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Modeling dynamic interactions between pre-exposure prophylaxis interventions & treatment programs: predicting HIV transmission & resistance

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Clinical trials have recently demonstrated the effectiveness of Pre-Exposure Prophylaxis (PrEP) in preventing HIV infection. Consequently, PrEP may soon be used for epidemic control. We model the dynamic interactions that will occur between treatment programs and potential PrEP interventions in resource-constrained countries. We determine the consequences for HIV transmission and drug resistance. We use response hypersurface modeling to predict the effect of PrEP on decreasing transmission as a function of effectiveness, adherence and coverage. We predict PrEP will increase need for second-line therapies (SLT) for treatment-naïve individuals, but could significantly decrease need for SLT for treatment-experienced individuals. If the rollout of PrEP is carefully planned it could increase the sustainability of treatment programs. If not, need for SLT could increase and the sustainability of treatment programs could be compromised. Our results show the optimal strategy for rolling out PrEP in resource-constrained countries is to begin around the "worst" treatment programs.

Effective prevention strategies for controlling the HIV pandemic are urgently needed. One potential strategy, currently being investigated in phase III clinical trials, is pre-exposure prophylaxis (PrEP)[1]. PrEP is the administration of low levels of antiretrovirals (ARVs), specifically Tenofovir (TDF) or Truvada (TDF in combination with emtricitabine (FTC)) prior to HIV exposure[2,3]. Results from the first Phase III clinical trial of oral PrEP, the iPrEx trial, have recently been published[4]. The study involved 2,499 men who have sex with men (MSM) and transgender women who have sex with men from six countries in the Americas, Africa and Asia. Once-daily oral Truvada was found to reduce the risk of acquiring HIV infection by 44% in the study population overall. Recent results (currently unpublished) from two other clinical trials provide additional evidence PrEP can reduce risk. The TDF2 trial investigated the use of once-daily oral Truvada in 1,219 heterosexual men and women in Botswana; the Partners PrEP trial evaluated both TDF and Truvada in 4,758 HIV serodiscordant couples in Kenya and Uganda. Both studies showed significant reductions in risk of infection ranging from 62% for TDF (in the Partners PrEP study) to between 63% and 73% for Truvada (in the TDF2 and Partners PrEP studies, respectively)[5,6]. Based on the results from the clinical trials, PrEP may soon be rolled out in resource-constrained countries as an intervention to reduce heterosexual transmission of HIV. However there is concern this could generate drug resistance[7], because HIV-infected individuals may inadvertently use PrEP. Drug resistance has already arisen in many resource-constrained countries as a consequence of their HIV treatment programs[8,9]. Here we model the dynamic interactions that will occur between treatment programs and PrEP interventions in resource-constrained countries. We predict the consequences of these interactions for HIV transmission and drug resistance. We evaluate both TDF-based and Truvada-based PrEP. The implications of our results for the rollout of PrEP interventions in Sub-Saharan Africa are discussed.

For user-dependent prevention interventions (e.g., PrEP), phase III clinical trials measure the effectiveness of the product rather than efficacy[10,11]. Effectiveness is a function of the biological efficacy of the product and participants' adherence. Effectiveness is a reasonable measure of biological efficacy if adherence is ~100%[11]. The Phase III clinical trials of PrEP (iPrEx, TDF2, and Partners PrEP) all found significant differences in

effectiveness depending on participants' adherence to the study protocol. In the IPrEx trial, the overall effectiveness of Truvada-based PrEP was 44% (95% confidence interval (CI): 15 to 63%), but was extremely dependent upon adherence. PrEP adherence was defined in terms of the percentage of the daily doses of PrEP that were taken. Specifically, incidence was reduced by 73% if adherence was high ($\geq$ 90% of doses), 50% if adherence was intermediate ($\geq$50% of doses) and 32% if adherence was low ($<$ 50% of doses)[4]. Notably, PrEP was found to reduce incidence by 92% (95% CI: 40 to 99%) if the regimen was taken exactly as prescribed[4]. No resistance mutations for TDF were found among iPrEx participants, although three cases of resistance for FTC were found: one in the placebo arm and two in the Truvada arm. The case in the placebo arm appears to reflect transmitted resistance, and the two individuals who developed mutations in the Truvada arm appear to have begun PrEP before it was known they were infected with HIV[4]. Based on these results it remains unknown whether individuals who begin PrEP when they are uninfected, then fail PrEP and remain on PrEP are likely to develop resistance.

In the TDF2 trial, the effectiveness of Truvada-based PrEP was 63% (95% CI: 22 to 83%)[6]. However, among participants known to have a supply of study drugs, protection was even greater, with an effectiveness of 78% (95% CI: 41 to 94%). Although some gender differences were noted, the study was not large enough to draw definitive conclusions about the effectiveness of Truvada based on gender. Consistent with the IPrEx trial, there were no cases of drug resistance among participants taking Truvada who became infected after enrollment. One case of TDF and FTC resistance occurred in a participant who had unrecognized HIV infection at the time of enrollment. In Partners PrEP, the study found 62% (95% CI: 34 to 78%) effectiveness for TDF-based PrEP and 73% (95% CI: 49 to 85%) for Truvada-based PrEP[5]. Both PrEP regimens had similar effectiveness in men and women. Although it appeared Truvada provided more protection than TDF alone, this difference was not statistically significant. Adherence to the daily PrEP medication was very high – more than 97% of dispensed doses of the study medications were taken. Twelve participants who had tested HIV-negative at screening were found to have acute HIV infection; however information on drug resistance has not been released yet. Notably, the results of the Partners PrEP study and TDF2 contrast with those of the FEM-PrEP study, which failed to demonstrate that Truvada-based PrEP was effective in protecting against HIV acquisition among at-risk women in Kenya, Tanzania and South Africa[12]. In addition, the VOICE trial of PrEP in heterosexual African women recently discontinued the daily oral TDF arm and the TDF gel arm, although the oral Truvada arm of the study is still under way. Currently there are no publicly available data to explain why Truvada was not found to be effective in FEM-PrEP, nor TDF in the VOICE study.

Prior to the clinical trial results, the available data concerning PrEP efficacy were mainly from pre-clinical studies of PrEP in the rhesus macaque model of SHIV/SIV infection[13-17]. These studies investigated daily PrEP with TDF or Truvada[13,14,17]. Results showed the risk of simian human immunodeficiency virus (SIV) infection in macaques receiving daily PrEP with TDF or Truvada was 3.8- and 7.8-fold, respectively, lower than in untreated macaques[13]; indicating PrEP might significant reduce transmission. Results from another macaque study[15] suggest PrEP may be less effective in protecting against infection with drug-resistant viruses than against infection with wild-type viruses. In that study loss of protection to infection by TDF-based PrEP was observed in macaques exposed to a SIV isolate carrying the TDF resistance mutation, K65R[15]. Other studies of macaques have shown resistance can emerge while on PrEP[13], as can occur when an individual is receiving ARVs for therapeutic purposes[18]. Since mutations to TDF and FTC acquired during treatment have been observed to rapidly revert when treatment has stopped[19–21], it is likely that mutations selected while on PrEP will also revert once the pressure of PrEP is removed. We use the results from these empirical observations and studies, as well as the recent results from the Phase III trials, to inform our modeling of PrEP-based interventions.

