Modeling to Inform the Delivery of HIV Pre-Exposure Prophylaxis in Sub-Saharan Africa

David Allen Roberts

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Reading Committee:

Ruanne Barnabas, Chair

Adam Akullian

Grace John-Stewart

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Abstract

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David Allen Roberts

Chair of the Supervisory Committee:

Ruanne Barnabas

Departments of Epidemiology, Global Health, and Medicine

Daily oral tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) as HIV pre-exposure prophylaxis (PrEP) is a safe and effective method for HIV prevention and offers potential to substantially reduce HIV incidence in sub-Saharan Africa. Mathematical models are commonly used to project the cost-effectiveness of investments in PrEP in comparison to alternative resource allocation strategies. Predictive modeling can also identify individuals at elevated risk who may benefit most from PrEP. The studies contained in this dissertation address fundamental issues in estimating the cost and potential impact of PrEP implementation in sub-Saharan Africa.

First, we estimated the cost of routine PrEP delivery through maternal and child health (MCH) and family planning (FP) clinics in western Kenya (Chapter 1). PrEP delivery through MCH and FP leverages existing service delivery platforms that reach a large fraction of women at elevated HIV risk. Using data from over 20,000 PrEP encounters through 16 clinics, we estimated that the cost per client-month of PrEP dispensed to be $26.52 (2017 USD), with personnel (43%), drugs (25%), and laboratory testing (14%) accounting for the majority of costs. Postponing creatinine testing from PrEP initiation to the first follow-up visit could save 8% of total program

costs. Under Ministry of Health implementation, we projected costs would decrease by 38%, but estimates were sensitive to changes in PrEP uptake and retention.

Second, we used an individual-based transmission model calibrated to Eswatini to evaluate the sensitivity of model projections of PrEP impact and efficiency to specification HIV exposure heterogeneity (Chapter 2). A common method for introducing HIV exposure heterogeneity into a model is to stratify the population into “risk group” categories with different average sexual behavior parameters, allowing PrEP coverage to vary by risk group without having to explicitly represent individual partnerships. We found that this specification leads to a sharp tradeoff between total impact and efficiency depending on PrEP coverage levels in each risk group. In comparison, PrEP use among the general population is projected to be two times more efficient if PrEP use is prioritized during partnerships and over six times more efficient if use is further prioritized among individuals with HIV-positive partners. In addition, large incidence reductions can be achieved at low levels of PrEP coverage if PrEP use in the general population is concentrated when HIV exposure is more likely, but high levels of PrEP coverage are needed if time-varying individual risk is ignored.

Third, we developed and validated HIV risk prediction models incorporating individual-level and geospatial covariates using data from nearly 20,000 individuals in a population-based cohort in rural KwaZulu-Natal, South Africa (Chapter 3). Individual-level predictors included demographic, socioeconomic, and sexual behavior measures, while geospatial covariates included local estimates of community HIV prevalence and viral load. We compared full models to simpler models restricted to only individual-level covariates or only age and geospatial covariates. Models using only age group and geospatial covariates had similar performance (women: area under the receiver operating characteristic curve (AUROC) = 0.65, men: AUROC = 0.71) to the full models (women: AUROC = 0.68, men: AUROC = 0.72). In addition, geospatial models more accurately identified high incidence regions than individual-level models; the 20%

of the study area with the highest predicted risk accounted for 60% of the high incidence areas when using geospatial models but only 13% using models with only individual-level covariates.

These findings have implications for PrEP policies. Our primary costing study identified service delivery bottlenecks and cost drivers that can inform efforts to streamline PrEP delivery. By ignoring the alignment of PrEP use with time-varying individual HIV exposure, models using a risk group specification may overestimate the cost and underestimate the impact of widespread PrEP availability. Finally, local estimates of HIV prevalence can help identify individuals and areas to prioritize for PrEP services to maximize impact.

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DEDICATION

To my parents

INTRODUCTION

Human immunodeficiency virus (HIV) is a leading cause of mortality in sub-Saharan Africa, resulting in an estimated 460,000 deaths in 2020 [1]. Despite the advent of effective prevention and treatment methods, HIV incidence in sub-Saharan Africa remains high, with an estimated 870,000 people newly infected in 2020 [1]. Rapid scale-up of treatment and prevention is a global moral imperative to alleviate morbidity and mortality.

Background on HIV prevention methods

Several effective HIV prevention methods have been established. Male circumcision reduces the risk of HIV acquisition among men by 60% [2–4]. Antiretroviral therapy (ART), a lifesaving treatment for people living with HIV (PLHIV), also drastically reduces transmission to partners. Initially, ART was recommended only among PLHIV who had evidence of severe immunosuppression, either by clinical staging or by CD4+ immune cell count (e.g., < 200 cells/μL). In a landmark randomized trial among serodiscordant couples first published in 2011, early ART initiation (CD4 > 350) in the partner living with HIV reduced HIV transmission risk to their uninfected partner by 93% [5]. Subsequent cohort studies of over 2,000 serodiscordant couples with over 150,000 reported condomless sex acts found zero cases of phylogenetically-linked HIV transmission when the partner living with HIV was virally suppressed [6,7]. The evidence for HIV "treatment as prevention", in addition to accumulating evidence that earlier ART initiation reduces morbidity and mortality [8,9], spurred guidelines that recommended immediate ART initiation for all PLHIV as well as ambitious global treatment targets, such as the 2014 UNAIDS target of 90-90-90 (90% of PLHIV knowing their status, 90% of those knowing their status linked to care, and 90% of those linked to care virally suppressed) by 2020 [10].

In addition to reducing transmissibility among PLHIV, antiretroviral drugs can also be used as pre-exposure prophylaxis (PrEP) among HIV-negative individuals. In 2010, a trial of daily oral tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) among men who have sex with men (MSM) and transgender women reported that randomization to the TDF/FTC arm reduced HIV incidence by 44% relative to the placebo arm [11]. In 2012, a randomized trial among serodiscordant heterosexual couples in sub-Saharan Africa found a 75% reduction in incidence in the PrEP arm [12]. However, in the same issue of the *New England Journal of Medicine*, a separate randomized trial reported that the same intervention had no effect on HIV incidence among African women aged 18-35 [13]. The discrepant results between PrEP trials among MSM and serodiscordant couples compared to those among young African women were reproduced in subsequent trials [14]. Meta-analyses of PrEP trials found that medication adherence strongly predicted efficacy, such that young women with high adherence (>75%) had an estimated 61% risk reduction [15,16]. A sub study within the Partners PrEP trial found 100% efficacy (95% CI: 83.7%-100%) among participants with very high adherence (> 97% by electronic monitoring and by unannounced pill counts) [17]. Taken together, oral TDF/FTC as PrEP is a safe and highly efficacious HIV prevention intervention when taken regularly.

Despite the initial results from randomized trials, PrEP offers particular promise as a prevention tool for women. Circumcision, ART, and condom use require partner action to achieve prevention, whereas PrEP is controlled by the user. HIV incidence is disproportionately high among young women due to low ART use among male partners [18] as well as several interacting biological, behavioral, and structural factors [19]. Therefore, high uptake of effective HIV prevention strategies among young women would have considerable impact. Furthermore, the low adherence observed in placebo-controlled randomized trials of an unproven product tends to improve with open-label access and counseling on efficacy, and steep declines in incidence have been observed in open-label extensions and demonstration projects [20]. However, several of the same factors that increase vulnerability to HIV, including poverty, gender inequity, and intimate

partner violence, also act as barriers to regular PrEP use [21]. PrEP research has thus shifted to the development of new formulations and improved service delivery strategies that can circumvent barriers to use [22].

PrEP implementation

Following the clinical trial results, demonstration projects and implementation studies have studied PrEP delivery to subpopulations at elevated HIV risk, including serodiscordant couples, adolescent girls and young women (AGYW), pregnant and postpartum women, female sex workers (FSW), and MSM. By the end of 2019, PrEP was approved by drug regulatory authorities in 12 African countries, and over 130,000 individuals had initiated PrEP [23]. Early observations from implementation studies have shown considerable uptake of PrEP but high rates of discontinuation by six months after initiation. Reasons for discontinuation include low perceived risk, pill burden, side effects, stigma, or travel time [24–26]. However, predictors of initiation, continuation, and adherence include reporting a partner whose status is HIV-positive or unknown and perceiving to be at risk for acquiring HIV [24,25,27–30]. Additionally, many individuals who discontinue PrEP return to restart it later, suggesting a change in their perception of its benefits [31,32].

An important feature of PrEP is that high adherence is only necessary during periods of HIV exposure, and discontinuation is recommended when risk is low. This paradigm, known as "prevention-effective adherence" [33], complicates evaluation of the performance of PrEP programs, as the denominator for who should use PrEP requires some assessment of risk. Unlike ART programs, in which all PLHIV should initiate and adhere to treatment, PrEP programs may be highly effective even when a minority of HIV-negative individuals are highly adherent, if adherence is closely aligned with HIV exposure. Clinical risk prediction tools have been developed to guide PrEP delivery in sub-Saharan Africa, and several have been validated against HIV incidence [34–42]. These studies have informed screening tools to help providers counsel clients

on PrEP [43]. A major challenge with these tools is their reliance on self-reported sexual behavior measures, which are prone to misclassification and are also dynamic, requiring frequent reassessment [44]. Another approach has been to geographically prioritize resources for PrEP based. For example, national PrEP rollout in Kenya in 2017 considered county-level estimates of HIV incidence in order to determine where PrEP programs would focus on key populations and where it would be available to all [43].

Health economic evaluation of PrEP

The mix of benefits and challenges of PrEP implementation raise the question of how much spending should be allocated to PrEP versus other interventions, such as improving ART programs. With stagnating funding for HIV programs [45], policymakers need to determine how to best use resources to maximize impact on new infections and deaths. Mathematical models are an important tool for estimating the population-level impact of scaling up HIV interventions and have been widely used to inform funding decisions [46–51]. Modeling studies can account for the benefits conferred to both those receiving interventions as well as their contacts. For example, PrEP use among HIV-negative women can protect not only those women from HIV infection but also their partners and their children. By including both costs and health benefits, mathematical models can estimate the cost-effectiveness of interventions like PrEP. A health intervention is considered to be cost-effective if the additional health benefits provided by the intervention outweigh the incremental cost required to implement it [52]. The relation of costs to benefits is usually expressed in an incremental cost-effectiveness ratio (ICER) which divides the change in costs by the change in health benefits, generally measured in disability-adjusted life-years (DALYs) [53]. Determination as to whether an intervention is cost-effective requires comparing the associated ICER with a decision threshold. Such a threshold generally reflects the opportunity cost of health benefits foregone due to the addition of the intervention in question [52]. Selection and estimation of cost-effectiveness thresholds continue to be debated and revised;

recent analyses in sub-Saharan Africa have used thresholds of $500-$750/DALY averted [54–59]. Additionally, models can estimate the overall budget impact of scaling up an intervention, informing policymakers as to whether an intervention is affordable [60].

Numerous mathematical modeling analyses have estimated the cost-effectiveness and affordability of PrEP use in sub-Saharan Africa [61]. Several models have estimated that PrEP may be cost-effective if prioritized for key populations (small high incidence subgroups such FSW or serodiscordant couples) but that PrEP use in the general population is not [56,62–68]. These results have shaped World Health Organization (WHO) guidelines that recommend PrEP for populations with average annual HIV incidence of at least 3% [69]. A recent review of the modeling literature summarized that evidence for the affordability and cost-effectiveness of PrEP use in the general population is limited, especially in an era of expanding ART coverage and when thresholds of $500 or $750/DALY averted are used [61]. In modeling analyses of optimal prevention portfolios, PrEP is only included when the budgets are large, as other interventions (e.g., expanded ART coverage, male circumcision, or behavioral interventions) are estimated to be more cost-effective and are thus prioritized earlier [62,63,70–72].

To estimate the PrEP cost-effectiveness, models must specify the cost of PrEP. However, few studies have collected primary data on the cost to deliver PrEP services, and most of the evidence has come from programs for serodiscordant couples or sex workers [71,73,74]. In addition to drug costs and laboratory testing, PrEP delivery programs also incur costs for engagement and counseling. The cost may also depend on the platform used to deliver PrEP services. A program that integrates PrEP into schools or clinics may benefit from economies of scope, whereas an outreach program for key populations may incur additional costs. Primary costing data from PrEP programs can therefore fill a key evidence gap for cost-effectiveness analyses and budgetary planning.

In addition to PrEP costs, models must also specify how PrEP use aligns with HIV exposure. To understand this issue, it is first necessary to review how heterogeneity in HIV risk is specified in mathematical models.

Structure of HIV transmission models

HIV transmission models can be broadly classified into population-based (e.g., compartmental) or individual-based approaches [75]. Population-based models stratify the simulated population into mutually exclusive and exhaustive compartments based on characteristics such as age, sex, HIV status, and intervention use. During the simulation, the model keeps track of the size of each compartment (states) and the rate at which the size is changing over time (flows). Within each compartment, all individuals are assumed to be homogeneous, and the status of distinct individuals is not explicitly tracked. Population characteristics of interest are calculated directly from states (e.g., HIV prevalence) or flows (e.g., HIV incidence or mortality) for time points of interest.

In contrast, individual-based models (sometimes referred to as agent-based models or microsimulations) explicitly represent each individual in a simulated population [76]. Each individual is assigned a set of characteristics, such as age or HIV status, which can change over time based on interactions with other individuals or with the environment. Functions that govern changes in characteristics are defined at the level of the individual, and population measures of interest such as prevalence or incidence are computed directly by aggregating over individuals. Therefore, individual-based models represent a “bottom-up” approach, in which population-level phenomena emerge from the interactions and behaviors of individual units.

Modeling individual agents provides significant flexibility that can be useful for HIV applications. HIV transmission is influenced by numerous factors, including sexual behavior, intervention use, biological cofactors, demography, and geography. In compartmental models, each factor adds substantial model complexity, as the number of items that must be tracked by

the model increases exponentially [77]. In contrast, each additional attribute does not increase the number of agents that an individual-based model needs to track. Therefore, when heterogeneous transmission dynamics are important for the scientific question at hand, individual-based models may be preferred. However, computational requirements for individual-based models can be immense if on the number of agents and interactions to be simulated is large [78]. Compiled languages with efficient memory allocation like C or C++ can improve runtimes but may require user interfaces for wide applicability. Parallelization can speed up some processes, especially for assessing parameter uncertainty or sensitivity analyses, but requires distributed computing systems. If population totals are of interest, the number of simulated individuals can sometimes be substantially downscaled to speed up run time, but stochastic effects may become problematic as the simulated population becomes smaller. Therefore, compartmental models may be preferred when simpler approaches can address the scientific question of interest.

Representation of HIV exposure heterogeneity

Partnership dynamics are of particular importance in the modeling of sexually transmitted diseases. The number and types of partnerships an individual has primarily determines their baseline HIV risk, and the distribution of partnerships influences how heterogeneous HIV risk is in the population. Furthermore, decisions about intervention use are often made based on the number of partnerships (e.g., interventions for female sex workers) or the types of partnerships (e.g., interventions for serodiscordant couples). In individual-based models, partnership characteristics are modeled explicitly and can influence individual behaviors or interventions. Partnership patterns represented in individual-based models can also provide insight into transmission dynamics and population-level behavior. Additionally, network-level effects, such as network size, concurrency, centrality, and density, can dramatically affect transmission rate [79–82]. Network structures can be explicitly represented using individual-based models, with individuals serving as nodes and partnerships representing edges.

Compartmental models can also include heterogeneous partnership features, but implementation can be cumbersome for complex dynamics. To incorporate heterogeneity, compartmental models often stratify the population into 2-4 “risk groups”, in which higher risk groups have greater partner turnover and sexual frequency [83]. Within each risk group, all individuals are homogenous, giving them the same risk of transmission. Assortativity in sexual behavior can be represented with mixing matrices, which become exponentially more complex with each added feature (e.g., age, sex, race, or HIV status) [84]. Furthermore, network-level effects are ignored in compartmental models since specific partnerships are not represented.

Heterogeneity and intervention impact

A major area of research for HIV epidemic models has been to estimate the population-level impact of expanding ART coverage [85–90]. Several types of models have been used, and differences between modeled estimates have been attributed more to assumptions about infectivity in acute HIV infection and ART coverage by age and sex than to whether the model was compartmental or individual-based [85,91]. Several features may explain why simpler models can perform reasonably well for modeling ART coverage. Mechanistic HIV transmission models are generally underdetermined by the available data, with many more parameters than data points to fit to [92]. As such, simple compartmental models with basic risk heterogeneity can closely fit time trends in HIV prevalence [93]. Since HIV-infection is an absorbing state, and ART is recommended for all HIV-positive individuals for their lifetime, models of ART coverage can generally be simpler than models of interventions of shorter durations and for which eligibility is dynamic. However, in the era of universal test-and-treat, accurate representation of individual characteristics of those not engaged in care, such as mobility and sexual networks, may become increasingly important, and more flexible models may be desired [94,95].

Modeling PrEP coverage has several challenges that may be more amenable to individual-based approaches. Unlike ART, the appropriate duration of PrEP use varies for each

individual depending on number of partnerships, partner HIV status, partner viral suppression, sexual frequency, condom use, and other factors [73,96]. As discussed previously, dynamic partnership factors are difficult to represent in compartmental models, which have instead generally investigated PrEP coverage prioritized to specific risk groups [61]. Models estimate that PrEP use among subsets of the population at highest risk for infection, such as sex workers, greatly increases cost-effectiveness but limits overall impact, since the proportion of the population covered is small [97]. In contrast, models of widespread PrEP use in the population, including models focused on adolescent girls and young women, have not found PrEP to be cost-effective [61]. However, the structure of these models does not allow for dynamic changes in risk within strata defined by age, sex, and risk group. For example, the largest fraction of the population is usually assigned to the lowest risk group, with low rates of partner turnover. However, such categorization masks substantial within-group heterogeneity based on factors such as partner HIV status, viral load, and condom use. Since the cost-effectiveness of PrEP delivery is highly dependent on how well PrEP use is aligned with HIV risk [68], accurate modeling of partnership dynamics in generalized epidemics is essential. If PrEP use is correlated with transient periods of HIV exposure, widespread PrEP availability may both have substantial impact and be cost-effective.

Individual-based models have also been used to model PrEP delivery to MSM in the US based on specific guidelines. One study estimated the impact of CDC guidelines for PrEP use, which included number of partnerships (sexual network degree), knowledge of partner HIV status, serodiscordancy, and history of unprotected anal intercourse [98]. This analysis required an individual-based model that tracked each of these partnership characteristics and allowed them to influence the probability of PrEP use. However, individual-based models have seen comparatively little use for modeling PrEP use in sub-Saharan Africa. A notable exception is a recent analysis from South Africa used an IBM to estimate the cost-effectiveness of PrEP use concentrated during periods of condomless sex [99]. Contrary to the results of most prior

analyses, they found that PrEP use among 15–64-year-olds was cost-effective across all simulations, whereas simulations that assumed that PrEP use was unrelated to condomless sex were never cost-effective. This model allows time-varying individual HIV risk to influence PrEP use, but it does not explicitly represent partnerships formed between individuals and therefore does not allow partner HIV status to impact PrEP coverage.

In summary, individual-based models offer a promising approach for realistically modeling PrEP usage. Since partnerships can be explicitly tracked, characteristics such as number of partners, partner HIV status, and condom usage can serve as triggers for PrEP use or discontinuation, reflecting either guideline-based delivery strategies or merely individual self-selection based on HIV risk. Compartmental models can also incorporate risk heterogeneity, but specific partnership characteristics are much more difficult to include. The extent to which model structure matters will depend on the specific of the research question of interest, and direct comparisons of model structure have not been conducted for PrEP specifically.

Aims of this dissertation

This dissertation contains three studies to inform the delivery of PrEP in sub-Saharan Africa. In Chapter 1, we estimate the cost of PrEP delivery to women accessing maternal and child health and family planning clinics in Kenya. In Chapter 2, we investigate how model representation of HIV exposure heterogeneity influences estimates of PrEP impact and efficiency. In Chapter 3, we develop and evaluate HIV risk prediction tools that incorporate geospatial data to identify individuals and areas at the highest risk for HIV infection in South Africa.

CHAPTER 1

Cost of HIV pre-exposure prophylaxis delivery through routine maternal and child health and family planning clinics in western Kenya

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Abstract

Introduction

Understanding the cost of strategies to reach and deliver pre-exposure prophylaxis (PrEP) to priority populations is essential to assess the cost-effectiveness and budget impact of HIV prevention programs. Providing PrEP through maternal and child health and family planning clinics offers a promising strategy to reach women in high HIV burden settings. We estimated incremental costs and explored the cost drivers of integrating PrEP delivery into routine maternal and child health and family planning services in Kenya.

Methods

We conducted a costing study from the provider perspective within the PrEP Implementation for Young Women and Adolescents program in western Kenya. We identified all within- and above-facility activities supporting PrEP delivery and measured clinical service time using time-and-motion studies. We obtained input costs from program budgets, expenditure records and staff interviews. We estimated changes in costs if creatinine testing were postponed from initiation to first follow-up visit and if PrEP were prioritized to clients at high HIV risk using a behavioral risk assessment tool. We also projected costs under Ministry of Health (MOH) implementation assuming MOH salaries and program supervision. We estimated annual numbers of PrEP visits from program data abstracted from 16 facilities between November 2017 and June 2018. We report the cost per client-month of PrEP dispensed in 2017 USD.

Results

For an annual program output of 24,005 screenings, 4198 PrEP initiations and 4427 follow-up visits, the average cost per client-month of PrEP dispensed in the study was $26.52. Personnel, drugs and laboratory tests comprised 43%, 25% and 14% of program costs respectively. Postponing creatinine testing and prioritizing PrEP delivery to clients at high HIV risk reduced total

program costs by 8% and 14% respectively. In the MOH scenario assuming no changes in outputs, the projected cost per client-month of PrEP dispensed decreased to $16.54 and total program costs decreased by 38%.

Conclusions

Incremental PrEP costs are sensitive to the service delivery strategy used to engage priority populations. Postponing creatinine testing and prioritizing PrEP delivery to clients at high HIV risk may reduce costs. Context-specific cost data are crucial to assess the cost-effectiveness and affordability of PrEP delivery models.

Introduction

Despite remarkable progress in expanding access to antiretroviral therapy (ART), an estimated 200,000 women aged 15 to 24 in sub-Saharan Africa were newly infected with HIV in 2017 [100]. Pre-exposure prophylaxis (PrEP) prevents HIV infection and offers promise as a female-controlled HIV prevention strategy [15,21]. Effective models for PrEP delivery to young women are needed to maximize population-level benefits. Budgets have competing demands, and evidence on the cost, affordability and potential impact of PrEP programs is necessary to guide policy decisions about the choice and implementation of prevention interventions [22].

PrEP programs that achieve widespread coverage and adherence among individuals at high risk of acquiring HIV infection (priority populations) will maximize population-level impact [46,63,65,66,101–103]. However, the cost and yield of engaging priority populations will vary across settings, affecting cost-effectiveness and budget impact conclusions [68]. While several studies have projected the potential cost-effectiveness of PrEP delivery in sub-Saharan Africa, few service delivery models for identifying and providing PrEP to priority populations have been defined that could substantiate the costs assumed in modelling studies [62,70,104–107]. Primary costing studies of PrEP delivery are sparse, and research describing how costs vary across outreach and service delivery strategies is limited [73,71,74].

Integrating PrEP into other medical and nonmedical services may be an efficient strategy for reaching priority populations. For example, offering PrEP to women through maternal and child health (MCH) or family planning (FP) programs may have low incremental costs. Pregnant and postpartum women in sub-Saharan Africa have high HIV incidence, and recent evidence suggests that HIV risk may be elevated in pregnancy and postpartum periods [108–110]. However, no prior studies have estimated the cost of delivering PrEP to women through MCH and FP clinics. A previous modelling study of PrEP administration to pregnant and breastfeeding women varied PrEP program costs per patient-year from $80 to $720 per year, reflecting large uncertainty in the absence of data [111].

We present the results from a costing study for the PrEP Implementation for Young Women and Adolescents (PrIYA) program, an implementation project delivering PrEP in 16 MCH and FP clinics in western Kenya. We estimated the incremental cost of integrating PrEP delivery into routine MCH and FP services. Furthermore, we explored the cost implications of service delivery modifications such as timing of creatinine monitoring and prioritized delivery to women identified as having high risk for HIV infection.

Methods

Study setting

The PrIYA program is an implementation project to evaluate PrEP delivery strategies to young women through MCH and FP clinics in Kenya [112]. PrIYA is part of the DREAMS Innovation Challenge funded by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and managed by JSI Research & Training Institute, Inc. In collaboration with Department of Health and Sanitation, Kisumu County and the Kenya National AIDS and STI Control Program (NASCOP), PrIYA has been implemented in 16 facilities (nine public hospitals, four mission hospitals, one private hospital, one health center and one dispensary) in Kisumu County and involves centralized supervision and administration by program staff. This region has an estimated adult HIV prevalence of 16% and high incidence of HIV among pregnant women [113,114]. Women attending MCH and FP clinics are screened by nurses for behavioral risk factors for HIV and willingness to consider PrEP. All medically eligible (HIV-negative and creatinine clearance <50 mL/min by national guidelines) women who are interested in PrEP are offered same-day PrEP initiation and can return to the same clinic for monthly follow-up visits and refills [115]. PrEP is delivered either by the same nurse providing routine MCH and FP services or by a separate nurse in an adjoining room. Nurses perform point-of-care creatinine testing at initiation and dispense medication directly to clients. Additional program details have been described elsewhere [116]. The PrIYA protocol was approved by the University of Washington

Human Subjects Division and the Kenyatta National Hospital/University of Nairobi Ethical Review Committee. Participants provided oral informed consent.

Costs

We estimated the incremental economic cost of PrEP delivery from the provider perspective following the principles outlined in the Global Health Cost Consortium Reference Case [117]. We categorized costs as either fixed (constant irrespective of program output over the course of one year) or variable (costs directly related to program output). To estimate variable costs, we measured resource use at a sample of eight facilities representative of clinic size, ownership (public, mission or private), and type (MCH vs FP). For each PrEP clinical activity (behavioral screening and counselling, initiation, and follow-up visits), we measured the cost of drugs, clinical personnel, laboratory testing and other supplies. We estimated clinical personnel unit costs using time-and-motion studies and multiplying the average time spent in each activity (in minutes) by the cost per minute (including both salary and benefits). For supplies and commodity costs, we observed resource use for each activity and multiplied the relevant quantity by input costs obtained from program budgets or centralized price lists. Drug costs for oral co-formulated tenofovir disoproxil fumarate/emtricitabine ($6.75 per 30 days) included the cost of purchase from the manufacturer as well as central storage and distribution costs. Fixed costs included centralized start-up costs (microplanning and training), capital (equipment, furniture), overheads (e.g., building costs, transportation and airtime) and administrative and supervisory personnel supporting PrEP delivery. We annualized start-up and capital costs over the expected useful life (assumed to be five years or fewer) using a discount rate of 3% [117]. We allocated building space based on the proportion of all MCH or FP visits that included a PrEP encounter. We multiplied the average size of the room in which PrEP screening and initiation were conducted by a rental rate estimated from nearby commercial properties. This analysis excludes the cost of any research activities that would not be part of routine PrEP service delivery.

We calculated program-level average unit costs for each clinical activity (screening, initiation, and follow-up visits) by allocating fixed costs to each activity and adding the activity's average variable cost. Fixed costs that could not be assigned exclusively to a single activity were apportioned using hourly rate allocation based on clinical service time [118]. We adjusted all costs to 2017 currency using GDP deflators and converted to US dollars (USD) using the 2017 average exchange rate (1 USD = KSh 103.40) [119]. We analyzed costs in Excel 2018 (Microsoft, Redmond, USA). Additional details about the costing methodology are available in Appendix A. The Excel file used for the analysis is available at:

https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fjia2.25296&file=jia225296-sup-0002-Spreadsheet.xlsx

Program volume

We used data collected as part of routine monitoring to estimate the numbers of women screened, initiated, and dispensed PrEP over a one-year period. Study staff abstracted standardized client records in all 16 facilities from 20 November 2017 to 15 June 2018. We extrapolated program volume to one year assuming no changes in the pattern of visits. We analyzed program volume using R version 3.5.1 [120]. Further details are available in Appendix A.

Cost metrics

We estimated the total program cost (across 16 facilities) by multiplying the number of screening, initiation and follow-up visits by their respective average unit costs and summing the total. We then calculated the cost per client-month of PrEP dispensed as follows:

$$\text{Cost per client-month of PrEP dispensed} = \frac{\text{Total program cost}}{\text{\# months of PrEP dispensed}}$$

Scenarios

To evaluate the potential cost ramifications of different delivery scenarios, we projected costs incurred under the following conditions: (1) postponing creatinine testing to the first follow-up visit rather than initiation; (2) restricting PrEP initiation to clients identified as having high risk for acquiring HIV; and (3) if the program were entirely implemented through the Ministry of Health (MOH).

The first scenario (postponing creatinine testing) is motivated both by the low prevalence (8/4007) of ineligible creatinine tests among PrIYA clients at initiation as well as the considerable proportion of clients who choose to discontinue PrEP within a month after initiating. This scenario is expected to decrease program costs by reducing the number of creatinine tests conducted. For the second scenario, we categorized clients as having high risk of HIV infection based on reporting at least one of the following risk factors assessed at their first PrEP screening visit: (1) current partner with unknown or positive HIV status; (2) positive rapid plasma regain syphilis test; or (3) reporting at least one of the following in the prior six months: (a) exchanging sex for money or other favors; (b) diagnosis or treatment for a sexually transmitted infection; (c) forced to have sex against will; (d) experiencing intimate partner violence; (e) sharing needles while engaging in injection drug use; or (f) using post-exposure prophylaxis more than twice. Assessment of these specific risk factors for PrEP consideration is recommended as part of national guidelines [115]. This scenario is expected to decrease total program costs by reducing the number of clients who initiate and continue on PrEP.

