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Comparative Effectiveness of Interventions to Improve the HIV Continuum of Care and HIV Preexposure Prophylaxis in Kenya: A Model-Based Analysis

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Background. In Western Kenya up to one-quarter of the adult population was human immunodeficiency virus (HIV)-infected in 2012. The Ministry of Health, Médecins Sans Frontières, and partners implemented an HIV program that surpassed the 90-90-90 UNAIDS targets. In this generalized epidemic, we compared the effectiveness of preexposure prophylaxis (PrEP) with improving continuum of care.

Methods. We developed a dynamic microsimulation model to project HIV incidence and infections averted to 2030. We modeled 3 strategies compared to a 90-90-90 continuum of care base case: (1) scaling up the continuum of care to 95-95-95, (2) PrEP targeting young adults with 10% coverage, and (3) scaling up to 95-95-95 and PrEP combined.

Results. In the base case, by 2030 HIV incidence was 0.37/100 person-years. Improving continuum levels to 95-95-95 averted 21.5% of infections, PrEP averted 8.0%, and combining 95-95-95 and PrEP averted 31.8%. Sensitivity analysis showed that PrEP coverage had to exceed 20% to avert as many infections as reaching 95-95-95.

Conclusions. In a generalized HIV epidemic with continuum of care levels at 90-90-90, improving the continuum to 95-95-95 is more effective than providing PrEP. Continued improvement in the continuum of care will have the greatest impact on decreasing new HIV infections.

Keywords. HIV; preexposure prophylaxis; continuum of care; Kenya.

There continue to be 1.4 to 2.4 million new human immunodeficiency virus (HIV) infections per year worldwide, and HIV remains the leading cause of mortality in sub-Saharan Africa [1–3]. To reduce HIV infections, improvement in the HIV continuum of care is among the most effective interventions [2, 4]. The Joint United Nations Program on HIV and AIDS (UNAIDS) in 2014 advocated the 90-90-90 target for 2020, aiming to reach 90% HIV testing coverage of the infected population, 90% of those infected on antiretroviral therapy (ART), and 90% of those on ART achieving viral suppression [5].

Ndhiwa is a recently created subcounty, part of Homa Bay County, in Southwest Kenya, with one of the highest HIV prevalences in Kenya at 24.1% [6]. Médecins Sans Frontières (MSF) has scaled up its activity within Ndhiwa in partnership with the Kenyan Ministry of Health (MoH) since 2014. A recent MSF cross-sectional study, the Ndhiwa HIV Impact Population Survey (NHIPS), found that in 2018 the MoH, MSF, and other partners interventions had exceeded the 90-90-90 targets [7]. UNAIDS has now identified a more ambitious continuum set of fast-track targets for 2030; the goal is a reduction in new HIV infections by 89% and a decrease in AIDS-related deaths by 81% [8]. To achieve these goals, the new continuum of care targets are 95-95-95 by 2030.

Preexposure prophylaxis (PrEP) is another promising HIV prevention intervention. It consists of providing 2-drug ART to HIV-negative people to prevent transmission. Four major randomized controlled trials have been published on PrEP to prevent heterosexual transmission; 2 showed a decrease in HIV transmission in men and women [9, 10], while 2 others had negative results in younger adult women (including sex workers) [11, 12]. The discrepancy in the results of these trials has been explained mostly by differences in adherence to PrEP [11, 12].

The objective of this study is to compare the effectiveness of PrEP in a generalized epidemic like that in Ndhiwa, Southwest Kenya with achieving continuum of care targets of 95-95-95.

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METHODS

Analytic Overview

We developed a dynamic, open cohort, agent-based model of HIV disease progression and transmission to evaluate the effectiveness of PrEP compared with improved continuum targets or added to the current continuum of care [13]. We examined PrEP initially with 10% coverage in younger adults (defined below). Continuum of care intervention impact was modeled by calibrating model inputs to the NHIPS survey in 2012 and the 90-90-90 UNAIDS targets in 2020 [5, 6, 8]. We evaluated continuum of care, incidence, prevalence, and infections averted. The study time horizon was through 2030, 10 years after implementation of the interventions.