Previously we (VS & SB) designed a mathematical model to predict the effect of PrEP interventions in a "high-risk" community in a resource-rich country; specifically the MSM community in San Francisco[22]. Our new model is designed to investigate the dynamic interactions between HIV treatment programs and potential PrEP interventions in resource-constrained countries. The model tracks the transmission dynamics of wild-type and resistant strains of HIV in a generalized epidemic driven by heterosexual transmission. Generalized epidemics are characterized by a high prevalence of HIV in the general population and occur in many African countries. In our analyses, PrEP interventions are implemented when treatment programs are in place, resistant strains are evolving in treated individuals, and resistant strains are being transmitted. Previous models of PrEP have been based on unrealistic assumptions. Specifically, treatment will be unavailable in resource-constrained countries when PrEP is rolled out[23–26], all infected individuals are eligible for PrEP[24,26] or neither treatment programs nor PrEP interventions can generate drug resistance[27].

We use our model to investigate the effect of the "quality" of the PrEP interventions and the effect of the "quality" of the treatment programs on transmission and resistance by using uncertainty and sensitivity analyses (see Methods). We characterize the "quality" of PrEP interventions in terms of four of the models' parameters: (i) coverage (specified by the proportion of sexually active individuals adopting PrEP each year), (ii) the effectiveness of PrEP for individuals who are highly adherent to the regimen (defined as taking $\geq$90% of daily doses), (iii) the proportion of individuals who are highly adherent to PrEP and (iv) the average level of adherence in individuals who have low/moderate adherence (defined as taking $<$ 90% of daily doses). We characterize the "quality" of treatment programs in terms of two of the models' parameters: (i) the proportion of treated individuals who achieve complete viral suppression ($<$400 copies/ml) and (ii) the rate of developing resistance in treated individuals who only achieve partial viral suppression. Parameter values used to define the "quality" of PrEP interventions and the "quality" of treatment programs are given in Table S6 and Table S7 in the Supplementary Material (SM).

Our model includes behavioral heterogeneity with respect to adherence to PrEP regimens. We define adherence, as in the clinical trials, in terms of the number of daily doses that are taken. We model adherence for each gender independently. We assume a certain proportion of individuals on PrEP are highly adherent (i.e., take $\geq$90% of daily doses) and the remaining proportion on PrEP are low to moderately adherent (i.e., take less than 90% of daily doses). We vary the degree of behavioral heterogeneity in adherence to PrEP regimens by letting: (i) the size of the high adherence group vary from 0% to 100% of the individuals taking PrEP, (ii) the average level of adherence (in the high adherence group) vary from 90% to 100% and (iii) the average level of the adherence (in the low/moderately adherent group) vary from zero to 89%. Our model is designed to use data from clinical trials; consequently, we model effectiveness of PrEP rather than efficacy. We model effectiveness as a function of adherence and whether the strain is wild-type or resistant; see Section 1e and Figure S2 in the SM for technical details. Based on data from the macaque studies[15] we assume PrEP is less effective against resistant strains than against wild-type. We also assume that below a certain level of adherence there are not enough ARVs present to protect against infection or to select for resistance. Therefore, when modeling the effectiveness of PrEP and the risk of developing a DRM on PrEP, we include an adherence threshold below which effectiveness is very low and resistance unlikely. Our modeling of this threshold is described in detail in Sections 1e and 1f in the SM, and shown in Figures S2 and S3 in the SM.

We assume to begin PrEP and/or to renew a prescription an individual has to test negative for HIV. However, none of the currently available HIV antibody tests can detect infection during the first few weeks after infection (i.e., during the "window period")[28,29]. In Botswana, HIV testing is by parallel rapid tests or parallel ELISAs: in the first case, Uni-Gold Recombigen HIV (Trinity Biotech, Bray, Ireland) and Determine HIV 1/2 (Abbott Diagnostics, Abbott Park, IL) tests are used. If the results are discordant, then parallel tests are repeated. If the rapid tests are still discordant, the OraQuick (OraSure Technologies, Bethlehem, PA) test is used as a tie-breaker[30]. These tests have shown very high sensitivity and specificity (~100%) in Botswana in detecting HIV in individuals whose infection is outside the "window period"[31,32]. Consequently, when modeling PrEP interventions we assume tests are 100% accurate in detecting HIV when testing occurs after the "window period" and do not detect HIV when testing occurs during the "window period". Hence in our analyses, recently infected individuals tested during the "window period" could inadvertently be prescribed PrEP, but infected individuals tested after the "window period" would not be prescribed PrEP. The Center for Disease Control and Prevention in the United States recommends that individuals who take PrEP should be tested every three months to check whether they have become infected. Testing frequency in resource-constrained countries is unlikely to be more frequent than in the US. Therefore in our analyses we explored a range of testing frequencies varying from every three months to every six months.

Our model includes two mechanisms for selecting for a drug-resistant mutation (DRM) on PrEP. A DRM can be selected if (i) an HIV-infected individual in the "window period" of infection inadvertently begins taking PrEP or (ii) an individual acquires infection when they are on PrEP and then remains on the regimen. We model the risk of an individual developing a DRM on PrEP as a function of: their level of adherence to the regimen, their stage of HIV infection (primary or chronic), the specific PrEP regimen they take (TDF-based or Truvada-based) and the time they spend on PrEP once infected with HIV; see Section 1f and Figure S3 in the SM for technical details. As well as modeling the emergence of resistant strains due to the selective pressure of PrEP, we model the emergence of resistant strains in treated individuals taking first-line therapies. We also model reversion of resistant strains to wild-type in infected individuals who: i) develop resistance while on PrEP and then come off PrEP or ii) acquire transmitted resistance. Reversion occurs because wild-type strains out-compete the resistant strains in the absence of ARVs. In addition, we model (after reversion has occurred) the reemergence of resistant strains under the selective pressure of treatment. Resistance can reemerge quickly as resistant strains are maintained in reservoirs as minority strains within the individual. For the technical details of our modeling of resistance see SM.

