 95% CI 1.01 to 1.14) or African American (7.1% vs. 4.5%; PR = 1.12, 1.02 to 1.24) than white (see Table 1). Trans women were significantly more likely than MSM to be living at or below the poverty level (70.7% vs. 15.8%; PR = 1.47; 1.41 to 1.53), unemployed (50% vs. 26%; PR = 1.18, 1.13 to 1.24) and homeless (8.4% vs. 3.5%; PR = 1.15, 1.06 to 1.25), and trans women were more likely to have ever been incarcerated than MSM (52.6% vs. 15.3%; PR = 1.31, 1.26 to 1.37). Trans women were also significantly more likely than MSM to have less than a college degree (PR = 1.41 for a high school degree or GED, and PR = 1.27 for some college or a technical degree).

In terms of health care, trans women were significantly more likely than MSM to have health insurance (95.7% vs. 89.7%, PR = 1.17, 1.06 to 1.28) and to have public rather than private health insurance (64.8% vs. 21.8%, PR = 1.35, 1.23 to 1.49), but significantly less likely than MSM to have seen a healthcare provider in the last 12 months (86.9% vs. 92.5%, PR = 0.91, 0.85 to 0.98).

3.2 | PrEP continuum among trans women compared to MSM overall

Trans women reported significant disparities along the PrEP continuum compared to MSM (see Figure 1). Significantly fewer trans women than MSM were aware of PrEP (292/369 = 79.1% vs. 386/399 = 96.7%, aPR = 0.83, 0.77 to 0.88, $p < 0.01$), had used PrEP within the last six months (54/369 = 14.6% vs. 159/399 = 39.9%, PR = 0.36, 0.28 to 0.47, $p < 0.01$), talked with a provider about PrEP (131/369 = 35.5% vs. 219/399 = 54.9%; PR = 0.62, 0.53 to 0.73, $p < 0.01$). Among the 54 trans women and 159 MSM PrEP users, trans women were less likely to report being adherent to PrEP (70.4% vs. 87.4%; PR = 0.82, 0.68 to 0.99, $p = 0.04$).

3.3 | PrEP candidacy for trans women and MSM

Over one-half of MSM in our data set would be considered PrEP candidates based on CDC criteria (212/399, 53.1%), but only 15.7% of trans women (58/369) would have been considered candidates. Based on CDC guidelines, significantly fewer trans women would be PrEP candidates due to fewer trans women than MSM reporting any male sexual partners in the last six months (157/369 = 42.5% vs. 277/369 = 69.4%, $p < 0.01$). Similarly, fewer trans women compared with MSM reported having one or more PrEP candidacy criteria (non-monogamous sex with a HIV-negative male partner and condomless anal intercourse; having a sexually transmitted disease; or having a primary partner who was living with HIV) (15.7% vs. 53.1%, $p < 0.01$).

3.4 | PrEP continuums among trans women and MSM candidates based on CDC criteria

Figure 1 depicts the PrEP continuum for MSM from the overall sample and from the PrEP-eligible sample; Figure 2 accomplishes this for trans women from the overall sample and from the PrEP-eligible sample. Of MSM PrEP candidates, 98.6% (209/212) were aware of PrEP, 69.3% (147/212) had talked with a provider about PrEP, 56.1% (119/212) had used PrEP in the last six months and 91.6% (109/119) of PrEP users reported being adherent to PrEP. Of trans women candidates, 87.9% (51/58) were aware of PrEP, 56.9% (33/58) had talked with their provider about PrEP, 25.9% (15/58) had used PrEP in the last six months and 60.0% (9/15) of PrEP users reported being adherent to PrEP. When comparing trans women and MSM candidates, there were significantly fewer trans women candidates aware of PrEP than MSM (87.9% vs.

Table 1. Participant characteristics for MSM in NHBS and trans women in Trans*National

	MSM		Trans women		Bivariable comparison	
	N	%	N	%	PR	95% CI
Total	399	100.00	369	100.00		
Demographic						
Age (years), Median & IQR	36	29 to 49	37	27 to 51	1.00	1.00 to 1.00
Race/ethnicity						
White	205	51.4	145	39.3	Ref	
Black or African American	18	4.5	26	7.1	1.12	1.02 to 1.24*
Hispanic/Latino/a	103	25.8	112	30.4	1.08	1.02 to 1.14*
Other	72	18.1	86	23.3	1.09	1.03 to 1.16**
Education						
Some college/technical degree	83	20.8	127	34.4	1.27	1.21 to 1.35**
College degree and above	274	68.7	96	26.0	Ref	
HS/GED or less	42	10.5	146	39.6	1.41	1.34 to 1.48**
Annual income						
Above poverty limit	335	84.0	99	26.8	Ref	
At or below poverty limit	63	15.8	261	70.7	1.47	1.41 to 1.53**
Employed						
No	105	26.3	185	50.1	1.18	1.13 to 1.24**
Yes	294	73.7	184	49.9	Ref	
Currently homeless						
No	385	96.5	338	91.6	Ref	
Yes	14	3.5	31	8.4	1.15	1.06 to 1.25**
Ever incarcerated						
No	337	84.5	175	47.4	Ref	
Yes	61	15.3	194	52.6	1.31	1.26 to 1.37**
Health care						
Saw a healthcare provider in the last 12 months						
No	30	7.5	46	12.5	Ref	
Yes	369	92.5	321	87.0	0.91	0.85 to 0.98*
Currently has health insurance						
No	41	10.3	16	4.3	Ref	
Yes	358	89.7	353	95.7	1.17	1.06 to 1.28**
Insurance type						
None	41	10.3	16	4.3	Ref	
Public	87	21.8	239	64.8	1.35	1.23 to 1.49**
Private	258	64.7	100	27.1	1.00	0.91 to 1.10
Public + private	13	3.3	6	1.6	1.03	0.86 to 1.23
Sexual behaviours & health outcomes						
# condomless anal intercourse partners, last six months	1	0 to 2	0	0 to 0	0.88	0.86 to 0.89**
Median and IQR						
Percent of HIV-uninfected partners on PrEP						
0	152	38.1	191	51.8	Ref	
(0, 25]	36	9.0	7	1.9	0.75	0.68 to 0.83**
(25, 50]	50	12.5	4	1.1	0.69	0.64 to 0.74**
(50, 75]	40	10.0	1	0.3	0.66	0.62 to 0.70**
(75, 100]	42	10.5	6	1.6	0.72	0.66 to 0.79**
No uninfected partner	79	19.8	160	43.4	1.07	1.02 to 1.1388

Percentages column-calculated out of total sample (n = 399 for NHBS; n = 369 for T × N). CI, 95% confidence interval; PR, crude prevalence ratio from Poisson binomial regression comparing prevalence of PrEP continuum steps for trans women to that for MSM; Ref, reference group.
*$p < 0.05$.
**$p < 0.01$. MSM: men who have sex with men; HS: high school; GED: General Educational Development; PrEP: pre-exposure prophylaxis; NHBS: National HIV Behavioral Surveillance

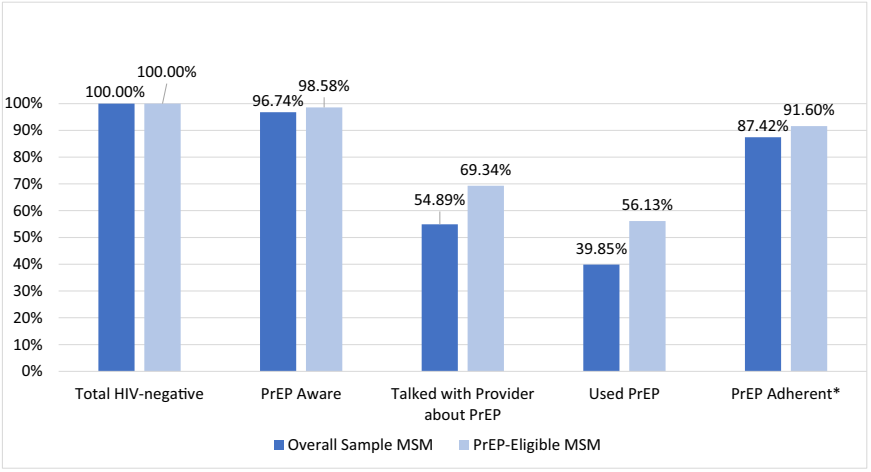

Figure 1. PrEP continuum indicators for MSM, overall and by PrEP-eligibility, San Francisco, USA, 2016/2017.
*Denominator: those who reported using PrEP in the last six months. MSM, men who have sex with men; PrEP, pre-exposure prophylaxis