Model Structure

The model has 2 different modules: the HIV disease module and the dynamic transmission module. The HIV disease module divides the population into 6 health states stratified by sex: no HIV infection, primary HIV infection not treated, chronic infection not treated, chronic infection suppressed on ART, chronic infection not suppressed on ART, and death. HIV-infected patients not diagnosed have a monthly probability of HIV diagnosis by routine testing, linkage to care if tested, and treatment if linked. Patients have a monthly probability of hospitalization related to HIV infection, and a probability of being diagnosed with HIV when hospitalized. For treated patients, we included 2 sequential ART regimens, because third-line treatment is rarely accessible in this setting [14, 15].

The dynamic transmission module divides the population into 2 risk groups. The younger adult (YA) group is defined by a high incidence of HIV infection and high number of contacts (Table 1). It is made up of women aged 15–30 years and men aged 20–40 years. The rest of the adult population, men aged 15–19 and 40+ years, and women aged 30+ years, defines the older adult (OA) group. The YA group is characterized by a higher incidence but lower prevalence compared to the OA group. Because most infected patients from the YA group survive and become part of the OA group, where HIV infection still occurs, prevalence is higher in OAs than in YAs. Contacts can occur within the same risk group, or with individuals of the other risk group (Table 1). The probability of transmission by health state is calculated using the methods of McCormick et al [16]. The structure of the model is further detailed in the Supplementary Material.

Table 1. Input Parameters for a Modeling Analysis of Combination HIV Prevention Strategies in Rural Kenya

Parameter	Base Case Value	Reference
Baseline cohort characteristics		
Mean age, y (range)	31.5 (15–99)	[6]
Female/male, %	55/45	From [6]
Mean CD4 count at diagnosis, cells/μL (SD)	560 (230)	[37]
Transmission characteristics		
Probability of transmission per contact		
Acute infection	0.0082	Adapted from [16]
Infected, not treated	0.0023	Adapted from [16]
Treated, suppressed	0.0001	Adapted from [16]
Treated, not suppressed	0.001	Adapted from [16]
Older adult population		
Proportion, %	53	[7]
Number of contacts, monthly	4.5	Calibration to [6]
Proportion of contacts with older adult, %	93	Calibration to [6]
Younger adult population		
Proportion, %	47	[7]
Number of contacts, monthly	6	Calibration to [6]
Proportion of contacts with younger adult, %	91	Calibration to [6]
Parameter	Base case value	Reference
Baseline continuum of care		
Probability of being diagnosed if major event	0.40	Calibration to [6]
Probability of being diagnosed through background testing, monthly	0.03	Calibration to [6]
Probability of linkage to care when tested	0.90	Calibration to [6]
Probability of retention in care when linked, monthly	0.99	Calibration to [6]
Viral suppression rate at 1 y	0.99	Calibration to [6]
PrEP interventions		
Risk reduction, %	0.75	[10]
Coverage, among high-risk population, %	10	Assumption

Abbreviation: PrEP, preexposure prophylaxis.

Input Data

Cohort

The modeled cohort mirrors the adult population (> 15 years) of Ndhiwa: 55% female with a population increase of 3.8%/year. Characteristics of the study cohort were drawn from the NHIPS, a cross-sectional study conducted by MSF in 2012 (Table 1) [6, 7].

Natural History

The natural history input data for CD4 count decline, non-AIDS mortality, and AIDS-related mortality were derived from literature on African cohorts (Supplementary Table 1) [18, 19]. We calibrated the HIV testing probability based on the median CD4 count at diagnosis and the proportion of patients diagnosed with World Health Organization (WHO) clinical stage 3 or 4 disease, as well as MSF data for the continuum of care (Table 1) [6, 7].

Continuum of Care

We ran the model for an initialization period of 30 years (roughly the beginning of the HIV epidemic in the region to the beginning of ART distribution in the late 1990s), and calibrated HIV prevalence, incidence and continuum of care to fit the 2012 epidemiological data from the Kenyan AIDS Indicator Survey and the NHIPS studies [6].