In the third scenario, we revised costs to reflect a program implemented entirely through the MOH. First, we adjusted clinical personnel salaries to reflect government cadre-specific salary scales (including benefits). Second, we estimated the cost of facility, sub-county and county

supervisory activities that are planned to subsume PrIYA administrative staff responsibilities. Last, we replaced the cost of the point-of-care assay used in PrIYA with the average facility price for creatinine testing. These projections assume no changes in program output. We conducted a sensitivity analysis under the MOH scenario to explore how costs might change with varying uptake and retention, assuming constant fixed costs.

Results

Overall program costs and unit costs

For an annual program output of 24,005 screenings, 4,198 PrEP initiations, and 4,427 follow-up visits, the estimated total annual program cost as implemented was $204,253 (Table 1.1). Personnel (43%), drugs (25%), and lab tests (14%) comprised the largest cost categories. Supervision and administration accounted for nearly two-thirds of personnel costs. The average cost per client-month of PrEP dispensed was $26.52. The unit costs of PrEP screening, initiation, and follow-up encounters were $2.91, $19.18, and $12.16, respectively (Table 1.2).

Cost implications of service delivery modifications

Table 1.3 shows the estimated impact of postponing creatinine testing to the first follow-up visit or prioritizing PrEP initiation to clients at high risk of HIV infection on the total program cost and cost per month of PrEP dispensed. Postponing creatinine testing would reduce the annual number of tests by two-thirds (from 4,198 to 1,370) and decreases estimated program costs by 7.5%, resulting in a cost of $24.53 per client-month of PrEP dispensed. Clients at high risk for HIV infection (at least one baseline risk factor) accounted for 34% of screening encounters but 68% of PrEP initiations. The most common risk factor was having a partner of unknown status (89% of clients with at least one baseline risk factor). Restricting PrEP initiation to clients at high risk of HIV lowered total program costs by 14%. Under this scenario, the cost per client-month of PrEP dispensed only to clients with high risk of HIV infection was $31.88.

Projected costs under MOH implementation

We projected how program costs might change under Kisumu County MOH implementation assuming no changes in outputs. Substituting public-sector clinical staff salaries for PrIYA nurse salaries decreased the cost per client-month of PrEP dispensed from $26.52 to $25.92 (Table 1.4). Using the estimated cost of planned MOH supervision in place of PrIYA administration lowered the cost per client-month of PrEP dispensed from $25.92 to $18.00. Replacing the cost of the point-of-care creatinine assay with facility creatinine prices further decreased the cost per client-month of PrEP dispensed to $16.54. Overall, we estimated the total program cost under the MOH scenario to be $127,421, which constitutes a 38% decrease compared to PrIYA implementation, and the average cost per client-month of PrEP dispensed decreased to $16.54. The largest cost components were drugs (41%), personnel (33%), and lab tests (15%) (Figure 1.1 and Appendix A, Figure A.3). Overall personnel costs were 52% lower under the assumption that project coordinator staff activities would be subsumed under existing facility and above-facility supervisory structures.

We evaluated the sensitivity of costs under the MOH scenario to assumptions about program output. Doubling both the proportion of screening encounters that result in an initiation (from 17% as observed to 34%) and the average number of follow-up visits within a year among clients with at least one follow-up visit (from 2.6 as observed to 5) increases estimated program costs by 224% and lowers the cost per client-month of PrEP dispensed to $12.96. In comparison, halving both uptake and retention increases the cost per client-month of PrEP dispensed to $25.31 while reducing total program costs by 42%.

Discussion

We explored the relationship between costs and service delivery strategies using primary data from an implementation study of integrating PrEP into MCH and FP clinics, as part of the

DREAMS Innovation Challenge funded by PEPFAR. Offering PrEP to women through MCH and FP clinics as done in this study would cost on average $26.52 per client-month of PrEP dispensed, with personnel and drugs accounting for 43% and 25% of program costs, respectively. In comparison, an analysis of PrEP delivery to female sex workers and men who have sex with men (MSM) in Nairobi that found that drugs accounted for 15-19% of total costs [71]. The Nairobi study estimated higher unit costs ($33-44 per client-month of PrEP dispensed) than our study despite similar drug unit costs. The difference in the two program costs may reflect the increased resources used in outreach efforts needed to contact FSW and MSM compared to a clinic-based strategy that integrated PrEP within existing services. However, our estimated unit costs are higher than analyses among FSW and MSM conducted in South Africa, which estimated costs per client-month of $17-18 [65,73]. This program had substantially lower drug costs (< $5 per month) as well as high uptake and retention, both of which contributed to lower unit costs. Additional efforts are needed to better understand differences between delivery strategies and to standardize cost reporting.

Prioritizing PrEP delivery to clients at high risk for HIV infection can reduce total costs if these clients are easily identified. In our study, total program costs decrease by 14% if initiation occurs only among clients with baseline behavioral risk factors. Clients with baseline risk factors were more likely to initiate PrEP, demonstrating that risk prioritization is to some extent occurring as these clients self-select to initiate PrEP when universally offered [112]. Eighty-nine percent of clients with a baseline risk factor had a partner with unknown HIV status, highlighting that increasing partner testing could improve client risk assessment. Given the low cost of HIV self-test kits ($2 as negotiated by the Bill and Melinda Gates Foundation), providing HIV self-test kits to promote partner testing might be an efficient method for refining client decisions about PrEP [121,122]. The utility of these strategies will depend on the how well risk can be evaluated by both client and provider. An ongoing randomized trial using an HIV risk assessment tool designed for peripartum women and self-testing to guide PrEP delivery among pregnant women will help

evaluate the potential impact of this strategy [34,123]. In the process of risk assessment, it is also important that PrEP delivery programs do not stigmatize women or suggest they are the primary population responsible for HIV prevention. Validated and context-specific risk assessment tools for a range of populations, including men, are needed to guide prevention programs.

Creatinine testing consumed significant resources, and previous studies of reducing the frequency of kidney function monitoring have not shown harm [124]. Due to high numbers of clients discontinuing PrEP after initiation, deferral of creatinine testing from initiation to the first follow-up visit would save an estimated 7.5% of overall program costs. Notably, only 0.2% of clients in the program had creatinine clearance measured at less than 50 mL/min at initiation (the NASCOP threshold for PrEP ineligibility). Postponing creatinine testing by one month does not present a major departure from Kenya national guidelines, which recommend baseline and then annual testing but permit PrEP delivery without testing if laboratory facilities are unavailable [115].

Implementation projects are essential for demonstrating the impact and costs of strategies for introducing PrEP to at-risk populations; however, their costs may not reflect typical MOH settings. Our analysis projects overall program costs could decrease by 38% under routine MOH implementation. This large potential cost reduction is consistent with previous PrEP costing studies that have compared observed costs to projections in an MOH scenario. A demonstration project of PrEP as a bridge to ART among serodiscordant couples in Uganda reported estimated unit costs of $408 (as studied) and $92 (MOH scenario) per couple per year [74]. However, the projected costs in the MOH scenario were highly sensitive to assumptions about program volume. The degree to which unit costs will change will depend on how program output is affected by changes in staff and supervision.

Within a facility-based setting, additional service delivery modifications may affect PrEP costs. For example, providing multiple months of PrEP prescription for established clients could improve retention by requiring fewer visits, as has been demonstrated in some ART programs [125,126]. Additionally, task shifting PrEP screening counselling to HTS counsellors may reduce

costs and alleviate nurse time burden. HIV testing provides a natural entry point for discussions about HIV prevention and PrEP use, as PrEP initiation is contingent upon a negative test and behavioral assessment. While task shifting HIV services has demonstrated efficiency gains across a wide variety of settings [127,128], it is possible that program output would be affected. Implementation studies are needed to evaluate the utility of these models.

Our analysis has several limitations. The baseline behavioral risk factors used to classify clients are not based on a validated risk score and may not fully capture HIV risk. The unit cost of client-month of PrEP dispensed reflects neither the client's true HIV risk nor drug adherence, both of which are crucial parameters for cost-effectiveness studies. In addition, our assumption of constant volume with reduced costs under MOH implementation may be unrealistic. Program output may decrease without PrIYA clinical staff and program support. Alternatively, PrEP uptake and retention may increase over time with expanded community awareness and sensitization, and counselling time may decrease as clients become more familiar with the intervention. Improving demand generation, messaging, and support strategies will be critical to increasing PrEP usage in this population [21,129]. We did not address whether additional MOH clinical staff would be required to support PrEP initiation, which would add human resource costs. Last, the 16 facilities involved in PrIYA were primarily hospitals in urban and semi-urban environments that may benefit from economies of scale. These facilities may not be representative of all MCH and FP clinics in western Kenya, so caution must be taken in generalizing these cost estimates to other settings. We were not able to address facility-level variation in PrEP service delivery costs given the centralized implementation of the program; further research under routine conditions is needed to identify facility-level drivers of service delivery costs.

Despite these limitations, cost projections are useful to evaluate the relative impact that program modifications may have on budgets. Benefits of offering PrEP through MCH and FP services include potential economies of scope and convenient access to a priority population, without ancillary outreach activities to needed reach them. However, the degree to which women

perceive themselves at risk and choose to take PrEP as part of routine MCH and FP services will critically affect costs, coverage, and impact. While our study focused on a PrEP delivery strategy for women, ongoing cost data collection efforts nested in implementation science evaluations are needed to provide up-to-date evidence on the costs of delivery strategies to reach other priority populations, including adolescents, serodiscordant couples, FSW and MSM. Such data will be critical for understanding the potential success of PrEP programs at the country level and will serve as invaluable inputs to mathematical models that aim to produce more accurate estimates of potential cost-effectiveness.

Conclusions

MCH and FP services offer a potential PrEP delivery platform to efficiently reach large numbers of at-risk women in high HIV burden settings. Postponing creatinine testing and prioritizing PrEP delivery to clients at high HIV risk are potential strategies to reduce costs. Subpopulation-specific costing studies are needed to evaluate the costs of delivering PrEP to priority populations in other settings. Cost-effectiveness studies of PrEP scale-up need context-specific costing data in order to accurately inform policy.

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Table 1.1: Total program cost and average cost per client-month of PrEP dispensed (2017 USD)

	Total annual cost (USD)	Average cost per client-month of PrEP dispensed (USD)
Variable		
Personnel (clinical)	37,535	4.87
Drugs	51,997	6.75
Laboratory testing	27,830	3.61
Other supplies	3,616	0.47
Sub-total	*120,978*	*15.71*
Fixed		
Microplanning	1,366	0.18
Training	2,898	0.38
Personnel (supervision and administration)	50,924	6.61
Capital (e.g., creatinine machines, furniture)	3,925	0.51
Overhead (e.g., building, airtime, transportation)	24,162	3.14
Sub-total	*83,275*	*10.81*
Summary	**204,253**	**26.52**

Table 1.2: Unit cost breakdown by clinical activity (2017 USD)

	Screening	Initiation	Follow-up[†]
Variable unit cost			
Personnel (clinical)	0.91	1.47	2.14
Drugs	0.00	6.75	5.34
Laboratory testing	0.00	5.76	0.83
Other supplies	0.02	0.32	0.41
Sub-total	*0.93*	*14.30*	*8.71*
Fixed unit cost	1.98	4.88	3.45
Total unit cost (variable + fixed)	**2.91**	**19.18**	**12.16**
Number	24,005	4,198	4,427
Total annual cost	**69,876**	**80,525**	**53,852**

[†]Follow-up unit costs are weighted averages of the costs of visits with (79%) and without (21%) PrEP dispensation

Table 1.3: Estimated cost implications of service delivery modifications

Scenario	Total annual cost (USD)	Cost per client-month of PrEP dispensed (USD)
As implemented	204,253	26.52
Postponed creatinine†	188,932	24.53
Prioritized delivery to clients at high risk for HIV infection‡	175,793	31.88¶

†Creatinine testing postponed from initiation to first follow-up visit

‡ High risk is defined as having at least one of the following risk factors at baseline: Current partner with unknown or positive HIV status, positive rapid plasma reagin syphilis test, or reporting at least one of the following in the prior six months: exchanging sex for money or other favors, diagnosis or treatment for a sexually transmitted infection, forced to have sex against will, experiencing intimate partner violence (IPV), sharing needles while engaging in injection drug use, using post-exposure prophylaxis more than twice

¶Unit cost is calculated by dividing the total program cost by the number of person-months of PrEP dispensed to clients at high risk of HIV infection

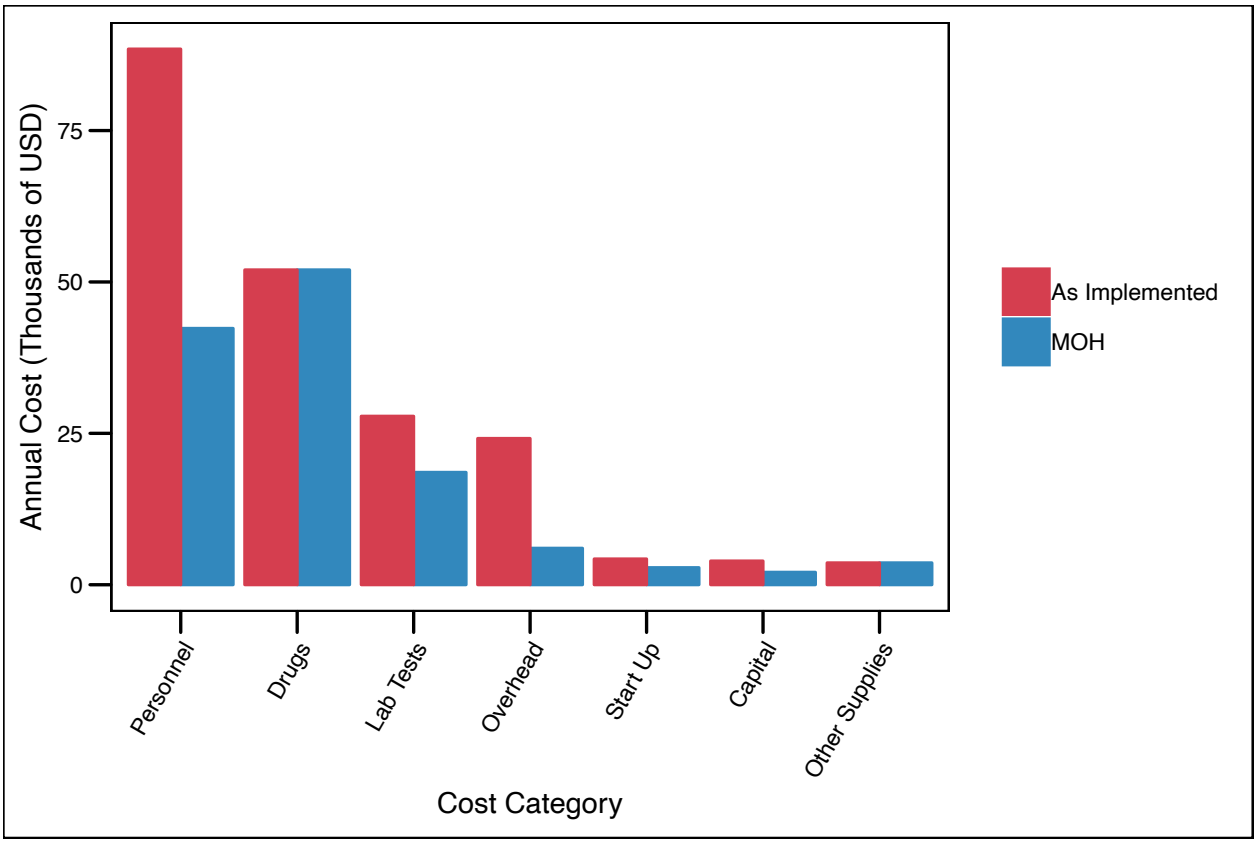
Table 1.4: Cost projections under Ministry of Health (MOH) implementation assuming constant output

Scenario	Total annual cost (USD)	Cost per client-month of PrEP dispensed (USD)
As implemented	204,253	26.52
With public-sector clinical staff salaries	199,613	25.92
With MOH supervision† and public-sector clinical staff salaries	138,609	18.00
With facility creatinine testing‡, MOH supervision†, and public-sector clinical staff salaries	127,421	16.54

†PrIYA administrative staff responsibilities are subsumed into routine facility, sub-county, and county supervision

‡Using prices for facility-based creatinine testing instead of a point-of-care assay

Figure 1.1: Total annual program cost (2017 USD) by category as implemented and in the Ministry of Health (MOH) scenario. The MOH scenario assumes public sector clinical staff salaries instead of study salaries; study administrative staff responsibilities are subsumed into routine facility, sub-county, and county supervision; and facility-based creatinine testing instead of point-of-care.



CHAPTER 2

The impact of prevention-effective PrEP use on HIV incidence: A mathematical modeling study

Abstract

Introduction

Models that project the impact and cost-effectiveness of HIV pre-exposure prophylaxis (PrEP) must specify how PrEP use aligns with HIV exposure. We hypothesize that varying PrEP use according to individual-level partnership dynamics rather than prioritization to population subgroups based on average risk will result in larger HIV incidence reductions and greater efficiency.

Methods

We used an individual-based network transmission model calibrated to HIV dynamics in Eswatini to simulate PrEP use among individuals ages 15-34 between 2022 to 2031 under two paradigms of PrEP delivery: “Risk Group” and “Partnership.” In the “Risk Group” paradigm, we varied PrEP coverage by risk groups (low, medium, and high) defined by average partnership frequency and concurrency. In the “Partnership” paradigm, all individuals are potentially eligible for PrEP, but we assumed use occurs only during partnerships and varied prioritization by partner HIV status (no prioritization to high prioritization with HIV-positive partners). We calculated person-time on PrEP and incidence relative to a no PrEP scenario and estimated efficiency as the person-years of PrEP needed to avert one additional infection (NNT).

Results

In the Risk Group paradigm, restricting PrEP to the high-risk group was the most efficient (NNT = 17), but the number of infections averted was limited by the small size of the high-risk group. Expanding PrEP use to all risk groups averted up to three times more infections but with lower efficiency (NNT = 202). PrEP use under the Partnership paradigm was 2 to 6 times more efficient (NNT = 33 to 102) than the Risk Group paradigm with all groups eligible for PrEP. A 33% reduction in incidence among 15-34-year-olds was achieved at 46% (95% CI: 39%-52%) PrEP coverage in

the Risk Group paradigm and 6% (95% CI: 5%-7%) to 17% (95% CI: 14%-20%) in the Partnership paradigm.

Conclusions

Modeling PrEP use based on risk groups resulted in a sharp tradeoff between PrEP efficiency and impact, whereas PrEP use predicated on partnerships resulted in much higher efficiency for widespread PrEP availability. Model estimates of PrEP impact and cost-effectiveness in generalized epidemics are strongly influenced by assumptions about how PrEP use aligns with individual-level HIV exposure heterogeneity.

Introduction

HIV incidence remains high in sub-Saharan Africa, with an estimated 870,000 people newly inflected in 2020 [1]. Daily oral tenofovir disoproxil fumarate (TDF) in combination with emtricitabine (FTC/TDF) as HIV pre-exposure prophylaxis (PrEP) is a safe and effective prevention strategy, and early implementation has begun in sub-Saharan Africa [15,23,130]. Policymakers must decide how to allocate finite HIV budgets to PrEP programs versus other interventions to maximize impact on HIV incidence and mortality. To guide policy, mathematical modeling analyses have estimated that PrEP may be cost-effective if prioritized to subgroups with higher risk (e.g., female sex workers). However, widespread PrEP use in generalized epidemics is seen as prohibitively expensive, because the eligible population is large and the average incidence rate is lower [61,104]. These results have influenced World Health Organization (WHO) guidelines that recommend PrEP for populations with average HIV incidence of at least 3 per 100 person-years (PY), as well as national guidelines that specify risk criteria for PrEP eligibility [131].

To estimate the cost-effectiveness of PrEP use among subgroups with different levels of risk, mathematical models must specify heterogeneity in HIV exposure. A common approach is to stratify the simulated population into a few broadly defined “risk group” categories with different average levels of partnership turnover, mixing patterns, sexual frequency, and condom use [83,132]. As a result, strata (e.g., age/gender/risk group) with unique sets of sexual activity parameters have different HIV incidence rates, but all individuals within a given stratum are subject to the same average incidence rate. This specification is common in compartmental models because it introduces some HIV exposure heterogeneity without needing to explicitly represent individuals in computer memory.

Despite its convenience, the risk group approach imposes restrictions for modeling PrEP. HIV exposure is highly dynamic depending on an individual’s current number and types of partnerships, partner HIV status, or use of other preventive interventions. In the “prevention-effective” paradigm, these time-varying behaviors also influence individual decisions to start and

stop PrEP [33]. Individual partnerships are not explicitly simulated in the risk group approach, removing a component of heterogeneity that may be important for modeling PrEP. If, within risk groups, PrEP use is higher among individuals with higher probability of HIV exposure, then models ignoring this heterogeneity may overestimate the cost and underestimate the impact of PrEP use. Individual-based models that allow PrEP use to be contingent on dynamic partnership characteristics have been used for men who have sex with men in the US [98] but rarely in generalized epidemics in sub-Saharan Africa.

Here, we use an individual-based model calibrated to the HIV epidemic in Eswatini to evaluate the effect of aligning PrEP use with HIV exposure on estimates of impact and efficiency of PrEP scale-up in young men and women. We compared models in which PrEP coverage varies by risk group to models in which PrEP use occurs only while individuals are in partnerships and varies by partner HIV status. We estimated HIV incidence and person-years on PrEP for each PrEP implementation paradigm at increasing levels of PrEP coverage and compared the projected relationship between additional PrEP use and impact across model assumptions.

Methods

Model description

We used Epidemiological MODelling Software (EMOD), an open-source, stochastic individual-based model that simulates demography, disease progression, partnership networks, and intervention use among a collection of individuals [77]. For this analysis, we used a model recently calibrated to transmission dynamics in Eswatini, which has been described in detail previously [133]. Individuals in this model are stratified into three risk groups with different sexual activity parameters: a small “high-risk” group intended to represent sex workers and clients, a “medium-risk” group with short-term partnerships, and a large “low-risk” group with fewer, longer-term partnerships. Additional details on risk group sizes, incidence rates, and partnership dynamics are provided in Appendix B (Tables B.1-B.3). HIV transmission occurs through

heterosexual partnerships formed between individuals, which are governed by age, sex, and risk group-specific pair formation parameters [134,135]. Partnerships formed between individuals are stratified by types with specific duration distributions, condom use probabilities, and concurrency propensity. Marital partnerships are of longer duration and involve older individuals, while informal and transitory partnerships are shorter and tend to involve younger individuals. Commercial partnerships are the shortest and can be formed between individuals in the highest risk group, with high turnover and concurrency. Among 15-34-year-olds, on average 35% of men and 52% of women in the model have at least one partner at a given moment in time, similar to observed data from cohorts in southern Africa [136,137]. Partnership dynamics in EMOD also recapitulate age-specific transmission patterns observed in from cohort studies conducted in KwaZulu-Natal, South Africa [18,138,139]. The model was calibrated using a parallel simultaneous optimization algorithm, and 250 sets of 24 fitted parameters were selected using roulette resampling in proportion to the likelihood to capture stochastic and parameter uncertainty [140]. We assume that antiretroviral therapy (ART) coverage reached UNAIDS 90-90-90 targets by 2020 and voluntary medical male circumcision (VMMC) coverage remains constant at 2016 levels [10]. Transmission from individuals on ART is assumed to be reduced by 92% per coital act [141]. Further details on the model parameters and calibration are available in Appendix C.

PrEP paradigms and scenarios

We focused this analysis on individuals ages 15-34 and restricted our analyses to a 10-year period from 2022 through 2031. We simulated PrEP use among 15–34-year-olds according to two paradigms (Figure 2.1). In the “Risk Group” approach, PrEP coverage can vary by risk group, but PrEP use within risk group is independent of partnership status. In the “Partnership” approach, low- and medium-risk individuals are assumed to only use PrEP while in a partnership. Furthermore, because reporting a partner with HIV or a partner of unknown status is a strong predictor of PrEP use [24,25,27,28], we allow partner HIV status to modify the probability of PrEP

use. Specifically, we applied a multiplier for PrEP coverage among individuals with HIV-positive partners relative to those with only HIV-negative partners. We varied this multiplier from 1 (partner HIV status has no impact on PrEP coverage) to 5 (individuals with an HIV-positive partner are five times more likely to use PrEP than individuals with only HIV-negative partners) (Table 2.1), reflecting uncertainty in the relationship between actual HIV partner status and PrEP use. These multipliers lead to different levels of prioritization of PrEP use during periods of HIV exposure (Appendix B, Figure B.1). In sensitivity analyses, we apply this multiplier only to individuals in partnerships with HIV-positive individuals who have been diagnosed. Based on our model parameterization, high-risk individuals are nearly always in partnerships and cycle in and out of short-term commercial partnerships on a faster time scale than PrEP refill schedules (typically one to three months), making the Partnership paradigm infeasible for the high-risk group. Instead, we assigned high-risk individuals the same PrEP coverage as low- and medium-risk individuals with an HIV-positive partner. Therefore, the Partnership paradigm differs from the Risk Group paradigm primarily in how low- and medium-risk individuals (~95% of the population) are assumed to use PrEP. For each scenario, we systematically vary PrEP coverage from low levels up to a maximum 90% coverage in any subgroup (Appendix B, Tables B.4 and B.5). In all scenarios, PrEP use occurs in month-long intervals according to the timestep of the model; therefore, initiation and discontinuation on shorter time scales (e.g., “on-demand PrEP”) is not modeled. We assumed that PrEP confers a 75% reduction in HIV acquisition risk per coital act [12]. We simulated each PrEP coverage level under each PrEP scenario, as well as a scenario without PrEP, for each of the 250 parameter sets.

Analysis

For each PrEP simulation, we calculated total person-time on PrEP, PrEP coverage among 15–34-year-olds, the percentage of infections averted relative to a scenario without PrEP, and the relative risk (RR) of infection among 15–34-year-olds compared to a scenario without

PrEP (Table 2.2). As a proxy for cost-effectiveness, we estimated the relationship between person-time on PrEP (cost) and infections averted (impact) for each PrEP scenario by fitting a one-knot natural spline regression model with a random intercept on parameter set (Appendix B, Figure B.2). We used an analogous model to describe the relationship between PrEP coverage and RR among 15–34-year-olds. We calculated the additional person-years of PrEP needed to avert one infection (number needed to treat, NNT) as the average slope between infections averted and person-years on PrEP (Appendix B, Figure B.3). We summarized parameter and stochastic uncertainty by calculating 95% credible intervals (CI) for each metric. We additionally conducted stratified analyses by gender. All statistical analysis was conducted in R version 4.0.2 [142].

Results

PrEP scenario results

The relationship between additional person-time on PrEP and infections averted depended strongly on the PrEP scenario assumed (Figure 2.2). In the Risk Group scenarios, prioritizing PrEP to the high-risk group was most efficient (NNT = 17, Table 2.3), but the percentage of infections averted at the highest PrEP coverage modeled (90% of high-risk individuals) was limited to 9% (95% CI: 6% – 12%). The percentage of infections averted at 90% coverage was higher with PrEP uptake among other risk groups (high and medium: 19% (95% CI: 16%-21%); all: 25% (95% CI: 22%-27%)), but the efficiency was lower (high and medium: NNT = 86; All: NNT = 202). In the Partnership paradigm, the efficiency depended on the multiplier governing the prioritization of PrEP during periods of higher risk (multiplier = 1: NNT = 102; multiplier = 5: NNT = 33). The Partnership scenarios were 2-6 times more efficient than the Risk Group scenario with all individuals eligible for PrEP. However, the total impact of the Partnership scenarios (>25% of infections averted at the highest coverage modeled in all scenarios) was not limited by the size of the risk groups, since all individuals are potentially eligible

for PrEP. The contrast between the Risk Group and Partnership paradigms was similar when stratified by gender (Appendix B, Figure B.4 and Table B.6).

The incidence reduction among 15-34-year-olds at given PrEP coverage levels also depended strongly on the assumed PrEP scenario (Figure 2.3). To achieve a RR of 0.67 (a 33% reduction in incidence relative to a no PrEP scenario) in the Risk Group scenario with equal coverage across risk groups, PrEP coverage needed to reach 46% (95% CI: 39%-52%). In the Partnership scenarios, the same incidence reduction was achieved at 17% coverage (95% CI: 14%-20%) with a multiplier of 1 and 6% coverage (95% CI: 5%-7%) with a multiplier of 5. At 10% coverage, the impact on incidence was smaller in the Risk Group scenarios (high and medium: RR = 0.83 (95% CI: 0.79-0.88); all: RR = 0.92 (95% CI: 0.88-0.97)) than in the Partnership scenarios (multiplier = 1: RR = 0.78 (95% CI: 0.74-0.83); multiplier = 5: RR = 0.52 (95% CI: 0.48-0.57). In the Risk Group scenario in which PrEP is restricted to the high-risk group, the largest impact on incidence (RR = 0.82, 95% CI: 0.77-0.87) occurred at 90% coverage among high-risk HIV-negative individuals, which corresponded to 3% coverage among HIV-negative 15-34-year-olds. Similar patterns were observed when stratifying by gender (Appendix B, Figure B.5). In the Partnership scenario, incidence reductions were larger among men than among women at the same level of coverage. A 50% reduction in incidence (RR = 0.5) was achieved at 9% (multiplier = 5; 95% CI: 8%-11%) to 21% (multiplier = 1; 95% CI: 17%-25%) coverage among men and 11% (multiplier = 5; 95% CI: 10%-13%) to 41% (multiplier = 1; 95% CI: 35%-46%) among women.