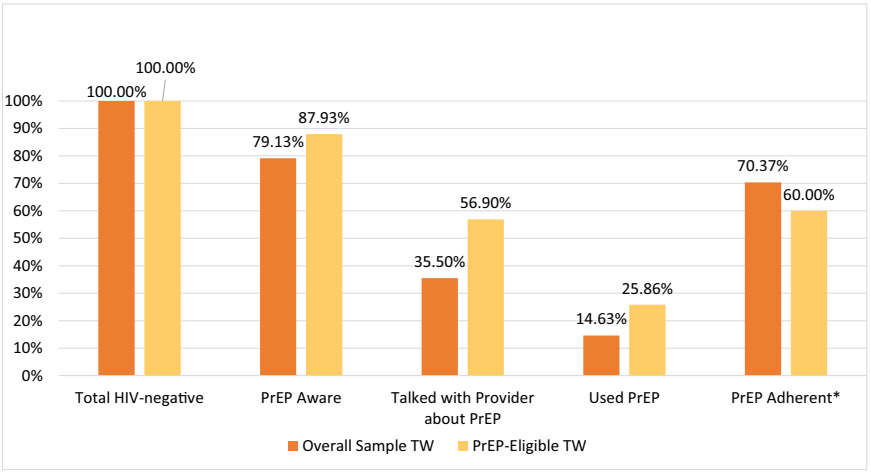

Figure 2. PrEP continuum indicators for trans women (TW), overall and by PrEP-eligibility, San Francisco, USA, 2016/2017.
*Denominator: those who reported using PrEP in the last six months. PrEP, pre-exposure prophylaxis

98.6%, aPR = 0.90, CI = 0.81 to 0.99, $p = 0.04$), and significantly fewer trans women than MSM candidates who had used PrEP (25.9% vs. 56.1%) in the last six months (aPR = 0.50, CI = 0.31 to 0.78, $p < 0.01$) after adjusting for race/ethnicity and homelessness. There were no significant adjusted differences in the prevalence of trans women vs. MSM who had spoken to their provider about PrEP (56.9% vs. 69.3%, aPR = 0.85, CI-.66 to 1.09, $p = 0.19$) or of being adherent to PrEP if taking it (60% vs. 91.6%, aPR = 0.79, CI = 0.58 to 1.08, $p = 0.14$).

4 | DISCUSSION

Our data point to marked disparities in the PrEP continuum for trans women compared to MSM in San Francisco. Data on lower awareness among trans women are consistent with other local research showing that trans women did not believe PrEP was for them because PrEP social marketing campaigns initially focused exclusively on MSM in San Francisco [8]. Conversely, a PrEP campaign inclusive of trans women in Chicago, Illinois did not find differences in awareness between MSM and trans women [33]. Low reporting of trans women's participation in efficacy trials may have also impacted the community's awareness of PrEP [34].

Provider willingness to prescribe and healthcare avoidance due to stigma may have presented additional barriers to awareness and uptake of PrEP among trans women. Research finds that providers support the provision of PrEP as a HIV prevention public health intervention, but knowledge, acceptance and willingness to prescribe it has been limited [35]. Many providers also do not offer PrEP in the course of their clinical practice [36]. Lower education was also found among trans women in our study compared to MSM, which may have impacted trans women's health literacy and power to engage in a discussion with providers about PrEP [37]. Trans women in our study were also less likely than MSM to have seen a health care provider in the last year, despite having higher

levels of health insurance. Studies have found that trans women face considerable stigma from medical providers, which may cause healthcare avoidance [38,39]. Discrimination from HIV care providers created reluctance of African American trans women in one study to see their doctor [40]. Healthcare avoidance may have also been precipitated by fear of disclosing trans identity, lack of cultural competence by providers or structural barriers like transportation costs [41,42]. Trans women may also have avoided asking for PrEP because of discomfort discussing sexual and drug use behaviours with their primary care providers [37]. Provider barriers and healthcare avoidance among trans women are an important focus of efforts to better engage trans women in PrEP.

Although the two data sets are different for MSM and trans women, they each point to factors that influenced PrEP awareness, access and uptake for the respective populations that allow for comparisons. Structural barriers of having low income, unemployment, homelessness and incarceration were all significantly more prevalent among trans women than MSM. More than half of trans women in our sample had been previously incarcerated compared to 15% of MSM. High incarceration among trans women in our sample is consistent with findings from other studies of trans women [43,44]. Having a history of incarceration may have impacted trans women's current housing, income and employment opportunities. The elevated presence of competing priorities for survival from lack of income may have limited trans women's awareness or interest in PrEP. Structural barriers may have also impacted adherence among those on PrEP. Trans women reported disproportionately high homelessness compared to MSM. Unstable housing was similarly a barrier to viral suppression among trans women in a recent analysis from San Francisco [32]. Not having a place to store and privately take medication may explain the lower PrEP adherence among trans women compared to MSM in our study [45].

We also found that significantly fewer trans women would be considered candidates for PrEP compared to MSM based on CDC guidelines. Research is increasingly uncovering that HIV transmission among trans women is varied and different from MSM [46]. CDC guidelines for the population given the high HIV prevalence of HIV and specific risks trans women face remain inadequate [32].

The primary limitation to this study is that it was not designed to compare the PrEP continuum in these populations. Measures, and therefore, data compared for this analysis had differences in how the survey questions were asked in Trans*National compared to NHBS. For example the adherence measure from the sample of trans women asked how many days participants took their medications in the last week. We tried to address differences in how the data were captured by creating measures as conservatively as possible. This measure was then re-categorized to a month-long recall window to be comparable to the MSM sample, and re-grouped to be qualitatively comparable to the "every day or almost every day" versus "less often" language used in the survey of MSM. It is possible that trans women's adherence fluctuated week to week, and therefore those who reported four to seven days of PrEP, but actually averaged 16 days of PrEP in the last 30 would be misclassified as PrEP adherent. Even so, this would actually over-represent the number of trans women who were PrEP adherent, and therefore produce more conservative estimates for the hypothesized differences between trans women and MSM. Thus, the disparity in PrEP adherence that we found may actually be more severe and stronger in magnitude, but our conclusion would remain qualitatively the same (i.e. that MSM are more adherent to PrEP than trans women). For the PrEP-eligible sample, this misclassification could have biased results toward the null and may, in addition to the smaller number of trans women in this restricted analysis, explain why we did not find statistically significant differences in PrEP adherence for PrEP-eligible MSM compared to PrEP-eligible trans women. Also, study data collection periods overlapped and were not entirely synced, which we could not account for in the measures or analysis. All PrEP continuum indicators were by self-report, including PrEP use and adherence, so we do not know conclusively if PrEP was used and adhered to at levels we observed in each population. Lastly, for the comparison of PrEP use and adherence levels between MSM and trans women, there are power limitations given that only 15 trans women reported using PrEP. Despite limitations, this data-informed approach to assessing the PrEP continuum was a useful tool for identifying PrEP disparities between trans women and MSM and helped identify potential points of intervention.

5 | CONCLUSIONS

Our study points to the need for differentiated PrEP implementation strategies to meet the barriers trans women face that are different from MSM. Inclusion of trans women in PrEP campaigns are needed to increase awareness. Changes to CDC guidelines for PrEP that are based on evidence regarding trans women's HIV risks may positively impact provider knowledge and interest in prescribing PrEP to trans women [47]. Alternatively, PrEP accessibility could be offered to any trans woman who wants it and does not demonstrate medical contraindications. This approach is well justified given high HIV prevalence and persistent HIV incidence in this disproportionately impacted population [2].

New delivery models, like pharmacy-delivered PrEP could address provider barriers and trans women's justifiable healthcare avoidance [48,49]. Pharmacy-delivered PrEP programs will have to accept public health insurance and facilitate application to PrEP access programs if they are to be inclusive of trans women in San Francisco. PrEP-only clinics for trans women may mitigate barriers related to anticipated discrimination or discomfort discussing sexual health and drug use with primary care providers. Structural barriers will also need to be addressed. Trans women most at risk of HIV are those facing daily threats to their survival. In order for trans women to prioritize HIV prevention and access it, interventions will need to address trans women's housing and income needs as well. Finally, inclusion of trans women in HIV prevention safety and efficacy trials from the outset [34] is needed to ensure their equitable access to the next generation of biomedical prevention.

