Strengthening the HIV prevention cascade to maximise epidemiological impact in eastern Zimbabwe: a modelling study

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Summary

Background HIV prevention cascades provide a systematic understanding of barriers to prevention. In this study we used mathematical modelling to understand the consequences of these barriers and how the cascade could be strengthened to maximise epidemiological impact, providing potentially important insights for programmes.

Methods We used an individual-based model of HIV transmission (PopART-IBM), calibrated to data from the Manicaland cohort from eastern Zimbabwe. HIV prevention cascade estimates from this cohort were used as probabilities for indicators in the model representing an individual's motivation, access, and capacity to effectively use pre-exposure prophylaxis, voluntary male medical circumcision, and condoms. We examined how current barriers affect the number and distribution of HIV infections compared with a no-barrier scenario. Using assumptions about how interventions could strengthen the HIV prevention cascade, we estimated the reduction in HIV infections over a 10-year period through addressing different elements of the cascade.

Findings 21 200 new potentially avertable HIV infections will occur over the next 10 years due to existing HIV prevention cascade barriers, 74·2% of the 28 500 new infections that would occur with existing barriers in a population of approximately 1·2 million adults. Removing these barriers would reduce HIV incidence below the benchmarks for epidemic elimination. Addressing all cascade steps in one priority population is substantially more effective than addressing one step across all populations.

Interpretation Interventions exist in eastern Zimbabwe to reduce HIV towards elimination, but barriers of motivation, access, and effective use prevent their full effect being realised. Interventions need to be multilayered and address all steps along the HIV prevention cascade. Models incorporating the HIV prevention cascade can help to identify the main barriers to greater effectiveness.

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Introduction

Substantial effort has been put into promoting HIV prevention tools including condoms, pre-exposure prophylaxis (PrEP), and voluntary male medical circumcision (VMMC), all of which greatly reduce the risk of HIV infection when used effectively.[1–3] However, uptake often remains below targets, affecting progress in meeting goals for reductions in new HIV infections.[4]

Understanding the barriers that individuals experience is crucial in facilitating effective use of these methods. Analogous to the HIV treatment cascade, the HIV prevention cascade has been proposed as a means to identify barriers and inefficiencies, and to develop actionable strategies to increase effective use of HIV prevention methods.[5,6] Developed in consultation with key local and international stakeholders,[7] one articulation of the HIV prevention cascade framework[8] describes how, for each prevention method, a cascade exists across three overarching domains: motivation, access, and capacity to use effectively. Each domain represents a cascade step, and consists of multiple barriers; for example, the step representing motivation comprises barriers related to knowledge, risk perception, consequences of use, and social norms.[8] An individual experiencing a barrier in any domain might not use that method effectively. Importantly, the HIV prevention cascade framework is applicable to all prevention methods, reflecting that individuals fall within a cascade for each possible HIV prevention method.

However, it remains unclear to what extent barriers combine to frustrate the potential effectiveness of available HIV prevention methods, the degree to which these barriers might be mitigated by intervention efforts,[9] and the consequences these mitigations could have for

Research in context

Evidence before this study

We searched PubMed and Embase from database inception to April 14, 2023, using the terms "HIV prevention" AND "cascade" AND "model*". We identified three papers that used a HIV prevention cascade formulation in a mathematical model. Two examined the HIV prevention cascade for pre-exposure prophylaxis (PrEP) only, and each used an instance of the HIV prevention cascade where uptake was taken as a single step, showing how hypothetical improvements in each cascade step (uptake, adherence, retention, and reengagement; and initiation, adherence, and persistence) would affect the impact of PrEP. Both models included voluntary male medical circumcision and condom use, but neither method was examined using a prevention cascade methodology. The third study used a difference equation model, where changes take place on a 1-year timescale, and the same HIV prevention cascade as the present study in the context of couples' voluntary counselling. This study showed that mitigating interventions to successive cascade steps have a diminishing effect.

Added value of this study

In this study we used a prevention cascade with separate steps for motivation, access, and effective use. We used an individual-based model of HIV transmission, calibrated to cohort data from eastern Zimbabwe, and examined the cascade for the three currently available prevention methods in this setting. The study highlights the need to address all steps in the prevention cascade, and that existing prevention methods in this setting could reduce HIV towards elimination if all steps are overcome.

Implications of all the available evidence

The combination of the HIV prevention cascade framework and mathematical modelling provides a detailed quantitative understanding of how barriers hold back HIV prevention efforts. These insights can help to guide efforts towards elimination of HIV.

reducing the individual-level risk of HIV infection and achieving milestones towards eliminating HIV as a public health threat.[10,11] In order to address these questions, we used an individual-based model simulating the HIV prevention cascade and HIV transmission[12] in the well characterised population of Manicaland, eastern Zimbabwe to (1) quantify the extent to which existing barriers in the cascade limit the effectiveness of prevention methods (tenofovir-based oral PrEP, VMMC, and condom use), and (2) estimate the potential effect on HIV incidence of addressing these barriers with interventions.