We investigate the two PrEP regimens that are currently being investigated in clinical trials: TDF and Truvada. A full listing of PrEP trials is given in Table 1. In our modeling of the evolution of resistance on TDF-based PrEP, we model the DRM that has been observed to be selected for by TDF, K56R. In our analysis of Truvada-based PrEP we model the risk of developing M184V. In infected humans and non-human primates taking Truvada, the first DRM that has generally been observed is M184V; K65R has been observed to arise subsequently, if the infected primate or human remains on Truvada[7]. We do not model the possibility of further selection for K65R because we include frequent testing in our model. If individuals on PrEP, in our model, are found to be infected with HIV they will not be given further PrEP regimens. If testing is frequent, it is unlikely that an HIV-infected individual would remain on PrEP long enough to select both M184V and K65R. We note that in the iPrEx trial (where trial participants were tested approximately monthly) it was found that among HIV-infected individuals on Truvada-based PrEP only M184V was selected[4]; the virus did not evolve further and acquire K65R. In TDF2, there was one case of a participant who started taking Truvada while having acute HIV infection and had several false negative HIV tests in the months following enrollment[6]. The individual tested positive for K65R and M184V, and also had a broad-spectrum NNRTI mutation A62V, which suggests that the virus they had contracted was not wild-type. One seroconverter in the placebo arm was also found to have low levels of K65R. We note that the complexity of our model could be increased to include the sequential evolution of multiple DRMs.

The Government of Botswana is considering implementing public health interventions based on PrEP if several of the Phase III trials demonstrate effectiveness, PrEP is shown to be cost effective and the health system is able to deliver such services. Botswana has one of the

Table 1 | Ongoing and Planned daily oral PrEP Trials[1]

Location	Sponsor/Founder	Population	PrEP strategies being tested	Status/Results expected
Phases III, IIb (safety and effectiveness)				
Kenya, South Africa, Tanzania, Zimbabwe (FEM-PrEP)	BMGF, FHI, USAID	3,900 heterosexual women	Daily oral TDF/FTC	Data Analysis/TBD[a]
Uganda, Kenya (Partners PrEP)	BMGF	4758 serodiscordant heterosexual couples	Daily oral TDF; daily oral TDF/FTC	Data Analysis/TBD[b]
Thailand (CDC 4370)	CDC	2,400 injecting drug users	Daily oral TDF	Fully enrolled/Q1 2012
South Africa, Uganda, Zimbabwe (VOICE MTN 003)	NIH/MTN	5,000 heterosexual women	Daily oral TDF;daily oral TDF/FTC;daily TDF gel	Fully enrolled[c]/Q1 2013
Phases I, II (safety, adherence, acceptability, feasibility)				
Botswana (TDF2; CDC 4940)	CDC	1,200 heterosexual men & women	Daily oral TDF/FTC	Data Analysis/TBD
United States HPTN069	HPTN, NIH	400 MSM	MVC; MVC+FTC; MVC+TDF; TDF/FTC	in development
Uganda (IAVI E002)	IAVI	72 heterosexual men & women	Daily and intermittent TDF/FTC	Ongoing/TBD
Open Label				
Peru, Ecuador, US, South Africa, Brazil, Thailand (iPrEx OLE)	NIH	iPrEx and ATN 082 participants offered opportunity to enroll in open-label extension	Daily oral TDF/FTC	Enrolling/2013

DAIDS: Division of Acquired Immunodeficiency Syndrome; BMGF: Bill & Melinda Gates Foundation; CDC: US Centers for Disease Control; MTN: Microbicide Trials Network; NIH: US National Institutes of Health; MSM: Men who have Sex with Men; IAVI: International AIDS Vaccine Initiative; ATN: Adolescent Trial Network; USAID – United States Agency for International Development; FHI – Family Health International; TDF: TDF; FTC: emtricitabine; MVC: maraviroc; TBD: To be determined.
[a]stopped early due to futility.
[b]stopped early for efficacy of Truvada and TDF.
[c]oral TDF and TDF gel arms stopped early.

highest levels of HIV in the world. The most recent World Health Organization report[33] and the Botswana AIDS Impact Survey[34] indicate that: (i) ~30% of women (aged 15–49 years) and ~20% of men (aged 15–49 years) are infected with HIV, (ii) HIV incidence is high, ~4.4% in women and ~2.5% in men[34] and (iii) transmitted drug resistance has reached ~4%[35]. Botswana is a relatively rich country with one of the best healthcare systems in Africa and, potentially, has the resources available to provide PrEP to the general population. In addition, the population size is small, only ~1 million adults aged between 15 and 49 years old, live in Botswana. Therefore, it is a feasible strategy for the entire population to be offered PrEP. In addition, since it has the highest HIV treatment coverage of any African country it may now be able to afford to concentrate on prevention. In 2002 it was the first African country to offer free ARVs to everyone in need of treatment; treatment was rapidly scaled up and now 70–80% of those in need are receiving ARVs[36,37].

Treatment programs in Botswana have been very successful; a study of the first 5 years of treatment found the percentage of patients with viral loads less than 400 copies/ml at one, three and five years was 91%, 90% and 98%, respectively[38]. However some patients on first-line regimens are now virologically failing treatment and developing resistance to TDF[39], although the number of patients needing second-line therapies (SLT) is currently low[35]. In Botswana, as well as in many other Sub-Saharan African countries, the potential problem of PrEP increasing resistance is of particular concern since their first-line treatment regimens are based on TDF[40]. For example, Atripla (efavirenz/FTC/TDF) has been used, since 2008, as the first-line treatment regimen in Botswana. A rise in TDF-resistance could challenge future treatment options and potentially increase the need for SLT regimens in Botswana, as well as could occur in other countries in Sub-Saharan Africa. We use our model to investigate the consequences, for HIV transmission and drug resistance, of the dynamic interactions between potential PrEP interventions and current treatment programs in Botswana.

Results

Model validation. To assess the validity of our model we began the simulations of our model in 2002 when the rollout of treatment began in Botswana. We then assessed the goodness of fit of the model by comparing its outputs (for 2010) against current empirical data from Botswana. Specifically, we compared the outputs against seven epidemiological measures of the current HIV epidemic. The model outputs are an excellent fit to current empirical data from Botswana; see Table S9 in the SM. For example, the model predicts: (i) HIV prevalence in women is 32% (compared with actual prevalence of ~30%), (ii) HIV prevalence in men is 23% (compared with actual prevalence of ~20%), (iii) HIV incidence in women is 4.5% (compared with actual incidence of ~4.4%) and (iv) HIV incidence in men is 2.7% (compared with actual incidence of ~2.5%). This goodness-of-fit analysis demonstrates that our model is a valid representation of the current transmission dynamics of HIV in Botswana in the presence of their treatment programs and pre-PrEP interventions.