The distribution of averted infections by risk group also depended on the assumed PrEP scenario (Appendix B, Figure B.6). In the Risk Group scenario in which all individuals were eligible for PrEP, 41% of the infections averted were among low-risk individuals and 41% among medium-risk individuals. In contrast, restricting PrEP to either the medium- and high-risk groups or just the high-risk group primarily averted infections among high- and medium-risk individuals, with only 8-13% of averted infections among low-risk individuals. In the Partnership scenarios, PrEP use

primarily averted infections among low- (39%) and medium-risk (42%) individuals, similar to the Risk Group scenario in which all individuals were eligible for PrEP.

Sensitivity analysis

The results from the Partnership scenarios were similar when we restricted the multiplier on PrEP coverage among individuals with HIV-positive partners to only be applied when the partner had previously been diagnosed (Appendix B, Figure B.7). Since over 90% of HIV-positive individuals are assumed to know their status by 2020, changing this assumption had little impact on the distribution of PrEP person-time (Appendix B, Figure B.8).

Discussion

Our results indicate that model projections of the impact and efficiency of PrEP programs are highly sensitive to how closely PrEP use is assumed to align with HIV exposure. Compared to a model that ignores partnerships, PrEP use among the general population is projected to be two times more efficient if PrEP use is prioritized during partnerships and over six times more efficient if use is further prioritized among individuals with HIV-positive partners. In addition, large incidence reductions can be achieved at low levels of PrEP coverage if PrEP use in the general population is concentrated when HIV exposure is more likely, but high levels of PrEP coverage are needed if time-varying individual risk is ignored.

The differences in the results from the Risk Group and Partnership paradigms are driven by the low- and medium-risk groups, which represent most of the population but collectively have lower average incidence rates (0.29/100 PY for men and 1.04/100 PY for women). These average incidence rates determine the efficiency of PrEP use in the Risk Group paradigm, whereas the Partnership paradigm prioritizes PrEP use during times of higher HIV risk by further considering whether the individual has a partner and the partner's HIV status. This model specification allows individuals to cycle on and off PrEP in accordance with their time-varying HIV risk.

Estimates of the cost-effectiveness of PrEP use in sub-Saharan Africa will depend on the assumed alignment of PrEP use and HIV risk. While most prior models of PrEP use in sub-Saharan Africa have used risk groups to reflect HIV exposure heterogeneity, a recent analysis from South Africa used an individual-based model to estimate the cost-effectiveness of PrEP use concentrated during periods of condomless sex [99]. Under this paradigm, PrEP use among 15–64-year-olds was cost-effective across all simulations, whereas simulations that assumed that PrEP use was unrelated to condomless sex were never cost-effective. As with the Partnership paradigm in our analysis, their model allowed time-varying individual HIV risk to influence PrEP use. Our model differs by explicitly representing a network of partnerships formed between individuals, allowing partner HIV status to impact PrEP coverage. Taken together, our results indicate that PrEP may be more cost-effective than previously estimated if use aligns with potential HIV exposure.

Evidence from PrEP implementation studies suggest that the Partnership paradigm may better reflect patterns of PrEP use compared to the Risk Group paradigm. PrEP uptake, continuation, and adherence is higher among clients who report a partner with known HIV-positive status or of unknown status [24,25,27,28] or who have higher predicted risk using validated risk scoring tools [30,35]. Common reasons for PrEP discontinuation include low perceived HIV risk or reporting a known HIV-negative partner [24,27,143–146]. Furthermore, HIV incidence in many PrEP implementation studies has been substantially lower than expected in the absence of PrEP despite a minority of participants adhering to PrEP. HIV incidence among all participants was 55% lower after PrEP became available during the Evidence for Contraceptive Options in HIV Outcomes (ECHO) trial in South Africa despite only 26% of participants reporting PrEP use [147]. In a study of young women in South Africa and Zimbabwe, only 21% of participants had high adherence (≥ 700 fmol/punch by dried blood spot) at six months after initiation, but observed incidence (1.0/100 PY) was 73% lower than expected based on a modeled counterfactual

[148,149]. Our modeling results suggest that such incidence reductions at low coverage levels are possible when PrEP use is concentrated during times of higher HIV risk.

To achieve the impact estimated in the Partnership scenarios, individuals must be able to start and stop PrEP in accordance with HIV risk. Therefore, PrEP must be widely available in convenient locations with minimal barriers to use. Increased distance to PrEP services is a barrier to use [26,150], and PrEP delivery at community locations (e.g., pharmacies) may facilitate access [151]. Increased awareness and normalization of PrEP use, as well as new formulations that may mitigate adherence challenges, may increase uptake among those who need it [152,153]. Furthermore, risk perception must align with underlying HIV risk, and PrEP must be perceived as a means to achieving sexual health and relationship goals [154]. Partner HIV testing, including secondary distribution of HIV self-testing kits, can also improve prioritization of PrEP use during times of HIV exposure [155]. Furthermore, high rates of discontinuation and re-initiation that have been observed in PrEP implementation studies [31] may in part reflect episodic use in accordance with risk rather than low adherence. In contrast, the Risk Group scenarios imply that a small subpopulation of “high-risk” individuals should be prioritized for PrEP use. Even if such a subgroup can be identified and engaged in PrEP services, the population-level impact is projected to be much smaller than if PrEP is used more generally due to the relatively smaller size of the high-risk population. Furthermore, policies that associate PrEP with specific key populations may introduce stigma for other users [156].

Our results have several limitations. First, we chose a model recently calibrated to Eswatini that allowed comparative modeling of PrEP use based on risk groups versus individual partnerships across a wide range of scenarios in a high HIV incidence setting. As such, our results do not correspond to a specific PrEP delivery program in Eswatini. For this reason, we did not produce formal cost-effectiveness estimates, as program costs will depend on the platform used to provide PrEP services [157]. Second, we did not explicitly model knowledge of partner HIV status; instead, we allowed the true HIV status of partners to affect PrEP uptake. Knowledge of

partner HIV status is low in southern Africa [158], so individuals considering PrEP often make decisions with considerable uncertainty about their HIV risk. However, quantitative and qualitative evidence supports that beliefs about partner status, even in the absence of disclosure, are strong determinants of PrEP use [24,25,27,28,143,144]. For this reason, we varied the multiplier for PrEP uptake by partner HIV status across a wide range, including scenarios in which partner HIV status had no impact on PrEP use. Further research is needed to understand the degree to which decisions about PrEP use align with HIV exposure and to incorporate them into mathematical models. Third, the Partnership paradigm does not capture many of the reasons that individuals may choose to start or stop PrEP. Within partnerships, PrEP use is assumed to be independent of condom use and partner viral suppression. Our model may underestimate efficiency and impact if PrEP is preferentially used during periods of condomless sex or with partners with unsuppressed viral loads. Additionally, pill burden, side effects, travel times, stigma, or fear of intimate partner violence act as barriers to PrEP use [25,28,144,145,159], which may limit prioritization of PrEP use with HIV exposure. Finally, our model also does not include HIV drug resistance; however, prior analyses have estimated limited impact of drug resistance on PrEP cost-effectiveness estimates when dolutegravir is used in first-line ART regimens [99].

Conclusions

Model assumptions that govern the alignment of PrEP use with HIV exposure strongly influence projections of PrEP impact. Prioritizing PrEP use based on risk groups results in a substantial tradeoff between infections averted and efficiency and may underestimate cost-effectiveness. Assuming instead that PrEP use is prioritized based on partnership characteristics results in much higher efficiency for use in the general population. Individual-based models may allow better representation of the dynamics of PrEP use in relation to time-varying individual-level heterogeneity in HIV exposure to improve estimates of the cost-effectiveness of PrEP programs.

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Figure 2.1: Illustration of PrEP use assumptions according to two model paradigms. Four example individual trajectories over a ten-year period are shown in each paradigm. In the Risk Group paradigm, PrEP coverage can vary according to behavioral risk group, but PrEP use within risk group is independent of partnership status. In the Partnership paradigm, PrEP use occurs only during partnerships and may be prioritized with HIV-positive partners. In this example, PrEP coverage is twice as high during partnerships with HIV-positive individuals compared to during partnerships with HIV-negative individuals. The high-risk group is not shown. PrEP coverage levels are systematically varied in the main analysis. Pr(PrEP) = PrEP coverage.

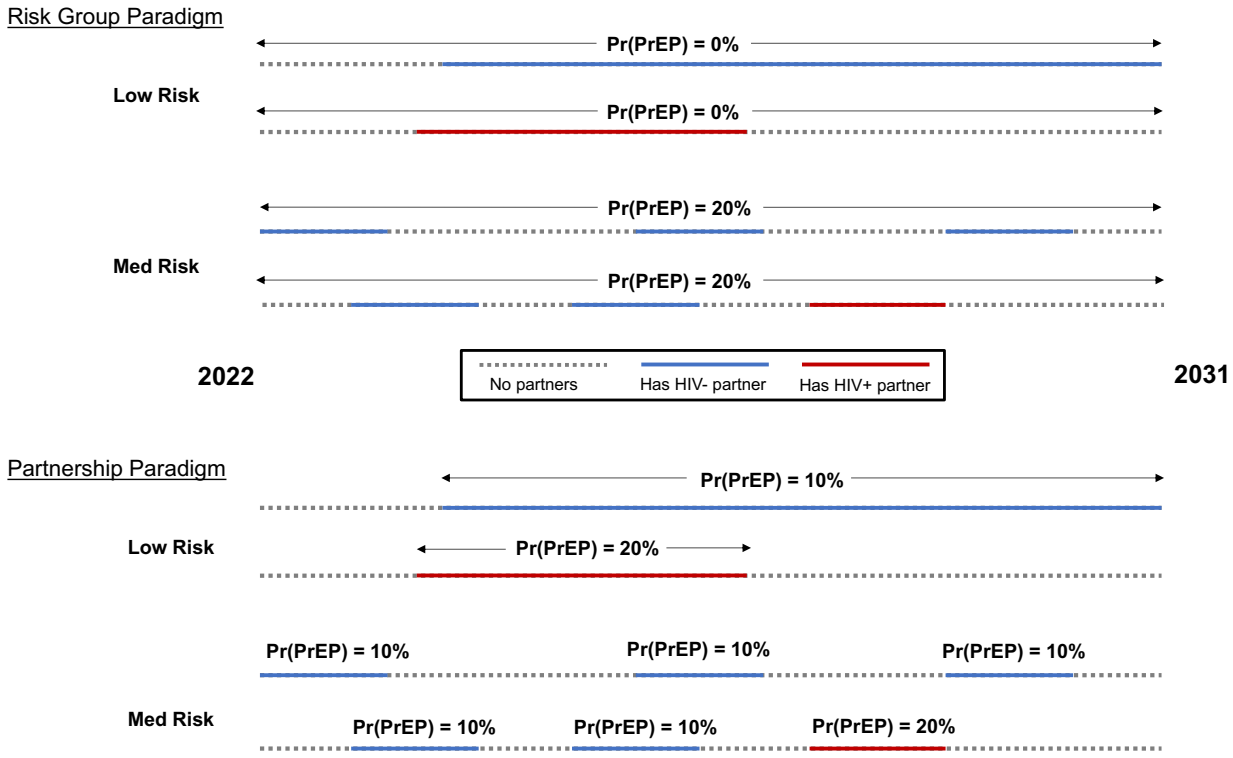


Table 2.1: Model assumptions for PrEP use according to the Risk Group and Partnership paradigms. In the Risk Group paradigm, PrEP use can differ according to risk group, but within risk group PrEP use is assumed to be independent of partnerships and partner characteristics. In the Partnership paradigms, PrEP use is assumed to only occur during partnerships, and a multiplier is applied to PrEP coverage among individuals with one or more HIV-positive partners relative to PrEP coverage among individuals with only HIV-negative partners.

Paradigm	Risk Group	Partnership requirement	Multiplier for PrEP use with HIV+ partners relative to PrEP use with HIV- partners
Risk Group	All	No	-
Risk Group	High and medium	No	-
Risk Group	High	No	-
Partnership	All	Yes	1
Partnership	All	Yes	2
Partnership	All	Yes	3
Partnership	All	Yes	5

Table 2.2**:** Metrics calculated for each PrEP simulation. Each metric represents a different construct (e.g., impact, cost) through which PrEP programs are evaluated.

Metric	Definition	Interpretation
Person-time on PrEP	Total person-years of PrEP use from 2022-2031	Program cost
PrEP coverage	Proportion of HIV-negative 15–34-year-olds currently on PrEP, averaged from 2022-2031	Reach among potential users
% of infections averted	Percentage of total infections (all age groups) occurring between 2022 and 2031 in a simulation with no PrEP that are averted in a given PrEP simulation	Total impact
Relative risk (RR)	Average HIV incidence rate among all 15-34-year-olds (regardless of PrEP use) between 2022 and 2031 in a given PrEP simulation divided by the same incidence rate in a simulation with no PrEP	Impact among potential users
Number needed to treat (NNT)	Average additional person-years of PrEP use in a given PrEP simulation needed to avert one additional HIV infection between 2022 and 2031 relative to a simulation with no PrEP	Efficiency or cost-effectiveness

Figure 2.2: Relationship between additional person-time on PrEP and percentage of infections averted relative to a no PrEP scenario, by PrEP paradigm. Person-years on PrEP and percentage of infections averted are cumulative across a ten-year period spanning 2022 to 2031. Shaded regions indicate 95% credible intervals. Mult = multiplier on the probability that an individual with an HIV-positive partner will use PrEP relative to the probability than an individual with only HIV-negative partners will use PrEP.

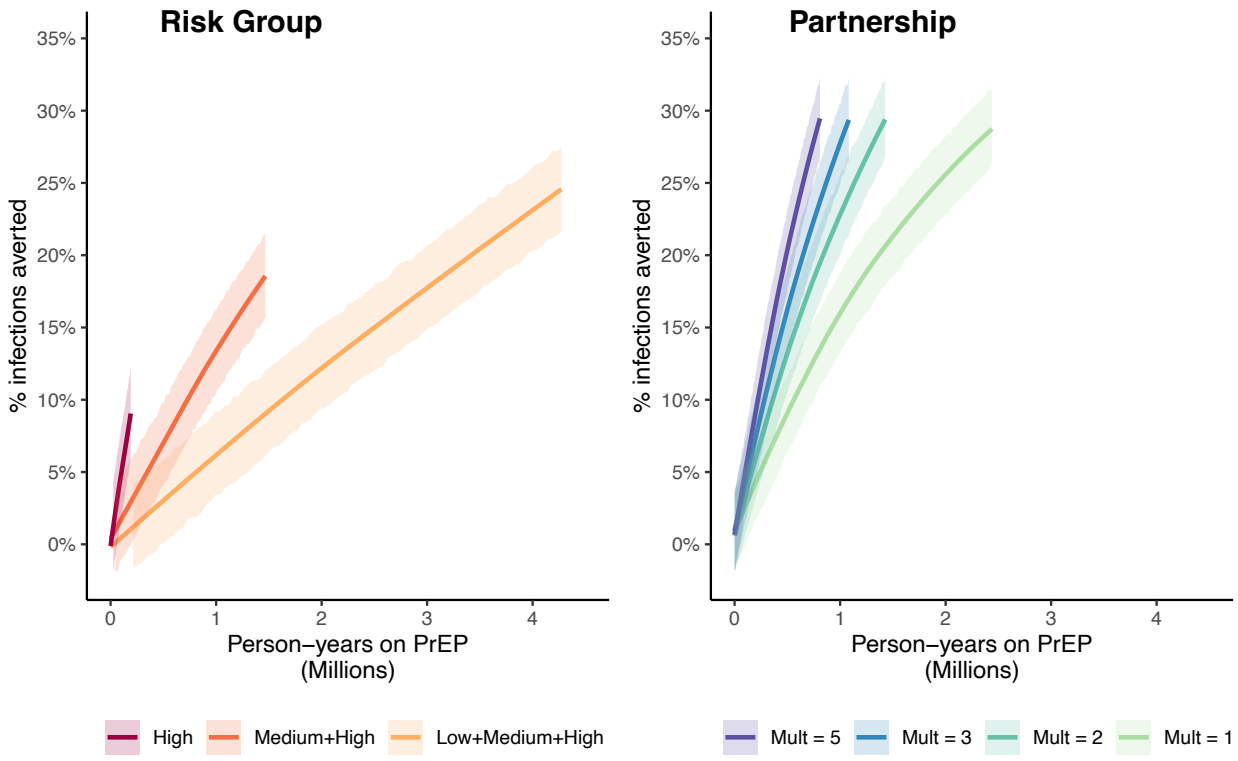
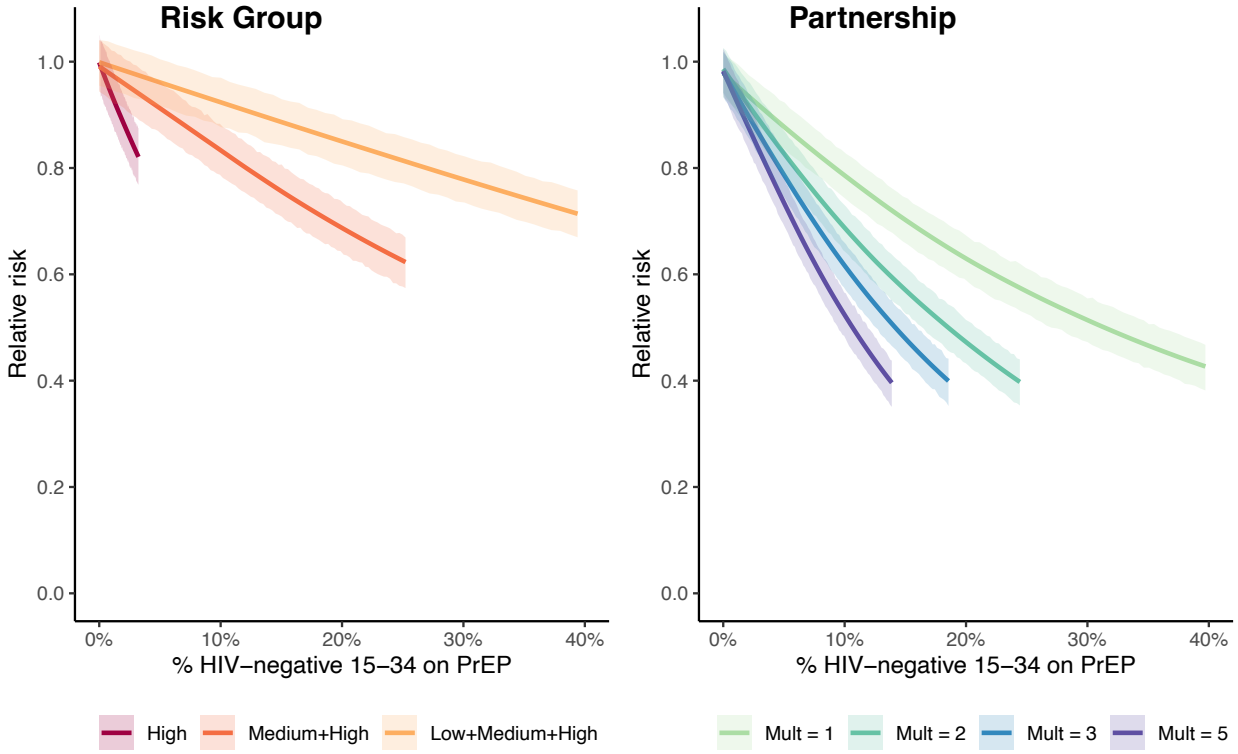


Table 2.3**:** Number of additional person-years of PrEP needed to avert one additional HIV infection (number needed to treat, NNT), by PrEP scenario. CI = credible interval. Mult = multiplier on the probability that an individual with an HIV-positive partner will use PrEP relative to the probability than an individual with only HIV-negative partners will use PrEP.

Paradigm	Scenario	NNT (95% CI)
Risk Group	All	202 (200-204)
	High and medium	86 (85-87)
	High	17 (17-18)
Partnership	Mult = 1	102 (101-103)
	Mult = 2	58 (57-58)
	Mult = 3	45 (44-45)
	Mult = 5	33 (32-33)

Figure 2.3: Relationship between PrEP coverage among all HIV-negative 15–34-year-olds and the relative risk of HIV infection compared to a no PrEP scenario, by PrEP paradigm. Relative risk is averaged across 2022 to 2031. Shaded regions indicate 95% credible intervals. Mult = multiplier on the probability that an individual with an HIV-positive partner will use PrEP relative to the probability than an individual with only HIV-negative partners will use PrEP.



CHAPTER 3

Predicting the risk of HIV-1 acquisition in rural South Africa using geospatial data

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Abstract

Background

Accurate HIV risk assessment can guide optimal HIV prevention. We evaluated the performance of risk prediction models incorporating geospatial measures.

Methods

We developed and validated HIV risk prediction models in a population-based cohort in South Africa. Individual-level covariates included demographic and sexual behavior measures, and geospatial covariates included community HIV prevalence and viral load estimates. We trained models on 2012-2015 data using LASSO Cox models and validated predictions on 2016-2019 data. We compared full models to simpler models restricted to only individual-level covariates or only age and geospatial covariates. We compared the spatial distribution of predicted risk to that of high incidence areas (≥ 3/100 person-years (PY)).

Results

Our analysis included 19,556 individuals contributing 44,871 PY and 1,308 seroconversions. Incidence among the highest predicted risk quintile using the full model was 6.6/100 PY (women) and 2.8/100 PY (men). Models using only age group and geospatial covariates had similar performance (women: AUROC = 0.65, men: AUROC = 0.71) to the full models (women: AUROC = 0.68, men: AUROC = 0.72). Geospatial models more accurately identified high incidence regions than individual-level models; the 20% of the study area with the highest predicted risk accounted for 60% of the high incidence areas when using geospatial models but only 13% using models with only individual-level covariates.

Conclusions

Geospatial models with no individual measures other than age group predicted HIV risk nearly as well as models that included detailed behavioral data. Geospatial models may help guide HIV prevention efforts to individuals and geographic areas at highest risk.

Introduction

Despite progress in expanding access to treatment and prevention services, HIV incidence in sub-Saharan Africa remains high. An estimated 870,000 people were newly infected in 2020, and annual incidence among adults exceeds five per 1000 population in several countries [1]. HIV prevention programs that prioritize services such as pre-exposure prophylaxis (PrEP) to individuals at the highest risk of infection will maximize benefits given available resources. The World Health Organization (WHO) has recommended that PrEP be offered to populations with HIV incidence of at least 3 per 100 person-years (PY) [110].

Accurate and efficient identification of individuals at high risk remains a key challenge for HIV prevention programs. Several model-based HIV risk prediction tools have been developed for women [35,37,41], men who have sex with men [160], serodiscordant couples [38], pregnant women [34], and the general population [39]. Existing tools rely primarily on age, sexual behavior, alcohol and drug use, and testing for sexually transmitted infections (STIs). These individual-level measures have several limitations. Behavioral risk factors are dynamic, require frequent reassessment, and are generally self-reported and thus prone to misclassification [161,162]. Nucleic acid amplification testing for STIs is often not available outside of research studies or specialized clinics. The importance of specific individual risk factors may also vary across settings [163], which may diminish the performance of risk scores when applied in new populations [164].

Community-level measures of HIV prevalence, viral load, and treatment coverage offer an alternative approach to identifying individuals at elevated HIV risk. These measures are associated with HIV incidence [165–167] and act as proxies for local HIV transmission potential. Models based on geospatial measures may allow prioritization of prevention interventions to individuals and communities without the need to collect detailed behavioral data. However, existing HIV risk scores have generally not incorporated community-level HIV indicators, and the utility of geospatial measures in HIV risk prediction is unclear.

Using population-based data from a large prospective HIV cohort in South Africa, we developed and evaluated the predictive performance of gender-specific HIV risk prediction models. We compared the performance of models including both geospatial and individual-level covariates (full models) with models using only individual-level covariates (individual-level models) and models restricted to age and geospatial covariates (geospatial models). We also mapped the geospatial distribution of predicted risk from each model and compared the alignment with high incidence areas, as defined by the 2015 WHO PrEP guidelines (≥ 3 per 100 PY).

Methods

Study population

We used data from a large demographic surveillance system (DSS) run by the Africa Health Research Institute (AHRI) in the Hlabisa sub-district of KwaZulu-Natal, South Africa [168]. The southern surveillance area of the AHRI DSS, which has been followed since 2000, contains about 90,000 individuals in 11,000 households over a 438 km^2 area. We excluded data from a northern surveillance area that was added in 2017. The study area is primarily rural with several peri-urban settlements and a single urban township. All households in the study area are contacted three times each year to interview the household head, who provides information on household attributes, births, deaths, and migration of residents. Since 2004, field workers have conducted annual surveys among household participants aged 15 years or older to assess demographics, sexual health, relationship history, and use of HIV prevention strategies. Participants then provide a dried blood spot (DBS) sample for anonymized HIV testing. Viral load testing has been conducted since 2011. In 2017, HIV prevalence among individuals aged 15-54 was 20% for men and 41% for women, and overall HIV incidence was 2.3 per 100 PY [169].

Eligible individuals for this analysis were aged 15-54 years with an initial HIV-negative test and at least one subsequent HIV test. For individuals with a subsequent positive HIV test, we randomly imputed a single seroconversion date from a uniform distribution defined between the

last HIV-negative test and first HIV-positive test [170]. Follow-up time was right censored at the earliest of the last HIV negative test, first HIV positive test, date of death, or 55th birthday. To train the HIV risk prediction models, we used follow-up time occurring between January 1, 2012, and December 31, 2015 (development dataset). We validated the models using follow-up time occurring between January 1, 2016, and December 31, 2019 (validation dataset).

Covariates

We constructed our models using a suite of time-varying individual-level and geospatial covariates. Individual-level predictors included five-year age group, gender, marital status, education, employment, migration history, prior pregnancies or children, circumcision status, contraception use, number of sexual partners, and characteristics of the most recent partner. A full list of covariates and missingness frequency is available in Appendix D, Table D.1. We estimated missing covariate values using multiple imputation by chained equations with 10 imputations [171]. Multiple imputation was carried out separately for the development and validation datasets to avoid bias from contamination between the two datasets [172]. Geospatial covariates included local estimates of HIV prevalence and population prevalence of detectable viremia (PPDV) [166], urban or rural designation, and distances from residence to the nearest roads, clinic, and schools. We produced annual estimates of local HIV prevalence and PPDV using moving two-dimensional Gaussian kernels of a 3-km search radius [173]. We chose the kernel radius *a priori* based on extensive previous work in the study area [165,166,174]. For each calendar year of follow-up time, we defined HIV prevalence and PPDV covariates by extracting the value of the prior year's estimated surface at the coordinates of each individual's residence.

Model development and validation

We modeled time to seroconversion separately for men and women using Cox proportional hazards with least absolute shrinkage and selection operator (LASSO) penalties

[175]. We selected optimal LASSO penalties via 10-fold cross-validated mean area under the receiver operating characteristic curve (cv-AUROC) evaluated at one year [176]. We fit four models with different covariate restrictions: all covariates (full model), only individual-level covariates, only age group and geospatial covariates, and only age group and local HIV prevalence. We finalized our models by fitting to the full development dataset using the optimal LASSO penalties and averaging the estimated hazard ratios across the 10 imputed datasets.

We validated each of the models by predicting hazard ratios in the validation dataset, and we evaluated model discrimination using AUROC. We evaluated model sensitivity by calculating the proportion of incident infections that occur within fixed percentiles of predicted risk for each model. We also calculated HIV incidence rates across quintiles of predicted HIV risk for each model.

Geospatial distribution of risk

We evaluated how well our models identified geographic areas of high HIV risk by comparing the spatial distribution of predicted risk to the areas in which observed incidence exceeded 3 per 100 PY. We estimated the spatial distribution of incidence by separately smoothing counts of cases and total person-time at risk using Gaussian kernels and then dividing the value from the cases surface by the value of the person-time surface across the study area. Since the number of incident cases is smaller and therefore leads to noisier geospatial estimates, we generated a single incidence surface across the study area by combining data from both men and women from 2012 to 2019 and increased the kernel bandwidth to 10 km. We compared this surface to the spatial distribution of predicted risk over the same time period from each of the four models. For each modeled surface, we calculated the percentage of the area with incidence at least 3 per 100 PY that was contained within the 20%, 40% or 60% of the area with the highest predicted risk. We varied the incidence kernel bandwidth in sensitivity analyses. Geospatial

analyses were conducted using ArcGIS (ESRI Inc, Redlands, USA), while all other analyses used R version 4.0.2.

Ethics Approval

All participants provided written informed consent prior to the household-based interview and collection of dried blood spots. Approval for data collection and use was obtained from the biomedical and ethics committee (BREC) of the University of KwaZulu-Natal, Durban, South Africa (BREC approval number BE290/16).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The development datasets contained 9,623 individuals (5,910 women and 3,713 men) with 841 seroconversions (679 among women 162 among men) (Table 3.1). The validation datasets included 9,933 individuals (6,023 women and 3,910 men) and 467 seroconversions (381 among women and 86 among men). Descriptive characteristics were similar between development and validation datasets, except for increases in educational attainment, circumcision, and contraception use (Table 3.2). Missingness was less than 5% for most variables but ranged as high as 46% for condom use at last sex (Table D.1). HIV incidence was 3.34/100 PY in the development dataset and 2.37/100 PY in the validation dataset, reflecting recent declines in incidence in the study area [169].