Methods

Model

We used PopART-IBM, an individual-based model simulating HIV transmission in a growing population.[12] The model code used in this study is available from https://doi.org/10.5281/zenodo.7258438 under the GNU General Public License 3.0. Full details of the model are in the appendix (pp 2–24). Below we give brief descriptions of each of the major components.

See Online for appendix

HIV transmission, natural history, and antiretroviral therapy

HIV-negative people in sexual partnership with a person living with HIV are at risk of acquiring HIV infection at each timestep; the risk of transmission is determined by the treatment status and stage of infection of the partner living with HIV, as well as use of prevention methods (described below). Once infected, individuals enter the early HIV infection period, following which they are assigned a set-point viral load, which determines both their infectiousness[13] and the rate at which they pass through stages of infection, defined by the ranges of CD4 cell count in peripheral blood.[14] In the absence of antiretroviral therapy (ART), individuals will die after passing through the final stage of infection. However, individuals can undergo HIV testing and, if they test as HIV-positive, can initiate ART.

Population structure

The model simulated a growing population of adults aged 14 years or more. Each modelled adult has a sex and date of birth, from which their age is calculated. Individuals are exposed to an age-specific risk of death due to non-HIV-related causes. Certain priority populations were defined for each prevention method (men aged 15–29 and 30–54 years, and women aged 15–24 and 25–54 years, with additional method-specific eligibility conditions; see appendix p 8 for full definitions). Accordingly, individuals entered and left priority populations over time as they aged or their status otherwise changed.

Sexual partnerships

Two distinct types of heterosexual partnerships between individuals were modelled: long-term (including marriages, cohabiting partnerships, or other partnerships lasting more than a year) and casual (all other types). Partnerships can be concurrent (ie, an individual can be simultaneously in partnerships with two or more individuals). Rates of partnership formation are dependent on age and sex, and age-mixing matrices govern who partners with whom (appendix pp 18–19); a graphical representation is shown in the appendix (p 13). These mixing matrices produce realistic age disparities between partners,[15] where men tend to have younger partners.

HIV prevention cascades

We represented the HIV prevention cascade framework of Schaefer and colleagues[6] by assigning, to each modelled individual, Boolean indicators for their

motivation (desire to use a given method), access (ability to access the method), and capacity to use effectively (possession of the skills and self-efficacy to use the method effectively) for each HIV prevention method (appendix p 4). These three indicators were then combined to determine whether the given method will be used by the individual in the model. We assumed that prevention methods are independent.

Table 1 provides the distributions of these indicators, estimated from the Manicaland cohort.[16,17] This is an open general population HIV survey conducted in Manicaland Province, eastern Zimbabwe, collecting detailed socio-demographic, HIV risk, and health-seeking behaviour, and HIV prevalence data from adults over seven rounds between 1999 and 2019. The probabilities corresponding to the cascade steps are calculated using data from the 2019 round, as described in the appendix (pp 25–27) and as illustrated for male condoms[18] and for young women.[19]

	Men aged 15–29 years	Men aged 30–54 years	Women aged 15–24 years	Women aged 25–54 years
PrEP				
Motivation	0·06	0·05	0·09	0·07
Access	0·04	0·04	0·11	0·10
Capacity to use effectively	1·00	1·00	0·00	0·60
VMMC				
Motivation	0·33	0·21	..	..
Access	0·36	0·33	..	..
Capacity to use effectively	0·39	0·30	..	..
Condoms (in casual sexual partnerships)				
Motivation	0·97	0·84	0·93	0·85
Access	0·67	0·68	0·56	0·81
Capacity to use effectively	0·71	0·72	0·80	0·71

The time period for each probability is as follows: for VMMC, this is an annual probability of receiving VMMC; for PrEP it is the probability of using PrEP at the current model timestep; and for condoms it is use within the current sexual partnership. All values derived from the 2019 round of the Manicaland cohort. PrEP=pre-exposure prophylaxis. VMMC=voluntary male medical circumcision.

Table 1: **Probabilities of overcoming barriers for each prevention method in each priority population**

Model parameterisation and calibration

Parameters used in the model, including sources, are tabulated in the appendix (pp 14–23), and analyses underlying the parameterisation are shown in figures in the appendix (pp 6, 10–11, 13, 16). The means by which the HIV prevention cascade-related parameters were estimated from the data available in the study setting are described in the appendix (pp 25–27).

The model was calibrated to other data from the Manicaland cohort (age-specific and sex-specific HIV prevalence in 1999, 2003, 2005, 2008, 2011, 2013, and 2019; age-specific and sex-specific awareness of HIV status in 2005, 2008, 2011, 2013, and 2019; and age-specific and sex-specific ART coverage in 2008, 2011, 2013, and 2019; these ensured that the model captured changes in treatment coverage over time). The procedure by which the model was calibrated to these data is as follows: the model was run using 50 000 parameter sets generated using Latin hypercube sampling[20] in which certain parameters are allowed to vary within defined ranges (appendix p 24); for each parameter set the likelihood of the observed survey data given the corresponding modelled outputs was calculated. The ten parameter sets with the highest likelihood were selected for use in all further model analyses.