Predictions from the uncertainty analysis: incidence & prevalence. Figure 1 shows model predictions for Botswana obtained from three uncertainty analyses (see Methods). Each of the three sets of predictions are based on different conditions: (i) only current treatment programs and no PrEP interventions, (ii) current treatment programs plus the introduction of TDF-based PrEP interventions, and (iii) current treatment programs plus the introduction of Truvada-based PrEP interventions. Ten year predictions are shown for incidence in women (Figure 1A), prevalence in women (Figure 1B), incidence in men (Figure 1C), and prevalence in men (Figure 1D).

The model predicts that even without PrEP interventions, incidence and prevalence will decrease slightly over the next decade due to the effect of the current treatment programs on reducing infectivity of treated individuals (Figure 1). If PrEP interventions are implemented in Botswana, along with the current treatment programs, incidence and prevalence could decrease significantly; irrespective of whether the interventions are based on TDF or Truvada (Figure 1). If Truvada-based PrEP interventions are implemented, incidence could drop from 4.5% (median; IQR 3.2%–6.1%) to 1.6% (median; IQR 1.1%–2.4%) in women and from 2.7% (median; IQR 1.9%–3.8%) to 1.0% (median; IQR 0.7%–1.6%) in men; very similar results were found for TDF-based PrEP interventions (Figure 1). Notably, these reductions in incidence (i.e., reductions in transmission) and prevalence are due to both the PrEP interventions and the treatment programs. As the incidence falls, prevalence decreases. If Truvada-based PrEP interventions are implemented, prevalence could decrease from 32% (median; IQR 26%-39%) to 20% (median; IQR 15%–25%) in women and from 23% (median; IQR 17%–29%) to 14% (median; IQR 10%–18%) in men; very similar results were found for TDF-based PrEP interventions (Figure 1).

Our modeling shows that the introduction of Truvada-based PrEP interventions, over a decade, could prevent 39% (median; IQR 29%–49%) of new infections in women and 40% (median; IQR 30%–50%) of new infections in men in Botswana. Predictions for the number of infections prevented are not significantly different for TDF-based PrEP versus Truvada-based PrEP.

Key parameters in reducing transmission. To determine which parameters were most important in decreasing transmission (i.e., the key parameters) we conducted two types of sensitivity analyses. One was based on calculating Partial Rank Correlation Coefficients (PRCCs), the other based calculating Standardized Regression Coefficients (SRCs) and response hypersurface modeling[41]; see Methods. We defined key parameters as those with a PRCC greater than 0.4 or less than minus 0.4. Both types of sensitivity analyses identify the key parameters; however the results from response hypersurface modeling provide additional insights. Three dimensional response hypersurfaces were generated by using multivariate analysis to identify linear and nonlinear relationships among the key parameters. Each color-coded plot of a response hypersurface shows the predictions from the model for one specified outcome variable (Z) as a function of two of the models' key parameters (Y_1 and X_1); where $Z = \alpha_1 Y_1 + \alpha_2 X_1 + \alpha_3 Y_1 X_1$ and α_1, α_2 and α_3 specify the coefficients in the regression equation. The interaction effect between the two key parameters is shown by the curvature of the hypersurface.

The key parameters which affect transmission, after the introduction of PrEP interventions in the presence of treatment programs, are shown in bold in Table 2 and Table S10 in the SM. There are no significant differences between TDF-based PrEP and Truvada-based PrEP with respect to their values of PRCCs or their SRCs. Not surprising, the key parameters in determining the success of PrEP interventions in reducing transmission are the parameters that specify adherence, coverage and the effectiveness of PrEP for women who are highly adherent to the regimen (Table 2). The response hypersurfaces in Figure 2 reveal the independent and interaction effects of these key parameters on the percentage of infections prevented in women 10 years after Truvada-based PrEP interventions have been introduced. Plots are color-coded based on the predicted degree of reduction in transmission; regression equations used to construct the hypersurfaces are given in the Figure Legend. The introduction of PrEP interventions could have very little effect on reducing transmission (shown by the dark blue region) or a substantial effect (~55%) on reducing transmission (shown by the dark red region) or anywhere in between (Figure 2). Figure S4 in the SM shows results for Truvada-based PrEP interventions for men. Results for