Strategies

95-95-95 Interventions

We modeled this intervention by calibrating the continuum of care to the 95-95-95 targets in 2030.

PrEP Interventions

Risk reduction in HIV infection with PrEP was 75%, as found in the Partners-PrEP study, which studied heterosexual couples in Uganda and Kenya [10]. This risk reduction includes the combination of PrEP adherence and efficacy. Coverage is defined by the proportion of the population reached by the PrEP intervention. We examined a 10% level of coverage in the YA group in the base case.

95-95-95 + PrEP Interventions

We modeled both continuum of care and PrEP interventions together.

Sensitivity Analyses

In sensitivity analyses we assessed uncertainty in parameter estimates.

One-Way Sensitivity Analyses

We first considered uncertainties in input variables, such as inputs to the transmission module (numbers of contacts, proportion of contact between risk groups). Second, we varied the efficacies of the intervention strategies to assess how changes in these parameters affected the overall results, such as PrEP adherence, coverage, and also the continuum of care. In particular, MoH, MSF, and partners continuum of care metrics are already high in Ndhiwa, with 93.4% tested, 96.8% on ART among tested, and 97.7% suppression among those on ART in 2018 [7]; we used these levels in a sensitivity analysis.

Two-Way and Multiway Sensitivity Analyses

We varied all interventions to the upper bound (optimistic case scenario) or the lower bound (pessimistic case scenario) of expected efficacies.

RESULTS

Model Validation

In 2012, the HIV prevalence in the modeled population in Ndhiwa subcounty was 20.9% in the overall population, 18.5% in the YA population and 26.1% in the OA population, compared to 24.1%, 22.0%, and 26.7% in the NHIPS study [6]. HIV incidence in the modeled population was 1.77/100 person-years (PY) in 2012, compared to 1.90/100 PY in the NHIPS study [6]. Testing coverage of the infected population in 2012 was 61.3% in the model and 61.8% in the NHIPS study, the proportion of patients on ART was 39.8% versus 42.2%, and proportion of patients who achieved virological suppression was 33.4% versus 28.2%.

Impact of Improved Continuum of Care Interventions

Scaling-up continuum of care interventions from 90-90-90 in 2020 to 95-95-95 in 2030 would decrease incidence from 0.77/100 PY in 2020 to 0.27/100 PY, or a 66% reduction, by 2030 in the YA group (22.5% of infections averted) (Figure 1 and Table 2), from 0.43 to 0.20/100 PY, or 58% reduction, in the OA group (18.2% of infections averted), and from 0.66 to 0.24/100 PY, or 63% reduction, in the overall population (21.5% of infections averted) (Figure 1 and Table 2).

Impact of Adding PrEP Intervention

In the YA group, in 2030, PrEP interventions with 10% coverage decreased incidence to 0.34/100 PY (56% reduction), which resulted in 9.9% of infections averted (Figure 1 and Table 2). In the OA group, in 2030, PrEP interventions with 10% coverage in YA group decreased incidence to 0.28/100 PY (34% reduction), resulting in 2.0% of infections averted. The PrEP intervention was more effective in the YA group than in the OA group. In the overall population, in 2030, PrEP with 10% coverage in the YA group decreased incidence to 0.32/100 PY (51% reduction), which resulted in 8.0% of infections averted (Figure 1 and Table 2).

Impact of Improved Continuum of Care Combined With PrEP

In the YA group, in 2030, improved continuum of care to 95-95-95 with the PrEP interventions decreased incidence to 0.22/100 PY (71% reduction), which resulted in 33.7% of infections