In an individual-based model, events were determined by drawing random numbers. The same parameters, but with different random numbers, give different epidemics. We incorporated this stochastic variation as follows: immediately after the final cohort round in 2019 we reseeded the random number generator ten times, producing ten different sets of random numbers for the same parameters. In the appendix (pp 28–29), we compared the relative magnitudes of the variation due to this stochasticity compared with that arising from different calibrated parameters, to ensure that ten reseedings sufficiently accounted for stochastic variation in subsequent analyses (appendix p 29).

All model results are presented as medians and 95% credible intervals (CrIs) of the 100 runs (ten parameter sets times ten stochastic runs).

Modelling analysis

To quantify the extent to which the barriers in the HIV prevention cascade limit the effectiveness of HIV prevention methods (aim 1), we ran the model under our estimates for the current state of the cascade and compared the resulting number and distribution of HIV infections over a 10-year period (July 1, 2020–June 30, 2030) with an alternative run in which every barrier was entirely removed. The difference between these scenarios was attributed to the joint effect of all the barriers. As we used a dynamic model, this approach also captured indirect effects, unlike, for example, Markov models.

To estimate the potential effect on HIV incidence of addressing the barriers with interventions (aim 2), we first formed assumptions on the extent to which the HIV prevention cascade for each method might be strengthened by plausible interventions that address the barriers associated with each of motivation, access, and capacity to use the method effectively (table 2). We then compared the status quo scenario (per table 1, reflecting the current state of the HIV prevention cascade) with scenarios in which each intervention is applied individually, or in combination, for each HIV prevention method and priority population, and compare the number of HIV infections in individuals 15–54 years of age over a 10-year period (July 1, 2020–June 30, 2030).

For three scenarios (status quo, barriers removed from aim 1, and mitigating all barriers for all methods from aim 2), we compare model estimates of four metrics in 2030 (HIV incidence, incidence:prevalence ratio,

	Proportion of people who overcome barrier	Justification
PrEP		
Motivation	0·30	Similar to coverage levels achieved in SEARCH and ECHO trials,[21,22] and assuming that barriers to access and capacity to use effectively were small in the trial context
Access	0·90	Assumption informed by targets such as the first 90 of 90–90–90,[23] reflecting the challenges in implementing universal access
Capacity to use effectively	0·90	Reach 90% among women 15–29 years of age (maintain at existing value when >0·90)
VMMC		
Motivation	0·56	Overall annual rate of 0·175 found to produce 90% VMMC coverage after 5 years, comparable to traditional circumcision in other sub-Saharan African countries (eg, van der Straten and colleagues, 2016[24]), through improving understanding of risk and evolving social norms around VMMC; to create an overall rate from the cascade, we assume that the three cascade steps are equal, giving a value of $0{\cdot}175^{1/3}=0{\cdot}56$ per step
Access	0·56	To produce 90% VMMC coverage after 5 years, through expansion of VMMC services through other channels
Capacity to use effectively	0·56	To produce 90% VMMC coverage after 5 years, through interventions to address partner disapproval and interpersonal perception of VMMC
Condoms (in casual sexual partnerships)		
Motivation	0·97	Corresponds to highest current value among priority populations in Manicaland[17]
Access	0·90	Assumption that same value as for PrEP can be reached
Capacity to use effectively	0·90	Assumption that training can be used to improve negotiation skills with partners, address norms, and provide training on how to use effectively

For a given prevention method and domain, the same values are used for each priority population, reflecting the assumption that once barriers related to age and sex are mitigated, the residual barriers would be similar across populations. PrEP=pre-exposure prophylaxis. VMMC=voluntary male medical circumcision.

Table 2: **Probabilities of overcoming barriers in the presence of interventions to strengthen HIV prevention cascade domains**

reduction in new infections compared with 2010, and incidence:mortality ratio) with benchmarks for epidemic transition[11] and control.[25]

Written informed consent to take part was obtained from all participants for whom survey data were used in the model. For participants aged under 18, written informed consent was obtained from a parent or guardian and assent was obtained from the child. Ethical approval was granted by the Imperial College Research Ethics Committee (17IC4160), and the Medical Research Council of Zimbabwe (MRCZ/A/2243).

Role of the funding source

The funders of the study had no role in data collection, data analysis, data interpretation, writing of the report, or decision to submit for publication.

Results

Overall, the model reproduced well the increase in HIV prevalence by age and sex, and also reproduced the overall pattern of ART coverage by age for each sex. The results of the calibration of the model with data for the year 2019 are shown in the appendix (p 30). Furthermore, a comparison between model and cohort HIV incidence, to which the model was not calibrated, shows (appendix p 31) that the model also reproduced changes over time in incidence by age and sex.

The model also reproduced the percentage of the population using each prevention method (appendix p 30). Self-reported condom use with casual partners was slightly higher among women (47%) than men (44%) in the survey. However, since condom use is a partnership-level property in the model, and thus must balance between sexes, there was less variation between men and women in the model than was reported in the survey.