AUTHORS' AFFILIATIONS

[1]Center for Public Health Research, San Francisco Department of Public Health, San Francisco, CA, USA; [2]Division of Prevention Science, Center for AIDS Prevention Studies, University of California, San Francisco, CA, USA; [3]HIV Epidemiology, San Francisco Department of Public Health, San Francisco, CA, USA;

[4]Rutgers University, New Jersey, USA; [5]Bridge HIV, San Francisco Department of Public Health, San Francisco, CA, USA

AUTHORS' CONTRIBUTIONS

ECW and AL designed the study. CMT conducted the analysis and wrote the results. ML, SS, HFR and SA reviewed all results and contributed to writing the manuscript. All authors reviewed and approved the final version.

ACKNOWLEDGEMENTS

The authors have no conflict of interest to declare. We acknowledge the trans women and MSM participants who gave their time and information to the respective studies from which these data were drawn.

FUNDING

Funding for this project was provided through an administrative supplement from the National Institute of Mental Health, award #P30MH062246.

REFERENCES

1. (SFDPH) SFDoPH. HIV semi-annual report December, 2018. 2018.
2. McFarland W, Wesson P, Turner C, Lin J, Veras MA, Yan H, et al. High HIV incidence among young and racial/ethnic minority transgender women in San Francisco: results of a longitudinal cohort study. J Acquir Immune Defic Syndr. 2020;84(1),e7–10.
3. Snowden JM, Chen YH, McFarland W, Raymond HF. Prevalence and characteristics of users of pre-exposure prophylaxis (PrEP) among men who have sex with men, San Francisco, 2014 in a cross-sectional survey: implications for disparities. Sexually transmitted infections. 2017;93(1):52–55.
4. Santos GM, Wilson EC, Rapues J, Macias O, Packer T, Raymond HF. HIV treatment cascade among transgender women in a San Francisco respondent driven sampling study. Sexually transmitted infections. 2014;90(5):430–3.
5. Raifman J, Dean LT, Montgomery MC, Almonte A, Arrington-Sanders R, Stein MD, et al. Racial and ethnic disparities in HIV Pre-exposure prophylaxis awareness among men who have sex with men. AIDS Behav. 2019;23(10):2706–9.
6. Schueler K, Ferreira M, Nikolopoulos G, Skaathun B, Paraskevis D, Hatzakis A, et al. Pre-exposure prophylaxis (PrEP) awareness and use within high HIV TRANSMISSION NETWORKs. AIDS Behav. 2019;23(7):1893–903.
7. Chen YH, Guigayoma J, McFarland W, Snowden JM, Raymond HF. Increases in pre-exposure prophylaxis use and decreases in condom use: behavioral patterns among HIV-negative san Francisco men who have sex with men, 2004–2017. AIDS Behav. 2019;23(7):1841–5.
8. Sevelius JM, Keatley J, Calma N, Arnold E. 'I am not a man': trans-specific barriers and facilitators to PrEP acceptability among transgender women. Glob Public Health. 2016;11(7–8):1060–75.
9. Sevelius J, Johnson M. A Qualitative Investigation of Barriers to Treatment Initiation and Engagement among Transgender Women Living with HIV. 8th International Conference on HIV Treatment and Prevention Adherence; June, 2013; Miami Beach, FL.
10. Mereish EH, O'Cleirigh C, Bradford JB. Interrelationships between LGBT-based victimization, suicide, and substance use problems in a diverse sample of sexual and gender minorities. Psychol Health Med. 2014;19(1):1–13.
11. Nemoto T, Bodeker B, Iwamoto M. Social support, exposure to violence and transphobia, and correlates of depression among male-to-female transgender women with a history of sex work. Am J Public Health. 2011;101 (10):1980–8.
12. Erickson M, Shannon K, Sernick A,Pick N, Ranville F, Martin RE, et al. Women, incarceration and HIV: a systematic review of HIV treatment access, continuity of care and health outcomes across incarceration trajectories. AIDS. 2019;33(1):101–11.
13. Kenagy GP. Transgender health: findings from two needs assessment studies in Philadelphia. Health Soc Work. 2005;30(1):19–26.
14. Wilson EC, Iverson E, Garofalo R, Belzer M. Parental support and condom use among transgender female youth. J Assoc Nurs AIDS Care. 2012;23(4):306–17.
15. Ackerley CG, Poteat T, Kelley CF. Human immunodeficiency virus in transgender persons. Endocrinol Metab Clin North Am. 2019;48(2):453–64.
16. Kosenko K, Rintamaki L, Raney S, Maness K. Transgender patient perceptions of stigma in health care contexts. Med Care. 2013;51(9):819–822.
17. Logie CH, James L, Tharao W, Loutfy MR. HIV, gender, race, sexual orientation, and sex work: a qualitative study of intersectional stigma experienced by HIV-positive women in Ontario, Canada. PLoS Med. 2011;8:e1001124.
18. Raymond HF, Wilson EC, Packer T, Ick T, Lin J, McFarland W. High and stable human immunodeficiency virus prevalence among transwomen with low income recruited with respondent-driven sampling, San Francisco, 2010–2016. Sex Transm Dis. 2019;46(2):118–24.
19. Wilson EC, Turner C, Arayasirikul S, Woods T, Nguyen T, Lin R, et al. Housing and income effects on HIV-related health outcomes in the San Francisco Bay Area - findings from the SPNS transwomen of color initiative. AIDS Care. 2018;30(11):1356–9.
20. Jalil EM, Wilson EC, Luz PM, Velasque L, Moreira RI, Castro CV, et al. HIV testing and the care continuum among transgender women: population estimates from Rio de Janeiro, Brazil. J Int AIDS Soc. 2017;20(1):21873.
21. Cruz TM. Assessing access to care for transgender and gender nonconforming people: a consideration of diversity in combating discrimination. Soc Sci Med. 2014;110:65–73.
22. Angela Davidson JF, Freeman Mark, Lin Royce, Martinez Linette, Monihan Mary, Porch Maria, et al. Tom Waddell Health Center protocols for hormonal reassignment of gender. Tom Waddell Health Center. 2013.
23. Melendez RM, Pinto RM. HIV prevention and primary care for transgender women in a community-based clinic. J Assoc Nurs AIDS Care. 2009;20(5):387–97.
24. Sevelius JM, Patouhas E, Keatley JG, Johnson MO. Barriers and facilitators to engagement and retention in care among transgender women living with human immunodeficiency virus. Ann Behav Med. 2014;47(1):5–16.
25. Deutsch MB, Glidden DV, Sevelius J, Sevelius J, Keatley J, McMahan V, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. Lancet HIV. 2015;2:e512–9.
26. Raymond HF, Snowden JM, Guigayoma J, McFarland W, Chen YH. Community levels of PrEP Use among men who have sex with men by race/ethnicity, San Francisco, 2017. AIDS Behav. 2019;23(10):2687–93.
27. Office of Management and Budget. Office of Management and Budget. Revisions to the standards for the classification of federal data on race and ethnicity. Federal Registrar; 1997.
28. Housing and Urban Development (HUD). FY 2018 income limits documentation system. 2019. [cited 2019 Jun 28]. Available from: https://www.huduser.gov/portal/datasets/il/il2018/2018summary.odn?states=%24states%24&data=2018&inputname=&stname=%24stname%24&statefp=%24statefp%24&year=2018&selection_type=%24selection_type%24
29. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama J R, Guanira J V, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med. 2012;4(151): 151ra125.
30. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis. 2014;14(9):820-9.
31. (CDC) CfDCaP. Pre-exposure Prophylaxis (PrEP). 2018 [cited 2018 May 3]. Available at: https://www.cdc.gov/hiv/risk/prep/index.html
32. Baguso GN, Turner CM, Santos GM, Raymond HF, Dawson Rose C, Lin J, et al. Successes and final challenges along the HIV care continuum with transwomen in San Francisco. J Int AIDS Soc. 2019;22:e25270.
33. Phillips G II, Raman AB, Felt D, McCuskey D J, Hayford C S, Pickett J, et al. PrEP4Love: the role of messaging and prevention advocacy in PrEP attitudes, perceptions, and uptake among YMSM and transgender women. J Acquir Immune Defic Syndr. 2020;83(5):450–6.
34. Grant RM, Sevelius JM, Guanira JV, Aguilar JV, Chariyalertsak S, Deutsch MB. Transgender women in clinical trials of pre-exposure prophylaxis. J Acquir Immune Defic Syndr. 2016;72 Suppl 3:S226–9.
35. Krakower DS, Mayer KH. The role of healthcare providers in the roll out of preexposure prophylaxis. Curr Opin HIV AIDS. 2016;11(1):41–8.
36. Calabrese SK, Willie TC, Galvao RW, Tekeste M, Dovidio JF, Safon CB, et al. Current US guidelines for prescribing HIV pre-exposure prophylaxis (PrEP) disqualify many women who are at risk and motivated to use PrEP. J Acquir Immune Defic Syndr. 2019;81(4):395–405.
37. Brookfield S, Dean J, Forrest C, Jones J, Fitzgerald L. Barriers to accessing sexual health services for transgender and male sex workers: a systematic qualitative meta-summary. AIDS Behav. 2020;24(3):682–96.
38. Poteat T, German D, Kerrigan D. Managing uncertainty: a grounded theory of stigma in transgender health care encounters. Soc Sci Med. 2013;84:22–9.
39. Wilson EC, Jalil E, Castro C, Fernandez NM, Kamel L, Grinsztejn B. Discrimination in the health care system as the main barrier to PrEP implementation withfor Transwomen in the context of Brazil. Global Public Health. 2017.
40. Wilson EC, Arayasirikul S, Johnson K. Access to HIV care and support services for African American transwomen living with HIV. Int J Transgender. 2014;14(4):182–195.