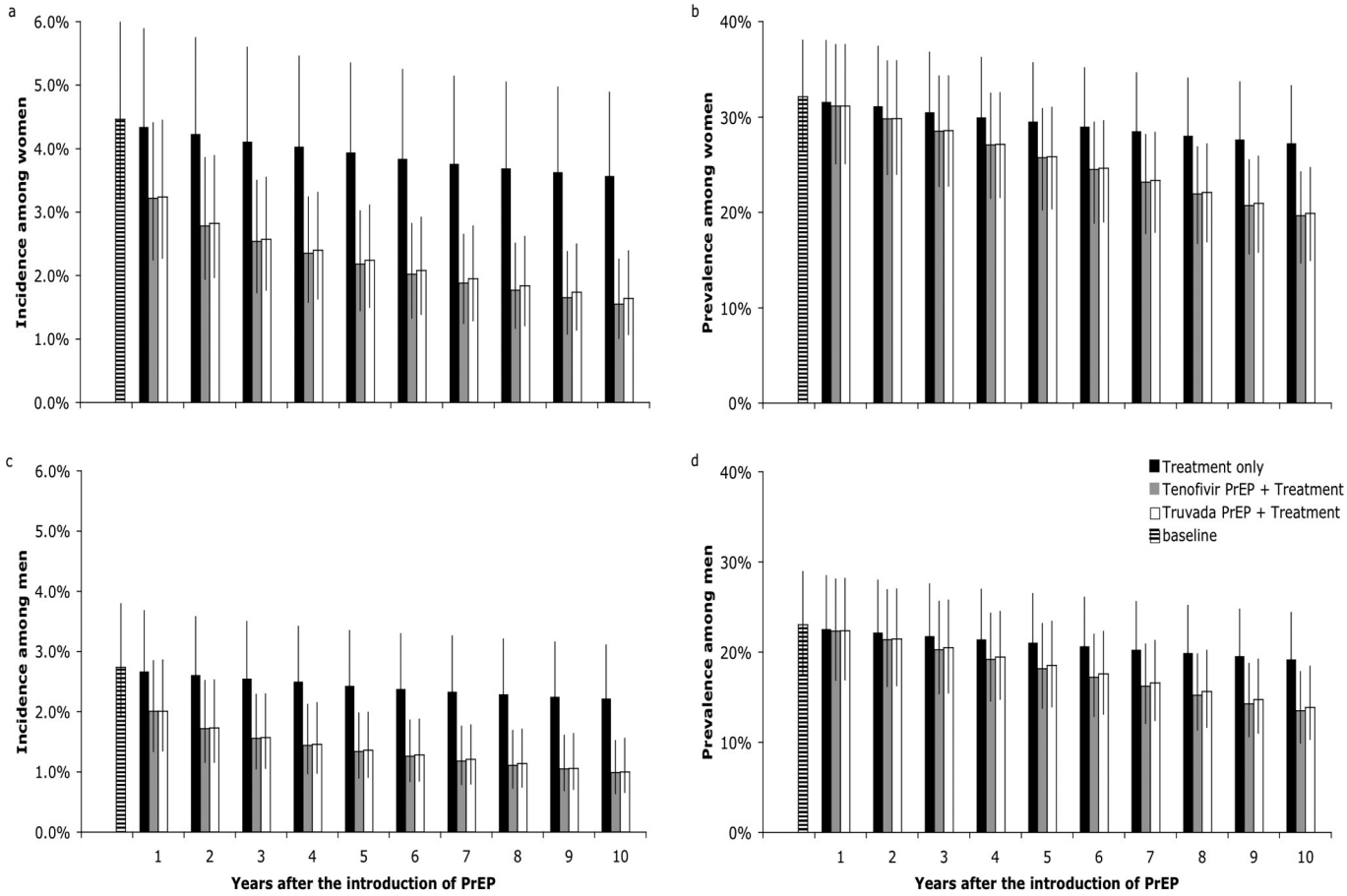

Figure 1 | Model predictions from the uncertainty analysis for women in Botswana for 10 years from when Truvada-based PrEP interventions are introduced: (a) HIV incidence and (b) HIV prevalence. Bars with black stripes show the values of HIV incidence in (a) and prevalence in (b) in women before the introduction of PrEP-based interventions. Model predictions are shown for the following conditions: treatment only (black bars), treatment plus Tenofovir-based PrEP (grey bars) and treatment plus Truvada-based PrEP (white bars). (c) same as (a) but for men. (d) same as (b) but for men.

TDF-based PrEP interventions for women and the corresponding results for men are shown in Figure S5 in the SM.

Figure 2A shows the effect of any specific PrEP intervention on reducing transmission as a function of the effectiveness of the regimen for women who are highly adherent (see Y-axis) and coverage (i.e., the proportion of sexually active women who adopt PrEP each year) (see X-axis). Figure 2B shows the effect of the PrEP intervention on reducing transmission as a function of the adherence level of women specified in terms of: (i) the proportion of women who are highly adherent (see Y-axis) and (ii) the average level of adherence in women who have low/moderate adherence (see X-axis). The curvature of the hypersurface shows there is a strong interaction effect between these two key adherence parameters. Notably, Figure 2B shows a wide variety of adherence patterns could cause similar reductions in transmission. For example, transmission could be reduced by ~40% if ~70% of the women taking Truvada-based PrEP are highly adherent (i.e., take ≥90% of daily doses) and the other women have extremely low adherence (i.e., on average take ~10% of daily doses). Transmission could also be reduced by ~40%, if ~40% of the women are highly adherent (i.e., take ≥90% of daily doses) and the other women are only moderately adherent (i.e., on average take ~60% of daily doses).

Change in need for Second-Line Therapies (SLT) for treatment-naïve individuals. Our results from the uncertainty analyses show the number of treatment-naive individuals in need of SLT is very likely to increase in the decade after implementing PrEP interventions; this occurred in 99% of the 937 simulations conducted for the uncertainty analyses. The result is regardless of whether the PrEP regimen was based on TDF or Truvada. Our sensitivity analyses show only one parameter is important in determining the degree of increase in need (Table 2). This key parameter reflects the "quality" of the PrEP intervention; specifically, the average level of adherence in individuals who have low/moderate adherence to the regimen. The sensitivity of the results to this parameter is similar for TDF-based PrEP and Truvada-based PrEP (Table 2 and Table S10 in the SM).

The predictions of the model showing the increase in the number of treatment-naive women in need of SLT (shown in Figure 3A for TDF-based PrEP and in Figure 3B for Truvada-based PrEP), after the introduction of PrEP interventions, is shown in terms of a ratio (see Methods). Corresponding results for treatment-naïve men are shown in Figures S6A and S6B in the SM. Each prediction shown in Figure 3 is from one of the 937 simulations conducted for the two uncertainty analyses where PrEP interventions were introduced when treatment programs were in place. Results are stratified based on whether the average level of adherence for the group of women who take < 90% of daily doses was low (<40%; shown by the blue bars) or moderate to high (between 40% and 89%; shown by the red bars). If adherence was low, the increase in the number of treatment-naive women in need of SLT was ~50% (Figure 3). When Truvada-based PrEP interventions were simulated (Figure 3A) the increase in need was slightly less than when TDF-based PrEP interventions were simulated (Figure 3B). Specifically, the SLT need ratio was 1.4

Table 2 | Table of Partial Rank Correlation Coefficients (PRCCs) for key experimental parameters identified in the sensitivity analysis of the two PrEP regimens studied: Tenofovir-based PrEP (TDF) and Truvada-based PrEP (TDF+FTC). PRCCs for men and women were calculated separately; values for men are shown in ()'s. IP: % of cumulative infections prevented; SLTN: ratio of need for second-line therapies for treatment-naïve individuals; SLTE: ratio of need for second-line therapies for treatment-experienced individuals

	Model outcome variables					
	IP		SLTN		SLTE	
	TDF	TDF+FTC	TDF	TDF+FTC	TDF	TDF+FTC
Proportion (average) of sexually active men who are tested HIV-negative and adopt PrEP each year (proxy for coverage)	0.27 **(0.57)**	0.22 **(0.56)**	−0.02 (0.30)	0.02 (0.28)	−0.21 **(−0.59)**	−0.22 **(−0.50)**
Proportion (average) of sexually active women who are tested HIV-negative and adopt PrEP each year (proxy for coverage)	**0.56** (0.25)	**0.57** (0.25)	0.24 (−0.10)	0.21 (−0.09)	**−0.65** (−0.26)	**−0.62** (−0.37)
Proportion of women highly adherent to PrEP	**0.80** (0.38)	**0.80** (0.39)	−0.02 (−0.09)	−0.06 (−0.12)	**−0.73** (−0.22)	**−0.77** (−0.26)
Proportion of men highly adherent to PrEP	0.43 **(0.82)**	0.44 **(0.82)**	−0.05 (0.00)	−0.08 (0.00)	−0.27 **(−0.74)**	−0.28 **(−0.79)**
Level of PrEP adherence among partially adherent men	0.30 **(0.66)**	0.23 **(0.65)**	−0.01 **(0.56)**	0.04 **(0.54)**	−0.21 **(−0.64)**	−0.17 **(−0.55)**
Level of PrEP adherence among partially adherent women	**0.69** (0.27)	**0.69** (0.25)	**0.59** (0.01)	**0.56** (0.05)	**−0.66** (−0.15)	**−0.62** (−0.20)
Effectiveness of PrEP against wild-type strains among individuals who are highly adherent	**0.42** **(0.43)**	**0.44** **(0.44)**	−0.30 (−0.31)	−0.32 (−0.32)	−0.36 (−0.27)	−0.39 (−0.39)
Proportion of individuals who are virally suppressed on treatment	0.12 (0.10)	0.10 (0.09)	0.33 (0.35)	0.34 (0.37)	**0.67** **(0.63)**	**0.64** **(0.64)**
Proportion of individuals only partially virally suppressed on treatment who develop resistance on treatment per year	0.02 (0.05)	0.02 (−0.05)	−0.26 (−0.23)	**−0.61** **(−0.53)**	**−0.61** **(−0.53)**	**−0.59** **(−0.54)**