Our first aim was to quantify how barriers in the HIV prevention cascade limit the maximal effectiveness of HIV prevention methods. Figure 1 shows the distribution of avertable infections over 10 years. Overall, completely removing all barriers for all HIV prevention methods combined in Manicaland would avert a median of 21 200 infections (74·2% of the 28 500 infections that would otherwise occur) over this period (95% CrI 11 600–33 000; 2·5–97·5 percentile 64·6–80·9%) from a total adult population of approximately 1·2 million. Almost half of these 28 500 infections (median 10 600, representing 48·6%; 95% CrI 36·8–55·5%) were in women 25–54 years of age, while only a median of 1475 (7·6%) of avertable infections were in men 15–29 years of age. The largest number of avertable infections occur through removing barriers to PrEP, as PrEP has the largest existing barriers (appendix p 32). With the barriers in place, there is no chance of the epidemic transition benchmarks being met, but with the complete removal of all barriers, HIV incidence among adults would be reduced to less than 0·1 per 100 person-years by 2030, below the benchmark for HIV epidemic control suggested by Galvani and colleagues,[25] as well as meeting benchmarks for other metrics of epidemic transition[11] (appendix p 33).

Our second aim was to estimate the potential effect of interventions to mitigate barriers seen in the HIV prevention cascade. Figure 2 illustrates the effect of intervening to strengthen the HIV prevention cascade by addressing and mitigating barriers for PrEP in women 25–54 years of age with one or more casual partners (analogous figures for other priority populations and interventions are shown in appendix p 34). Figure 2A shows the strengthening of the HIV prevention cascade in this population under intervention scenarios wherein the existing barriers are sequentially mitigated. The dark grey bars show the estimates for the status quo: only 48 (7%) of 645 women in this priority population reported being motivated to use PrEP, and three (<1%) were using PrEP. An intervention to increase motivation to use PrEP, for example through increasing knowledge of PrEP and more accurate risk perception, as well as addressing social norms around PrEP use,[8] results in an increase in the first bar (to the orange "mitigate motivation barriers" level). However, if the intervention does not address barriers to access and capacity to use effectively, then overall PrEP use remains low in this population (2%). Addressing both motivation and access barriers together (green) leads to higher PrEP usage (16%). Of the five women who were in the last step of the cascade in the survey, two (40%) reported that capacity to use effectively, capturing skills and self-efficacy to use PrEP, as well as issues around partner approval remained barriers; adding components to the intervention to improve capacity to use PrEP effectively can increase PrEP usage to 24·3%. Figure 2B shows how these cascades translate into PrEP usage over time in the model, and figures 2C and 2D show the modelled rate of HIV incidence among women 25–54 years of age and among the adult population, respectively, under the different intervention scenarios. Since we assume that barriers are only affected in the specific priority population under consideration, even mitigating all barriers has a modest effect in terms of incidence rate. Figure 2E gives the cumulative number of HIV

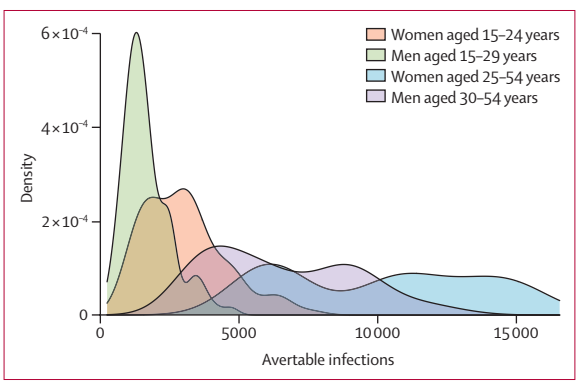

Figure 1: **Distribution of avertable infections over 10 years across model runs in each population group through removing all barriers to use for all prevention methods**