The full models retained 38 predictors for men and 28 predictors for women (Table D.2). The strongest predictors included age group, marital status, circumcision (men), contraception use (women), sexual debut, number of partners in the last 12 months, number of current

relationships (men), most recent partner residing outside of the household, and PPDV (men). The cv-AUROC for the full model in the development data was estimated as 0.74 (men) and 0.71 (women) (Table D.3). Models with covariate restrictions had cv-AUROC values ranging from 0.71 to 0.73 among men and 0.68 to 0.71 among women. In validation, the full models (AUROC = 0.72 for men and 0.68 for women) and models restricted to individual-level covariates (AUROC = 0.72 for men and 0.68 for women) had similar performance. Models restricted to age and geospatial covariates (AUROC = 0.71 for men and 0.65 for women) or age and HIV prevalence (AUROC = 0.68 for men and 0.64 for women) had slightly lower performance.

The sensitivity of the models at varying predicted risk thresholds is shown in Figure 3.1. Among the 40% of individuals with the highest predicted risk, the full model identified 77% of all new infections among men and 65% of new infections among women. Sensitivity at the 40% threshold was the same for models with only individual-level covariates (men: 77%, women: 65%) and slightly lower for geospatial models without individual-level covariates other than age (men: 68%-72%, women: 60%). Incidence rates increased monotonically with increasing predicted risk quintiles (Table 3.3). Among men, the incidence rate in the validation data (per 100 PY) among the 20% of individuals with the highest predicted risks ranged from 2.1 (95% CI: 1.4-2.9) using the age + HIV prevalence model to 2.8 (95% CI: 1.9-3.6) using the full model. Among women, incidence in the highest predicted risk quintile ranged from 4.9 (95% CI: 4.0-5.7) using the age and geospatial covariates model to 6.6 (95% CI: 5.4-7.5) in the full model (Table 3.3). These incidence rates were between 5 and 11 times higher than the incidence rates in the lowest predicted risk quintile among women and 7 to 9 times higher among men.

The geographic distribution of predicted risk from models incorporating geospatial covariates aligned much more closely to the geographic distribution of observed HIV incidence than predictions from models using only individual-level covariates (Figure 3.2). The 20% of the map with the highest predicted risk captured 60% of the area with high incidence ($\geq$ 3/100 PY) when using the full model and 59-60% when using the models with only age and geospatial

covariates (Figure D.1). In contrast, the geospatial distribution of predicted risk using the individual model did not align closely with incidence, and the 20% of the map with the highest predicted risk only accounted for 13% of the area with high incidence. These results were robust to varying the incidence kernel bandwidth (Figure D.2).

Discussion

We developed and validated HIV-1 risk prediction models using a suite of individual-level and geospatial covariates to identify men and women at very high risk for HIV acquisition in rural KwaZulu-Natal, South Africa. Men and women within the top 20% of predicted risk had incidence rates of at least 2.1 and 4.9 per 100 PY, respectively, across all models. Simple models using only age group and geospatial covariates (including a model with only age and local HIV prevalence) predicted individual-level risk of HIV infection nearly as accurately as models that included demographic, sexual behavioral, and socioeconomic predictors. Furthermore, spatially smoothed predictions from models that included geospatial covariates aligned closely with high incidence areas while predictions from models with only individual-level covariates did not.

Few HIV risk prediction models have incorporated geospatial measures, but those that have considered HIV prevalence have consistently found it to be predictive. An analysis from the communities in the vicinity of Rakai District in rural Uganda found that a one percentage point increase in community HIV prevalence was associated with a three percent increase in the hazard for HIV acquisition [177]. A risk score developed from the ECHO study, which used data from nine South African sites spanning five provinces, found site-level HIV prevalence to be one of the strongest predictors of HIV risk [37]. Our analysis, which used micro-scale spatial variation in HIV prevalence and community viral load, extends these findings to a much smaller geographic scale, allowing identification of “corridors of HIV transmission” with high incidence [178]. While community viral load has been strongly associated with HIV incidence in multiple settings [166,167], georeferenced viral load data is not widely available, and we found that predictive

performance was largely maintained in a model with only age and HIV prevalence. This result may reflect that PPDV is a function of HIV prevalence, and the two measures tend to be closely correlated in settings with low ART coverage such as AHRI (51% among women and 38% among men in 2017) [169]. However, as ART scales up, PPDV may become a more sensitive measure of local transmission potential.

Risk scores based on detailed clinical and sexual behavior measures rely on accurate reporting of sensitive and potentially stigmatizing behaviors. Such approaches are best suited to clinical settings with sufficient resources for lengthy individual-based assessment. Our results indicate that similar predictive performance may be obtained from models using age group and smoothed HIV test results from population-based surveys. These models enable HIV prevention strategies focused more on geographic context than on individual risk behaviors. Additional investment in routine population-based HIV and viral load testing could facilitate resource prioritization to communities with the highest need.

While our model identified individuals and geographic areas at the highest risk, incidence was still elevated among women even at lower predicted risk thresholds. Women in the second lowest quintile of predicted risk using the full model experienced an incidence rate of 1.9/100 PY between 2016 and 2019, and women in the middle quintile had an incidence rate of 3/100 PY. Our results indicate that, in a hyperendemic South African setting, incidence was high even among women who reported few individual-level risk factors. Similar gender disparities have been demonstrated across sub-Saharan Africa [179], and our findings underscore the continuing need for widespread coverage of combination HIV prevention services, especially for women.

Our analysis has several strengths. We used a robust internal validation strategy on a large dataset to develop our models, and we validated our predictions on data from subsequent years that were not used in model development. This validation strategy was chosen to estimate performance in prospective prediction, and our models performed well despite temporal changes in incidence and risk factor distribution. For future predictions, the models can easily be retrained

using the same methods on an updated dataset. Additionally, our suite of models with different covariate restrictions allows for prediction in a variety of settings with different data availability. Models based solely on individual-level covariates could be applied in a clinical setting where geospatial covariates may not be available. In contrast, models based on age and geospatial covariates could guide geographic prioritization of interventions, such as focused community HIV testing campaigns, home-based antiretroviral therapy (ART) delivery, or community PrEP services [28,180,181]. Approaches that combine both geographic and individual factors may be needed to achieve both widespread coverage to those at risk as well as efficient resource allocation. Additional research is needed to optimize implementation of risk prediction tools in low-resource settings.

Our analysis also has limitations. Some of the sexual behavior variables had high amounts of missing data, and we lacked other indicators that have been previously incorporated into risk scoring tools, such as alcohol use, whether sex partners provide financial support, and whether sex partners have other partners [35]. Therefore, our models based on individual-level covariates may have lower performance than ones trained on richer data. We did not have STI testing, which has been incorporated into risk scores trained using clinical trial data but is not widely available, even in routine clinical care settings. We did not compare other algorithms for training our predictive models. Even so, the predictive performance of our individual-level covariate models (AUROC 0.68-0.71) was similar to the performance of models developed in other sub-Saharan Africa settings (AUROC 0.67-0.73) [35,37,39]. We also did not validate our models using data from other settings, so the generalizability of our findings is uncertain. Further research could evaluate predictions in other locations with routine population-based HIV surveillance at small spatial scales, such as ALPHA Network sites or universal test-and-treat trial locations [182,183]. Additionally, small area HIV prevalence estimates have been generated for all of sub-Saharan Africa [184]; however these estimates derive from sparser data, and their predictive performance at small geographic scales is unknown. Additional investment in population-based surveys and

surveillance may be needed to improve estimates of local HIV prevalence and viremia in other settings. In addition to informing HIV risk prediction, these measures are directly applicable to HIV treatment targets and would have tangible benefits to ART programs [185].

In summary, we developed and validated a suite of risk prediction models informed by individual-level and geographic covariates that identified individuals and geographic areas at high risk for HIV acquisition. These results may guide efforts to prioritize HIV prevention resources to maximize impact.

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Data Sharing

The datasets used in this analysis are contained in the AHRI data repository ([165]). To access the licensed datasets, the applicant must agree to the terms and conditions of use by completing an Application for Access to a Licensed Dataset. This request will be reviewed by the AHRI Data Release Committee, who may decide to approve the request, to deny access to the data, or to request additional information from the applicant.

Table 3.1: Cohort sizes and HIV incidence rates

		Development (2012-2015)	Validation (2016-2019)
Women	# individuals	5,910	6,023
	# seroconversions	679	381
	# person-years	16,183	12,239
	Incidence rate (per 100 PY)	4.20	3.11
Men	# individuals	3,713	3,910
	# seroconversions	162	86
	# person-years	9,013	7,436
	Incidence rate (per 100 PY)	1.80	1.16

Table 3.2: Descriptive characteristics of individuals in the development and validation datasets.

		Men		Women	
		Dev.	Val.	Dev.	Val.
Age	15-19	36.1%	33.9%	23.8%	25.3%
	20-29	38.0%	37.5%	32.1%	32.0%
	30-39	11.7%	15.7%	14.0%	16.3%
	40-54	14.3%	12.8%	30.0%	26.5%
Education	Less than primary	7.1%	4.6%	8.1%	4.9%
	Primary	47.5%	39.6%	37.7%	31.0%
	Secondary or greater	45.5%	55.8%	54.2%	64.1%
Married		5.8%	4.3%	17.3%	15.3%
Employed		27.4%	22.7%	22.5%	17.0%
Prior outmigration		8.3%	13.5%	8.3%	11.7%
Ever had sex		59.3%	59.4%	76.5%	75.5%
Ever fathered children		24.7%	27.7%	-	-
Ever pregnant		-	-	64.4%	64.9%
Circumcised		7.4%	28.7%	-	-
Prior contraception use		-	-	19.6%	44.1%
1+ partners in last 12 months		53.9%	52.7%	65.7%	65.2%
MRP casual*		30.1%	25.9%	18.4%	16.6%
MRP member of household*		20.6%	16.5%	39.9%	35.2%
Rural**		68.0%	66.0%	72.9%	70.0%
Mean local HIV prevalence**		24.6%	34.6%	23.8%	34.0%
Mean local PPDV***		15.3%	14.5%	14.7%	14.1%

Percentages are averaged across 10 imputed datasets. Dev = development dataset (2012-2015); Val = validation dataset (2016-2019); MRP = most recent partner; PPDV = population prevalence of detectable viremia. *Evaluated among those reporting ever having sex. **< 400 residents per square km. ***Estimated from a 2-dimensional Gaussian kernel with 3 km bandwidth

Figure 3.1: Percentage of new infections identified (sensitivity) within varying percentages of the population with the highest predicted risks. Estimated in the validation dataset (2016-2019). Full = no covariate restriction; Individual = only individual-level covariates; Age + Geo = only age group and geospatial covariates; Age + HIV prev = only age group and local HIV prevalence.

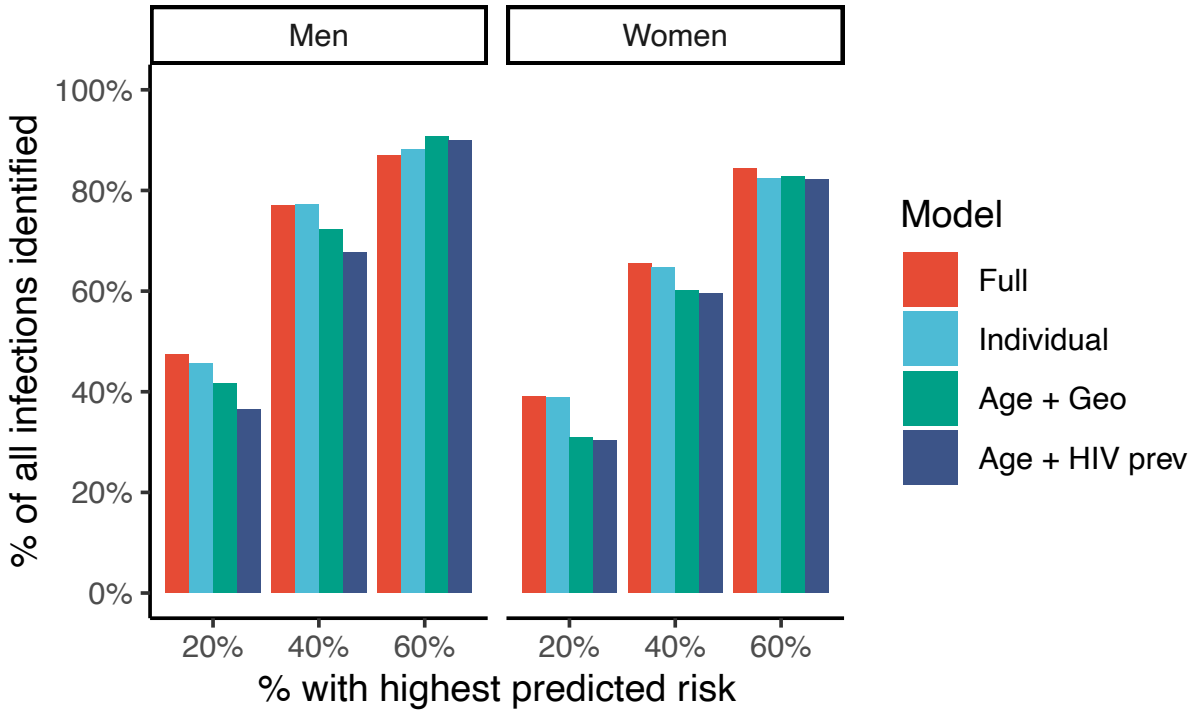
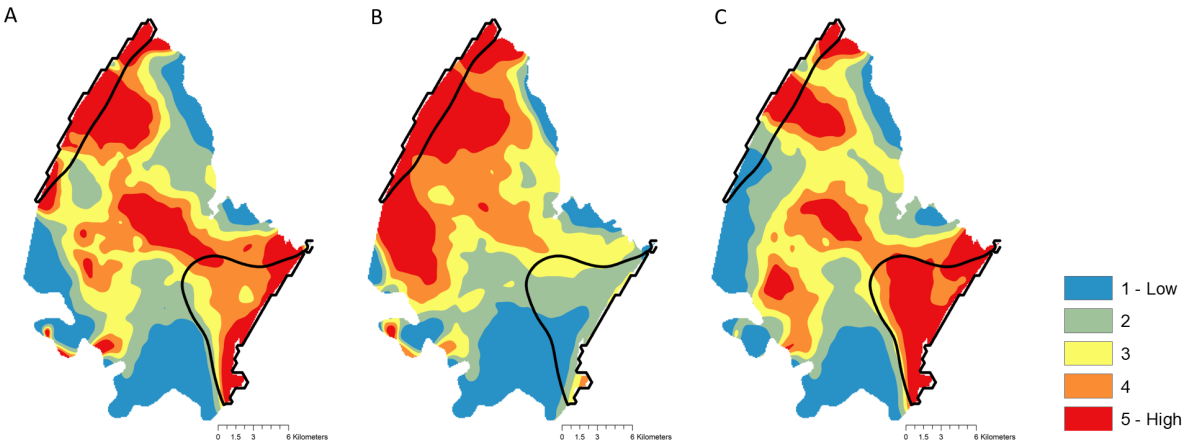


Table 3.3: Incidence rate (per 100 person-years) in validation dataset by quintiles of predicted risk. Parentheses indicate 95% confidence intervals. Full = no covariate restriction; Individual = only individual-level covariates; Age + Geo = only age group and geospatial covariates; Age + HIV prev = only age group and local HIV prevalence

		Full	Individual	Age + Geo	Age + HIV prev
Men	Predicted risk quintile				
	1 (low)	0.3 (0.0, 0.5)	0.3 (0.0, 0.6)	0.3 (0.0, 0.6)	0.3 (0.0, 0.5)
	2	0.5 (0.1, 0.9)	0.4 (0.1, 0.8)	0.3 (0.0, 0.5)	0.3 (0.0, 0.5)
	3	0.6 (0.1, 1.0)	0.6 (0.2, 1.0)	1.0 (0.5, 1.6)	1.3 (0.7, 1.9)
	4	1.7 (1.0, 2.5)	1.8 (1.0, 2.5)	1.7 (1.0, 2.3)	1.8 (1.1, 2.5)
	5 (high)	2.8 (1.9, 3.6)	2.8 (1.8, 3.7)	2.4 (1.7, 3.2)	2.1 (1.4, 2.9)
Women					
	1 (low)	0.6 (0.3, 0.9)	0.5 (0.2, 0.8)	0.9 (0.5, 1.2)	0.8 (0.5, 1.2)
	2	1.9 (1.3, 2.5)	2.2 (1.6, 2.8)	2.0 (1.4, 2.5)	2.1 (1.5, 2.7)
	3	3.0 (2.3, 3.8)	2.9 (2.2, 3.6)	3.3 (2.6, 4.0)	3.3 (2.6, 4.1)
	4	3.9 (3.0, 4.7)	4.1 (3.2, 5.0)	4.8 (4.0, 5.7)	4.6 (3.7, 5.4)
	5 (high)	6.6 (5.4, 7.5)	6.2 (5.1, 7.2)	4.9 (4.0, 5.7)	5.0 (4.1, 5.9)

Figure 3.2: Geospatial distribution of predicted risk. A = full model (no covariate restriction); B = only individual covariates; C = only age group and geospatial covariates. Maps include predictions for both men and women from 2012-2019. Model predictions were spatially smoothed using a 2-dimensional Gaussian kernel. Colors indicate quantiles of spatially smoothed model predictions. Solid lines enclose areas with estimated incidence ≥ 3 per 100 person-years.



CONCLUSION

The studies included in this dissertation contribute to our understanding of PrEP delivery in sub-Saharan Africa. Our primary costing study identified service delivery bottlenecks and cost drivers that can inform efforts to streamline PrEP delivery. By disregarding the alignment of PrEP use with time-varying individual HIV exposure, models using a risk group specification may overestimate the cost and underestimate the impact of widespread PrEP availability. Finally, local estimates of HIV prevalence can help prioritize for PrEP services to maximize impact. This section summarizes implications for PrEP programs and outlines some future directions for research.

Together, these analyses have several implications for optimal PrEP delivery. In particular, our results highlight the limitations of PrEP programs that are focused on specific subgroups who meet certain criteria based on individual-level risk factors. In generalized epidemic settings, restricting PrEP to a small fraction of the population based on risk group criteria is likely to have limited impact. Furthermore, prospective identification of high incidence subgroups based on self-reported individual-level risk factors is challenging, and targeted delivery platforms may incur additional costs. When available, local estimates of community transmission may help PrEP programs prioritize services in high incidence geographic areas. Nevertheless, widespread PrEP availability is crucial to achieve substantial impact. This strategy allows individuals to choose when to use PrEP in accordance with risk perception. Furthermore, widespread availability will unlikely translate to widespread use among those not at risk, as evidenced by high rates of discontinuation and episodic use observed in implementation studies. Additionally, if self-selection leads to alignment of PrEP use with HIV exposure, then PrEP programs can have large impacts even at low levels of coverage.

Widespread PrEP access may require program adaptations to maximize impact. Integration of PrEP into existing clinic-based services has potential to reach large numbers without requiring additional outreach and engagement activities. However, health facilities in sub-

Saharan Africa are often understaffed and overburdened, and service delivery modifications to reduce provider time may be necessary. Emerging evidence from differentiated care models may inform PrEP service delivery. For example, multi-month prescribing for established clients could simplify follow-up by requiring fewer visits. Additionally, task shifting PrEP screening to HIV test counsellors may reduce costs and alleviate clinician time burden. HIV self-testing could potentially allow clients to determine eligibility for PrEP initiation and continuation, although further research is needed to evaluate concerns with decreased sensitivity during acute infection. In addition, postponing creatinine testing from initiation to a follow-up visit may save costs in programs with high rates of early discontinuation, especially when in settings with limited laboratory capacity.

Community-based PrEP services may also be needed to expand access, especially to young, healthy people who are not in disclosed serodiscordant relationships [186]. Pharmacies offer a promising venue for PrEP delivery, with numerous locations that cater to individuals seeking sexual health services [187]. Other community approaches to delivering PrEP include mobile health clinics and community health fairs [188–190]. In addition to providing services with flexible hours and locations, community sensitization, education, and counseling efforts may further improve individual decision-making around PrEP use. Additional implementation science research is needed to develop effective and efficient PrEP delivery platforms that are acceptable to a wide range of potential users.

Other formulations than daily oral tenofovir-based PrEP are forthcoming. A monthly dapivirine-containing vaginal ring reduces HIV incidence by 30% compared to placebo is currently under review by medical regulatory authorities in sub-Saharan Africa [191]. Intramuscular injection of cabotegravir every 8 weeks reduced incidence by 76% compared to oral TDF/FTC among cisgender MSM and transgender women and by 89% among African women [152,192]. Several other modalities are under investigation, including topical gels, implants, patches, and vaginal films [193]. As with contraception, a broad mix of modalities may facilitate choice and accommodate wide-ranging user preferences [194]. Delivery of these products will also incur

different costs depending on drug prices, visit frequency, and monitoring and provider needs. By facilitating adherence, long-acting PrEP formulations are likely to alter use patterns with respect to HIV risk, which will need to be elicited in future research. Mathematical modeling analyses must subsequently adapt to accurately reflect how PrEP use aligns with HIV exposure.

Future research can also extend the geospatial risk prediction analysis described in Chapter 3. A logical first step would be to evaluate model performance at other sites with routine population-based HIV surveillance at small spatial scales, such as ALPHA Network sites [182]. Such a validation exercise would test whether the geospatial distribution of HIV prevalence and viral load is similarly predictive in other sub-Saharan Africa settings, or whether other covariates are more important. The universal test-and-treat cluster-randomized trials may also provide another setting for model validation [195]. For example, a pooled analysis of four trials found that a 1% decrease in community-level viremia was statistically significantly associated with a decrease in HIV incidence of 0.07/100 PY [183]. This analysis could be extended to test the importance of HIV prevalence and population prevalence of detectable viremia in individual-level prediction.

A further step would be to evaluate whether model-based predictions of local HIV prevalence, which have been generated for all of sub-Saharan Africa [184], prospectively predict HIV incidence and at what scale. Such an analysis would need to consider validation of the HIV prevalence estimates themselves. Poor performance could be indicative of issues with the predicted surfaces, the geographic scale used for the analysis, or limitations with the predictive ability of geospatial covariates in general. More generally, our findings may motivate efforts to better estimate local HIV prevalence and viremia at small scales. Additional investment in population-based surveys and surveillance activities could inform efforts to map local HIV prevalence and viremia. Estimates of HIV prevalence and viral suppression are directly applicable to HIV treatment targets; therefore, investment in measuring the covariates needed for prediction also has tangible benefits to treatment programs.

Mathematical and predictive models are powerful tools with increasing influence on HIV policy decisions. This dissertation contributes new insight into the development and evaluation of models to inform PrEP programs in sub-Saharan Africa, with the goal of improving access to effective HIV prevention.

REFERENCES

1. UNAIDS. UNAIDS Estimates (2020) [Internet]. [cited 2021 Jan 14]. Available from: https://aidsinfo.unaids.org/

2. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet. 2007 Feb;369(9562):643–56.

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(11):1112–22.

4. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet. 2007 Feb;369(9562):657–66.

5. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 Infection with Early Antiretroviral Therapy. N Engl J Med. 2011 Aug;365(6):493–505.

6. Bavinton BR, Pinto AN, Phanuphak N, Grinsztejn B, Prestage GP, Zablotska-Manos IB, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. Lancet HIV. 2018 Aug 1;5(8):e438–47.

7. Rodger AJ, Cambiano V, Bruun T, Vernazza P, Collins S, Degen O, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. The Lancet. 2019 Jun 15;393(10189):2428–38.

8. Group TISS. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med. 2015 Aug;373(9):795–807.

9. Group TTA 12136 S. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med. 2015 Aug;373(9):808–22.

10. UNAIDS 90-90-90 treatment target [Internet]. 2020. Available from: https://www.unaids.org/en/90-90-90

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 Dec;363(27):2587–99.

12. 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 Aug;367(5):399–410.

13. 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 Aug 2;367(5):411–22.

14. Chou R, Evans C, Hoverman A, Sun C, Dana T, Bougatsos C, et al. Preexposure Prophylaxis for the Prevention of HIV Infection: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA. 2019 Jun 11;321(22):2214–30.

15. Fonner VA, Dalglish SL, Kennedy CE, Baggaley R, O'Reilly KR, Koechlin FM, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS. 2016 Jul;30(12):1973–83.

16. Hanscom B, Janes HE, Guarino PD, Huang Y, Brown ER, Chen YQ, et al. Brief Report: Preventing HIV-1 Infection in Women Using Oral Preexposure Prophylaxis: A Meta-analysis of Current Evidence. JAIDS J Acquir Immune Defic Syndr. 2016 Dec;73(5):606–8.

17. Haberer JE, Baeten JM, Campbell J, Wangisi J, Katabira E, Ronald A, et al. Adherence to Antiretroviral Prophylaxis for HIV Prevention: A Substudy Cohort within a Clinical Trial of Serodiscordant Couples in East Africa. PLoS Med. 2013 Sep 10;10(9):e1001511.

18. de Oliveira T, Kharsany ABM, Gräf T, Cawood C, Khanyile D, Grobler A, et al. Transmission networks and risk of HIV infection in KwaZulu-Natal, South Africa: a community-wide phylogenetic study. Lancet HIV. 2017 Jan;4(1):e41–50.

19. Abdool Karim Q, Sibeko S, Baxter C. Preventing HIV infection in women: a global health imperative. Clin Infect Dis Off Publ Infect Dis Soc Am. 2010 May 15;50 Suppl 3:S122-129.

20. Pyra MN, Haberer JE, Hasen N, Reed J, Mugo NR, Baeten JM. Global implementation of PrEP for HIV prevention: setting expectations for impact. J Int AIDS Soc [Internet]. 2019 Aug;22(8). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jia2.25370

21. 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.

22. 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 Jan;11(1):80–6.

23. Irungu EM, Baeten JM. PrEP rollout in Africa: status and opportunity. Nat Med. 2020 May;26(5):655–64.

24. 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 Med. 2019 Sep;16(9):e1002885.

25. 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 Jan;7(1):e38–48.

26. Mayer CM, Owaraganise A, Kabami J, Kwarisiima D, Koss CA, Charlebois ED, 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 Apr;22(4).

27. Pintye J, Kinuthia J, Abuna F, Mugwanya K, Lagat H, Dettinger JC, et al. Frequency and predictors of tenofovir-diphosphate detection among young Kenyan women in a real-world pre-exposure prophylaxis implementation program. Clin Infect Dis Off Publ Infect Dis Soc Am [Internet]. 2020 Feb; Available from: http://www.ncbi.nlm.nih.gov/pubmed/32109293

28. 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;0(0).

29. Koss CA, Havlir DV, Ayieko J, Kwarisiima D, Kabami J, Chamie G, et al. HIV incidence after pre-exposure prophylaxis initiation among women and men at elevated HIV risk: A population-based study in rural Kenya and Uganda. PLOS Med. 2021 Feb 9;18(2):e1003492.

30. Beesham I, Welch JD, Heffron R, Pleaner M, Kidoguchi L, Palanee-Phillips T, et al. Integrating oral PrEP delivery among African women in a large HIV endpoint-driven clinical trial. J Int AIDS Soc. 2020 May;23(5):e25491.

31. Reed JB, Shrestha P, Were D, Chakare T, Mutegi J, Wakhutu B, et al. HIV PrEP is more than ART-lite: Longitudinal study of real-world PrEP services data identifies missing measures meaningful to HIV prevention programming. J Int AIDS Soc. 2021 Oct;24(10):e25827.

32. Celum C. A Cohort for Evaluation of Open-label PrEP Delivery Among Kenyan and South African Women: The POWER Cohort [Internet]. clinicaltrials.gov; 2020 Nov [cited 2021 Oct 31]. Report No.: NCT03490058. Available from: https://clinicaltrials.gov/ct2/show/NCT03490058

33. Haberer JE, Bangsberg DR, Baeten JM, Curran K, Koechlin F, Amico KR, et al. Defining success with HIV pre-exposure prophylaxis: a prevention-effective adherence paradigm. AIDS Lond Engl. 2015 Jul;29(11):1277–85.

34. Pintye J, Drake AL, Kinuthia J, Unger JA, Matemo D, Heffron R, et al. A risk assessment tool for identifying pregnant and postpartum women who may benefit from pre-exposure prophylaxis (PrEP). Clin Infect Dis. 2016 Dec;64(6):ciw850.

35. Balkus JE, Brown E, Palanee T, Nair G, Gafoor Z, Zhang J, et al. An Empiric HIV Risk Scoring Tool to Predict HIV-1 Acquisition in African Women. J Acquir Immune Defic Syndr. 2016 Jul;72(3):333–43.

36. Balkus JE, Brown ER, Palanee-Phillips T, Matovu Kiweewa F, Mgodi N, Naidoo L, et al. Performance of a Validated Risk Score to Predict HIV-1 Acquisition Among African Women Participating in a Trial of the Dapivirine Vaginal Ring. Vol. 77, Journal of acquired immune deficiency syndromes (1999). NIH Public Access; 2018. e8–e10 p.

37. Peebles K, Palanee-Phillips T, Balkus JE, Beesham I, Makkan H, Deese J, et al. Age-Specific Risk Scores Do Not Improve HIV-1 Prediction Among Women in South Africa. J Acquir Immune Defic Syndr. 2020 Oct 1;85(2):156–64.

38. Kahle EM, Hughes JP, Lingappa JR, John-Stewart G, Celum C, Nakku-Joloba E, et al. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention. J Acquir Immune Defic Syndr. 2013 Mar;62(3):339–47.

39. Balzer LB, Havlir DV, Kamya MR, Chamie G, Charlebois ED, Clark TD, et al. Machine Learning to Identify Persons at High-Risk of Human Immunodeficiency Virus Acquisition in Rural Kenya and Uganda. Clin Infect Dis [Internet]. 2019 Nov; Available from: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciz1096/5614347

40. Wand H, Reddy T, Naidoo S, Moonsamy S, Siva S, Morar NS, et al. A Simple Risk Prediction Algorithm for HIV Transmission: Results from HIV Prevention Trials in KwaZulu Natal, South Africa (2002–2012). AIDS Behav. 2018 Jan;22(1):325–36.