(median; IQR 1.2–1.7) versus 1.5 (median; IQR 1.2–1.9). However, if the average level of adherence was between 40% and 89% the number of treatment-naive women in need of SLT could more than double after the introduction of PrEP interventions. Again, if Truvada-based PrEP was used the increase in the SLT need ratio was less than when TDF-based PrEP was used; 2.5 (median; IQR 1.9–3.7) versus 3.0 (median; IQR 2.3–4.5).

Change in need for Second-Line Therapies for treatment-experienced individuals. In contrast to our results for treatment-naïve individuals, our results show the number of treatment-experienced individuals in need of SLT is very likely to decrease in the decade after implementing PrEP interventions. This occurred in 927 of the 937 simulations conducted for the two uncertainty analyses where PrEP interventions were introduced when treatment programs were in place. The result is regardless of whether the regimen was based on TDF or Truvada. Our sensitivity analyses identified five key parameters that determined the decrease in need for SLT by treatment-experienced individuals; three parameters characterize the "quality" of PrEP interventions and two parameters characterize the "quality" of the treatment programs (Table 2 and S10 in the SM).

The three key parameters characterizing the "quality" of PrEP interventions were: (i) coverage (in terms of the proportion of sexually active individuals who adopt PrEP each year), (ii) the proportion of individuals taking PrEP who are highly adherent (i.e., who take ≥90% of daily doses) and (iii) the average level of adherence in individuals who have low/moderate adherence (i.e., who take < 90% of daily doses). Taken together these parameters determine the "quality" of PrEP interventions in terms of their effectiveness in reducing transmission. The more effective the PrEP intervention in reducing transmission, (i.e., the higher the "quality" of a PrEP intervention) the greater the expected reduction in the number of treatment-experienced women in need of SLT (Partial Correlation Coefficient (PCC) = −0.76) (Figure 4A). Decreases in need could be fairly substantial, up to a ~25% reduction (Figure 4A). Corresponding results for men and Truvada-based PrEP are shown in Figure S7A in the SM; results for TDF-based PrEP in Figure S7B (for women) and Figure S7C (for men).

The two key parameters characterizing the "quality" of treatment programs were: (i) the proportion of treated individuals who achieve complete viral suppression (<400 copies/ml) and (ii) the rate of developing resistance in treated individuals who only achieve partial viral suppression. Our sensitivity analyses show the greatest decreases in the number of treatment-experienced individuals in need of SLT will occur in treatment programs that currently are of low "quality". Specifically, programs that have a high percentage of patients who are only partially virally suppressed and a high rate of developing resistance in treated individuals who only achieve partial viral suppression (Table 2 and S10 in the SM).

Taken together our modeling results show a dynamic interaction between treatment programs and PrEP interventions will determine the magnitude of decrease in the number of treatment-experienced individuals in need of SLT. The effects of this interaction between the "quality" of the PrEP intervention and the "quality" of the treatment program is shown in the form of a response hypersurface in Figure 4B; this hypersurface shows the interaction between treatment programs and Truvada-based PrEP interventions on decreasing the need for SLT for treatment-experienced women. Corresponding results for men and Truvada-based PrEP are shown in Figure S7D in the SM; results for TDF-based PrEP in Figure S7E (for women) and Figure S7F (for men). The color-coded response hypersurface in Figure 4B shows the ratio of need decreases as the proportion of women on PrEP who are highly adherent (shown on the Y-axis) increases and/or the proportion of individuals who are virally suppressed on treatment decreases (shown on the X-axis). The interaction effect between these two key parameters is shown by the curvature of the hypersurface; the regression equation used to construct the hypersurface is given in the Figure Legend. These results show the greatest decrease in number of treatment-experienced individuals in