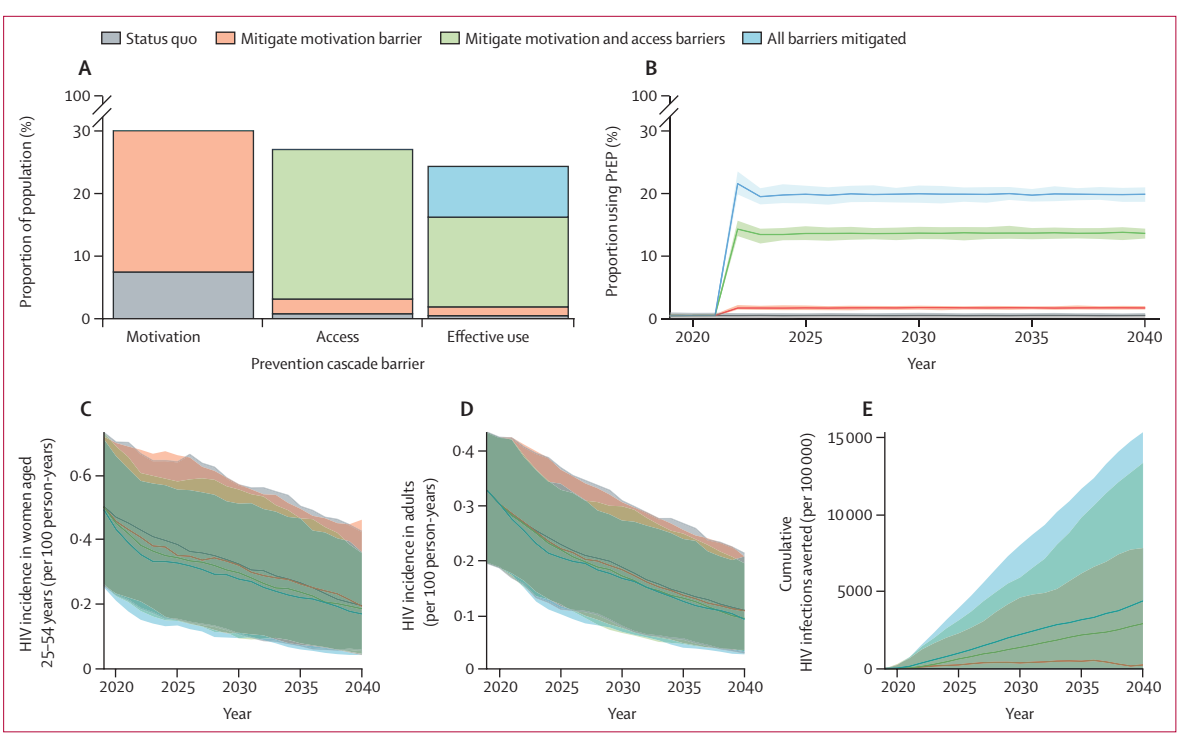

Figure 2: **Effect of intervening sequentially to strengthen the steps in the HIV prevention cascade for PrEP for women 25–54 years of age**
(A) HIV prevention cascade. (B) PrEP usage. HIV incidence in women 25–54 years of age (C) and all adults (D). (E) Cumulative infections averted in individuals 15–54 years of age per 100 000 population. For (B)–(E), solid lines show the median model output for each scenario, and shaded regions show the 2·5–97·5 percentiles. PrEP=pre-exposure prophylaxis.

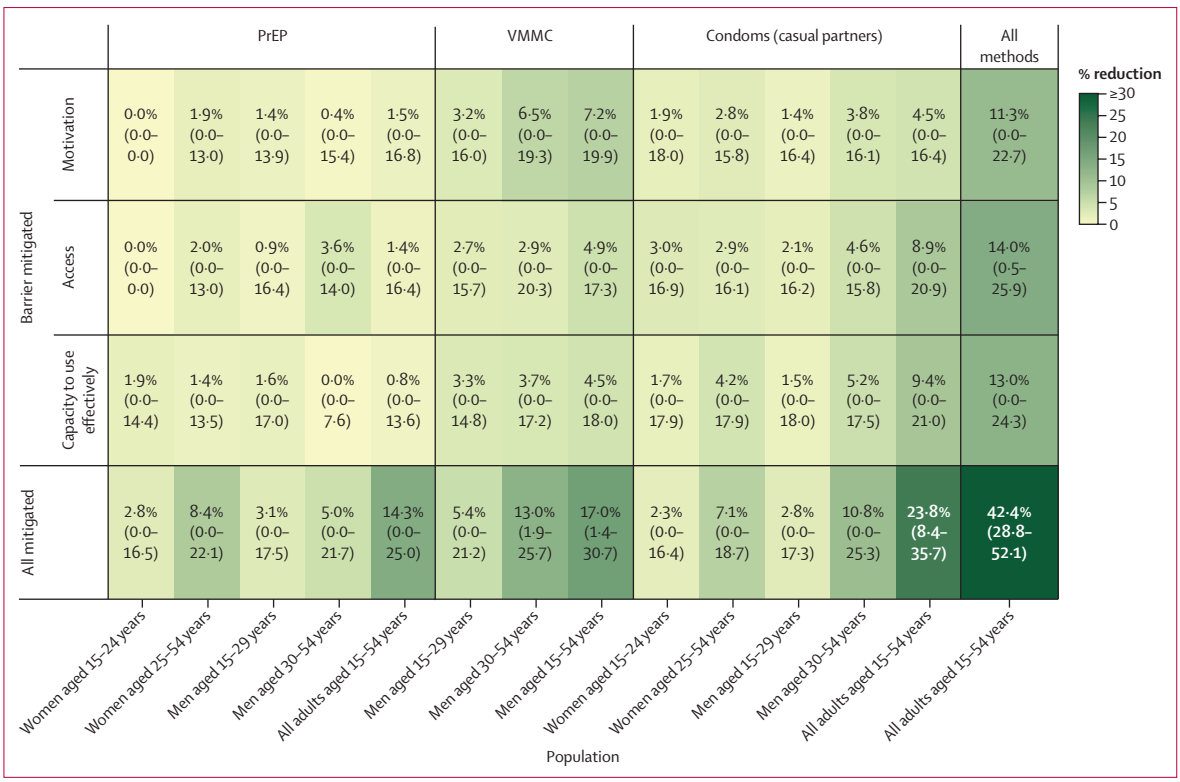

Figure 3: **Heatmap of median percentage reduction in infections in individuals 15–54 years of age over 10 years from reducing prevention cascade barriers**
Shading shows effect associated with reducing barriers in different cascade domains (rows) for different prevention methods (panels) in different priority populations (columns). Darker green indicates scenarios of greater effect. PrEP=pre-exposure prophylaxis. VMMC=voluntary male medical circumcision.

infections averted compared to status quo in individuals 15–54 years of age per 100 000 population under each scenario.