41. Ayton SG, Pavlicova M, Tamir H, Abdool Karim Q. Development of a prognostic tool exploring female adolescent risk for HIV prevention and PrEP in rural South Africa, a generalised epidemic setting. Sex Transm Infect. 2020 Feb;96(1):47–54.

42. Ayton SG, Pavlicova M, Abdool Karim Q. Identification of adolescent girls and young women for targeted HIV prevention: a new risk scoring tool in KwaZulu Natal, South Africa. Sci Rep. 2020 Aug 3;10(1):13017.

43. 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 Nov;15(6):578.

44. Zimmerman RS, Morisky DE, Harrison L, Mark HD. Validity of behavioral measures as proxies for HIV-related outcomes. J Acquir Immune Defic Syndr 1999. 2014 Aug;66 Suppl 3(0 3):S285-92.

45. Global Burden of Disease Health Financing Collaborator Network JL, Haakenstad A, Micah A, Moses M, Abbafati C, Acharya P, et al. Spending on health and HIV/AIDS: domestic health spending and development assistance in 188 countries, 1995-2015. Lancet Lond Engl. 2018 May;391(10132):1799–829.

46. Anderson S-J, 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 Lond Engl. 2014 Jul;384(9939):249–56.

47. Geffen N, Welte A. Modelling the human immunodeficiency virus (HIV) epidemic: A review of the substance and role of models in South Africa. South Afr J HIV Med. 2018;19(1):756.

48. Meyer-Rath G, Johnson LF, Pillay Y, Blecher M, Brennan AT, Long L, et al. Changing the South African national antiretroviral therapy guidelines: The role of cost modelling. Lima VD, editor. PLOS ONE. 2017 Oct;12(10):e0186557.

49. Schwartländer B, Stover J, Hallett T, Atun R, Avila C, Gouws E, et al. Towards an improved investment approach for an effective response to HIV/AIDS. The Lancet. 2011 Jun;377(9782):2031–41.

50. Anderson RM, Garnett GP. Mathematical models of the transmission and control of sexually transmitted diseases. Sex Transm Dis. 2000 Nov;27(10):636–43.

51. Easterbrook PJ, Doherty MC, Perriëns JH, Barcarolo JL, Hirnschall GO. The role of mathematical modelling in the development of recommendations in the 2013 WHO consolidated antiretroviral therapy guidelines. AIDS Lond Engl. 2014 Jan;28 Suppl 1:S85-92.

52. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the economic evaluation of health care programmes. 3 ed. Oxford, United Kingdom: Oxford University Press; 2005.

53. Gold MR, Stevenson D, Fryback DG. HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health. Annu Rev Public Health. 2002 Jan;23:115–34.

54. Marseille E, Larson B, Kazi DS, Kahn JG, Rosen S. Thresholds for the cost-effectiveness of interventions: alternative approaches. Bull World Health Organ. 2015 Feb;93(2):118–24.

55. Woods B, Revill P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. Value Health. 2016 Dec;19(8):929–35.

56. Meyer-Rath G, Van Rensburg C, Larson B, Jamieson L, Rosen S. Revealed willingness-to-pay versus standard cost-effectiveness thresholds: Evidence from the South African HIV Investment Case. PLoS ONE. 2017 Oct;12(10).

57. Phillips AN, Venter F, Havlir D, Pozniak A, Kuritzkes D, Wensing A, et al. Risks and benefits of dolutegravir-based antiretroviral drug regimens in sub-Saharan Africa: a modelling study. Lancet HIV. 2019 Feb;6(2):e116–27.

58. Rodriguez PJ, Roberts DA, Meisner J, Sharma M, Owiredu MN, Gomez B, et al. Cost-effectiveness of dual maternal HIV and syphilis testing strategies in high and low HIV prevalence countries: a modelling study. Lancet Glob Health. 2021 Jan 1;9(1):e61–71.

59. Meisner J, Roberts DA, Rodriguez P, Sharma M, Newman Owiredu M, Gomez B, et al. Optimizing HIV retesting during pregnancy and postpartum in four countries: a cost-effectiveness analysis. J Int AIDS Soc. 2021;24(4):e25686.

60. Bilinski A, Neumann P, Cohen J, Thorat T, McDaniel K, Salomon JA. When cost-effective interventions are unaffordable: Integrating cost-effectiveness and budget impact in priority setting for global health programs. PLOS Med. 2017 Oct;14(10):e1002397.

61. Case KK, Gomez GB, Hallett TB. The impact, cost and cost-effectiveness of oral pre-exposure prophylaxis in sub-Saharan Africa: a scoping review of modelling contributions and way forward. Vol. 22, Journal of the International AIDS Society. John Wiley and Sons Inc.; 2019.

62. Nichols BE, Baltussen R, van Dijk JH, Thuma PE, Nouwen JL, Boucher CAB, et al. Cost-effectiveness of PrEP in HIV/AIDS control in Zambia: a stochastic league approach. J Acquir Immune Defic Syndr 1999. 2014 Jun;66(2):221–8.

63. McGillen JB, Anderson S-J, Hallett TB. PrEP as a feature in the optimal landscape of combination HIV prevention in sub-Saharan Africa. J Int AIDS Soc. 2016 Oct;19(7 (Suppl 6)):21104.

64. Alistar SS, Grant PM, Bendavid E. Comparative effectiveness and cost-effectiveness of antiretroviral therapy and pre-exposure prophylaxis for HIV prevention in South Africa. BMC Med. 2014 Mar 17;12(1):46.

65. Meyer-Rath G, Jamieson L, Leuner R, Johnson L. Finding the right target population for PrEP: the cost-effectiveness of pre-exposure prophylaxis provision to female and male adolescents and young women in South Africa. In: 9th IAS Conference on HIV Science. Paris; 2017.

66. Pretorius C, Stover J, Bollinger L, Bacaër N, Williams B. Evaluating the Cost-Effectiveness of Pre-Exposure Prophylaxis (PrEP) and Its Impact on HIV-1 Transmission in South Africa. Myer L, editor. PLoS ONE. 2010 Nov;5(11):e13646.

67. Verguet S, Stalcup M, Walsh JA. Where to deploy pre-exposure prophylaxis (PrEP) in sub-Saharan Africa? Sex Transm Infect. 2013 Dec;89(8):628–34.

68. Cremin Í, Hallett TB. Estimating the range of potential epidemiological impact of pre-exposure prophylaxis. AIDS. 2015 Mar;29(6):733–8.

69. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. [Internet]. 2016 [cited 2020 Nov 8]. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf

70. Mitchell KM, Lépine A, Terris-Prestholt F, Torpey K, Khamofu H, Folayan MO, et al. Modelling the impact and cost-effectiveness of combination prevention amongst HIV serodiscordant couples in Nigeria. AIDS. 2015 Sep;29(15):2035–44.

71. Cremin I, McKinnon L, Kimani J, Cherutich P, Gakii G, Muriuki F, et al. PrEP for key populations in combination HIV prevention in Nairobi: a mathematical modelling study. Lancet HIV. 2017 May;4(5):e214–22.

72. Smith JA, Anderson S-J, Harris KL, McGillen JB, Lee E, Garnett GP, et al. Maximising HIV prevention by balancing the opportunities of today with the promises of tomorrow: a modelling study. Lancet HIV. 2016 Jul;3(7):e289–96.

73. 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. Bekker L-G, editor. PLOS Med. 2017 Nov;14(11):e1002444.

74. Ying R, Sharma M, Heffron R, Celum CL, Baeten JM, Katabira E, et al. Cost-effectiveness of pre-exposure prophylaxis targeted to high-risk serodiscordant couples as a bridge to sustained ART use in Kampala, Uganda. J Int AIDS Soc. 2015 Jan;18(4 Suppl 3):20013.

75. Garnett GP, Cousens S, Hallett TB, Steketee R, Walker N. Mathematical models in the evaluation of health programmes. Lancet Lond Engl. 2011 Aug 6;378(9790):515–25.

76. Willem L, Verelst F, Bilcke J, Hens N, Beutels P. Lessons from a decade of individual-based models for infectious disease transmission: A systematic review (2006-2015). BMC Infect Dis. 2017 Sep;17(1).

77. Bershteyn A, Gerardin J, Bridenbecker D, Lorton CW, Bloedow J, Baker RS, et al. Implementation and applications of EMOD, an individual-based multi-disease modeling platform. Pathog Dis. 2018 Jul;76(5).

78. Bonabeau E. Agent-based modeling: Methods and techniques for simulating human systems. Proc Natl Acad Sci U S A. 2002 May;99(SUPPL. 3):7280–7.

79. Luke DA, Harris JK. Network Analysis in Public Health: History, Methods, and Applications. Annu Rev Public Health. 2007 Apr;28(1):69–93.

80. Ghani AC, Swinton J, Garnett GP. The role of sexual partnership networks in the epidemiology of gonorrhea. Sex Transm Dis. 1997;24(1):45–56.

81. Eaton JW, Hallett TB, Garnett GP. Concurrent sexual partnerships and primary HIV infection: A critical interaction. AIDS Behav. 2011 May;15(4):687–92.

82. Leung KY, Kretzschmar M. Concurrency can drive an HIV epidemic by moving R0 across the epidemic threshold. AIDS. 2015 Jun;29(9):1097–103.

83. Rao DW, Wheatley MM, Goodreau SM, Enns EA. Partnership dynamics in mathematical models and implications for representation of sexually transmitted infections: a review. Ann Epidemiol. 2021 Jul 1;59:72–80.

84. Anderson RM, May RM (Robert M. Infectious diseases of humans : dynamics and control. Oxford University Press; 1991. 757 p.

85. Eaton JW, Menzies NA, Stover J, Cambiano V, Chindelevitch L, Cori A, et al. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. Lancet Glob Health. 2014;2(1):e23–34.

86. Eaton JW, Johnson LF, Salomon JA, Bärnighausen T, Bendavid E, Bershteyn A, et al. HIV Treatment as Prevention: Systematic Comparison of Mathematical Models of the Potential Impact of Antiretroviral Therapy on HIV Incidence in South Africa. Bartlett J, editor. PLoS Med. 2012 Jul 10;9(7):e1001245.

87. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet. 2009 Jan 3;373(9657):48–57.

88. Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by “test and treat” in hyperendemic settings. AIDS Lond Engl. 2010 Mar 13;24(5):729–35.

89. Hontelez JAC, Lurie MN, Bärnighausen T, Bakker R, Baltussen R, Tanser F, et al. Elimination of HIV in South Africa through Expanded Access to Antiretroviral Therapy: A Model Comparison Study. PLoS Med. 2013;10(10).

90. Akullian A, Morrison M, Garnett GP, Mnisi Z, Lukhele N, Bridenbecker D, et al. The effect of 90-90-90 on HIV-1 incidence and mortality in eSwatini: a mathematical modelling study. Lancet HIV. 2020 Feb 1;7(5):e348–58.

91. Eaton JW, Bacaër N, Bershteyn A, Cambiano V, Cori A, Dorrington RE, et al. Assessment of epidemic projections using recent HIV survey data in South Africa: a validation analysis of ten mathematical models of HIV epidemiology in the antiretroviral therapy era. Lancet Glob Health. 2015 Oct;3(10):e598-608.

92. Raftery AE, Bao L. Estimating and Projecting Trends in HIV/AIDS Generalized Epidemics Using Incremental Mixture Importance Sampling. Biometrics. 2010 Dec;66(4):1162–73.

93. Williams BG. Fitting and projecting HIV epidemics: Data, structure and parsimony. 2014 Nov 22;

94. Akullian A, Bershteyn A, Jewell B, Camlin CS. The missing 27%. Vol. 31, AIDS. Lippincott Williams and Wilkins; 2017. p. 2427–9.

95. 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 Jan 1;3:97–106.

96. Rutstein SE, Smith DK, Dalal S, Baggaley RC, Cohen MS. Initiation, discontinuation, and restarting HIV pre-exposure prophylaxis: ongoing implementation strategies. Lancet HIV [Internet]. 2020 Aug;0(0). Available from: https://linkinghub.elsevier.com/retrieve/pii/S2352301820302034

97. Grant H, Gomez GB, Kripke K, Barnabas RV, Watts C, Medley GF, et al. Time to Scale Up Preexposure Prophylaxis Beyond the Highest-Risk Populations? Modeling Insights From High-Risk Women in Sub-Saharan Africa. Sex Transm Dis. 2020 Nov;47(11):767–77.

98. Jenness SM, Goodreau SM, Rosenberg E, Beylerian EN, Hoover KW, Smith DK, et al. Impact of the centers for disease control's HIV preexposure prophylaxis guidelines for men who have sex with men in the United States. J Infect Dis. 2016 Dec;214(12):1800–7.

99. Phillips AN, Cambiano V, Johnson L, Nakagawa F, Homan R, Meyer-Rath G, et al. Potential Impact and Cost-Effectiveness of Condomless-Sex–Concentrated PrEP in KwaZulu-Natal Accounting for Drug Resistance. J Infect Dis. 2021 Apr 15;223(8):1345–55.

100. UNAIDS. UNAIDS Estimates [Internet]. 2018 [cited 2018 Sep 15]. Available from: http://aidsinfo.unaids.org/

101. Hallett TB, Baeten JM, Heffron R, Barnabas R, de Bruyn G, Cremin Í, et al. Optimal uses of antiretrovirals for prevention in HIV-1 serodiscordant heterosexual couples in South Africa: a modelling study. PLoS Med. 2011 Nov;8(11):e1001123.

102. Cremin I, Alsallaq R, Dybul M, Piot P, Garnett G, Hallett TB. The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis. Wolters Kluwer Health AIDS. 2013;27:447–58.

103. Schnure M, Kripke K, Forsythe S, Hamilton M, Dent J, Reidy M, et al. Oral Pre-Exposure Prophylaxis (PrEP) modeling for strategic planning: Results from thirteen countries. In: 22nd International AIDS Conference [Internet]. Amsterdam; 2018. Available from: http://programme.aids2018.org/Abstract/Abstract/6104

104. Gomez GB, Borquez A, Case KK, Wheelock A, Vassall A, Hankins C. The Cost and Impact of Scaling Up Pre-exposure Prophylaxis for HIV Prevention: A Systematic Review of Cost-Effectiveness Modelling Studies. Salomon JA, editor. PLoS Med. 2013 Mar;10(3):e1001401.

105. Cambiano V, Miners A, Phillips A. What do we know about the cost–effectiveness of HIV preexposure prophylaxis, and is it affordable? Curr Opin HIV AIDS. 2016 Jan;11(1):56–66.

106. Cremin I, Morales F, Jewell BL, O'Reilly KR, Hallett TB. Seasonal PrEP for partners of migrant miners in southern Mozambique: a highly focused PrEP intervention. J Int AIDS Soc. 2015;18(4 Suppl 3):19946.

107. Nichols BE, Boucher CAB, van Dijk JH, Thuma PE, Nouwen JL, Baltussen R, et al. Cost-Effectiveness of Pre-Exposure Prophylaxis (PrEP) in Preventing HIV-1 Infections in Rural Zambia: A Modeling Study. McBryde ES, editor. PLoS ONE. 2013 Mar;8(3):e59549.

108. Drake AL, Wagner A, Richardson B, John-Stewart G. Incident HIV during Pregnancy and Postpartum and Risk of Mother-to-Child HIV Transmission: A Systematic Review and Meta-Analysis. Mofenson LM, editor. PLoS Med. 2014 Feb;11(2):e1001608.

109. Thomson KA, Hughes J, Baeten JM, John-Stewart G, Celum C, Cohen CR, et al. Increased Risk of HIV Acquisition Among Women Throughout Pregnancy and During the Postpartum Period: A Prospective Per-Coital-Act Analysis Among Women With HIV-Infected Partners. J Infect Dis. 2018 Jun;218(1):16–25.

110. WHO | WHO expands recommendation on oral pre-exposure prophylaxis of HIV infection (PrEP). WHO [Internet]. 2018; Available from: https://www.who.int/hiv/pub/prep/policy-brief-prep-2015/en/

111. Price JT, Wheeler SB, Stranix-Chibanda L, Hosek SG, Watts DH, Siberry GK, et al. Cost-Effectiveness of Pre-exposure HIV Prophylaxis During Pregnancy and Breastfeeding in Sub-Saharan Africa. JAIDS J Acquir Immune Defic Syndr. 2016 Aug;72:S145–53.

112. Kinuthia J, Pintye J, Mugwanya KK, Serede M, Sila J, Abuna F, et al. High PrEP Uptake Among Kenyan Pregnant Women Offered PrEP During Antenatal Care. In: Conference on Retroviruses and Opportunistic Infections. Boston, Massachussetts; 2018.

113. National AIDS and STI Control Programme. Kenya HIV County Profiles 2016 [Internet]. Nairobi: Kenya Ministry of Health; 2016. Available from: https://www.fast-trackcities.org/sites/default/files/Kenya HIV County Profiles %282016%29.pdf

114. Kinuthia J, Drake AL, Matemo D, Richardson BA, Zeh C, Osborn L, et al. HIV acquisition during pregnancy and postpartum is associated with genital infections and partnership characteristics. AIDS. 2015 Sep;29(15):2025–33.

115. Kenya Ministry of Health. Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya [Internet]. 2016. Available from: https://aidsfree.usaid.gov/sites/default/files/kenya_art_2016.pdf

116. Pintye J, Kinuthia J, Roberts DA, Wagner AD, Mugwanya K, Abuna F, et al. Integration of PrEP Services Into Routine Antenatal and Postnatal care: Experiences from an Implementation Program in Western Kenya. J Acquir Immune Defic Syndr 1999 [Internet]. 2018 Sep; Available from: http://www.ncbi.nlm.nih.gov/pubmed/30204720

117. Vassall A, Sweeney S, Kahn J, Gomez GB, Bollinger L, Marseille E, et al. Reference Case for Estimating the Costs of Global Health Services and Interventions. Global Health Cost Consortium; 2017.

118. Finkler S, Ward D, Baker J. Essentials of Cost Accounting for Health Care Organizations. Third. Jones & Bartlett Learning; 2007.

119. OANDA. Average Exchange Rates [Internet]. [cited 2018 Sep 10]. Available from: https://www.oanda.com/currency/average

120. R Core Team. R: A language and environment for statistical computing. [Internet]. R Foundation for Statistical Computing; 2018. Available from: https://www.R-project.org/

121. 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. Tsai AC, editor. PLOS Med. 2016 Nov;13(11):e1002166.

122. Ngure K, Heffron R, Mugo N, Thomson KA, Irungu E, Njuguna N, et al. Feasibility and acceptability of HIV self-testing among pre-exposure prophylaxis users in Kenya. J Int AIDS Soc. 2017;20(1):21234.

123. John-Stewart G. PrEP Implementation for Mothers in Antenatal Care (PrIMA) [Internet]. ClinicalTrials.gov. [cited 2018 Sep 10]. Available from: https://clinicaltrials.gov/ct2/show/NCT03070600

124. Mugwanya KK, Baeten JM, Wyatt C, Mugo NR, Connie \P, Celum L, et al. Frequency of Monitoring Kidney Function in HIV-Uninfected Persons Using Daily Oral Tenofovir Disoproxil Fumarate Pre-exposure Prophylaxis [Internet]. 2017. Available from: www.jaids.com

125. Grimsrud A, Barnabas RV, Ehrenkranz P, Ford N. Evidence for scale up: the differentiated care research agenda. J Int AIDS Soc. 2017;20(Suppl 4):22024.

126. Prust ML, Banda CK, Nyirenda R, Chimbwandira F, Kalua T, Jahn A, et al. Multi-month prescriptions, fast-track refills, and community ART groups: results from a process evaluation in Malawi on using differentiated models of care to achieve national HIV treatment goals. J Int AIDS Soc. 2017;20(Suppl 4):21650.

127. Seidman G, Atun R. Does task shifting yield cost savings and improve efficiency for health systems? A systematic review of evidence from low-income and middle-income countries. Hum Resour Health. 2017 Dec;15(1):29.

128. Callaghan M, Ford N, Schneider H. A systematic review of task- shifting for HIV treatment and care in Africa. Hum Resour Health. 2010 Dec;8(1):8.

129. Eakle R, Venter F, Rees H. Pre-exposure prophylaxis (PrEP) in an era of stalled HIV prevention: Can it change the game? 2018;15:29.

130. PrEPWatch:Country Updates [Internet]. PrEPWatch. [cited 2021 Dec 15]. Available from: https://www.prepwatch.org/in-practice/country-updates/

131. WHO | Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection [Internet]. WHO. [cited 2014 Dec 29]. Available from: http://www.who.int/hiv/pub/guidelines/arv2013/en/

132. Knight J, Kaul R, Mishra S. Risk heterogeneity in compartmental HIV transmission models of ART as prevention in Sub-Saharan Africa: A scoping review [Internet]. 2021 Apr [cited 2021 Oct 27] p. 2021.03.29.21254586. Available from: https://www.medrxiv.org/content/10.1101/2021.03.29.21254586v1

133. Akullian A, Morrison M, Garnett GP, Mnisi Z, Lukhele N, Bridenbecker D, et al. The effect of 90-90-90 on HIV-1 incidence and mortality in eSwatini: a mathematical modelling study. Lancet HIV. 2020 Feb;7(5):e348–58.

134. Klein DJ. Relationship formation and flow control algorithms for generating age-structured networks in HIV modeling. In: Proceedings of the IEEE Conference on Decision and Control. 2012. p. 1041–6.

135. Bershteyn A, Klein DJ, Wenger E, Eckhoff PA, Bershteyn * A, Klein DJ. Description of the EMOD-HIV Model v0.7 [Internet]. Available from: https://arxiv.org/pdf/1206.3720.pdf

136. Francis SC, Mthiyane TN, Baisley K, Mchunu SL, Ferguson JB, Smit T, et al. Prevalence of sexually transmitted infections among young people in South Africa: A nested survey in a health and demographic surveillance site. PLOS Med. 2018 Feb 27;15(2):e1002512.

137. Houle B, Mojola SA, Angotti N, Schatz E, Gómez-Olivé FX, Clark SJ, et al. SEXUAL BEHAVIOR AND HIV RISK ACROSS THE LIFE COURSE IN RURAL SOUTH AFRICA: TRENDS AND COMPARISONS. AIDS Care. 2018 Nov;30(11):1435–43.

138. Bershteyn A, Klein DJ, Eckhoff PA. Age-dependent partnering and the HIV transmission chain: a microsimulation analysis. J R Soc Interface. 2013 Aug;10(88):20130613–20130613.

139. Akullian A, Bershteyn A, Klein D, Vandormael A, Bärnighausen T, Tanser F. Sexual partnership age pairings and risk of HIV acquisition in rural South Africa. AIDS. 2017 Jul;31(12):1755–64.

140. Alaeddini A, Klein DJ. Parallel Simultaneous Perturbation Optimization. 2017 Apr; Available from: http://arxiv.org/abs/1704.00223

141. Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. The Lancet. 2010 Jun;375(9731):2092–8.

142. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2019.

143. Ngure K, Thuo N, Ogello V, Kiptinness C, Kamolloh K, Burns BFO, et al. Dynamic Perceived HIV Risk and Sexual Behaviors Among Young Women Enrolled in a PrEP Trial in Kenya: A Qualitative Study. Front Reprod Health. 2021;3:52.

144. Rousseau E, Katz AWK, O'Rourke S, Bekker L-G, Delany-Moretlwe S, Bukusi E, et al. Adolescent girls and young women's PrEP-user journey during an implementation science study in South Africa and Kenya. PloS One. 2021;16(10):e0258542.

145. Beesham I, Heffron R, Evans S, Baeten JM, Smit J, Beksinska M, et al. Exploring the Use of Oral Pre-exposure Prophylaxis (PrEP) Among Women from Durban, South Africa as Part of the HIV Prevention Package in a Clinical Trial. AIDS Behav. 2021 Apr;25(4):1112–9.

146. Bärnighausen K, Geldsetzer P, Matse S, Hettema A, Hughey AB, Dlamini P, et al. Qualitative accounts of PrEP discontinuation from the general population in Eswatini. Cult Health Sex. 2021 Sep 1;23(9):1198–214.

147. Donnell D, Beesham I, Welch JD, Heffron R, Pleaner M, Kidoguchi L, et al. Incorporating oral PrEP into standard prevention services for South African women: a nested interrupted time-series study. Lancet HIV. 2021 Aug;8(8):e495–501.

148. Celum C, Hosek S, Tsholwana M, Kassim S, Mukaka S, Dye BJ, et al. PrEP uptake, persistence, adherence, and effect of retrospective drug level feedback on PrEP adherence

among young women in southern Africa: Results from HPTN 082, a randomized controlled trial. Amico K, editor. PLOS Med. 2021 Jun 18;18(6):e1003670.

149. Moore JR, Donnell DJ, Boily M-C, Mitchell KM, Delany-Moretlwe S, Bekker L-G, et al. Model-Based Predictions of HIV Incidence Among African Women Using HIV Risk Behaviors and Community-Level Data on Male HIV Prevalence and Viral Suppression. J Acquir Immune Defic Syndr 1999. 2020 Dec 1;85(4):423–9.

150. Haberer JE, Mugo N, Bukusi EA, Ngure K, Kiptinness C, Oware K, et al. Understanding Pre-Exposure Prophylaxis Adherence in Young Women in Kenya. J Acquir Immune Defic Syndr 1999. 2022 Mar 1;89(3):251–60.

151. Roche SD, Wairimu N, Mogere P, Kamolloh K, Odoyo J, Kwena ZA, et al. Acceptability and Feasibility of Pharmacy-Based Delivery of Pre-Exposure Prophylaxis in Kenya: A Qualitative Study of Client and Provider Perspectives. AIDS Behav. 2021 Dec 1;25(12):3871–82.

152. Delaney-Moretlwe S. Long acting injectable cabotegravir is safe and effective in preventing HIV infection in cisgender women: results from HPTN 084 [Internet]. HIV R4P; 2021 Jan 27; Virtual. Available from: https://www.hptn.org/sites/default/files/inline-files/210123%20HPTN%20084%20HIV%20R4P%20final%20final.pdf

153. Nair G. Adherence to the dapivirine vaginal ring and oral PrEP among adolescent girls and young women in Africa: interim results from the REACH study [Internet]. IAS Conference on HIV Science; 2021 Jul 18; Virtual. Available from: https://theprogramme.ias2021.org/Abstract/Abstract/2487

154. Warren EA, Paterson P, Schulz WS, Lees S, Eakle R, Stadler J, et al. Risk perception and the influence on uptake and use of biomedical prevention interventions for HIV in sub-Saharan Africa: A systematic literature review. Hills RK, editor. PLOS ONE. 2018 Jun;13(6):e0198680.

155. Pintye J, Drake AL, Begnel E, Kinuthia J, Abuna F, Lagat H, et al. Acceptability and outcomes of distributing HIV self-Tests for male partner testing in Kenyan maternal and child health and family planning clinics. AIDS. 2019 Jul;33(8):1369–78.

156. 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 Jan 15;20(1):69.

157. Roberts DA, Barnabas RV, Abuna F, Lagat H, Kinuthia J, Pintye J, et al. The role of costing in the introduction and scale-up of HIV pre-exposure prophylaxis: evidence from integrating PrEP into routine maternal and child health and family planning clinics in western Kenya. J Int AIDS Soc. 2019 Jul;22(S4).

158. Matthews LT, Moore L, Crankshaw TL, Milford C, Mosery FN, Greener R, et al. South Africans with recent pregnancy rarely know partner's HIV serostatus: implications for serodiscordant couples interventions. BMC Public Health. 2014 Aug 14;14(1):843.

159. Velloza J, Khoza N, Scorgie F, Chitukuta M, Mutero P, Mutiti K, et al. The influence of HIV-related stigma on PrEP disclosure and adherence among adolescent girls and young women in HPTN 082: a qualitative study. J Int AIDS Soc. 2020 Mar;23(3).

160. Wahome E, Thiong'o AN, Mwashigadi G, Chirro O, Mohamed K, Gichuru E, et al. An Empiric Risk Score to Guide PrEP Targeting Among MSM in Coastal Kenya. AIDS Behav. 2018 Jul;22(S1):35–44.

161. Minnis AM, Steiner MJ, Gallo MF, Warner L, Hobbs MM, van der Straten A, et al. Biomarker Validation of Reports of Recent Sexual Activity: Results of a Randomized Controlled Study in Zimbabwe. Am J Epidemiol. 2009 Oct;170(7):918–24.

162. Roberts DA, Hawes SE, Bousso Bao MD, Ndiaye AJ, Gueye D, Raugi DN, et al. Trends in Reported Sexual Behavior and Y-Chromosomal DNA Detection Among Female Sex Workers in the Senegal Preexposure Prophylaxis Demonstration Project. Sex Transm Dis. 2020 May;47(5):314–20.

163. Mavedzenge SN, Olson R, Doyle AM, Changalucha J, Ross DA. The Epidemiology of HIV Among Young People in Sub-Saharan Africa: Know Your Local Epidemic and Its Implications for Prevention. J Adolesc Health. 2011 Dec 1;49(6):559–67.

164. Giovenco D, Pettifor A, MacPhail C, Kahn K, Wagner R, Piwowar-Manning E, et al. Assessing risk for HIV infection among adolescent girls in South Africa: an evaluation of

the VOICE risk score (HPTN 068). J Int AIDS Soc [Internet]. 2019 Jul;22(7). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jia2.25359

165. Tanser F, Bärnighausen T, Grapsa E, Zaidi J, Newell M-L. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 2013 Feb;339(6122):966–71.

166. Tanser F, Vandormael A, Cuadros D, Phillips AN, de Oliveira T, Tomita A, et al. Effect of population viral load on prospective HIV incidence in a hyperendemic rural African community. Sci Transl Med. 2017 Dec;9(420):eaam8012.