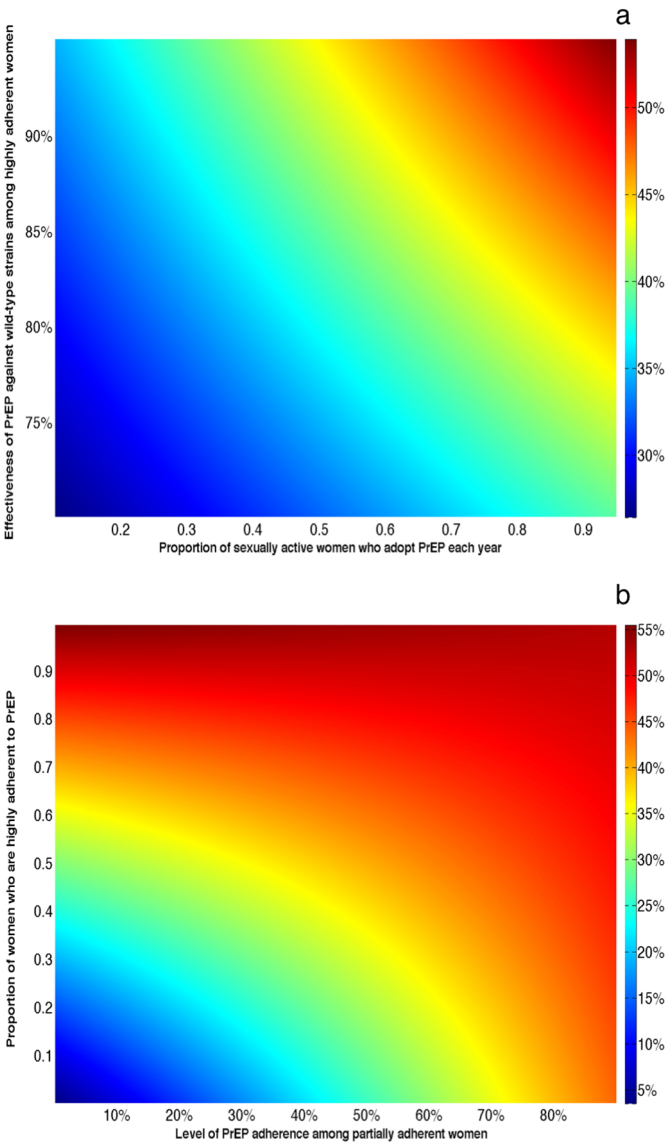

Figure 2 | Sensitivity analysis results, presented as response hypersurfaces, derived from the results, 10 years after the introduction of a Truvada-based PrEP intervention, of the uncertainty analysis. Color-coded response hypersurfaces show the percentage of infections prevented in women in Botswana (Z) as a function of: (a) the effectiveness of PrEP in protecting women who are highly adherent to PrEP against infection with wild-type strains of HIV (Y_1) and the proportion of sexually active women who adopt PrEP each year (X_1) ($Z = 0.24Y_1 + 0.32X_1 + 0.04Y_1X_1$), (b) the proportion of women on PrEP who are highly adherent (Y_2) and the level of PrEP adherence among women who are only partially adherent (X_2), ($Z = 0.62Y_2 + 0.41X_2 - 0.26Y_2X_2$).

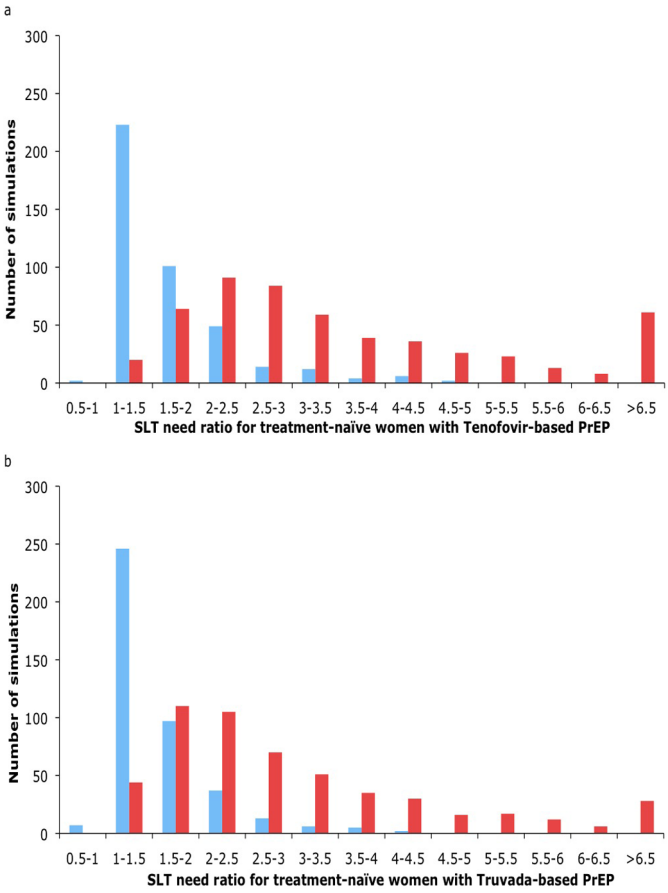

Figure 3 | Histogram of the number of simulations from the uncertainty analysis showing values for the ratio of need for second-line therapies (SLT) for treatment-naïve women when PrEP interventions are based on: (a) Tenofovir or (b) Truvada. Blue bars represent values when the level of adherence to PrEP is less than 40% among women with only moderate adherence; red bars represent values when the level of adherence to PrEP is between 40% and 89% among the women who are only moderately adherent.

need of SLT will occur if high "quality" PrEP interventions are rolled out around the "worst" treatment programs.

Notably, we find that there is no correlation between changing the need for SLT for treatment-naïve individuals and changing the need for treatment-experienced individuals (PCC = 0.20).

Discussion

In our comparison of TDF and Truvada-based PrEP we found both regimens would lead to an increase in the number of treatment-naïve individuals infected with resistant strains. Regardless of the level of adherence to the regimen, we found the increase would be greater if TDF-based PrEP was used than if Truvada-based PrEP was used. Our results indicate that Truvada-based PrEP would be a more optimal regimen. In addition, the specific mutations that arise will influence subsequent treatment and therefore need to be considered when choosing between regimens; K65R will be selected by TDF and M184V by Truvada. K65R may limit the utility of TDF in combination therapy for a newly infected individual. This may lead to greater use of alternative agents such as zidovudine with variable costs, toxicities and effectiveness. If K65R limits TDF effectiveness then the convenience of TDF co-formulated products may be lost and the use of more complex regimens with more pills or multiple daily administrations may be required; this might influence medication adherence. In addition, a widely spread K65R mutation would limit TDF as an effective agent for PrEP. M184V may have less subsequent clinical impact on the use of co-formulated pills for the treatment of infected individuals or for the need for alternative treatment regimens. Thus the implications of our modeling suggest that Truvada-based PrEP if well tolerated and affordable would be the more optimal regimen, as it would cause less clinical complexities than TDF-based PrEP.

In a previous modeling study, we (VS & SB) found that if PrEP is widely used in a "high-risk" community in San Francisco (i.e., in a resource-rich country) the number of treatment-naïve individuals infected with resistant strains is likely to decrease (if risk behavior does not increase). In contrast, in this study we have found that after the introduction of PrEP interventions in Botswana, the number of