Figure 3 is a heatmap showing the median percentage of all HIV infections over 10 years averted by interventions to reduce barriers associated with each cascade domain for each method in each priority population.

Addressing a single domain for one prevention method in one priority population has a very modest effect on HIV incidence overall. The single intervention with the largest effect is for addressing motivation barriers to VMMC among men 30–54 years of age, which averts a median 6·5% of infections over 10 years (95% CrI 0·0–19·3), corresponding to 1780 of the 28 500 infections in this period; this result is unsurprising, since it is a large priority population, and this domain has the largest barriers to VMMC in this group. However, to maximise the effect, the barriers across all three domains need to be addressed. For the PrEP example above, addressing only motivation barriers among all priority populations averts a median of 1·5% of infections over 10 years (0·0–16·8), whereas removing all barriers among just women 25–54 years of age averts a median of 8·4% of infections (0·0–22·1). Indeed, for any prevention method, strengthening all steps across the HIV prevention cascade in a single priority population is more impactful than strengthening a single step across all priority populations.

Figure 3 also shows how HIV prevention cascades can be used to identify which barriers are most important to address in different populations. For example, mitigating barriers to motivation for VMMC is more important for men 30–54 years of age than 15–29 years, but mitigating barriers affecting capacity to use VMMC effectively has a similar effect in the two age groups.

Overall, the median effect of mitigating all barriers for all prevention methods in all populations with plausible interventions is a reduction of 42·4% (95% CrI 28·8–52·1), 12 200 of the 28 500 HIV infections among individuals 15–54 years of age, over the next 10 years compared to the current states of the HIV prevention cascades in Manicaland. Mitigating these barriers would meet all benchmarks for metrics of epidemic transition by 2030[11] in almost half (48 of 100) of the model runs (appendix p 33), meaning that mitigating these barriers might be sufficient to eliminate HIV as a public health threat.

Discussion

In this study we have shown that overcoming current barriers in the HIV prevention cascade for existing prevention methods could avert approximately 21 200 extra HIV infections in Manicaland over the next 10 years (76·1% of all new infections in a population of 1·2 million, most among women 25–54 years of age). This is the difference between reaching and not reaching milestones

towards elimination of HIV as a public health threat[10,11] (appendix p 33). We also find that only strengthening a single step in the prevention cascade leads to minimal effects on HIV incidence. However, addressing all steps in a single priority population is more impactful in this setting than addressing a single step across all populations.

These findings underscore the need for multilayered and differentiated service delivery options that address, via more client-centred care, the full spectrum of barriers across the HIV prevention cascade, as has been recently recommended for PrEP.[26] HIV prevention is complex, and successfully increasing effective use of a method in a population will involve addressing individual, interpersonal, and societal barriers.[27] Failing to address a single barrier can lead to severely weakened overall effectiveness. Modelling analyses that leverage the concept of the HIV prevention cascade can identify the steps in the cascade, and the related barriers, that most severely reduce overall effectiveness.

This study also shows that barriers can manifest themselves differently for different groups (eg, age groups). For example, mitigating barriers to motivation for VMMC is more important for men 30–54 years of age than those 15–29 years of age, perhaps reflecting that the latter are the focus of national guidelines for VMMC, but mitigating barriers affecting capacity to use VMMC effectively (those related to disapproval of partners, family, and friends) has a similar effect in both age groups. Similarly, no women 15–24 years of age in the study reported capacity to use PrEP effectively; although based on a small number of women, this finding, if replicated elsewhere, is crucial for programmes to address. Thus, responses need to be tailored to specific groups.

HIV programmes, and those planning trials of HIV prevention methods, should note that a single unmitigated barrier can affect uptake and effectiveness, and should collect information to examine how they are modifying the prevention cascades, as illustrated in a recent trial to improve risk perception among adolescent girls and young women.[28] Such analyses might highlight positive results relating to removal of some barriers. Similarly, HIV prevention programmes would benefit from using prevention cascades integrated into an implementation or programme science approach[29,30] to identify and mitigate barriers in an iterative and data-driven manner, and hence optimise programme effectiveness.

The present study also highlights the need to understand how different combinations of interventions might interact. Further work is needed to understand whether there are tipping points, either at the individual level (where sufficient barriers to an individual's use of a method have been alleviated, allowing them to use the method effectively) or at the community level, when social norms around risk and HIV prevention change. Past experiences suggest that this might sometimes be the case; for example, HIV testing has become much more accepted in the era of test-and-treat.[31]

In this study we use an articulation of the HIV prevention cascade framework that has already been applied in the Manicaland context,[18,19] and that can provide detailed insight into the underlying barriers.[6,8] We embed the resulting cascades into a model that reproduces multiple rounds of data on HIV prevalence and treatment status in Manicaland by age and sex. As a dynamic individual-based model, it directly incorporates varying individual-level risk behaviour, for example as individuals form and break up casual partnerships, so that there is continuous turnover in the priority populations. An additional advantage of an individual-based over a compartmental model, another widely used type of mathematical model, is the explicit representation of partnerships, which is important both for condoms, as usage is dependent on both partners, and scenarios in which the eligibility of a prevention method is partner-dependent, such as for PrEP under the Partnership paradigm.[32]