167. Solomon SS, Mehta SH, McFall AM, Srikrishnan AK, Saravanan S, Laeyendecker O, et al. Community viral load, antiretroviral therapy coverage, and HIV incidence in India: a cross-sectional, comparative study. Lancet HIV. 2016 Apr;3(4):e183–90.

168. Gareta D, Baisley K, Mngomezulu T, Smit T, Khoza T, Nxumalo S, et al. Cohort Profile Update: Africa Centre Demographic Information System (ACDIS) and population-based HIV survey. Int J Epidemiol. 2021 Feb 1;50(1):33–4.

169. Vandormael A, Akullian A, Siedner M, de Oliveira T, Bärnighausen T, Tanser F. Declines in HIV incidence among men and women in a South African population-based cohort. Nat Commun. 2019 Dec;10(1):5482.

170. Vandormael A, Dobra A, Bärnighausen T, de Oliveira T, Tanser F. Incidence rate estimation, periodic testing and the limitations of the mid-point imputation approach. Int J Epidemiol [Internet]. 2017 Aug; Available from: http://www.ncbi.nlm.nih.gov/pubmed/29024978 http://academic.oup.com/ije/article/doi/10.1093/ije/dyx134/4079903/Incidence-rate-estimation-periodic-testing-and-the

171. van Buuren S. Flexible Imputation of Missing Data [Internet]. Boca Raton: Chapman and Hall/CRC; 2012. Available from: https://stefvanbuuren.name/fimd/

172. Wahl S, Boulesteix A-L, Zierer A, Thorand B, van de Wiel MA. Assessment of predictive performance in incomplete data by combining internal validation and multiple imputation. BMC Med Res Methodol. 2016 Oct 26;16(1):144.

173. Waller LA, Gotway CA. Applied Spatial Statistics for Public Health Data [Internet]. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2004. (Wiley Series in Probability and Statistics). Available from: http://doi.wiley.com/10.1002/0471662682

174. Tanser F, Bärnighausen T, Cooke GS, Newell M-L. Localized spatial clustering of HIV infections in a widely disseminated rural South African epidemic. Int J Epidemiol. 2009 Aug;38(4):1008–16.

175. Tibshirani R. The lasso method for variable selection in the Cox model. Stat Med. 1997 Feb 28;16(4):385–95.

176. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics. 2000;56(2):337–44.

177. Kagaayi J, Gray RH, Whalen C, Fu P, Neuhauser D, McGrath JW, et al. Indices to Measure Risk of HIV Acquisition in Rakai, Uganda. Law M, editor. PLoS ONE. 2014 Apr;9(4):e92015.

178. Tanser F, Bärnighausen T, Dobra A, Sartorius B. Identifying “corridors of HIV transmission” in a severely affected rural South African population: a case for a shift toward targeted prevention strategies. Int J Epidemiol. 2018;47(2):537–49.

179. Joshi K, Lessler J, Olawore O, Loevinsohn G, Bushey S, Tobian AAR, et al. Declining HIV incidence in sub-Saharan Africa: a systematic review and meta-analysis of empiric data. J Int AIDS Soc. 2021 Oct;24(10):e25818.

180. Medina-Marino A, Daniels J, Bezuidenhout D, Peters R, Farirai T, Slabbert J, et al. Outcomes from a multimodal, at-scale community-based HIV counselling and testing programme in twelve high HIV burden districts in South Africa. J Int AIDS Soc. 2021 Mar;24(3):e25678.

181. Barnabas RV, Szpiro AA, van Rooyen H, Asiimwe S, Pillay D, Ware NC, et al. Community-based antiretroviral therapy versus standard clinic-based services for HIV in South Africa and Uganda (DO ART): a randomised trial. Lancet Glob Health. 2020 Oct;8(10):e1305–15.

182. Reniers G, Wamukoya M, Urassa M, Nyaguara A, Nakiyingi-Miiro J, Lutalo T, et al. Data Resource Profile: Network for Analysing Longitudinal Population-based HIV/AIDS data on Africa (ALPHA Network). Int J Epidemiol. 2016 Feb 1;45(1):83–93.

183. Petersen M. Population-level Viremia Predicts HIV Incidence across Universal Test & Treat Studies [Internet]. CROI; 2020. Available from: https://www.croiconference.org/abstract/population-level-viremia-predicts-hiv-incidence-across-universal-test-treat-studies/

184. 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 May;1.

185. Jain V, Petersen M, Havlir DV. Population HIV viral load metrics for community health. Lancet HIV. 2021 Sep;8(9):e523–4.

186. 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 Apr 1;16(2):141–50.

187. Ortblad KF, Mogere P, Bukusi E, Ngure K, Baeten JM. Pharmacy delivery to expand the reach of PrEP in Africa. J Int AIDS Soc. 2020 Sep 30;23(9):e25619.

188. Rousseau E, Bekker L-G, Julies RF, Celum C, Morton J, Johnson R, et al. A community-based mobile clinic model delivering PrEP for HIV prevention to adolescent girls and young women in Cape Town, South Africa. BMC Health Serv Res. 2021 Aug 28;21(1):888.

189. Medina-Marino A, Bezuidenhout D, Hosek S, Barnabas RV, Atujuna M, Bezuidenhout C, et al. The Community PrEP Study: a randomized control trial leveraging community-based platforms to improve access and adherence to pre-exposure prophylaxis to prevent HIV among adolescent girls and young women in South Africa—study protocol. Trials. 2021 Jul 26;22(1):489.

190. Koss CA, Ayieko J, Mwangwa F, Owaraganise A, Kwarisiima D, Balzer LB, 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 Nov;67(12):1853–60.

191. Baeten JM, Palanee-Phillips T, Mgodi NM, Mayo AJ, Szydlo DW, Ramjee G, et al. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. Lancet HIV. 2021 Feb 1;8(2):e87–95.

192. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, et al. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women. N Engl J Med. 2021 Aug 12;385(7):595–608.

193. Beymer MR, Holloway IW, Pulsipher C, Landovitz RJ. Current and Future PrEP Medications and Modalities: On Demand, Injectables, and Topicals. Curr HIV/AIDS Rep. 2019 Aug;16(4):349–58.

194. Delany-Moretlwe S, Mullick S, Eakle R, Rees H. Planning for HIV preexposure prophylaxis introduction: lessons learned from contraception. Curr Opin HIV AIDS. 2016 Jan;11(1):87–93.

195. Perriat D, Balzer L, Hayes R, Lockman S, Walsh F, Ayles H, et al. Comparative assessment of five trials of universal HIV testing and treatment in sub-Saharan Africa. J Int AIDS Soc. 2018 Jan;21(1):e25048.

196. Hollingsworth TD, Anderson RM, Fraser C. HIV-1 Transmission, by Stage of Infection. J Infect Dis. 2008 Sep;198(5):687–93.

197. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis. 2005 May 1;191(9):1403–9.

APPENDIX A

Supplementary material to Chapter 1: Cost of HIV pre-exposure prophylaxis delivery through routine maternal and child health and family planning clinics in western Kenya

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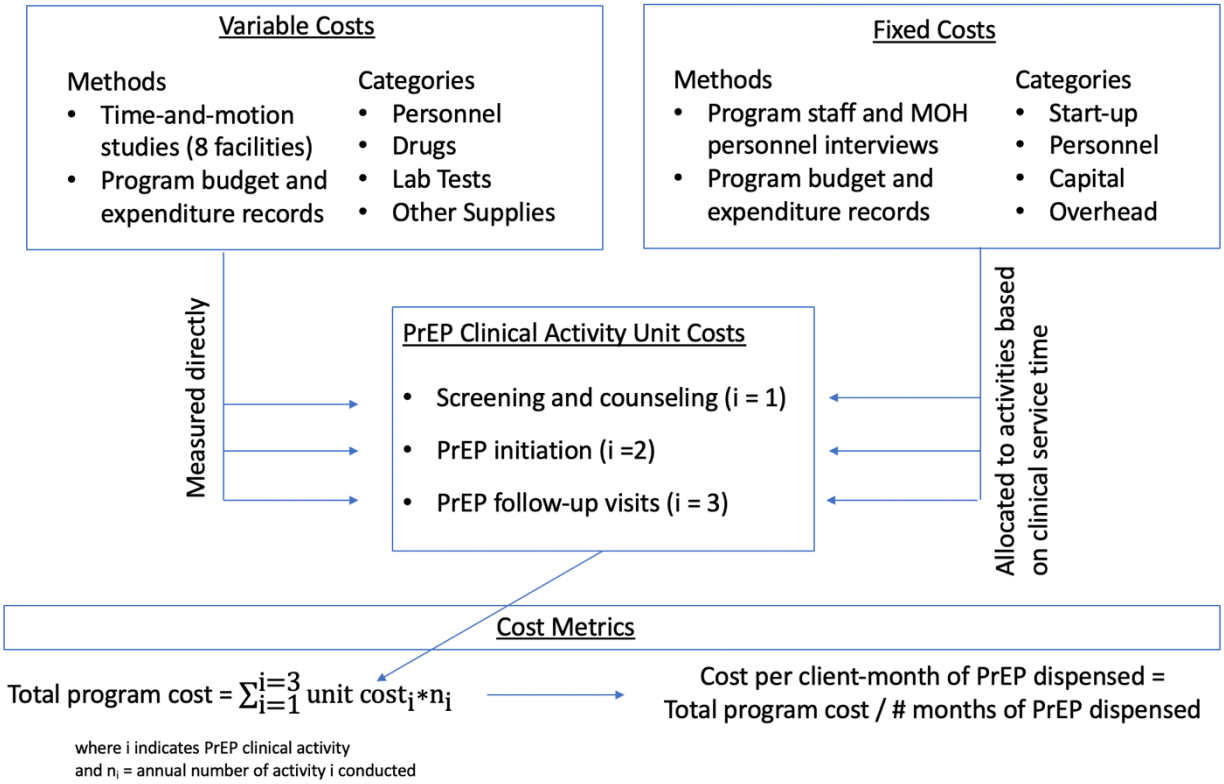
https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fjia2.25296&file=jia225296-sup-0001-Supinfo.docx

Costing methodology

Figure A.1: Overview of Costing Methodology



Variable cost categories

1) Estimates of resource use for variable costs were obtained from a sample of eight of the 16 PrIYA facilities.
2) *Personnel:* Included clinical staff costs for PrEP screening, initiation, HIV testing, and follow-up visits Personnel time was estimated via time-and-motion studies. In the MOH scenario, PrIYA nurse salaries were replaced by MOH salaries.
3) *Drugs:* Drug costs for oral co-formulated tenofovir disoproxil fumarate/emtricitabine ($6.75 per 30 days) included the cost of purchase from the manufacturer as well as storage and transportation costs (charged at 8% of the cost of the product).
4) *Laboratory tests:* Included the cost of the Determine HIV test to confirm HIV-negative status for clients at initiation and follow-up visits as well as the cost of point-of-care

creatinine test strips. Also included consumable supplies used in test administration (ie, gloves, lancets, etc). In the MOH scenario, the point-of-care creatinine cost was replaced by the average facility charge for creatinine testing across PrIYA facilities.

5) *Other Supplies:* Included printing cost of appointment cards, prescription pads, and PrEP encounter records.

Fixed Cost Categories

1) Start-up (annualized over five years)

a. *Microplanning:* Included meetings with county-level officials (i.e., technical working group and task force meetings), onboarding meetings with facility personnel, and printing costs to update standardized MOH reporting tools in order to include TDF/FTC.

b. *Training:* Included staff, venue, and supplies costs for initial nurse trainings as well as commodities and logistics management and information systems (LMIS) facilitation trainings for county and sub-county pharmacists and health records officers.

2) *Personnel*: Included facility staff costs spent on routine reporting, drug accounting, and conducting weekly phone meetings between nurses and program coordinators to debrief on PrEP delivery. Also included the annual salaries and benefits of three PrIYA program staff multiplied by the fraction of their time spent on service delivery management as opposed to research-specific activities (estimated from staff interviews). In the MOH scenario, weekly phone meetings between PrIYA staff were replaced by quarterly PrEP refresher trainings at each facility and PrIYA coordinator salaries were replaced by estimated costs for quarterly supervisory visits from county- and sub-county level health management teams (estimated from interviews with MOH staff).

3) *Capital:* Included the cost of creatinine machines, control solutions, and furniture used during PrEP encounters. Furniture costs were multiplied by the fraction of all MCH and FP encounters recorded at each facility that included PrEP activities. Useful life years assumed to be five years for most items (select items that needed to be replaced yearly, such as creatinine control solutions, were assigned useful life of one year).
4) *Overhead:* Included transportation costs for weekly facility visits conducted by PrIYA program staff, airtime, printing costs for reporting tools, and building and utility costs (estimated using nearby rental properties and multiplied by the fraction of all MCH and FP encounters recorded at each facility that included PrEP activities). Weekly transportation costs were excluded from the MOH scenario under the premise that PrEP supervisory activities would be integrated within existing scheduled visits for PMTCT and reproductive health supervision.

Key input costs

Table A.1: Input costs of key PrEP delivery components (2017 USD)

Item	Cost (2017 USD)	Source
30 days TDF/FTC	6.75*	MOH Personal Communication
Point-of-care creatinine test strip†	4.50	Project budget
Determine HIV test	0.83	Project budget
Project nurse monthly salary + allowances	819	Project budget
Facility-based creatinine test‡	2.51	PrIYA facility survey
MOH nurse monthly salary + allowances	718	Central MOH Salary Scale

*Purchase price from manufacturer of $6.25 per 30-day prescription plus 8% storage and distribution cost

†XPress StatSensor® Creatinine Meter

‡Based on average charge for creatinine test across PrIYA facilities

Time-and-motion studies

Time-and-motion studies were conducted in a sample of eight of the 16 PrIYA facilities (Figure A.2). Facilities were selected to be representative of clinic size, ownership (public, mission, or private), and type (MCH vs FP). A trained PrIYA staff member directly observed screening, PrEP initiation, PrEP follow-up visits, and HIV testing and counselling sessions and recorded the clinical provider time spent in each encounter. Time spent on any research-related activities outside the scope of routine PrEP service delivery were excluded. The average encounter time across all observations was multiplied by the hourly personnel cost to estimate personnel costs per clinical encounter. Time-and-motion results are displayed in Table A.2. In addition to personnel time, input resource usage (e.g., lab tests, consumables, etc) were observed and combined with personnel costs to estimate variable unit costs.

Table A.2: Time (minutes) for clinical service delivery components estimated from time-and-motion studies

Activity	Mean	Median	25th percentile	75th percentile
Screening	8	7	4	11
Initiation†	13	11	8	15
Creatinine	4	3	2	4
HIV testing and counselling	13	12	10	15
Follow-up visit	9	9	8	10

†Includes completing PrEP medical record, point-of-care creatinine testing, and medication dispensation

Figure A.2: Map of PrIYA health facilities in Kisumu County, Kenya

Red markers indicate facilities visited for time-and-motion studies

Program Volume

We used data collected as part of routine monitoring to estimate the numbers of women screened, initiated, and dispensed PrEP over a one-year period. Study staff abstracted standardized client records in all 16 facilities from November 20, 2017 to June 15, 2018. These records included behavioral risk assessment results for all clients counselled about PrEP and standard Ministry of Health records recording PrEP initiation and follow-up visits. Initiation and follow-up visit records included whether PrEP was dispensed as well as the next scheduled visit date. Out of 2586 follow-up visit records, 1963 (76%) indicated that PrEP was dispensed. We assumed that the remainder 24% of visits had no dispensation (regardless of whether dispensation status was recorded or missing).

To estimate annual output, we extrapolated the seven months of data to a full year (until November 19, 2018) assuming no temporal changes in volume. To do this, we created a synthetic cohort of clients entering the program between June 16, 2018, and November 19, 2018 assuming a pattern identical to the observed data starting November 20, 2017. However, the 248 clients

who were continuing on PrEP as of June 15, 2018, were right censored. We assumed that right-censored clients who had fewer than two consecutive follow-up visits did not return for additional follow-ups, while right-censored clients who had at least two consecutive follow-up visits with recorded dispensation (post initiation) would continue PrEP until November 19, 2018. Our results were not sensitive to this assumption. Assuming instead that all right-censored clients never return to the clinic changes the cost per client-month of PrEP delivered only slightly (from $27 to $28).

To calculate the number of client-months of PrEP dispensed, we calculated the median time between recorded visits with PrEP dispensation and the next scheduled follow-up visit to be 28 days (interquartile range: 28-31). Therefore, we assumed that one month of PrEP were dispensed at each follow-up visit. As such, the total number of client-months of PrEP dispensed was calculated by summing the number of PrEP initiations and the number of PrEP follow-up visits with dispensation.

MOH Scenario results

Table A.3: Total annual program cost and unit cost per client-month of PrEP dispensed (2017 USD) in Ministry of Health (MOH) scenario*

	Total annual cost (USD)	Average cost per client-month of PrEP dispensed (USD)
Variable		
Personnel (clinical)	32,895	4.27
Drugs	51,997	6.75
Laboratory testing	18,560	2.41
Other supplies	3,616	0.47
Sub-total	*107,068*	*13.90*
Fixed		
Microplanning	843	0.11
Training	1,978	0.26
Personnel (supervision and administration)	9,438	1.23
Capital (e.g. creatinine machines, furniture)	2,065	0.27
Overhead (e.g. building, airtime, transportation)	6,029	0.78
Sub-total	*20,353*	*2.64*
Summary	**127,421**	**16.54**

*The MOH scenario assumes public sector clinical staff salaries instead of study salaries; study administrative staff responsibilities are subsumed into routine facility, sub-county, and county supervision; and facility-based creatinine testing instead of point-of-care

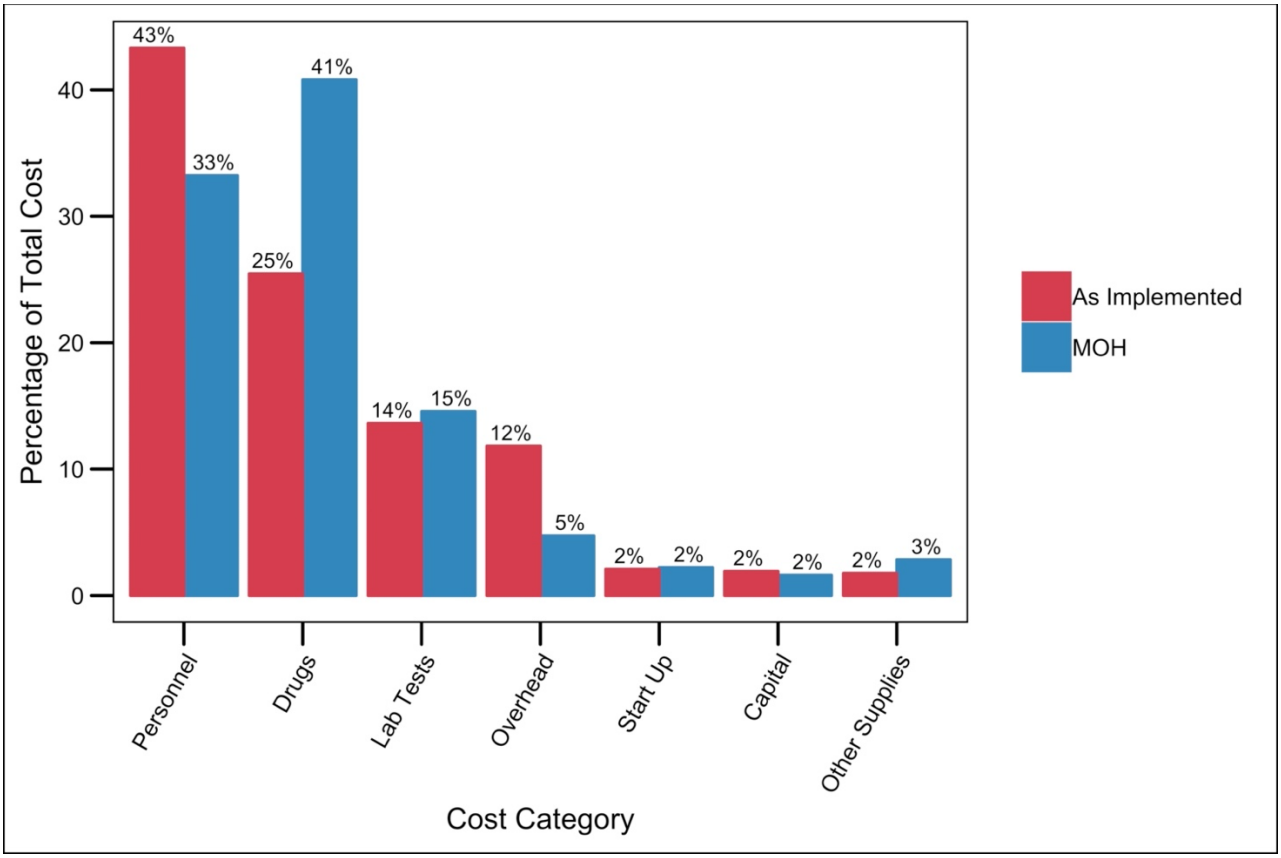
Table A.4: Unit cost breakdown by clinical activity (2017 USD) under Ministry of Health (MOH) scenario*

Cost by Clinical Activity (2017 USD)			
	Screening	**Initiation**	**Follow-up†**
Variable unit cost			
Personnel (clinical)	0.80	1.29	1.87
Drugs	0.00	6.75	5.34
Laboratory testing	0.00	3.55	0.83
Other supplies	0.02	0.32	0.41
Sub-total	***0.82***	***11.91***	***8.45***
Fixed unit cost	0.43	1.37	0.97
Total unit cost (variable + fixed)	**1.25**	**13.28**	**9.42**
Number	24,005	4,198	4,427
Total annual cost	**29,948**	**55,764**	**41,709**

†Follow-up unit costs are weighted averages of visits with and without PrEP dispensation

*The MOH scenario assumes public sector clinical staff salaries instead of study salaries; study administrative staff responsibilities are subsumed into routine facility, sub-county, and county supervision; and facility-based creatinine testing instead of point-of-care

Figure A.3: Percentage of total program cost across cost categories as implemented and under Ministry of Health (MOH) scenario*



*The MOH scenario assumes public sector clinical staff salaries instead of study salaries; study administrative staff responsibilities are subsumed into routine facility, sub-county, and county supervision; and facility-based creatinine testing instead of point-of-care

Sensitivity analysis of As Implemented costing results using different discount rates (2017 USD)

Table A.5: 5% Discount Rate

	Total annual cost (USD)	Average cost per client-month of PrEP dispensed (USD)
Variable		
Personnel (clinical)	37,535	4.87
Medication	51,997	6.75
Laboratory testing	27,830	3.61
Other supplies	3,616	0.47
Sub-total	*120,978*	*15.71*
Fixed		
Microplanning	1,445	0.19
Training	3,066	0.40
Personnel (supervision and administration)	50,924	6.61
Capital (e.g. creatinine machines, furniture)	3,987	0.52
Overhead (e.g. building, airtime, transportation)	24,162	3.14
Sub-total	*83,584*	*10.85*
Summary	**204,562**	**26.56**

Table A.6: 10% Discount Rate

	Total annual cost (USD)	Average cost per client-month of PrEP dispensed (USD)
Variable		
Personnel (clinical)	37,535	4.87
Medication	51,997	6.75
Laboratory testing	27,830	3.61
Other supplies	3,616	0.47
Sub-total	*120,978*	*15.71*
Fixed		
Microplanning	1,650	0.21
Training	3,501	0.45
Personnel (supervision and administration)	50,924	6.61
Capital (e.g. creatinine machines, furniture)	4,149	0.54
Overhead (e.g. building, airtime, transportation)	24,162	3.14
Sub-total	*84,387*	*10.96*
Summary	**205,365**	**26.66**

Table A.7: 15% Discount Rate

	Total annual cost (USD)	Average cost per client-month of PrEP dispensed (USD)
Variable		
Personnel (clinical)	37,535	4.87
Medication	51,997	6.75
Laboratory testing	27,830	3.61
Other supplies	3,616	0.47
Sub-total	*120,978*	*15.71*
Fixed		
Microplanning	1,866	0.24
Training	3,959	0.51
Personnel (supervision and administration)	50,924	6.61
Capital (e.g. creatinine machines, furniture)	4,319	0.56
Overhead (e.g. building, airtime, transportation)	24,162	3.14
Sub-total	*85,231*	*11.07*
Summary	**206,209**	**26.77**

APPENDIX B

Additional results from Chapter 2: The impact of prevention-effective PrEP use on HIV incidence: A mathematical modeling study

Table B.1: Population fraction and incidence rates among HIV-negative 15-34-year-old men and women in the model in 2022, stratified by risk group. CI = credible interval.

	Men		Women	
Risk group	Population fraction	Incidence per 100 PY (95% CI)	Population fraction	Incidence per 100 PY (95% CI)
Low	0.66	0.26 (0.15-0.39)	0.72	0.84 (0.55-1.15)
Medium	0.26	0.59 (0.32-0.85)	0.27	2.29 (1.64-2.92)
High	0.08	2.70 (1.70-4.09)	0.01	12.12 (5.24-22.82)

Table B.2**:** Proportion of person-time spent in at least one partnership among HIV-negative 15-34-year-olds between 2022 and 2031, stratified by risk group. Parentheses indicate 95% credible intervals.

Risk Group	Men	Women
Low	0.33 (0.28-0.37)	0.48 (0.42-0.53)
Medium	0.36 (0.32-0.39)	0.55 (0.50-0.58)
High	0.85 (0.79-0.88)	1 (1-1)

Table B.3**:** Proportion of relationship-time in which at least one partner was HIV-positive among HIV-negative 15-34-year-olds between 2022 and 2031, stratified by risk group. Parentheses indicate 95% credible intervals.

Risk Group	Men	Women
Low	0.08 (0.06-0.10)	0.07 (0.06-0.08)
Medium	0.13 (0.10-0.15)	0.12 (0.10-0.13)
High	0.24 (0.20-0.27)	0.39 (0.35-0.43)

Figure B.1: Prioritization of PrEP use by multiplier value. In the Partnership scenario, prioritization of PrEP use during periods of HIV exposure is governed by a multiplier relating PrEP coverage among individuals with HIV-positive partners relative to those with only HIV-negative partners. As the multiplier increases, PrEP is increasingly used when a low- or medium-risk individual has an HIV-positive partner (turquoise bar), while use during HIV-negative partnerships (purple bar) decreases. Since high-risk individuals cycle in and out of very short commercial partnerships, we applied the same level of PrEP coverage as among low- and medium-risk individuals with an HIV-positive partner. Therefore, PrEP use among high-risk individuals (yellow bars) also is prioritized as the multiplier increases. Error bars indicate 95% credible intervals across 250 parameter sets.

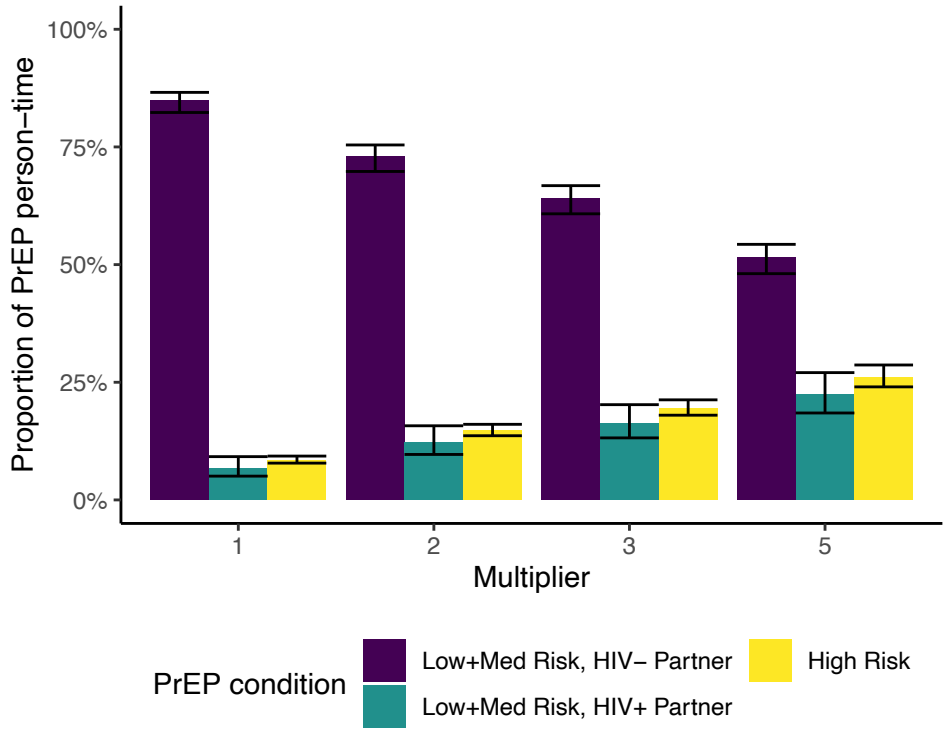


Table B.4: Simulated PrEP coverage levels for scenarios under the Risk Group paradigm. Coverage was scaled from the lowest level to the highest level in even increments. Each coverage level was simulated for each of 250 parameter sets to capture uncertainty.

		PrEP coverage		
Scenario	Scale	Low Risk	Medium Risk	High Risk
High	Lowest	0	0	10%
High	Highest	0	0	90%
Medium + High	Lowest	0	10%	10%
Medium + High	Highest	0	90%	90%
Low + Medium + High	Lowest	10%	10%	10%
Low + Medium + High	Highest	90%	90%	90%

Table B.5: Simulated PrEP coverage levels for scenarios under the Partnership paradigm. Multiplier indicates the multiplier for PrEP coverage level for individuals with at least one HIV-positive partner relative to PrEP coverage for individuals with only HIV-negative partners. The same multiplier was applied to PrEP coverage among high-risk individuals. Coverage was scaled from the lowest level to the highest level in even increments. Each coverage level was simulated for each of 250 parameter sets to capture uncertainty.