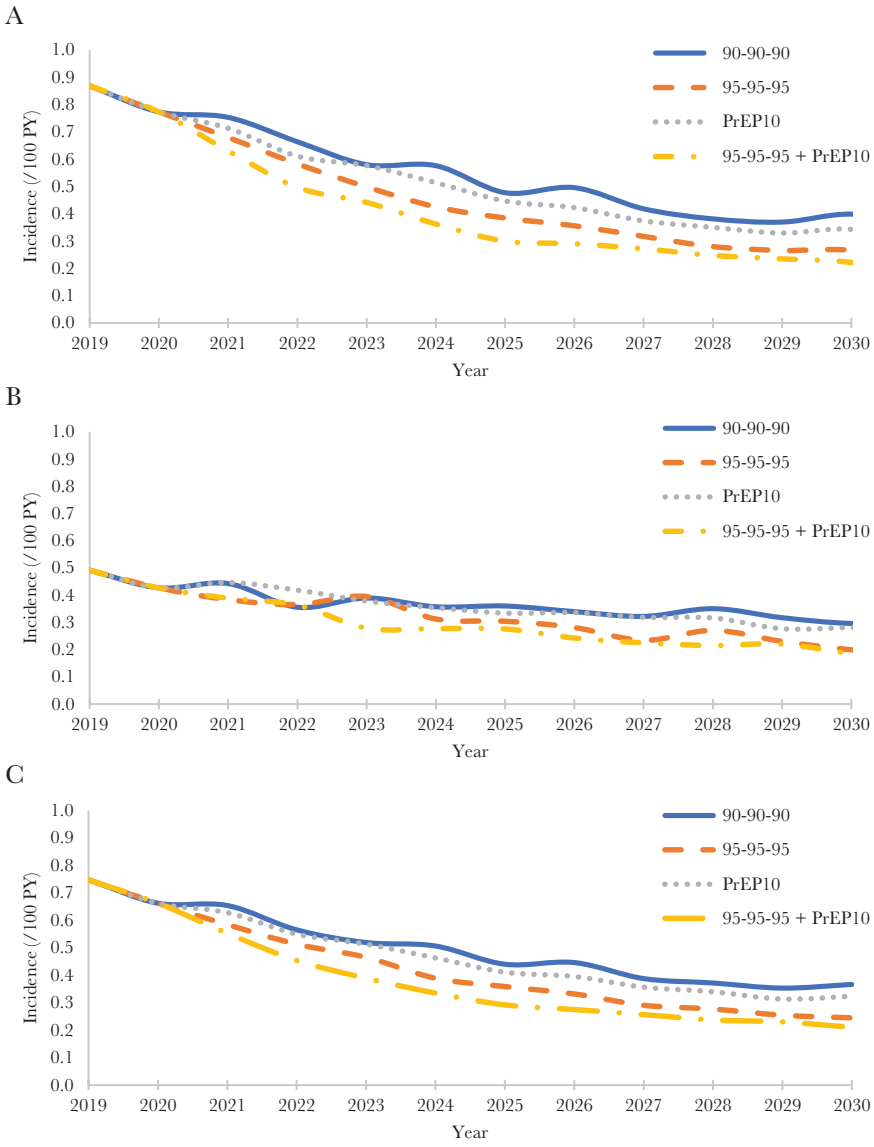

Figure 1. HIV incidence per 100 PY over time for 3 strategies compared to the base case (90-90-90), in the younger adult group (A), older adult group (B), and overall population (C) with 10% PrEP coverage, 95-95-95, and 95-95-95 plus 10% PrEP % coverage. Abbreviations: 90-90-90, 90% HIV testing coverage, 90% of those infected on ART, and 90% of those on ART achieving viral suppression; 95-95-95, 95% HIV testing coverage, 95% of those infected on ART, and 95% of those on ART achieving viral suppression; ART, antiretroviral therapy; HIV, human immunodeficiency virus; PrEP10, preexposure prophylaxis 10% coverage; PY, person year.

averted. In the OA group, in 2030, improved continuum of care and PrEP interventions decreased incidence to 0.19/100 PY (56% reduction), which resulted in 25.8% of infections averted. In the overall population, in 2030, incidence decreased to 0.21/100 PY (68% reduction), which resulted in 31.8% of infections averted (Figure 1 and Table 2).

Impact on Prevalence

Improved Continuum of Care Interventions

We projected a prevalence in 2030 of 8.6% in the overall population, with 3.6% in the YA and 19.3% in the OA group (Table 2).