Incorporating the HIV prevention cascade framework into a mathematical model provides important broad insights into HIV prevention. This approach can quantify the extent to which barriers from different steps of the cascade are responsible for HIV infections[21,33,34] and the effect of interventions to mitigate these barriers, and can be adapted for new prevention modalities such as long-acting injectable cabotegravir–rilpivirine PrEP, where such modelling can help in planning the steps needed for successful roll-out. This study, the first to combine modelling and the HIV prevention cascade for multiple prevention methods, also highlights existing challenges and the steps needed to provide more contextualised application of prevention cascades in mathematical modelling. We do not know the extent to which barriers can be mitigated, for which we need trials and programme evaluations to measure changes in the HIV prevention cascade. In the data used, there were few individuals in the later cascade steps, particularly capacity to use effectively for PrEP, so the corresponding probabilities come with large uncertainty. More work, both data collection and modelling, is needed to understand the correlation between steps in the cascade. To date, prevention cascades have focused on each prevention method separately, and in this study we have assumed independence, yet it is likely that there are correlations between different methods for a given step in the cascade that would be important considerations for combination prevention programmes. Furthermore, data for the HIV prevention cascade in this study are self-reported, and effective use of PrEP might be overestimated,[22–24] though the prevention cascade could be adapted to use pharmacological measures as outcomes. Finally, as more data become available on the HIV prevention cascade, so that the uncertainty in an individual step reflects true uncertainty rather than the small numbers seen in the latter steps of the cascades in the present study, it will be important to incorporate the measured uncertainty into model estimates.

Strengthening the HIV prevention cascade across all areas can be very effective. Mathematical modelling, incorporating the HIV prevention cascade, can help to guide prevention efforts to maximise effectiveness.

Contributors

MP, SG, and TBH conceptualised the study. MP and LM analysed the cohort data to parameterise the model. MP wrote the model code and did the modelling analyses. SG, LM, TD, FD, PM, RM, TM, RS, MS, RT, BT, OM, and CN had major roles in acquisition and interpretation of data used by the model. MP, TH, and SG interpreted model results. MP prepared figures and tables with inputs from all coauthors. MP wrote the initial draft of the report, which was revised by all coauthors. LM and TD directly accessed and verified the underlying data reported in the manuscript. All authors had access to all data and final responsibility for the decision to submit for publication. All authors read and approved the final version of the manuscript.

Declaration of interests

SG declares shareholdings in pharmaceutical companies GlaxoSmithKline and AstraZeneca. All other authors declare no competing interests.

Data sharing

The model code and corresponding prior parameter ranges used in this study are available from https://doi.org/10.5281/zenodo.7258438 under the GNU General Public License 3.0. The model parameterisation is largely derived from analysis of the Manicaland cohort. Due to the sensitive nature of data collected, including information on HIV status, treatment, and sexual risk behaviour, the Manicaland Centre for Public Health does not make full analysis datasets publicly available. Summary datasets of household and background sociodemographic individual questionnaire data, covering rounds 1–7 (1998–2019), are publicly available for download via the Manicaland Centre for Public Health website (http://www.manicalandhivproject.org/data-access.html). Quantitative data for independent analyses are available on request following completion of a data access request form (http://www.manicalandhivproject.org/data-access.html).

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References

1 Siegfried N, Muller M, Deeks J, et al. HIV and male circumcision—a systematic review with assessment of the quality of studies. *Lancet Infect Dis* 2005; **5:** 165–73.

2 Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. *AIDS* 2016; **30:** 1973–83.

3 Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev* 2002; **1:** CD003255.

4 UNAIDS. Global commitments, local action. June 3, 2021. https://www.unaids.org/en/resources/documents/2021/global-commitments-local-action (accessed June 28, 2022).

5 Auerbach JD, Gerritsen AA, Dallabetta G, Morrison M, Garnett GP. A tale of two cascades: promoting a standardized tool for monitoring progress in HIV prevention. *J Int AIDS Soc* 2020; **23** (suppl 3)**:** e25498.

6 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:** e60–66.

7 Manicaland Centre for Public Health Research. HIV prevention cascades: stakeholder consultation meeting and workshop. Sept 17, 2017. http://www.manicalandhivproject.org/uploads/4/7/1/9/4719905/hpc_consultation_workshop_report_final.pdf (accessed May 18, 2022).

8 Moorhouse L, Schaefer R, Thomas R, 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.

9 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:** e307–17.

10 UNAIDS. Miles to go. Global AIDS update 2018. Geneva, Aug 13, 2018. https://www.unaids.org/en/resources/documents/2018/global-aids-update (accessed Oct 7, 2022).

11 Ghys PD, Williams BG, Over M, Hallett TB, Godfrey-Faussett P. Epidemiological metrics and benchmarks for a transition in the HIV epidemic. *PLoS Med* 2018; **15:** e1002678.