41. Roberts TK, Fantz CR. Barriers to quality health care for the transgender population. Clin Biochem. 2014;47(10–11):983–7.
42. Safer JD, Coleman E, Feldman J, Garofalo R, Hembree W, Radix A, et al. Barriers to healthcare for transgender individuals. Curr Opin Endocrinol Diabetes Obes. 2016;23(2):168–71.
43. Hughto JMW, Reisner SL, Kershaw TS,Altice Fredrick L, Biello KB, Mimiaga MJ, et al. A multisite, longitudinal study of risk factors for incarceration and impact on mental health and substance use among young transgender women in the USA. J Public Health. 2019;41(1):100–9.
44. Reisner SL, Bailey Z, Sevelius J. Racial/ethnic disparities in history of incarceration, experiences of victimization, and associated health indicators among transgender women in the U.S. Women Health. 2014;54(8):750–67.
45. Philbin MM, Parker CM, Parker RG, Wilson PA, Garcia J, Hirsch JS. The Promise of pre-exposure prophylaxis for black men who have sex with men: an ecological approach to attitudes, beliefs, and barriers. AIDS Patient Care and STDs. 2016;30(6):282–90.
46. Deane KD, Samwell Ngalya P, Boniface L, Bulugu G, Urassa M. Exploring the relationship between population mobility and HIV risk: Evidence from Tanzania. Glob Public Health. 2018;13(2):173–88.
47. Wilson EC, Jin H, Liu A, Raymond HF. Knowledge, indications and willingness to take pre-exposure prophylaxis among transwomen in San Francisco, 2013. PLoS One. 2015;10:e0128971.
48. Okoro O, Hillman L. HIV pre-exposure prophylaxis: Exploring the potential for expanding the role of pharmacists in public health. J Am Pharm Assoc. 2018;58(4):412–20.e3.
49. Farmer EK, Koren DE, Cha A, Grossman K, Cates DW. The Pharmacist's Expanding role in HIV pre-exposure prophylaxis. AIDS Patient Care STDs. 2019;33(5):207–13.

Dumchev K et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25509
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25509/full | https://doi.org/10.1002/jia2.25509

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Operationalizing the HIV prevention cascade for PWID using the integrated bio-behavioural survey data from Ukraine

Kostyantyn Dumchev[1,§], Yana Sazonova[2], Pavlo Smyrnov[2*], Olga Cheshun[2*], Oksana Pashchuk[2*], Tetiana Saliuk[2*] and Olga Varetska[2]

[§]**Corresponding author**: Kostyantyn Dumchev, 5 Mala Zhytomyrska Str., Office 61a, Kyiv, 01001 Ukraine. Tel. +38 044 222 6271. (dumchev@uiphp.org.ua)
*These authors have contributed equally to the work.

Abstract

Introduction: People who inject drugs (PWID) remain at high risk of HIV in many countries. The HIV prevention cascades have been proposed to replicate the success of the treatment cascades and reinvigorate the prevention programmes through improved monitoring, planning and delivery. We adapted the cascade framework to the PWID context in Ukraine, assessed gaps and analysed factors associated with achieving "access" and "effective use" outcomes.

Methods: Self-reported data on the use of prevention services and risk behaviours from the 2017 integrated bio-behavioural survey among PWID in Ukraine were used to construct cascades for needle/syringe and condom programmes (NSP and CP). Socio-demographic and behavioural variables were evaluated as potential correlates of cascade outcomes.

Results: The NSP cascade analysis included 7815 HIV-negative PWID. Motivation to use clean syringes was not assessed and assumed at 100%. Access to clean syringes through NSP in the past 12 months was reported by 2789 participants (35.7%). Effective use of syringes (no sharing in the past 30 days) was reported by 7405 participants (94.8%). NSP access was higher among women, individuals older than 44, and mixed drug users; while effective use was reported more frequently by men and opioid users, with no difference by age. The CP cascade analysis included 6606 (85%) of the HIV-negative PWID who had sex in the past three months. Of those, 2282 (34.5%) received condoms, and 1708 (25.9%) reported consistent use with all partners in the past three months. Older PWID and mixed-drug users accessed condoms more frequently; whereas younger subgroups and opioid users used them more consistently.

Conclusions: Overall, the cascade framework was useful to describe the status of HIV prevention among PWID in Ukraine and to identify areas for improvement in the programming and evaluation of HIV prevention. Access to needle/syringe and condom programmes was substantially below the recommended levels. Effective use of clean syringes was reported by a vast majority of PWID, although likely affected by self-report bias; whereas consistent condom use was infrequent. Socio-demographic and behavioural variables showed significant associations in NSP and CP cascade analyses, with little consistency between the access and effective use outcomes.

Keywords: HIV prevention; prevention cascade; people who inject drugs; condoms; needle and syringe programmes; Ukraine

Received 7 October 2019; **Accepted** 20 April 2020

1 | INTRODUCTION

The number of new HIV infections is declining globally, although at a pace insufficient to reach the ambitious targets set by UNAIDS for 2020. Contrary to the global trend, some countries demonstrate an alarming growth of new infections. In Eastern Europe and Central Asia (EECA), the incidence has doubled since 2010 [1]. In EECA, and many other countries across the globe, new HIV cases remain highly concentrated among people who inject drugs (PWID) and their sexual partners [1-3].

Numerous interventions have been developed and proved to be efficacious in blocking all possible routes of HIV transmission in different populations [4]. However, their coverage, and thus the population-level effect, remain insufficient to achieve the global targets, prompting UNAIDS to announce a "prevention crisis."

In contrast, the progress in HIV treatment domain has been more pronounced. To a significant extent, it was achieved due to consolidated advocacy efforts instigated by the 90-90-90 target framework. In this framework, the key indicators are organized along the HIV treatment cascade, creating a simple and useful visualization of achievements and gaps at the main stages of HIV care [5]. This methodology was eagerly adopted by programme planners, advocacy groups, researchers and global policy makers [6].

The HIV prevention cascades have been proposed to replicate the success of the treatment cascades and reinvigorate

the prevention programmes through improved monitoring, planning and delivery [7,8]. The original concept proposed by Hargreaves and colleagues [9] was primarily informed by theory and data from the programmes addressing sexual transmission, such as condom distribution [10]. Considering other prevention methods, the authors acknowledged that some elements of the cascade may become irrelevant (e.g. adherence in voluntary medical male circumcision programmes [VMMC]) and advised to not "oversimplify HIV prevention" [8,9]. The diversity of target populations and corresponding prevention modalities was highlighted by some critical reviews [11], indicating that the multifaceted nature of HIV prevention is not fully compatible with the linear logic of the cascade approach.

Despite the apparent need to bolster HIV prevention, there is a notable scarcity of published literature on HIV prevention cascades. Aside from early publications on condom distribution, VMMC [10], and pre-exposure prophylaxis [12], there are a few conference abstracts [13] presenting cascades with actual program data. To the best of our knowledge, no previous publication has assessed an HIV prevention cascade for PWID, either theoretically or using real-world data.