		PrEP coverage		
Multiplier	Scale	All HIV- partners	≥1 HIV+ partner	High Risk
1	Lowest	10%	10%	10%
1	Highest	90%	90%	90%
2	Lowest	5%	10%	10%
2	Highest	45%	90%	90%
3	Lowest	5%	15%	15%
3	Highest	30%	90%	90%
4	Lowest	3%	15%	15%
4	Highest	18%	90%	90%

Figure B.2**:** Estimation of the relationship between additional PrEP use (x-axis) and percentage of infections averted relative to a scenario without PrEP (y-axis). Risk Group scenarios are on the top row while the Partnership scenarios are on the bottom row. Each black line represents one of 250 parameter sets. X-axis and y-axis scales vary for each plot to show model fit. The parameter set lines connect simulations run at various PrEP coverage levels (Tables B.4 and B.5). The red lines show the fit of a mixed-effects regression model using a natural spline with one knot and a random intercept for parameter set.

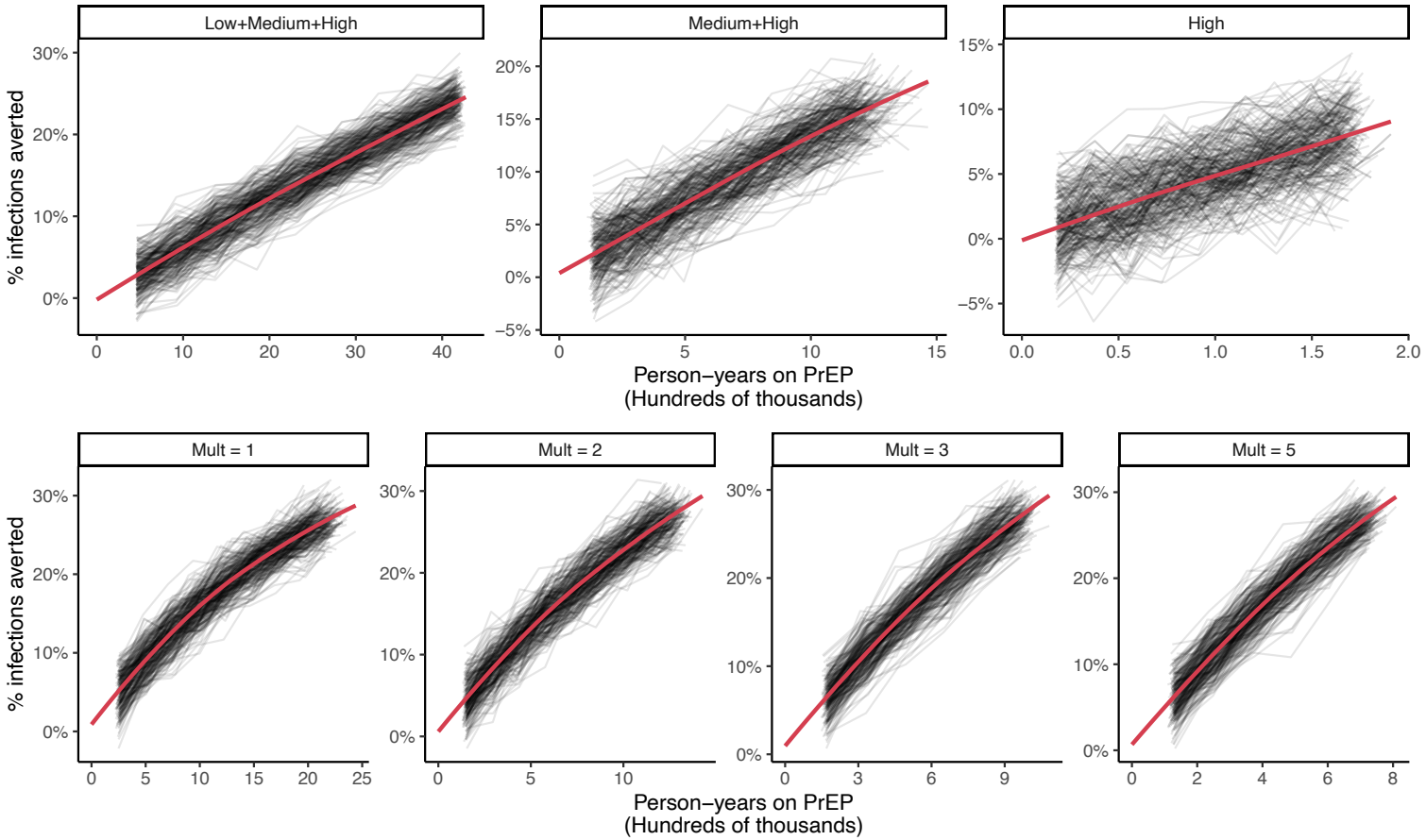
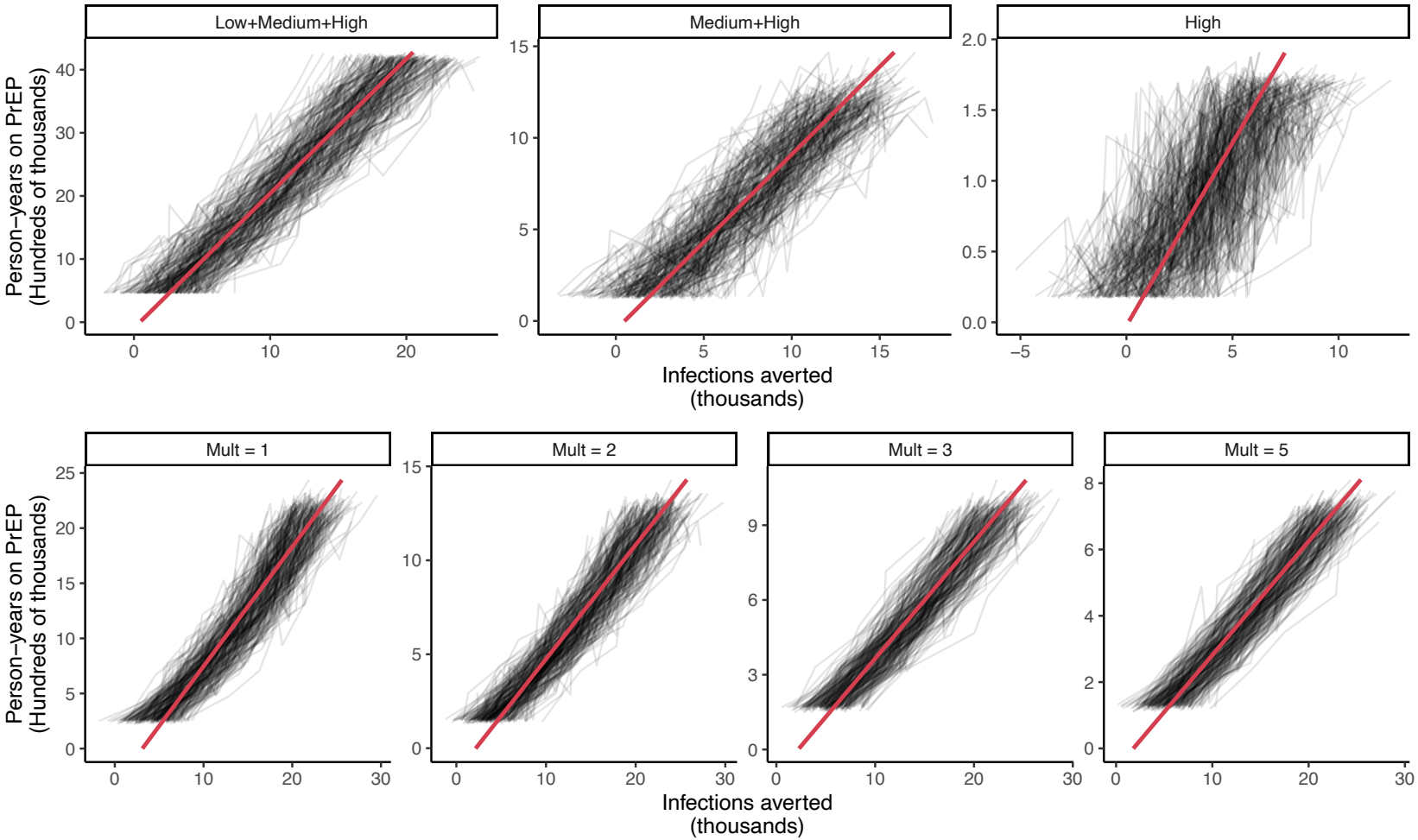


Figure B.3: Estimation of the additional person-years of PrEP use needed to avert one additional infection relative to a scenario without PrEP (number needed to treat, NNT). *Caption continued*



(*Figure B.3, continued*): Risk Group scenarios are on the top row while the Partnership scenarios are on the bottom row. Each black line represents one of 250 parameter sets. X-axis and y-axis scales vary for each plot to show model fit; note that the axes are reversed compared with Figure B.2. The parameter set lines connect simulations run at various PrEP coverage levels (Tables B.4 and B.5). The number needed to treat is estimated by fitting a linear model relating person-years on PrEP (as the outcome) to the number of infections averted (as the predictor), again with a random effect for parameter set. The estimated coefficient on the number of infections averted predictor indicates the NNT averaged across levels of PrEP coverage.

Figure B.4: Relationship between additional person-time on PrEP and percentage of infections averted relative to a no PrEP scenario, stratified by gender and by PrEP paradigm. Person-years on PrEP and percentage of infections averted are cumulative across a ten-year period spanning 2022 to 2031. Shaded regions indicate 95% credible intervals. Mult = multiplier on the probability that an individual with an HIV-positive partner will use PrEP relative to the probability than an individual with only HIV-negative partners will use PrEP.

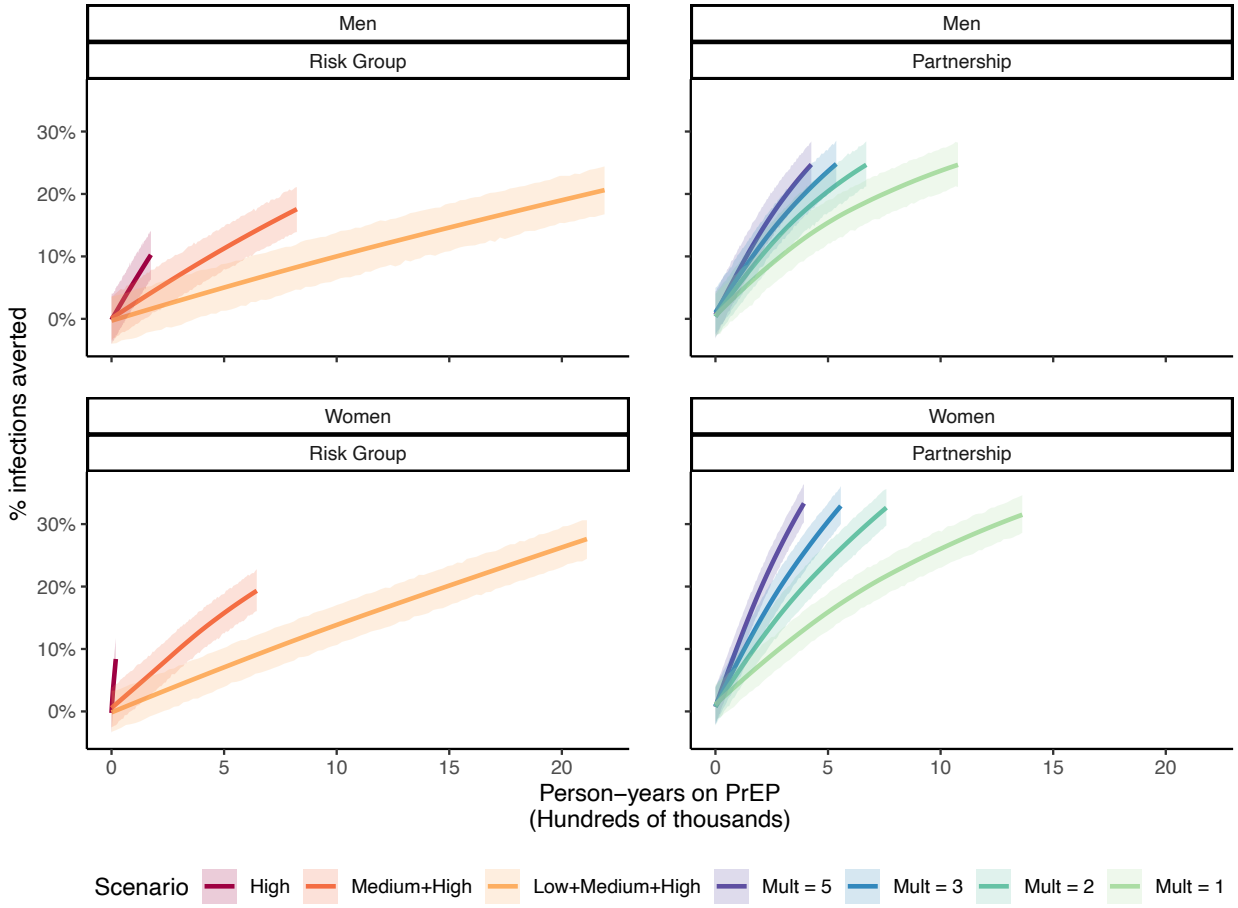


Table B.6**:** Number of additional person-years of PrEP needed to avert one additional HIV infection (number needed to treat, NNT), by PrEP scenario and by gender. CI = credible interval. For estimation details, see Appendix B, Figure B.3.

Paradigm	Scenario	Men NNT (95% CI)	Women NNT (95% CI)
Risk Group	All	283 (279-287)	151 (150-152)
	High and medium	118 (116-120)	60 (59-61)
	High	31 (30-32)	3 (3-3)
Partnership	Mult = 1	121 (119-123)	89 (88-90)
	Mult = 2	75 (74-76)	47 (47-48)
	Mult = 3	61 (60-62)	34 (34-35)
	Mult = 5	48 (47-49)	24 (24-24)

Figure B.5: Relationship between PrEP coverage among all HIV-negative 15–34-year-olds and the relative risk of HIV infection compared to a no PrEP scenario, by PrEP paradigm and by gender. Relative risk is averaged across 2022 to 2031. Shaded regions indicate 95% credible intervals. Mult = multiplier on the probability that an individual with an HIV-positive partner will use PrEP relative to the probability than an individual with only HIV-negative partners will use PrEP.

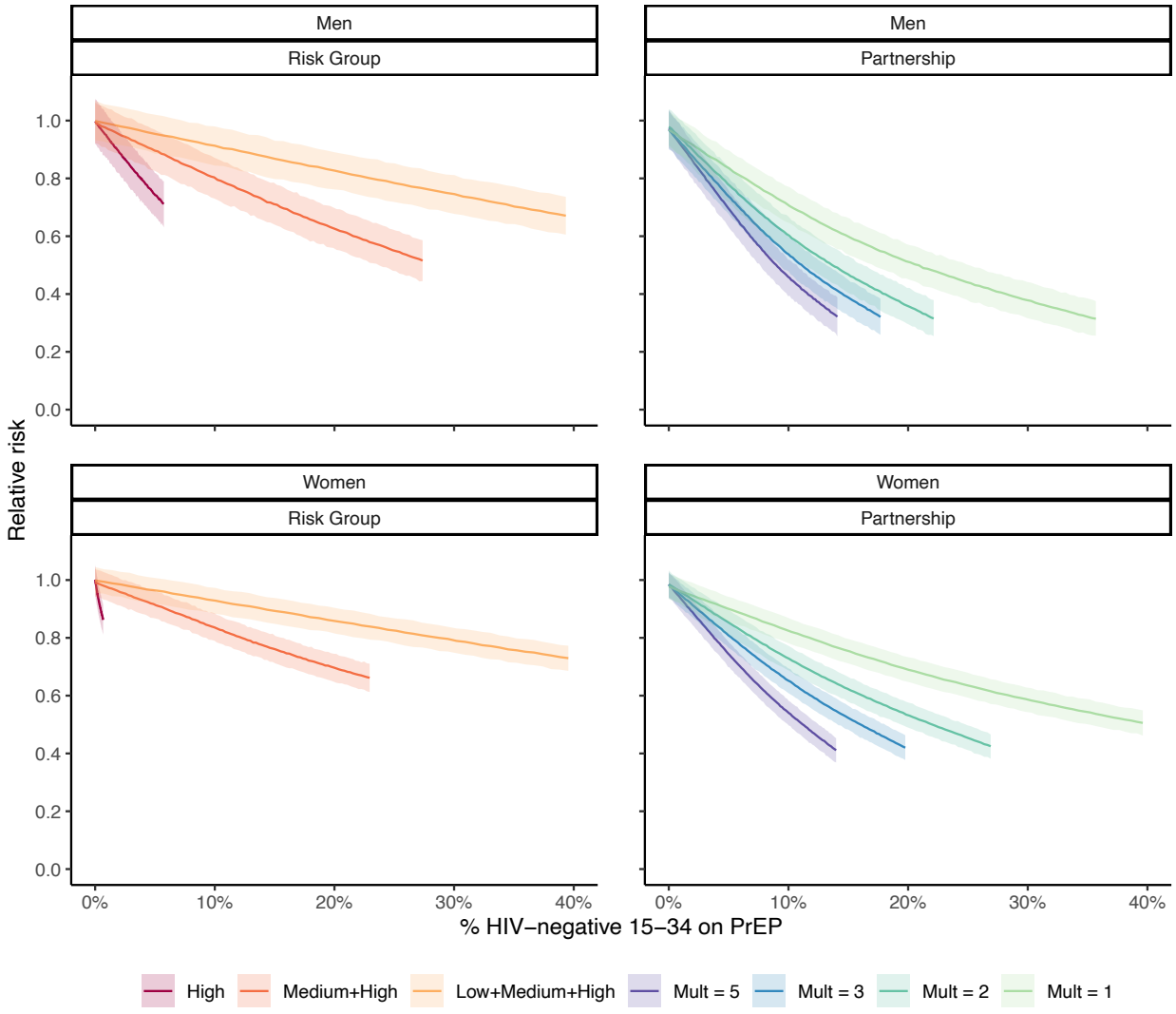


Figure B.6: Proportion of infections averted between 2022-2031 relative to a no PrEP scenario, disaggregated by risk group of the averted infections and stratified by PrEP scenario. Mult = multiplier on the probability that an individual with an HIV-positive partner will use PrEP relative to the probability than an individual with only HIV-negative partners will use PrEP.

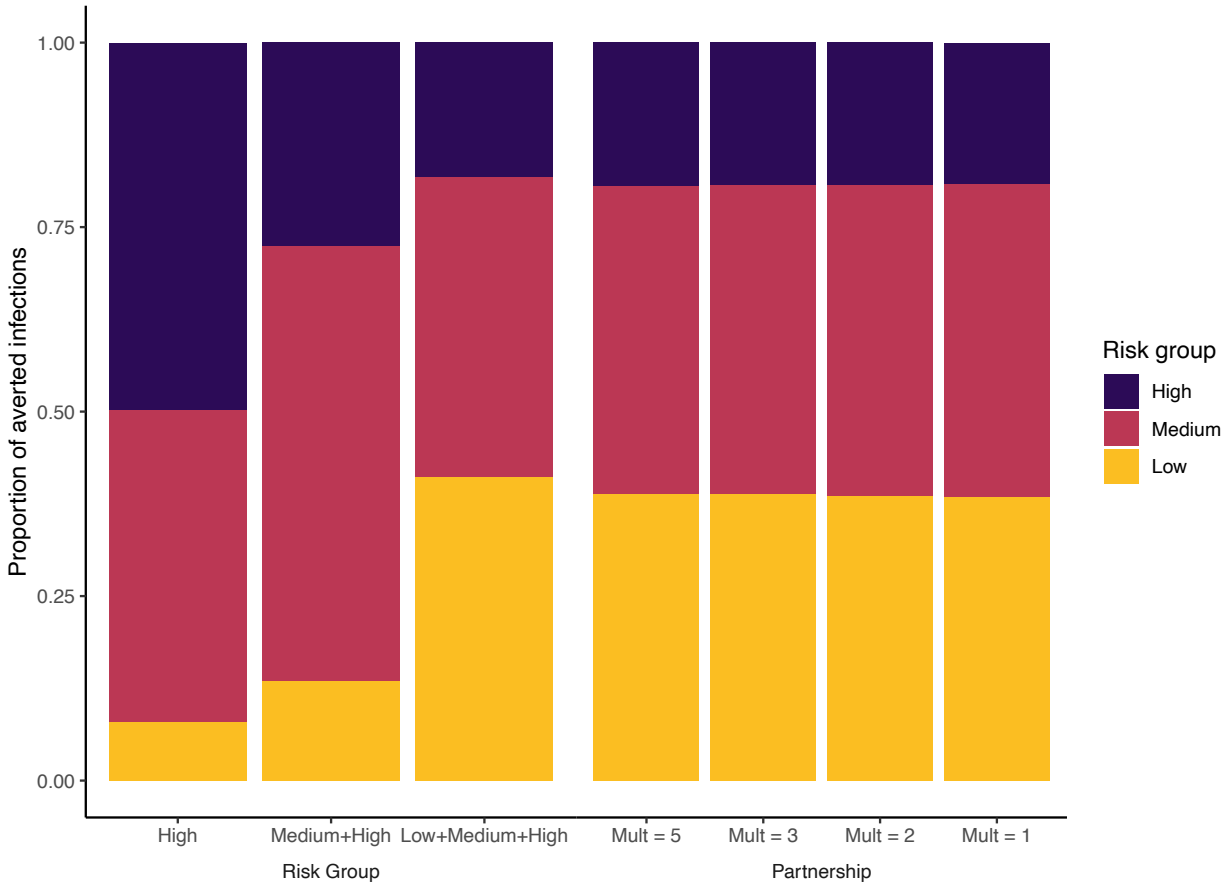


Figure B.7**:** Sensitivity analysis of applying the multiplier on PrEP coverage only to individuals with diagnosed HIV-positive partners but not undiagnosed HIV-positive partners. Plot displays the relationship between additional person-time on PrEP and percentage of infections averted relative to a no PrEP scenario in the Partnership paradigm. Solid lines indicate results when the multiplier is applied to individuals with any HIV-positive partner (main analysis), whereas dotted lines indicate that the multiplier is only applied to individuals with an HIV-positive partner who has previously tested positive. Person-years on PrEP and infections averted are cumulative across a ten-year period spanning 2022 to 2031. Shaded regions indicate 95% credible intervals. Mult = multiplier on the probability that an individual with an HIV-positive partner will use PrEP relative to the probability than an individual with only HIV-negative partners will use PrEP.

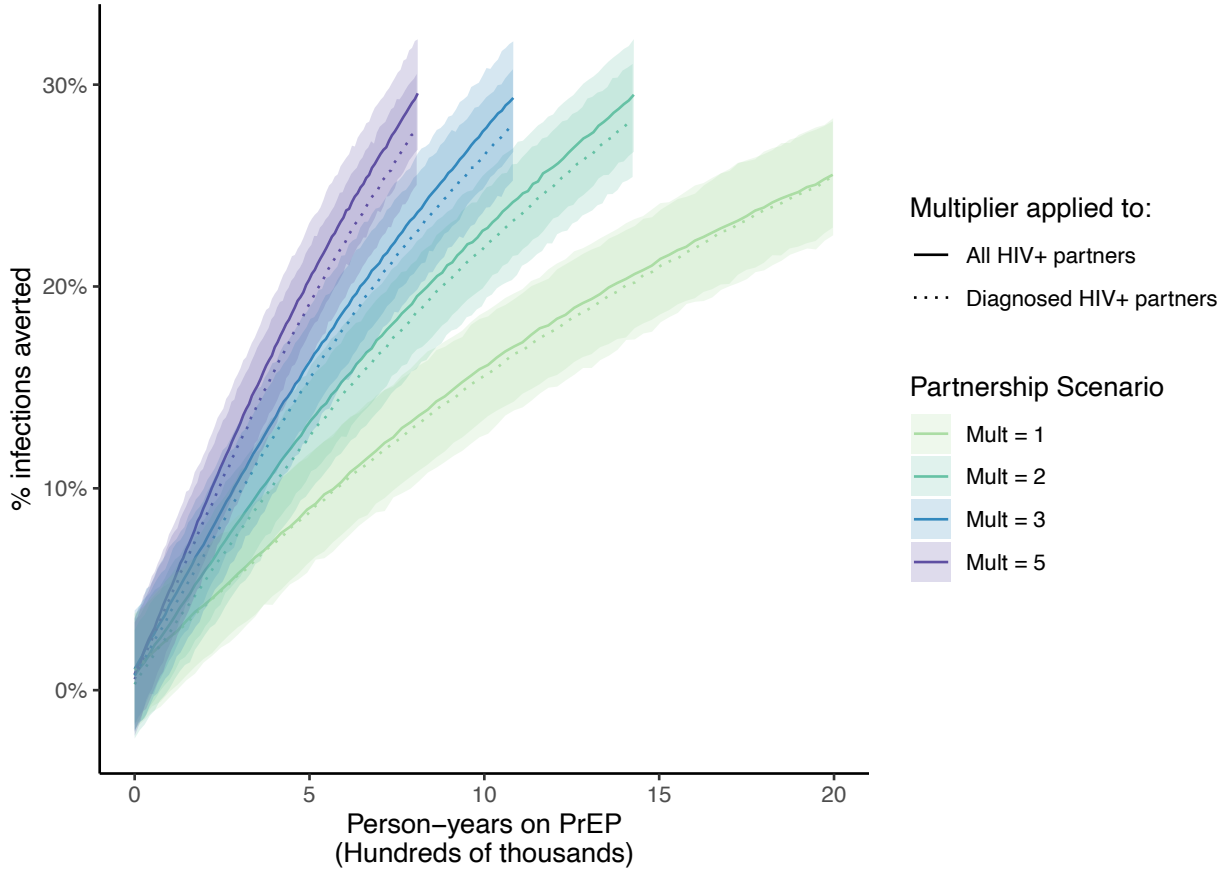
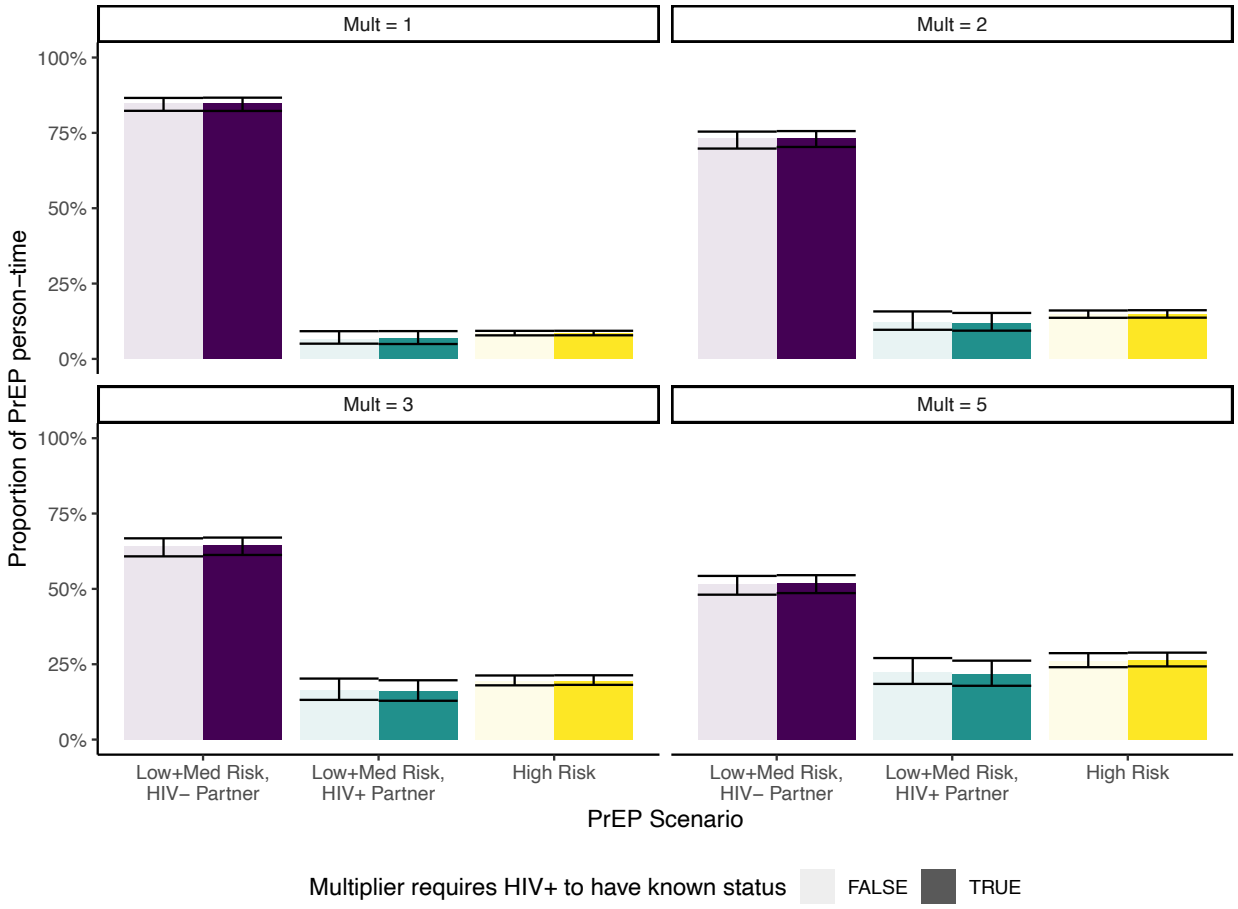


Figure B.8: Sensitivity of PrEP person-time distribution to restricting the multiplier on PrEP coverage among individuals with HIV-positive partners to require that the partner must have been previously diagnosed. Mult = multiplier on the probability that an individual with an HIV-positive partner will use PrEP relative to the probability than an individual with only HIV-negative partners will use PrEP. Error bars indicate 95% credible intervals across 250 parameter sets.