Adding PrEP Intervention

PrEP intervention with 10% coverage decreased prevalence in the overall population to 9.1%, in the YA group to 4.0%, and in the OA group to 20.0% (Table 2).

Improved Continuum of Care and PrEP Interventions

Prevalence decreased in the overall population to 8.4%, in the YA group to 3.3%, and in the OA group to 19.4% (Table 2).

Sensitivity Analyses

One-Way Sensitivity Analyses

First, we varied the value of key parameters used to calibrate the base case. Specifically, we changed transmission

Table 2. HIV Prevalence in 2020 and 2030 and Infection Averted in 2030 as a Function of Continuum of Care With Addition of PrEP in Rural Kenya

Population	2020	2030			
		90-90-90	95-95-95	PrEP 10%	95-95-95 + PrEP 10%
Younger adults[a]					
Incidence/100 PY	0.77	0.40	0.27	0.34	0.22
Infections averted, %		…	22.5	9.9	33.7
Prevalence, %	10.4	4.3	3.6	4.0	3.3
Older adults[b]					
Incidence/100 PY	0.43	0.30	0.20	0.28	0.19
Infections averted, %		…	18.2	2.0	25.8
Prevalence, %	26.9	20.1	19.3	20.0	19.4
Overall					
Incidence/100 PY	0.66	0.37	0.24	0.32	0.21
Infections averted, %		…	21.5	8.0	31.8
Prevalence, %	15.7	9.3	8.6	9.1	8.4

Abbreviations: 90-90-90, 90% HIV testing coverage, 90% of those infected on antiretroviral therapy (ART), and 90% of those on ART achieving viral suppression; 95-95-95, 95% HIV testing coverage, 95% of those infected on ART, and 95% of those on ART achieving viral suppression; PrEP, preexposure prophylaxis; PY, person-years.

[a]Younger adult: women 15–30 years, men 15–40 years.

[b]Older adult: women >30 years, men >40 years.

parameters by increasing the proportion of sexual contacts between the YA and OA groups, from 91% of sexual contacts of the YA group within the YA group in the base case to 59%, resulting in 51% of the sexual contacts of the OA group within the OA group (versus 93% for the base case, for details see Supplementary Material). This resulted in higher effectiveness of PrEP with 10% coverage in the OA: 11.0% of infections averted in the YA group, 4.2% in the OA group, and 9.5% in the overall population.

Two-Way Sensitivity Analyses

In two-way sensitivity analyses, we varied PrEP effectiveness and coverage to test the robustness of the results regarding infections averted. We found that PrEP was as effective as the 95-95-95 continuum of care when it reached 20% coverage, when using the same effectiveness as in the base case (Figure 2). Overall, the proportion of infections averted reached 85.5% in the YA group with 90% PrEP efficacy and 90% coverage, or 66.6% of infections averted in the overall population (Figure 2).

Multiway Sensitivity Analyses

In multiway sensitivity analyses, we adapted the base case to the continuum of care achieved by MoH, MSF, and partners in 2018 and maintained that through 2030, which would result in 98.3% tested among infected, 99.6% on ART among tested, and 98.2% with viral suppression among patients on ART (overall 96.3% viral suppression). With these continuum of care targets, in the model PrEP was as effective as in the base case scenario, with 11.4% of infections averted in YAs, 1.2% of infections averted in OAs, and 7.8% in the overall population.

Population	PrEP efficacy (%)	PrEP coverage (%)					
		10	20	30	50	70	90
YA	50	5.6	16.1	22.0	37.5	46.2	56.4
	75	9.9	24.1	33.5	52.5	64.2	77.4
	90	17.1	28.0	37.2	56.1	72.2	85.5
OA	50	0.0	2.9	2.3	3.0	3.3	7.6
	75	2.0	2.9	3.0	4.6	9.5	8.8
	90	5.1	9.0	8.0	9.6	12.1	12.4
Overall	50	4.2	12.9	17.4	42.0	35.6	44.4
	75	8.0	18.9	27.2	43.4	51.5	61.3
	90	14.2	23.3	28.6	35.6	56.8	66.6

Infections averted: : <25.0%, : 25.0% to 50.0%, : > 50.0%.