Ukraine has the second largest HIV epidemic in Europe, which contributed about 11% of 141,553 newly diagnosed cases in the WHO European Region in 2018 [2]. The epidemic was initially driven by PWID, who continue to have the highest prevalence among all key populations (22.6% in 2017) and to play a key role in ongoing HIV transmission [14-16]. The prevention programme, supported by international donors, expanded rapidly to reach 226,469 individual PWID with the minimum prevention package in 2017 [17]. The package is based on WHO recommendations [18] and includes provision of syringes (typically limited to 10 per day), condoms (3 per day) and peer or social worker counselling. The quality of the Ukrainian prevention programme has earned positive reviews and has been recognized as best practice in Europe by WHO [19].

In this study, we address this gap and adopt the HIV prevention cascade framework to the context of PWID programming. Using integrated bio-behavioural survey data from Ukraine, we have constructed cascades and analysed factors associated with achieving or not achieving each stage of the continuum for two prevention interventions – needle and syringe programmes and condom distribution.

2 | METHODS

2.1 | Study design

For this study, we used data from the integrated bio-behavioural survey (IBBS) among PWID conducted in November–December of 2017. Details on IBBS methodology in Ukraine are available elsewhere [16,20]. In brief, the cross-sectional survey was conducted in 30 cities (all 24 regional centres and six larger cities of regional significance) using respondent-driven sampling. Eligibility criteria included presence of injection marks (verified by study personnel), self-reported injection drug use in the past 30 days, and self-reported age of 14 years or older. All participants completed an interviewer-administered questionnaire and provided blood samples for the HIV test and other assessments.

2.2 | Cascade formulation

We constructed two separate cascades for the core components of HIV prevention among PWID: needle/ syringe programmes (NSP) and condom programmes (CP).

According to the original framework [8-10], the first element of the prevention cascade is the *population at risk of HIV* and in need of the intervention. Accordingly, the NSP cascade consisted of HIV-negative individuals who inject drugs at least once in 30 days. Considering the limitations of self-reporting (see Discussion), we did not use risky injection practices (e.g. syringe sharing) as a criterion. The CP cascade was restricted to those PWID who are sexually active, that is, had at least one sexual partner in the past three months.

The second element of the cascade is generally conceptualized as *awareness* of HIV risk and *willingness (motivation)* to use prevention tools such as syringes and condoms. The IBBS in Ukraine did not assess the perception of personal HIV risk, nor did it assess the motivation to use the prevention tools; hence, we could not analyse this indicator. However, to retain this important step in the cascade, we assumed the motivation to use clean needles to be 100% as an injection with a new needle is less traumatic and in most cases PWID would prefer a new one if they have it available. In contrast, willingness to use condoms is not universal [21] and we, therefore, conservatively assumed the motivation to be equal to the next indicator.

In the next stage of the cascade, characterizing *access* to prevention, we included PWID who received a syringe or a condom free of charge in a prevention programme in the past 12 months. It is important to note that in Ukraine syringes are openly available for purchase in pharmacies, which is the main source of clean syringes for PWID since, in most cases, the prevention programmes cannot provide enough for each injection. Similarly, PWID can and do obtain condoms outside of the prevention programmes. The IBBS questionnaire did not include questions about access to prevention tools elsewhere, therefore our cascade indicators were limited to the access to services in the prevention programmes.

The final stage of the cascade reflects the *effective use* of the services, such as safe injection practice or protected sex. For the NSP cascade, we defined it as using only clean syringes in the past 30 days. For the CP cascade, the final indicator included PWID who always used condoms with all types of partners in the past three months.

2.3 | Statistical analysis

2.3.1 | Outcome variables

All analyses were conducted in a subsample of IBBS participants who tested negative in the rapid HIV test, conducted in accordance with the WHO testing guidelines for HIV diagnosis in high prevalence settings. Access to clean syringes or condoms in prevention programmes was based on responses to the following questions: "Have you received a syringe free of charge in the past 12 months?" and "Have you received condoms free of charge in the past 12 months?". Effective use of syringes was determined by one question: "During the past 30 days, have you injected drugs with a syringe previously used by another person?". Consistent use of condoms was determined if the participant

answered "Always" to the question, "How frequently did you use condom with this partner in the past three months?" for each of the four types of partners – regular, casual and commercial, as a client or a sex worker.

2.3.2 | *Predictors*

We used key socio-demographic and behavioural variables as potential predictors for the cascade outcomes, including: age, sex, education, marital status, monthly income, duration of injection drug use and drug type that was injected during the past 30 days. The drug type was categorized as: exclusive opioid use – heroin, opium, desomorphine, home-made opioids, illegal methadone or buprenorphine; exclusive stimulant use – amphetamines, methamphetamines, cocaine, synthetic cathinones ("bath salts"); mixed use of opioids and stimulants in any combination during the same time period or other drug use.

In the bivariate analysis, the association was tested using chi-square test. Variables significant at $p < 0.1$ level were included in the multivariable logistic regression analysis. The final model with the best fit was selected via a backward stepwise technique using Wald test. Explanatory variables were removed one at a time if they were not associated with an outcome at 5% level of significance. Age and sex variables were retained in all models, even when they did not have a significant association with the outcomes.

Data were analysed using SPSS v.23 (IBM Corporation, Armonk, NY, USA).

2.4 | Ethical approval

All procedures in studies involving human participants were performed in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Prior to enrolment into the study, all participants were provided with comprehensive information about the study and signed a consent form. The study was approved by the Institutional Review Board of the Ukrainian Institute on Public Health Policy (Kyiv, Ukraine) and was reviewed for human subject issues in the research determination process by the Centers for Disease Control and Prevention (Atlanta, GA, USA).

3 | RESULTS

Of the total 10,076 PWID recruited in the IBBS, 2,261 tested HIV positive and 7,815 tested HIV negative, resulting in 22.4% HIV prevalence. The median age of participants was 35 years (IQR 30 to 40) and 18% of the sample were women.

Figure 1 shows the needle/syringe programmes (NSP) cascade and Table 1 provides disaggregation by key socio-demographic and drug use strata. Receiving clean syringes from the prevention programmes at least once in the past 12 months was reported by 2789 of participants (35.7%), whereas the exclusive use of clean syringes in the past 30 days was reported by 7405 (94.8%). Both behaviours were reported by 2685 participants (36.2% of those using only clean syringes or 96.2% of those receiving the service). Among the subcategories, NSP access was significantly higher among women, older individuals, those with longer injection careers, those with lower income, and opioid or mixed drug users (as compared to exclusive stimulant users). There was no statistical difference by family status and education. All variables in the multivariable model, except monthly income, demonstrated an independent and significant effect. Effective use of prevention was more prevalent among men, those with higher education, lower income, and opioid users. There was no difference by age, injection duration, and family status. The multivariable models largely confirmed the results of the univariate analysis, except for the effect of income.

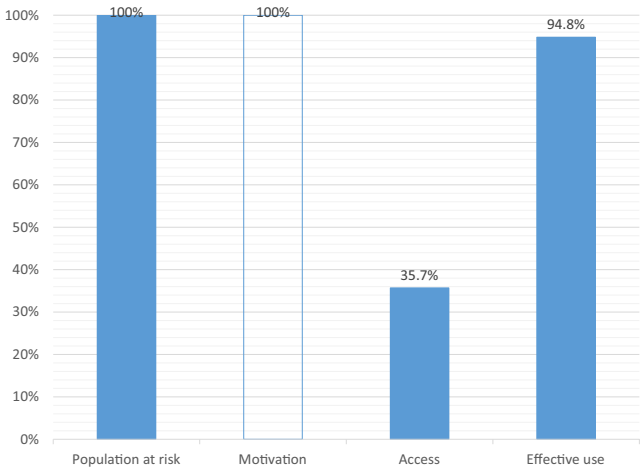

Figure 1. Needle/syringe programs cascade for HIV negative people who inject drugs in Ukraine. Population at risk is defined as people injecting drugs at least once in the past 30 days. Motivation is not measured and assumed at 100%. Access to service is defined as receiving syringes from prevention programs in the past 12 months. Effective use is defined as using only clean syringes in the past 30 days.