APPENDIX C

Model calibration details from Chapter 2: The impact of prevention-effective PrEP use on HIV incidence: A mathematical modeling study

Table C.1: Select model parameters used to fit the EMOD-HIV transmission model described in [133] to survey data on prevalence, incidence, and ART coverage from the Kingdom of Eswatini. Median and interquartile ranges (IQRs) across 25 best-fitting parameter sets are reported for the 24 dynamic parameters used in the calibration process. A full description of all parameters and references available is at: http://idmod.org/docs/hiv/parameter-configuration.html

Parameter	Description	Dynamic	Static value / fitted median (IQR)	Source
Acute_Duration_In_Months	The time since infection, in months, over which the Acute_Stage_Infectivity_Multiplier is applied to coital acts occurring in that time-period.	no	3	[196]
Acute_Stage_Infectivity_Multiplier	Multiplier acting on Base_Infectivity to determine the per-act transmission probability of an individual during acute stage	no	26	[196]
AIDS_Duration_In_Months	The length of time, in months, prior to an AIDS-related death over which the AIDS_Stage_Infectivity_Multiplier is applied	no	9	[196]
AIDS_Stage_Infectivity_Multiplier	Multiplier acting on Base_Infectivity to determine the per-act transmission probability of an individual during AIDS stage	no	4.5	[196]
ART_CD4_at_Initiation_Saturating_Reduction_in_Mortality	The duration from ART enrollment to on-ART HIV-caused death increases with CD4 at ART initiation up to a threshold determined by this parameter value.	no	350	
ART_dropout	Exponentially distributed mean number of days from ART initiation until ART dropout	no	7300	
ART_Link_Max	The right asymptote for the sigmoid trend of probability of ART linkage (given eligibility) over time.	yes	0.952 (0.948 - 0.955)	
ART_Link_Mid	The time of the inflection point in the sigmoid trend of probability of ART linkage (given eligibility) over time.	yes	2010.7 (2010.4 - 2010.9)	
ART_link_Min	The left asymptote for the sigmoid trend of probability of ART linkage (given eligibility) over time.	no	0	
ART_link_Rate	The slope of the inflection point in the sigmoid trend of probability of ART linkage over time. A Rate of 1 sets the slope to a 25% change in probability per year.	no	1	

ART_Viral_Suppression_Multiplier	Multiplier acting on Base_Infectivity to determine the per-act transmission probability of an individual on ART. Less-than-perfect (<100%) reduction in risk is attributed to sub-optimal adherence, drug resistance, and delay in viral load suppression from ART initiation.	no	0.08	[141]
Base_Infectivity	The probability of transmission when none of the transmission multipliers apply to a coital act (or when all multipliers are set to 1).	yes	0.00233 (0.00231 - 0.00234)	[197]
CD4_At_Death_LogLogistic_Heterogeneity	The inverse shape parameter of a Weibull distribution that represents the at-death CD4 cell count.	no	0.7	
CD4_At_Death_LogLogistic_Scale	The scale parameter of a Weibull distribution hat represents the at-death CD4 cell count.	no	2.96	
CD4_Post_Infection_Weibull_Heterogeneity	The inverse shape parameter of a Weibull distribution that represents the post-acute-infection CD4 cell count.	no	0.2756	
CD4_Post_Infection_Weibull_Scale	The scale parameter of a Weibull distribution that represents the post-acute-infection CD4 cell count.	no	560.43	
Circumcision_Reduced_Acquire	The reduction of susceptibility to HIV by voluntary male medical circumcision (VMMC)	no	0.6	[2–4]
Coital_Act_Rate	Number of coital acts per day for all relationships except commercial ones	no	0.33	
Coital_Act_Rate_Commercial	Number of coital acts per day for commercial relationships	no	0.002739726	
Coital_Dilution_Factor_2_Partners	The multiplicative reduction in the coital act rate for all relationship types when an individual has exactly two current partners. Represents coital dilution.	no	0.75	
Coital_Dilution_Factor_3_Partners	The multiplicative reduction in the coital act rate for all relationship types when an individual has exactly three current partners. Represents coital dilution.	no	0.6	
Coital_Dilution_Factor_4_Plus_Partners	The multiplicative reduction in the coital act rate for all relationship types when an individual has exactly three current partners. Represents coital dilution.	no	0.45	
Commercial_Condom_Max	The maximum asymptote for commercial relationships	no	0.85	
Commercial_Condom_Mid	The year of the inflection point for commercial relationships	no	1999.5	
Commercial_Condom_Min	The minimum asymptote of the probability of condom use per coital act for informal relationships for commercial relationships	no	0.5	

Commercial_Condom_Rate	The rate proportional to the slope at the inflection point for commercial relationships	no	1
Commercial_Form_Rate	Exponentially distributed mean number new relationships formed per day for commercial relationships	no	0.15
Condom_Transmission_Blocking_Probability	The per-act multiplier of the transmission probability when a condom is used	no	0.8
Days_Between_Symptomatic_And_Death_Weibull_Heterogeneity	The time between the onset of AIDS symptoms and death is sampled from a Weibull distribution; this parameter governs the heterogeneity (inverse shape) of the Weibull.	no	0.5
Days_Between_Symptomatic_And_Death_Weibull_Scale	The time between the onset of AIDS symptoms and death is sampled from a Weibull distribution; this parameter governs the scale of the Weibull.	no	618.34
Delay_Period_Mean	Delay from HIV infection until ART initiation for future ART scale-up scenarios, post 2016 (in days).	no	180
HIV_Adult_Survival_Scale_Parameter_Intercept	Determines the intercept of the scale parameter for the Weibull distribution used to determine HIV survival time. Survival time with untreated HIV infection depends on the age of the individual at the time of infection, and is drawn from a Weibull distribution with shape parameter (see HIV_Adult_Survival_Shape_Parameter) and scale parameter. The scale parameter is allowed to vary linearly with age as follows λ = HIV_Adult_Survival_Scale_Parameter_Intercept + HIV_Adult_Survival_Scale_ Parameter_Slope * Age (in years).	no	21.182
HIV_Adult_Survival_Scale_Parameter_Slope	This parameter determines the slope of the scale parameter for the Weibull distribution used to determine HIV survival time.	no	-0.2717
HIV_Adult_Survival_Shape_Parameter	This parameter determines the shape of the Weibull distribution used to determine age-dependent survival time for individuals infected with HIV.	no	2

HIV_Age_Max_for_Adult_Age_Dependent_Survival	Survival time with untreated HIV infection depends on the age of the individual at the time of infection, and is drawn from a Weibull distribution with shape parameter and scale parameters (See HIV_Adult_Survival_Scale_Parameter_Intercept, HIV_Adult_Survival_Scale_ Parameter_Slope, and HIV_Adult_Survival_Shape_Parameter). Although the scale parameter for survival time declines with age, it cannot become negative. To avoid negative survival times at older ages, this parameter, HIV_Age_Max_for_Adult_Age_Dependent_Survival, determines the age beyond which HIV survival is no longer affected by further aging.	no	50
HIV_Age_Max_for_Child_Survival_Function	The maximum age at which an individual's survival will be fit to the child survival function. If the value of this parameter falls between zero and the age of sexual debut, model results are not sensitive to this parameter as there is no mechanism for children to become infected between infancy and sexual debut.	no	15
HIV_Child_Survival_Rapid_Progressor_Fraction	The proportion of HIV-infected children who are rapid HIV progressors.	no	0.57
HIV_Child_Survival_Rapid_Progressor_Rate	The exponential decay rate, in years, describing the distribution of HIV survival for children who are rapid progressors.	no	1.52
HIV_Child_Survival_Slow_Progressor_Scale	The Weibull scale parameter describing the distribution of HIV survival for children who are slower progressors.	no	16
HIV_Child_Survival_Slow_Progressor_Shape	The Weibull shape parameter describing the distribution of HIV survival for children who are slower progressors.	no	2.7
Informal_Condom_Max	The maximum asymptote for informal relationships	yes	0.337 (0.321 - 0.355)
Informal_Condom_Mid	The year of the inflection point for informal relationships	yes	1992.6 (1992.2 - 1992.9)
Informal_Condom_Min	The minimum asymptote of the probability of condom use per coital act for informal relationships	no	0
Informal_Condom_Rate	The rate proportional to the slope at the inflection point for informal relationships		3.003 (2.941 - 3.076)
Informal_Form_Rate	Exponentially distributed mean number new relationships formed per day for informal relationships	yes	0.00146 (0.00134 - 0.00155)

Male_To_Female_Relative_Infectivity_Multiplier_Old	An array of scale factors governing the susceptibility of females relative to males, by age ≥ 25	yes	2.844 (2.727 - 2.958)
Male_To_Female_Relative_Infectivity_Multiplier_Young	An array of scale factors governing the susceptibility of females relative to males, by age < 25	yes	4.894 (4.747 - 5.041)
Marital_Condom_Max	The maximum asymptote for marital relationships	yes	0.218 (0.207 - 0.231)
Marital_Condom_Mid	The year of the inflection point for marital relationships	yes	2001.8 (2001.5 - 2002.1)
Marital_Condom_Min	The minimum asymptote of the probability of condom use per coital act for informal relationships for marital relationships	no	0
Marital_Condom_Rate	The rate proportional to the slope at the inflection point for marital relationships	yes	2.407 (2.252 - 2.524)
Marital_Form_Rate	Exponentially distributed mean number new relationships formed per day for marital relationships	yes	0.00046 (0.00044 - 0.0005)
Maternal_Infection_Transmission_Probability	The probability of transmission of infection from mother to infant at birth.		0.3
Maternal_Transmission_ART_Multiplier	The maternal transmission multiplier for on-ART mothers.	no	0.03334
preART_Link_Max	The right asymptote for the sigmoid trend of probability of preART linkage (given eligibility) over time.	yes	0.807 (0.783 - 0.829)
preART_Link_Mid	The time of the inflection point in the sigmoid trend of probability of preART linkage (given eligibility) over time.	yes	1995.7 (1995.1 - 1996.4)
preART_link_Min	The left asymptote for the sigmoid trend of probability of preART linkage (given eligibility) over time.	yes	0.00325 (0 - 0.03031)
preART_link_Rate	The slope of the inflection point in the sigmoid trend of probability of preART linkage over time. A Rate of 1 sets the slope to a 25% change in probability per year.	no	1
Proportion_Low_Risk	Proportion of the intial population that is low risk	yes	0.73 (0.721 - 0.742)
Seed_Year	Year in which the epidemic is seeded into high risk groups	yes	1982.7 (1982.4 - 1983.2)
Sexual_Debut_Age_Female_Weibull_Heterogeneity	The inverse shape of the Weibull distribution for female debut age.	yes	0.309 (0.293 - 0.322)
Sexual_Debut_Age_Female_Weibull_Scale	The scale term of the Weibull distribution for female debut age.	yes	16.302 (16.166 - 16.396)
Sexual_Debut_Age_Male_Weibull_Heterogeneity	The inverse shape of the Weibull distribution for male debut age.	yes	0.042 (0.04 - 0.05)
Sexual_Debut_Age_Male_Weibull_Scale	The scale term of the Weibull distribution for male debut age.	yes	17.499 (17.357 - 17.699)
Sexual_Debut_Age_Min	The minimum age at which individuals become eligible to form sexual relationships.	no	13
Transitory_Condom_Max	The maximum asymptote for transitory relationships	yes	0.103 (0.089 - 0.117)

Transitory_Condom_Mid	The year of the inflection point for transitory relationships	yes	1996.7 (1996.1 - 1997)
Transitory_Condom_Min	The minimum asymptote of the probability of condom use per coital act for informal relationships for transitory relationships	no	0
Transitory_Condom_Rate	The rate proportional to the slope at the inflection point for transitory relationships	yes	2.998 (2.878 - 3.106)
Transitory_Form_Rate	Exponentially distributed mean number new relationships formed per day for transitory relationships	no	0.001047839
Transitory_Weibull_Heterogeneity	Inverse of the Weibull shape (1/kappa) parameter of relationship duration in years for transitory relationships	no	0.833333333
Transitory_Weibull_Scale	Weibull scale parameter of relationship duration in years for transitory relationships.	no	0.956774771

Figure C.1: Model HIV incidence rates per 100 person-years (colored lines) and 95% credible intervals (shaded regions) by gender among adults ages 15-49 compared to observed data (points and 95% confidence interval error bars). SHIMS = Swaziland HIV Incidence Measurement Survey

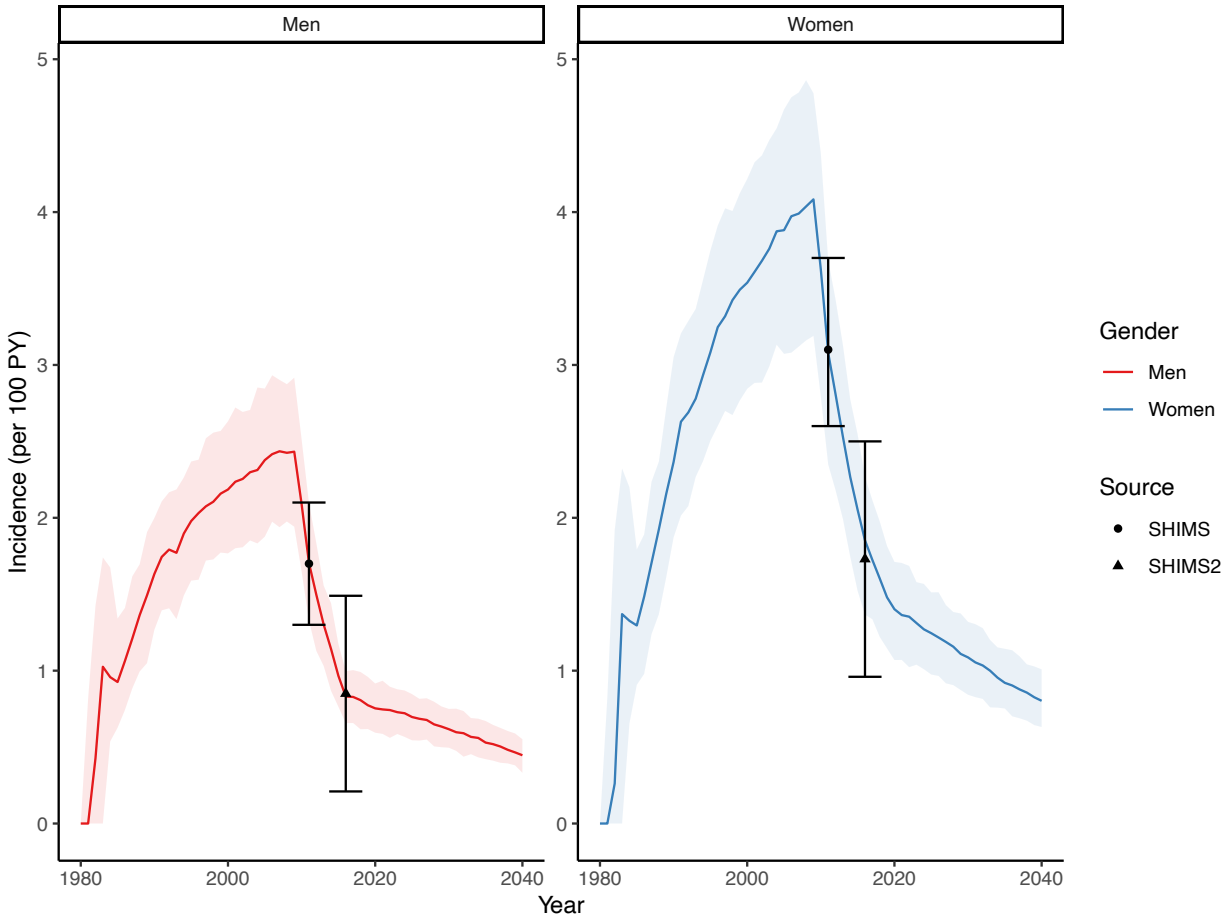


Figure C.2: Model HIV prevalence (colored lines) and 95% credible intervals (shaded regions) by gender and five-year age group compared to observed data (points and 95% confidence interval error bars). DHS = Demographic and Health Survey; SHIMS = Swaziland HIV Incidence Measurement Survey

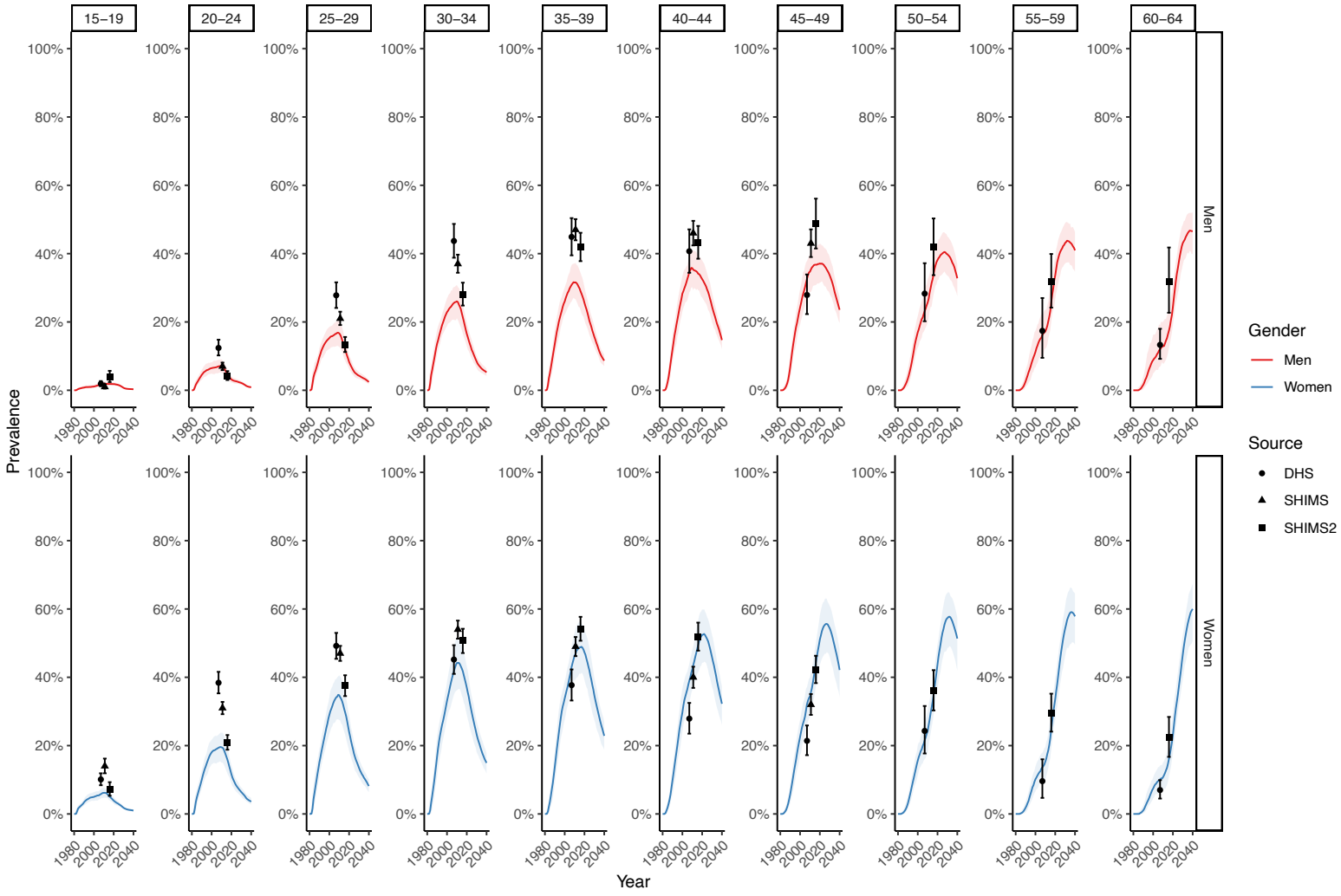
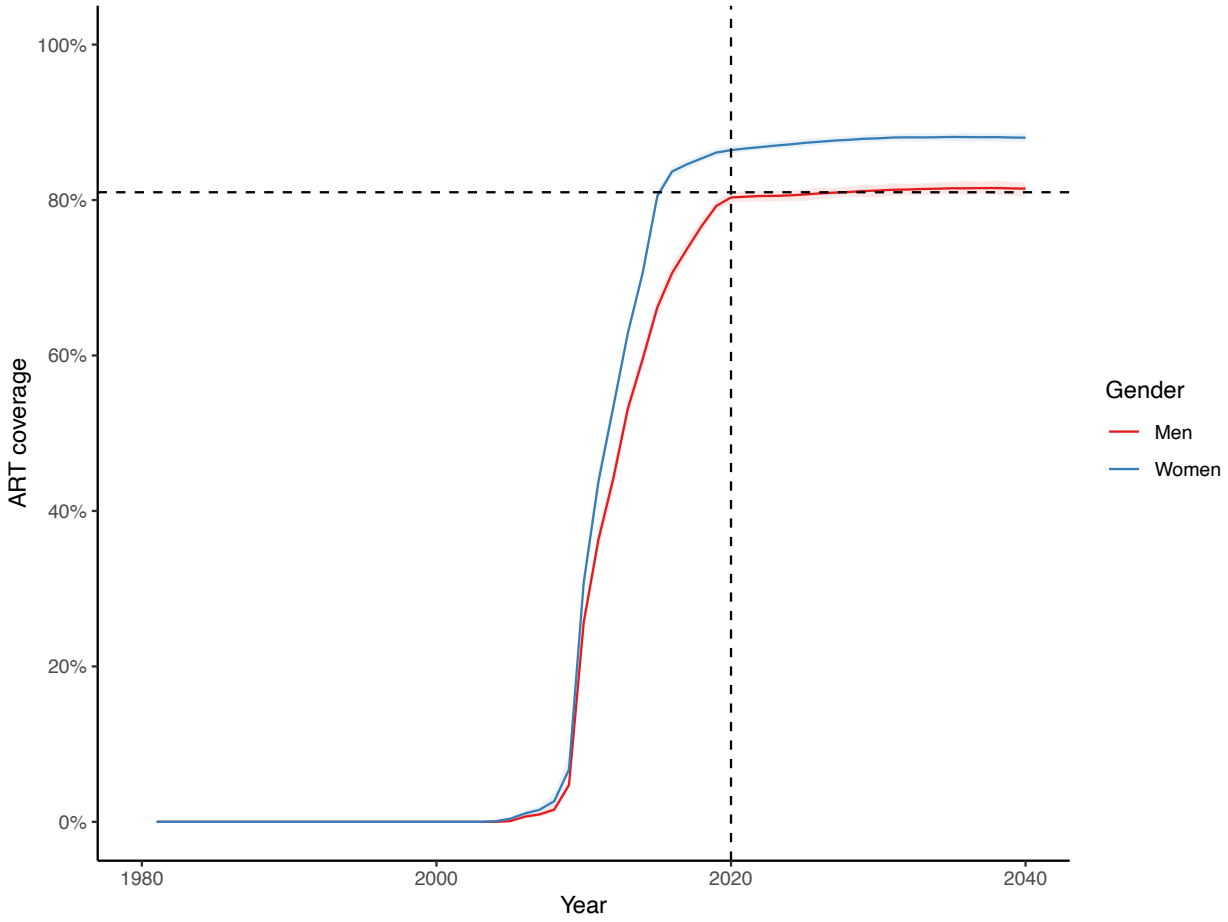


Figure C.3: Model ART coverage (colored lines) and 95% credible intervals (shaded regions) by gender, for adults ages 15-49. Dashed lines indicate UNAIDS ART coverage target (90% of HIV+ knowing status * 90% of HIV+ with known status on ART = 81% ART coverage among HIV+) by the year 2020.



APPENDIX D

Supplementary material to Chapter 3: Predicting the risk of HIV-1 acquisition in rural South Africa using geospatial data

Table D.1: Missingness frequency for variables considered in prediction models. Only variables with at least 1% missingness shown.

	Men		Women	
	Development	**Validation**	**Development**	**Validation**
Lifetime number of partners	31.3%	32.0%	32.5%	24.7%
Used condom at last sex with MRP	29.0%	38.1%	45.4%	45.6%
MRP member of household	17.9%	28.0%	19.5%	25.0%
MRP casual	17.7%	27.8%	19.3%	24.7%
# partners in last 12 months	17.6%	26.4%	18.6%	23.3%
# current relationships	17.1%	25.5%	17.6%	21.6%
Prior contraception use	-	-	5.3%	14.1%
Ever had sex	5.3%	9.1%	2.9%	5.4%
Married	3.4%	4.2%	2.5%	3.5%
Ever pregnant	-	-	2.3%	4.7%
Has fathered children	3.0%	8.0%	-	-
Is circumcised	2.8%	10.9%	-	-

Table D.2: Hazard ratios from coefficients retained in the final models. Full = no covariate restriction; Ind = only individual-level covariates; Age + Geo = only age group and geospatial covariates; Age + HIV prev = only age group and local HIV prevalence; Ref = reference group; SES = socioeconomic status; PPDV = population prevalence of detectable viremia

		Men				Women			
		Full	**Ind**	**Age + Geo**	**Age + HIV prev**	**Full**	**Ind**	**Age + Geo**	**Age + HIV prev**
Individual covariates									
Age (Ref = 15-19)	20-24	1.41	1.04	2.95	3.47	1.13	1.12	1.41	1.43
	25-29	1.79	1.12	5.26	6.32	1.08	1.06	1.38	1.40
	30-34	1.58	1.08	4.47	5.38	0.69	0.66	0.78	0.75
	35-39	0.99	1.00	2.51	3.00	0.56	0.52	0.52	0.45
	40-44	1.05	0.99	2.10	2.41	0.52	0.48	0.41	0.33
	45-49	0.83	0.96	1.47	1.62	0.54	0.51	0.41	0.33
	50-54	0.66	0.93	0.94	0.92	0.39	0.35	0.31	0.22
Education (Ref = < Primary)	Primary	1.49	-	-	-	1.27	1.28	-	-
	Secondary +	1.6	-	-	-	1.02	1.01	-	-
Married (Ref = No)		0.40	0.65	-	-	0.50	0.49	-	-
Employed (Ref = No)		0.87	-	-	-	-	-	-	-
Asset quintile (Ref = lowest)	2	0.99	-	-	-	-	-	-	-
	3	0.95	-	-	-	-	-	-	-
	4	0.80	-	-	-	-	-	-	-
	5 (highest)	0.83	-	-	-	-	-	-	-
SES quintile (Ref = lowest)	2	1.20	-	-	-	1.00	1.00	-	-
	3	1.14	-	-	-	0.99	1.00	-	-
	4	1.23	-	-	-	0.99	0.99	-	-
	5 (highest)	1.00	-	-	-	0.99	0.99	-	-
Prior non-resident (Ref = No)		1.10	-	-	-	1.09	1.10	-	-
Prior outmigration (Ref = No)		1.12	-	-	-	1.28	1.27	-	-
Ever had sex (Ref = No)		4.5	4.61	-	-	1.34	1.33	-	-
Ever pregnant (Ref = No)		-	-	-	-	-	-	-	-
Has fathered children (Ref = No)		1.25	-	-	-	-	-	-	-
Circumcised (Ref = No)		0.59	-	-	-	-	-	-	-
Prior contraception use (Ref = No)		-	-	-	-	1.47	1.48	-	-
# Partners in last 12 months (Ref = 0)	1	1.03	1.01	-	-	1.15	1.17	-	-
	2+	1.42	1.11	-	-	1.98	2.13	-	-
# Current relationships (Ref = 0)	1	1.15	1.04	-	-	1.04	1.07	-	-
	2+	1.87	1.34	-	-	0.95	0.90	-	-
MRP 5+ years younger (Ref = No)		0.97	-	-	-	-	-	-	-
MRP 5+ years older (Ref = No)		-	-	-	-	-	-	-	-
MRP casual (Ref = Regular)		0.77	0.99	-	-	1.08	1.14	-	-
MRP member of household (Ref = No)		0.79	0.97	-	-	0.58	0.58	-	-
MRP used condom last time (Ref = No)		0.92	-	-	-	0.99	0.98	-	-
Geospatial covariates									
HIV prevalence (per 10% increase)		1.09	-	1.06	1.39	1.08	-	1.09	1.16
PPDV (per 10% increase)		1.41	-	1.73	-	-	-	1.01	-
Rural (Ref = Urban)		0.81	-	0.88	-	-	-	-	-
Distance to clinic (per km)		1.09	-	1.09	-	-	-	-	-
Distance to level 1 road (per km)		0.99	-	0.99	-	-	-	-	-
Distance to level 2 road (per km)		0.95	-	0.97	-	0.92	-	0.94	-
Distance to primary school (per km)		-	-	-	-	0.95	-	0.97	-
Distance to secondary school (per km)		-	-	-	-	-	-	-	-

Table D.3: Area under the receiver operating characteristic curve (AUROC) estimated in the development and validation datasets. AUROC values are averaged over 10 imputed datasets. AUROC in the development dataset was estimated through 10-fold cross-validation.

	Men		Women	
Model	**Development cv-AUROC**	**Validation AUROC**	**Development cv-AUROC**	**Validation AUROC**
Full	0.74	0.72	0.71	0.68
Individual covariates only	0.73	0.73	0.71	0.68
Age + geospatial covariates	0.71	0.71	0.68	0.65
Age + HIV prevalence	0.71	0.68	0.68	0.64

Figure D.1: Percentage of high incidence area (≥ 3/100 PY) contained within varying percentages of the map with the highest predicted risk. Incidence and predicted risk estimated for men and women combined from 2012-2019 and smoothed using a 2-dimensional Gaussian kernel. Full = no covariate restriction; Ind = only individual-level covariates; Age + Geo = only age group and geospatial covariates; Age + HIV prev = only age group and local HIV prevalence