Figure 2. Two-way sensitivity analyses (heat map). Percent of HIV infections averted with PrEP compared to base case (90-90-90), projected to 2030 in younger adult and overall population, depending on PrEP coverage and efficacy. Red represents the situation where infections averted were <25.0%, yellow from 25.0% to 50.0%, and green > 50.0%. Abbreviations: 90-90-90, 90% HIV testing coverage, 90% of those infected on ART, and 90% of those on ART achieving viral suppression; HIV, human immunodeficiency virus; OA, older adult; PrEP, preexposure prophylaxis; YA, young adult.

DISCUSSION

The ambitious 90-90-90 continuum of care targets, set by UNAIDS in 2014, still leave a sizeable proportion of people with HIV with unsuppressed viremia [8]. To get closer to ending the HIV epidemic, additional strategies are being focused on, specifically PrEP [8, 20]. Kenya has started the most ambitious PrEP roll-out program in Africa, while on its way to reaching the 90-90-90 targets [21]. While PrEP has been presented as the best complementary intervention to 90-90-90, the comparative effectiveness of a high level of continuum of care interventions and PrEP, in the era of universal test and treat (UTT), is not well understood.

We expanded upon a model of the 90-90-90 targets to assess incidence, prevalence and infections averted with the addition of PrEP [13]. We found that maintaining the continuum of care to 90-90-90 would further substantially decrease incidence, by 63% in the overall population. This improved not only the survival of people with HIV, but also averted infections and therefore yielded additional years of life saved.

We found that in the context of a generalized epidemic, with high continuum of care targets already reached, PrEP has only modest additional effects on infections averted and decreasing incidence. We also found that achieving a 95-95-95 continuum of care will have a greater impact on the epidemic than achieving 90-90-90 targets with the addition of PrEP to a YA population, if PrEP coverage is below 20%. In a generalized HIV epidemic, transmission occurs more frequently in the OA group, compared to in a risk group-driven epidemic. Hence, PrEP is not as effective as it has been shown to be in epidemics driven by smaller risk groups, such as men who have sex with men (MSM) or people who inject drugs [22, 23]. Mixing between risk groups is higher in a generalized epidemic than in a concentrated epidemic because the proportion of sexual contacts between YA and OA groups is higher. Second, there is a competing mechanism between viral load suppression interventions, which control the source of transmission, and PrEP, which controls infection at "destination".

These competing efficacies have been described in previous model-based analyses [24–27]. In an early study in South Africa, Pretorius et al compared the effectiveness and cost-effectiveness of PrEP versus UTT, with 65% of the total HIV population treated, following WHO recommendations at that time [24]. With optimistic PrEP efficacy assumptions (90% overall efficacy), they found that PrEP benefit decreases rapidly as ART coverage increases and becomes negligible with UTT. However, this study did not model a generalized epidemic. Cremin et al used the same model to compare different ART expansion policies and PrEP coverage [25]. Their results favored ART expansion to 80% of infected individuals with CD4 count <350 cells/μL, and then PrEP. They also modeled PrEP targeted to an age-group population (age 15–24 years) and found that increasing PrEP coverage to 40% yields as few as 5% additional infections averted [25]. Alistar et al compared universal ART access and PrEP in South Africa and found, similar to our analysis, that PrEP effectiveness decreases with higher ART coverage, down to 20% of infections averted with PrEP added to ART coverage expansion [26]. More recently, Blaizot et al studied the comparative cost-effectiveness of ART expansion, voluntary medical male circumcision, and PrEP [28]. They used a compartmental model with no dynamic transmission, and ART expansion modeled to reach UNAIDS 90-90-90 targets. Their findings were consistent with ours: "ART for all" was the single most effective intervention to decrease incidence, and PrEP had a modest additional effect on incidence [28]. Our study adds importantly to this literature by including dynamic transmission, and by comparing continuum of care outcomes rather than treatment eligibility [28].