The condom programmes (CP) cascade is shown in Figure 2 and Table 2. The risk of sexual transmission, defined in this analysis as having at least one sexual partner in the past three months, was reported by 6606 (85%) of all HIV-negative PWID. Access to free condoms in the prevention programmes in the past 12 months was reported by 2282 (34.5%) of those at risk, which is only marginally lower than what was reported for NSP. Effective use of condoms, in contrast to syringes, was reported by only 1708 (25.9%) participants. Combination of access to services and effective use was reported by 673 participants, meaning that only 39.3% of all at-risk participants and 29.5% of those receiving the service report always using condoms. Receipt of condoms in prevention programmes in the past 12 months was higher among older individuals, those who have longer injection history, have lower income and are mixed drug users. These associations were confirmed in the multivariable model, where the effect of gender also became significant (aOR = 1.2 [95% CI 1.0 to 1.4] for women compared to men). Consistent condom use was higher among men, younger PWID, those with shorter injection history, living alone, having a lower income and among opioid users. The multivariable models confirmed the associations of consistent condom use with gender, age and family status.

Table 1. Needle/syringe programmes cascade and associated factors for HIV-negative people who inject drugs in Ukraine

	Population at Risk[a]	Access to service[b]						Effective use[c]					
					Multivariable model						Multivariable model		
	N	n	%	χ^2 *p*-value	AOR	95% CI	*p*-value	n	%	χ^2 *p*-value	AOR	95% CI	*p*-value
Total	7815	2789	35.7%					7405	94.8%				
Sex													
Male	6588	2310	35.1%	0.007	ref.			6278	95.3%	<0.001	ref.		
Female	1225	479	39.1%		1.4	1.2 to 1.6	<0.001	1127	92.0%		0.6	0.4 to 0.7	<0.001
Age													
≤24	656	130	19.8%	<0.001	ref.			619	94.4%	0.888	ref.		
25 to 44	6290	2292	36.4%		1.6	1.3 to 2.0	<0.001	5963	94.8%		0.9	0.7 to 1.3	0.719
≥45	869	367	42.2%		2.0	1.5 to 2.5	<0.001	823	94.7%		0.8	0.5 to 1.3	0.475
Injection duration													
≤2 years	716	127	17.7%	<0.001	ref.			676	94.4%	0.659			
>2 years	7078	2656	37.5%		2.3	1.8 to 2.8	<0.001	6711	94.8%				
Family status													
Live alone	3279	1164	35.5%	0.774				3111	94.9%	0.757			
Live with partner	4534	1625	35.8%					4294	94.7%				
Education													
<High school	1264	444	35.1%	0.843				1177	93.1%	0.01	0.6	0.4 to 0.8	0.002
High school	4893	1746	35.7%					4646	95.0%		0.8	0.6 to 1.1	0.222
>High school	1656	599	36.2%					1582	95.5%		ref.		
Monthly income													
<120 USD	3222	1228	38.1%	<0.001				3029	94.0%	0.03			
120 to 400 USD	3997	1381	34.6%					3815	95.4%				
401 to 800 USD	493	147	29.8%					468	94.9%				
>800 USD	101	33	32.7%					93	92.1%				
Type of drugs injected in 30 days													
Only opioids[d]	4788	1770	37.0%	<0.001	2.2	1.8 to 2.6	<0.001	4592	95.9%	<0.001	0.7	0.5 to 1.0	0.051
Only stimulants[e]	1053	232	22.0%		ref.			991	94.1%		ref.		
Mix or other[f]	1974	787	39.9%		1.8	1.6 to 2.2	<0.001	1822	92.3%		1.4	1.1 to 2.0	0.015

AOR, adjusted odds ratio; CI, confidence interval; USD: United States Dollars.

[a]People injecting drugs at least once in the past 30 days; [b]receiving syringes from prevention programmes in the past 12 months; [c]using only clean syringes in the past 30 days; [d]exclusive use of heroin, opium, desomorphine, home-made opioids, illegal methadone or buprenorphine;

[e]exclusive use of amphetamines, methamphetamines, cocaine, synthetic cathinones ("bath salts"); [f]use of opioids and stimulants in any combination during the same time period or other drug use.

Dumchev K et al. *Journal of the International AIDS Society* 2020, **23**(S3):e25509
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25509/full | https://doi.org/10.1002/jia2.25509

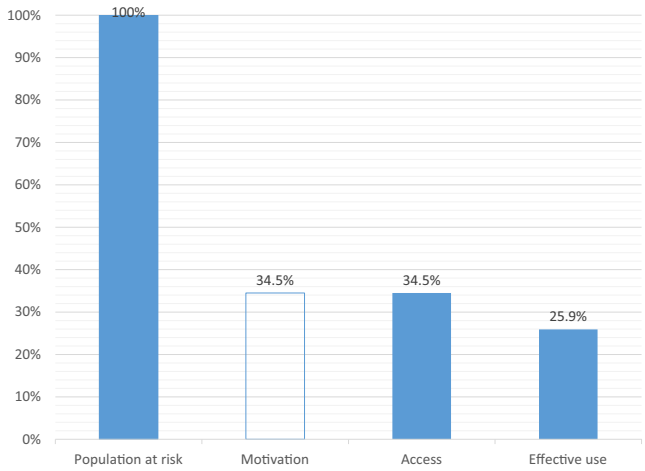

Figure 2. Condom programs cascade for HIV negative people who inject drugs in Ukraine. Population at risk is defined as people injecting drugs at least once in the past 30 days and having sex in the past 3 months. Motivation is not measured and assumed equal to the next indicator. Access to service is defined as receiving condoms from prevention programs in the past 12 months. Effective use is defined as always using condom with all partners in the past 3 months.

4 | DISCUSSION

4.1 | Cascade status and implications for programming

In this analysis, we applied the HIV prevention cascade framework to the data from the 2017 IBBS among PWID in Ukraine. Overall, the analysis was helpful to better understand the current status of HIV prevention among PWID in Ukraine. The cascade demonstrated that access to prevention interventions remains suboptimal, with just over one third of HIV-negative PWID accessing NSP to receive syringes in the past 12 months. The data also showed that the majority of PWID obtain clean injection equipment elsewhere, leading to the low reported level of syringe sharing. This last indicator has to be interpreted with caution, considering the self-reporting bias (see below).

Access to CP was similar to that of NSP, explained by the fact that these services are usually co-provided. However, in contrast to clean syringes, consistent use of condoms was reported by only a quarter of sexually active PWID. Similar to clean syringes, the majority of condom users were not covered by CP and purchased condoms at their own expense.

It should be noted that the service access indicators were based on the least stringent definition of receiving service at least once in the past 12 months. Applying more rigorous criteria, such as frequency or regularity, would decrease the estimates substantially.

The subgroup analysis revealed that uptake of NSP was higher among women, older and more experienced injectors, as well as users of opioids or a combination of drugs. However, the effective syringe use was slightly less frequent among women and mixed drug users. CP was more frequently accessed by older participants with longer injection history, and by opioid and mixed drug users. This also did not translate into higher rate of effective use, which was notably higher among males, young people and those living alone. Overall, the associations we found between the age and drug type with programme access and risk behaviour is consistent with other evidence indicating that PWID with riskier behaviour are seeking prevention services more intensively than those with lower risk [22,23].

Our findings confirm that HIV prevention efforts among PWID should be intensified through increase in both NSP and CP, particularly among specific subgroups such as young people and stimulant users. Unlike with treatment, which is indicated for all HIV-infected, universal coverage by most prevention interventions is not realistically attainable and may also not be necessary to achieve the reduction of incidence on the population level. The WHO tool [18] recommends a 60% NSP coverage target with at least 200 syringes per person per year, albeit recognizing that this number may not be sufficient to provide clean syringes for each injection.

4.2 | Framework adaptation and recommendations for evaluation

While the proposed cascade framework should be applicable to all key populations and prevention methods [8], we faced substantial challenges in adapting it to the PWID context. At the first step of the NSP cascade, the population in need of prevention services could be defined in several ways. We used the current definition of the PWID key population in Ukraine, which entails using drugs by injection at least once in the past month, regardless of specific behaviours directly associated with HIV transmission risk (e.g. syringe sharing). It can be speculated that other people who inject less frequently or are at risk of relapsing to injection (non-injection drug users, OAT patients) may also benefit from prevention services. Determination of sexual risk is no less complex, as it is affected not only by frequency of activity, but also by types of partners, specific practices, and use of protection. Similarly to non-injectors, people who have not had sex in the recent past may also re-engage in sexual activity and thus should not be excluded from condom provision.

Moreover the framework assumes that only HIV-negative population should be included in the cascade. In reality, the prevention programmes for PWID never distinguish clients based on HIV status and equally serve HIV positive, HIV negative, and people with unknown HIV status because risk reduction of HIV acquisition is as important as reduction of transmissibility among people living with HIV. From this standpoint, the inclusion of HIV-positive PWID in the cascade and analysis of HIV status as one of the factors influencing access to and effective use of services may be justifiable.