12 Pickles M, Cori A, Probert WJM, et al. PopART-IBM, a highly efficient stochastic individual-based simulation model of generalised HIV epidemics developed in the context of the HPTN 071 (PopART) trial. *PLoS Comput Biol* 2021; **17:** e1009301.

13 Fraser C, Hollingsworth TD, Chapman R, de Wolf F, Hanage WP. Variation in HIV-1 set-point viral load: epidemiological analysis and an evolutionary hypothesis. *Proc Natl Acad Sci USA* 2007; **104:** 17441–46.

14 Cori A, Pickles M, van Sighem A, et al. CD4+ cell dynamics in untreated HIV-1 infection: overall rates, and effects of age, viral load, sex and calendar time. *AIDS* 2015; **29:** 2435–46.

15 Probert W, Hall M, Xi X, et al. Quantifying the contribution of different aged men and women to onwards transmission of HIV-1 in generalised epidemics in sub-Saharan Africa: a modelling and phylogenetics approach from the HPTN071 (PopART) trial. *J Int AIDS Soc* 2019; **22:** 107.

16 Gregson S, Mugurungi O, Eaton J, et al. Documenting and explaining the HIV decline in east Zimbabwe: the Manicaland General Population Cohort. *BMJ Open* 2017; **7:** e015898.

17 Rao A, Moorhouse L, Maswera R, et al. Status of the HIV epidemic in Manicaland, east Zimbabwe prior to the outbreak of the COVID-19 pandemic. *PLoS One* 2022; **17:** e0273776.

18 Moorhouse L, Schaefer R, Eaton J, et al. Effective use and barriers to effective use of male condoms among HIV negative people in Manicaland, Zimbabwe: an HIV prevention cascade analysis. IUSSP International Population Conference; Dec 5–10, 2021.

19 Moorhouse L, Schaefer R, Eaton JW, et al. Male partners' influence on adolescent girls and young women's use of combination HIV prevention: insights from analysis of HIV-prevention cascade data collected in a general-population survey in Manicaland, Zimbabwe. AIDS; July 29–Aug 2, 2022.

20 McKay MD, Beckman RJ, Conover WJ. A comparison of three methods for selecting values of input variables in the analysis of output from a computer code. *Technometrics* 1979; **21:** 239–45.

21 Wall KM, Inambao M, Kilembe W, 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** (suppl 3)**:** e25522.

22 Baxi SM, Liu A, Bacchetti P, et al. Comparing the novel method of assessing PrEP adherence/exposure using hair samples to other pharmacologic and traditional measures. *J Acquir Immune Defic Syndr* 2015; **68:** 13–20.

23 Musinguzi N, Muganzi CD, Boum YI, et al. Comparison of subjective and objective adherence measures for preexposure prophylaxis against HIV infection among serodiscordant couples in East Africa. *AIDS* 2016; **30:** 1121–29.

24 van der Straten A, Brown ER, Marrazzo JM, et al. Divergent adherence estimates with pharmacokinetic and behavioural measures in the MTN-003 (VOICE) study. *J Int AIDS Soc* 2016; **19:** 20642.

25 Galvani AP, Pandey A, Fitzpatrick MC, Medlock J, Gray GE. Defining control of HIV epidemics. *Lancet HIV* 2018; **5:** e667–70.

26 World Health Organization. Differentiated and simplified pre-exposure prophylaxis for HIV prevention: update to WHO implementation guidance. July 27, 2022. https://www.who.int/publications/i/item/9789240053694 (accessed Sept 28, 2022).

27 Hargreaves JR, Delany-Moretlwe S, Hallett TB, 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.

28 Thomas R, Skovdal M, Galizzi MM, et al. Improving risk perception and uptake of pre-exposure prophylaxis (PrEP) through interactive feedback-based counselling with and without community engagement in young women in Manicaland, East Zimbabwe: study protocol for a pilot randomized trial. *Trials* 2019; **20:** 668.

29 Becker M, Mishra S, Aral S, et al. The contributions and future direction of Program Science in HIV/STI prevention. *Emerg Themes Epidemiol* 2018; **15:** 7.

30 Geng EH, Nash D, Phanuphak N, et al. The question of the question: impactful implementation science to address the HIV epidemic. *J Int AIDS Soc* 2022; **25:** e25898.

31 Bor J, Fischer C, Modi M, et al. Changing knowledge and attitudes towards HIV treatment-as-prevention and "undetectable= untransmittable": a systematic review. *AIDS Behav* 2021; **25:** 4209–24.

32 Roberts DA, Bridenbecker D, Haberer JE, Barnabas RV, Akullian A. The impact of prevention-effective PrEP use on HIV incidence: a mathematical modelling study. *J Int AIDS Soc* 2022; **25:** e26034.

33 Jenness SM, Le Guillou A, Lyles C, et al. The role of HIV partner services in the modern biomedical HIV prevention era: a network modeling study. *Sex Transm Dis* 2022; **49:** 801–07.

34 Bershteyn A, Sharma M, Akullian AN, et al. Impact along the HIV pre-exposure prophylaxis "cascade of prevention" in western Kenya: a mathematical modelling study. *J Int AIDS Soc* 2020; **23** (suppl 3)**:** e25527.