Although, the impact of "ART for all" on HIV incidence has been illustrated in model-based studies, results are more inconsistent in large-scale trials that have evaluated the effect of universal testing and treatment in the community. In the PopART study, a community-randomized trial conducted in Zambia and South-Africa, home-based HIV testing and universal ART did not lead to a lower incidence of HIV infection than standard care, although this was not anticipated and although the proportion of patients with viral suppression was 16% higher in the intervention group [29]. The Sustainable East Africa Research in Community Health (SEARCH) study in Kenya and Uganda, which embedded treatment as prevention in an integrated multidisease model, also did not show an effect on HIV incidence, even with 90% viral suppression among those on ART. This may have been related to intensive baseline community-based HIV testing in both the intervention and control groups [30]. The Ya Tsie study in Botswana had 88% viral suppression in the intervention group and showed a 30% lower incidence in the intervention compared to the control group, but the difference was not significant [31]. These clinical trials illustrate the challenge in achieving ART coverage targets in young people, men, and communities at high risk of HIV infection, such as those with increased mobility. Notably, linkage to care and retention are crucial in achieving high levels of viral suppression, and are difficult to achieve [32].

There are, in addition, important challenges to implementing PrEP in generalized epidemic settings such as in Southwest Kenya. The high-risk population is difficult to define, and so is the level of coverage [33]. This population represents a high proportion of the overall population, and to cover this population with PrEP is both difficult and costly. We considered PrEP coverage at 10% to be a realistic target. Even in developed countries, where the epidemic is driven by risk groups such as MSM, which are smaller in size, and with higher PrEP acceptability rates, few coverage rates achieve 20%: the EPIC-NSW prospective cohort study in Australia reached 19.6% of the sexually active gay-identifying men

[22]. In the United States, in the National Cohort of Gay and Bisexual Men, only 12.9% of eligible men were on PrEP [34]. In Kenya, oral PrEP has been included in national guidelines since 2016. As of October 2018, 1498 facilities provided PrEP nationally; in Homa Bay, which includes Ndhiwa, 156 facilities have delivered PrEP to 3906 clients [35]. PrEP coverage was assessed in the SEARCH study in Western Kenya in 2016 [36]. They classified 33.2% of the overall adult HIV-negative population as at elevated HIV risk, and achieved 24.0% PrEP uptake within 90 days. However, one-third of participants who self-reported adherence had drug concentrations that indicated low adherence; adolescents and young adults had the lowest uptake. Further, 17% of community members had neither HIV testing nor risk assessment. This suggests additional educational and outreach efforts will be needed, particularly in younger groups, but that PrEP coverage can be successfully increased.

Overall, despite competing efficacies, both UTT and PrEP face challenges in reaching key high-risk populations. Efforts to reach them could benefit both UTT and PrEP interventions.

As with all model-based studies, this analysis is subject to limitations. We derived natural history input parameters from different African cohorts [18, 19]. We structured the model based on assumptions including patients who become lost to follow-up, informed assumptions on risk group proportions and behavior, and transmission between individuals occurring randomly among risk groups. However, our sensitivity analyses on risk group proportions and transmission parameters did not change the overall results. Finally, we did not perform cost-effectiveness analysis, which would be valuable for health authorities. In the era of UTT and expected low HIV incidence, the cost-effectiveness of PrEP should be assessed depending on the context. As UNAIDS recommends that PrEP should be offered to high-risk groups, defined by incidence higher than 3.0/100 PY, cost-effectiveness studies can be used to weigh the value of PrEP roll-out compared to ART expansion in these populations [37].

In conclusion, based on current data for Southwest Kenya, we found that PrEP interventions have limited effect in the context of a high level of continuum of care coverage. Implementing PrEP, with its high cost and challenging feasibility, should be carefully weighed against efforts to further improve the HIV continuum of care in such settings.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contribution. L. B. L. N. has full access to all the data in the study and final responsibility for the decision to submit the manuscript for publication.

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