For the next step of the cascade, we assumed the motivation to use clean needles to be 100% because injecting with a new needle is less traumatic. Some studies have found that PWID may intentionally share needles in some circumstances [24,25]. However, reports of such practices became less frequent in the era of the grown HIV epidemic and nearly universal knowledge of HIV risk among PWID [21]. Motivation to use condoms, in contrast, is determined by other factors and is far from universal, leading to an assumption that only those who received the service were motivated.

The service access indicator appeared to be the most challenging to operationalize. Unlike treatment, prevention tools are available outside of prevention programmes and are widely used for purposes other than HIV prevention. The IBBS in Ukraine did not measure access to prevention tools

Table 2. Condom programmes cascade for HIV-negative people who inject drugs in Ukraine

	Population at risk[a]	Access to service[b]						Effective use[c]					
					Multivariable model						Multivariable model		
	N	n	%	χ^2 *p*-value	AOR	95% CI	*p*-value	n	%	χ^2 *p*-value	AOR	95% CI	*p*-value
Total	6606	2282	34.5%					1708	25.9%				
Sex													
Male	5543	1902	34.3%	0.379	ref.			1524	27.5%	<0.001	ref.		
Female	1063	380	35.7%		1.2	1.0 to 1.4	0.012	184	17.3%		0.7	0.5 to 0.8	<0.001
Age													
<25	574	130	22.6%	<0.001	ref.			188	32.8%	<0.001	ref.		
25 to 44	5427	1907	35.1%		1.3	1.1 to 1.7	0.009	1395	25.7%		0.7	0.5 to 0.8	<0.001
≥45	605	245	40.5%		1.6	1.2 to 2.1	0.001	125	20.7%		0.5	0.4 to 0.6	<0.001
Injection duration													
≤2 years	623	116	18.6%	<0.001	ref.			187	30.0%	0.014			
>2 years	5967	2162	36.2%		2.2	1.7 to 2.7	<0.001	1519	25.5%				
Family status													
Live alone	2241	771	34.4%	0.87				907	40.5%	<0.001	ref.		
Live with partner	4365	1511	34.6%					801	18.4%		0.3	0.3 to 0.4	<0.001
Education													
<High school	1014	339	33.4%	0.65				253	25.0%	0.182			
High school	4156	1437	34.6%					1057	25.4%				
>high school	1436	506	35.2%					398	27.7%				
Monthly income													
<120 USD	2528	933	36.9%	0.002				661	26.1%	0.01			
120 to 400 USD	3538	1192	33.7%					940	26.6%				
401 to 800 USD	446	129	28.9%					88	19.7%				
>800 USD	94	28	29.8%					19	20.2%				
Type of drugs injected in 30 days													
Only opioids[d]	3964	1407	35.5%	<0.001	1.9	1.6 to 2.3	<0.001	1071	27.0%	0.03			
Only stimulants[e]	920	213	23.2%		ref.			220	23.9%				
Mix or other[f]	1722	662	38.4%		1.7	1.4 to 2.0	<0.001	417	24.2%				

AOR, adjusted odds ratio; CI, confidence interval.

[a]People injecting drugs at least once in the past 30 days and had sex in the past three months; [b]receiving condoms from prevention programmes in the past 12 months; [c]always using condom with all partners in the past three months;[d]exclusive use of heroin, opium, desomorphine, home-made opioids, illegal methadone or buprenorphine;[e]exclusive use of amphetamines, methamphetamines, cocaine, synthetic cathinones ("bath salts"); [f]use of opioids and stimulants in any combination during the same time period or other drug use.

elsewhere; therefore, our cascade indicator was limited to receipt of the tools from the programmes. We believe that this approach is adequate to serve programming purposes, such as assessment and planning of coverage overall and in specific subgroups. It is also important to understand that, compared to individual purchase of prevention tools at a pharmacy, services provided by HIV prevention programmes are more complex and serve multiple synergistic purposes.

We defined the final element of the cascade, the effective use of prevention services, as consistent use of the condoms or the clean syringes. Unlike in the treatment cascade, where viral suppression is almost exclusively a result of treatment, behaviours that prevent HIV are often practiced without accessing specific programmes. As shown in our data, nearly two thirds of PWID reporting consistent use of prevention tools did not receive them through the prevention programmes. Such disconnect between the two indicators may seem to contradict the underlying sequential cascade logic. In the prevention context, however, it makes sense because safer behaviours are facilitated not only by direct provision of prevention services but also by educating about harm reduction approaches and motivating to obtain tools from other sources.

Several amendments to the IBBS instruments can be made in order to enable a more accurate and complete estimation of the HIV prevention cascade. To assess motivation, the second element of the cascade, IBBS should include questions to measure the perceived HIV risk and motivation to use prevention services. Additional questions are needed to comprehensively measure access to prevention tools within and outside of prevention programmes. It is also important to consider the temporal dimension and assess the frequency and regularity of tools uptake. Lastly, questions related to all cascade indicators should use the same time frame (i.e. past twelve or three or one month).

4.3 | Limitations

Several limitations should be considered in interpreting our findings. First, the IBBS data on service uptake are vulnerable to reporting bias. When responding to the questions, participants may not be fully aware that syringes acquired through pharmacy exchange sites or through secondary exchange volunteers may come from the prevention programmes. This could partially explain the notable discrepancy with the programmatic data indicating higher levels of access [17]. The risk behaviour indicators, especially the most straightforward ones regarding syringe sharing, are likely affected by the social desirability bias due to the ubiquitous exposure of Ukrainian PWIDs to HIV-related information and regular surveys. This could lead to a substantial overestimation of the effective use of services element.

As described in Methods, several limitations in the IBBS data source led to compromises in adapting the cascade methodology. These included the absence of motivation and risk perception measures, lack of data on the uptake of prevention tools outside of the programmes, and different time frames in the access and effective use-related questions.

Our analyses did not include other types of risk behaviours, such as back- and front-loading, using pre-filled syringes, or container sharing, because these practices are not directly affected by the availability of clean syringes. Substantial prevalence of these behaviours may contribute to ongoing HIV transmission among PWID despite active NSP in Ukraine. If the "effective use" definition would account for these practices, the estimates of the last stage of the cascade would decrease significantly.

5 | CONCLUSIONS

The generic HIV prevention cascade framework was proposed some time ago to reinvigorate the HIV prevention programme [7,8]. The first real-life cascade analyses used data from condom distribution and pre-exposure prophylaxis programmes [10,12], and this study is the first such example for PWID. We estimated the NSP and CP cascades for PWID in Ukraine using the IBBS survey data and analysed the programming gaps, as well as demographic and behavioural factors associated with achieving the cascade outcomes. Access to NSP and CP was substantially below the recommended level, especially among men and younger PWID. In contrast, effective use of clean syringes was reported by the vast majority of PWID, likely affected by self-report bias. Consistent use of condoms was infrequent.

The analysis also revealed conceptual challenges in applying the cascade framework to the context of HIV prevention among PWID, primarily caused by complex, non-linear causal pathways between the prevention interventions and desired outcomes. Overall, the cascade framework was useful to describe the status of HIV prevention among PWID in Ukraine and to identify areas for improvement in programming as well as evaluation of HIV prevention.

AUTHORS' AFFILIATIONS

[1]Ukrainian Institute on Public Health Policy, Kyiv, Ukraine; [2]Alliance for Public Health, Kyiv, Ukraine

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

KD, YS, OV, PS and TS conceptualized the analysis approach. KD and YS analysed the data. YS designed and managed all stages of IBBS survey. OC and OP managed program data, contributed to program data analysis. TS contributed to IBBS survey design. KD and YS wrote the paper. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors thank Aleksandr Milshteyn for editing the final draft of the manuscript, all of IBBS study team for their dedication and the participants for their willingness to share their experiences through the study.

FUNDING

This IBBS study has been supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through the U.S. Centers for Disease Control and Prevention under the terms of grant NU2GGH000840 (Engaging Local Indigenous Organizations in Developing HIV/AIDS Monitoring and Evaluation Capacity in Ukraine). The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the funding agencies.

REFERENCES

1. UNAIDS. Miles to go - The response to HIV in eastern Europe and central Asia. Geneva, Switzerland; 2018 [cited 2020 March 12]. Available from: http://www.unaids.org/en/resources/documents/2018/miles-to-go_eastern-europe-and-central-asia]

2. European Centre for Disease Prevention and Control, WHO Regional Office for Europe. HIV/AIDS surveillance in Europe 2019–2018 data Stockholm. ECDC; 2019 [cited 2020 March 1]. Available from: https://www.ecdc.europa.eu/en/publications-data/hivaids-surveillance-europe-2019-2018-data]
3. UNAIDS. UNAIDS Data 2019. 2019 [cited 2020 March 12]. Available from: https://www.unaids.org/en/resources/documents/2019/2019-UNAIDS-data]
4. Krishnaratne S, Hensen B, Cordes J, Enstone J, Hargreaves JR. Interventions to strengthen the HIV prevention cascade: a systematic review of reviews. Lancet HIV. 2016;3(7):e307–17.
5. Medland NA, McMahon JH, Chow EP, Elliott JH, Hoy JF, Fairley CK. The HIV care cascade: a systematic review of data sources, methodology and comparability. J AIDS Soc. 2015;18:20634.
6. World Health Organization. Cascade data use manual: to identify gaps in HIV and health services for programme improvement. Geneva, Switzerland: World Health Organization; 2018.
7. Isbell MT, Kilonzo N, Mugurungi O, Bekker L-G. We neglect primary HIV prevention at our peril. Lancet HIV. 2016;3(7):e284–5.
8. Schaefer R, Gregson S, Fearon E, Hensen B, Hallett TB, Hargreaves JR. HIV prevention cascades: a unifying framework to replicate the successes of treatment cascades. Lancet HIV. 2019;6(1):e60–6.
9. Hargreaves JR, Delany-Moretlwe S, Hallett TB, Johnson S, Kapiga S, Bhattacharjee P, et al. The HIV prevention cascade: integrating theories of epidemiological, behavioural, and social science into programme design and monitoring. Lancet HIV. 2016;3(7):e318–22.
10. Garnett GP, Hallett TB, Takaruza A, Hargreaves J, Rhead R, Warren M, et al. Providing a conceptual framework for HIV prevention cascades and assessing feasibility of empirical measurement with data from east Zimbabwe: a case study. Lancet HIV. 2016;3(7):e297–306.
11. Godfrey-Faussett P. The HIV prevention cascade: more smoke than thunder? Lancet HIV. 2016;3(7):e286–8.
12. Kelley CF, Kahle E, Siegler A, Sanchez T, Del Rio C, Sullivan PS, et al. Applying a PrEP continuum of care for men who have sex with men in Atlanta, Georgia. Clin Infect Dis. 2015;61(10):1590–7.
13. Weir SS. Condom cascades to monitor HIV prevention. 22nd International AIDS Conference; Amsterdam, the Netherlands: Abstract #THPEC253; 2018.
14. Vitek CR, Cakalo JI, Kruglov YV, Dumchev KV, Salyuk TO, Bozicevic I, et al. Slowing of the HIV epidemic in Ukraine: evidence from case reporting and key population surveys, 2005–2012. PLoS ONE. 2014;9:e103657.
15. Dumchev K, Varetska O, Kornilova M, Azarskova M. Improved ascertainment of modes of HIV transmission in Ukraine highlights importance of risk due to injecting and homosexual risk behavior among males. 16th European AIDS Conference; Milan, Italy: Abstract #PE23/33. 2017.
16. Dumchev K, Sazonova Y, Salyuk T, Varetska O. Trends in HIV prevalence among people injecting drugs, men having sex with men, and female sex workers in Ukraine. Int J STD AIDS. 2018;29(13):1337–44.
17. Alliance for public health: annual report. 2017 [2020 Mar 01]. Available from: http://aph.org.ua/wp-content/uploads/2018/08/Annual-Report-2017__15.08.2018.pdf]
18. World Health Organization. Tool to set and monitor targets for HIV prevention, diagnosis, treatment and care for key populations. Geneva, Switzerland: World Health Organization; 2015.
19. WHO. Good practices in Europe: HIV prevention for people who inject drugs implemented by the International HIV/AIDS Alliance in Ukraine 2014 [cited 2020 March 12]. Available from: http://www.euro.who.int/en/countries/ukraine/publications3/good-practices-in-europe-hiv-prevention-for-people-who-inject-drugs-implemented-by-the-international-hivaids-alliance-in-ukraine-2014
20. Barska J, Sazonova I. Monitoring of behaviour and HIV prevalence among people who inject drugs and their sexual partners: analytical report on 2015 study. Kyiv, Ukraine: Alliance for Public Health; 2016 [cited 2020 March 12]. Available from: http://aph.org.ua/wp-content/uploads/2015/09/monsin.pdf
21. Sereda YV, Sazonova YO.Monitoring of behaviour and HIV prevalence among people who provide sexual services for reward: a report on 2015 bio-behavioral survey Kyiv. Ukraine: Alliance for Public Health; 2017 [cited 2017 September 1]. Available from: http://aph.org.ua/wp-content/uploads/2017/06/Monitoryng-povedinky-ta-poshyrennya-VIL-infektsiyi-sered-RKS_22.06.2017_Natsyonalnaya-chast.pdf
22. Fernandes RM, Cary M, Duarte G, Jesus G, Alarcao J, Torre C, et al. Effectiveness of needle and syringe Programmes in people who inject drugs - an overview of systematic reviews. BMC Public Health. 2017;17(1):309.
23. MacArthur GJ, van Velzen E, Palmateer N, Kimber J, Pharris A, Hope V, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. Int J Drug Policy. 2014;25(1):34–52.
24. Magura S, Grossman JI, Lipton DS, Siddiqi Q, Shapiro J, Marion I, et al. Determinants of needle sharing among intravenous drug users. Am J Public Health. 1989;79(4):459–62.
25. Pasa MK, Alom KR, Bashri Z. Vermund SH. sharing of needles and syringes among men who inject drugs: HIV risk in Northwest Bangladesh. PLoS ONE. 2016;11:e0148276.

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

AUTHOR INDEX

T

V

W

Y

Journal Information

About the journal

The *Journal of the International AIDS Society*, the official journal of the Society, provides a peer-reviewed, open access forum for essential and innovative HIV research, across all disciplines. All articles published by the *Journal of the International AIDS Society* are freely accessible online. The editorial decisions are made independently by the journal's Editors-in-Chief.

Website: www.jiasociety.org

eISSN: 1758-2652

Contact details

Editorial office:
Avenue de France, 23
CH-1202 Geneva
Switzerland

Email: editorial@jiasociety.org

Tel: +41 (0) 22 710 0800

Publisher

The *Journal of the International AIDS Society* is published by John Wiley & Sons Ltd on behalf of the International AIDS Society

John Wiley & Sons Ltd
9600 Garsington Road
Oxford, OX4 2DQ UK

Telephone: +44 1865 776868

Email: customer@wiley.com

Production Editor

Maruthu Pandian Sankareswaran (email: maruthupandian@wiley.com)

Abstracting and Indexing Services

The *Journal of the International AIDS Society* is indexed in a variety of databases including PubMed, PubMed Central, MEDLINE, Science Citation Index Expanded and Google Scholar. The 2018 Journal Impact Factor is 5.192, *Journal Citation Reports* (Clarivate Analytics, 2019).

Advertising, sponsorship and donations

Please contact the editorial office if you are interested in advertising on our journal's website. We also gladly receive inquiries on sponsorship and donations to support open access publications from authors in low- and middle-income countries.

Supplements

The *Journal of the International AIDS Society* publishes supplements and thematic series on its own initiative or based on proposals by external organizations or authors. Inquiries can be sent to the editorial office at editorial@jiasociety.org.

All articles submitted for publication in supplements are subject to peer review. Published supplements are freely accessible online and can also be produced in print.

Disclaimer

Copyright and Copying

Wiley's Corporate Citizenship Initiative

Wiley's Corporate Citizenship Initiative seeks to address the environmental, social, economic, and ethical challenges faced in our business and which are important to our diverse stakeholder groups. Since launching the initiative, we have focused on sharing our content with those in need, enhancing community philanthropy, reducing our carbon impact, creating global guidelines and best practices for paper use, establishing a vendor code of ethics, and engaging our colleagues and other stakeholders in our efforts. Follow our progress at www.wiley.com/go/citizenship.

Research4Life

Wiley is a founding member of the UN-backed HINARI, AGORA, and OARE initiatives. They are now collectively known as Research4Life, making online scientific content available free or at nominal cost to researchers in developing countries.

Please visit Wiley's Content Access – Corporate Citizenship site:
www.wiley.com/WileyCDA/Section/id-390082.html

Editors

Editorial Board