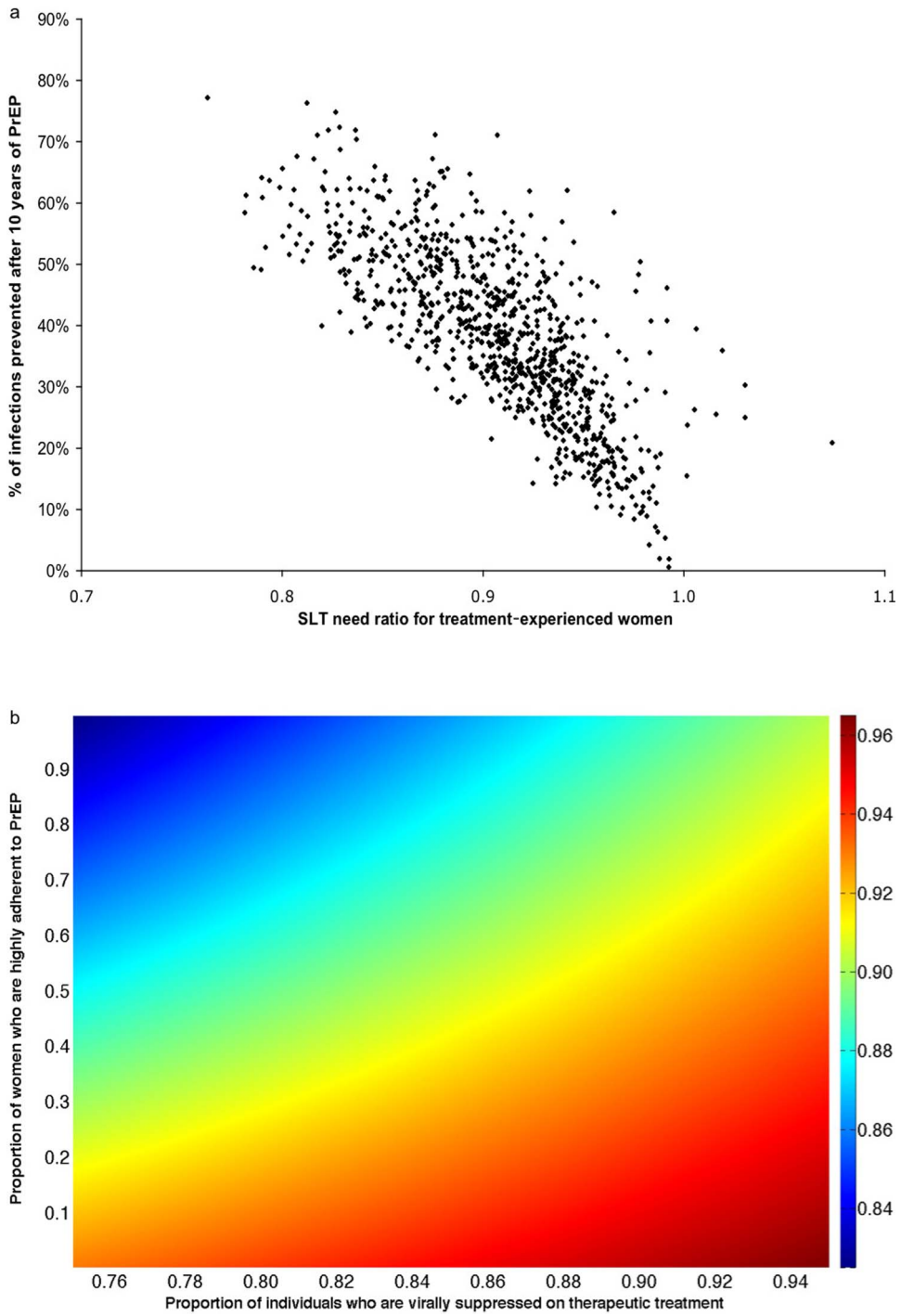

Figure 4 | Model predictions from the uncertainty analysis after ten years of Truvada-based PrEP. (a) Scatterplot of the percentage of infections prevented in women versus the ratio of need for second-line therapies (SLT) for treatment-experienced women. (b) Sensitivity analysis results, presented as response hypersurfaces, derived from the results of the uncertainty analysis. Color-coded response hypersurface shows the ratio of need for SLT for treatment-experienced women (Z) as a function of the proportion of women on PrEP who are highly adherent (Y_1) and the proportion of individuals who are virally suppressed on treatment (X_1); ($Z = -0.52\ Y_1 + 0.35\ X_1 + 0.08\ Y_1X_1$).

treatment-naïve individuals infected with resistant strains is likely to increase. This occurs because the level of ambient resistance is higher in San Francisco than in Botswana due to a longer treatment history. This comparison of results indicates that the impact of PrEP on transmitted resistance will be highly dependent on the number of years since treatment was first made available, as well as the current success of treatment programs. Consequently the impact of PrEP interventions on transmitted resistance may be beneficial in resource-rich countries, but detrimental in resource-constrained countries.

In this study, we have presented a novel mathematical model designed to predict the impact of PrEP interventions introduced into resource-constrained countries with generalized HIV epidemics and treatment programs already in place. We have parameterized our model using country-specific data in order to make predictions for the impact of PrEP interventions on transmission and resistance in Botswana. The response hypersurfaces that we have constructed can be used for policy and planning purposes by health officials in Botswana to predict the effect of TDF-based or Truvada-based

PrEP interventions on decreasing transmission for specified levels of effectiveness, adherence and coverage. Health officials can also use the model predictions to determine the number of SLT that will be needed by specific treatment programs. Our model can be reparameterized and used to make predictions for other countries in sub-Saharan Africa that have generalized HIV epidemics and treatment programs. Reparameterization of the model will enable country-specific response hypersurfaces to be constructed and for country-specific predictions to be made regarding changing needs for SLT. Therefore our model could be used as an important policy and planning tool in many resource-constrained countries. Although quantitative results will be country-specific, the qualitative insights we have gained regarding the impact of interactions between treatment programs and PrEP interventions will hold for other resource-constrained countries with generalized epidemics.

Our modeling shows it is essential to consider the dynamic interaction that will occur between treatment programs and PrEP interventions. The outcome of this interaction has significant implications for the success of PrEP interventions and the sustainability of treatment programs. We have found "high quality" PrEP interventions will substantially reduce the number of treatment-naïve individuals in need of first-line therapies and could also substantially reduce the number of treatment-experienced individuals in need of SLT. Hence "high quality" PrEP interventions are likely to reduce treatment costs which would contribute to the sustainability of treatment programs. However, if PrEP interventions are not "high quality" (for example, if - on average - individuals on PrEP only take between 40% and 89% of daily doses) the number of treatment-naïve individuals in need of SLT could significantly increase; even if individuals taking PrEP are frequently tested. Consequently poor "quality" PrEP interventions could reduce the success of current treatment programs. Our response hypersurface modeling shows PrEP interventions could prevent the same number of HIV infections whether behavior is very heterogeneous with respect to adherence (i.e., the majority of individuals are extremely adherent and the minority have very low adherence) or fairly homogeneous (i.e., all individuals are moderately adherent; none have extremely high, or low, adherence). These results indicate it will be difficult to assess the "quality" of PrEP interventions in terms of their effectiveness in reducing transmission by monitoring adherence.

Notably, our results indicate the most beneficial rollout strategy would be to begin introducing high "quality" PrEP interventions around poor "quality" treatment programs (i.e., programs with low success in viral suppression and high rates of acquired resistance). This rollout strategy would maximize the reduction in the number of treatment-experienced individuals in need of SLT. In summary our analysis shows that if the rollout of PrEP is carefully planned it could decrease the need for SLT and increase the sustainability of treatment programs. If it is not, the need for SLT could increase and the sustainability of treatment programs in resource-constrained countries could be compromised.

Methods

Before implementing PrEP interventions we modeled the rollout of HIV treatment based on empirical data of the numbers of patients that were treated each year in Botswana; we used empirical data beginning in 2002 when the roll-out began in Botswana[36,37]. After calibrating/validating our model we evaluated both TDF-based and Truvada-based PrEP interventions.

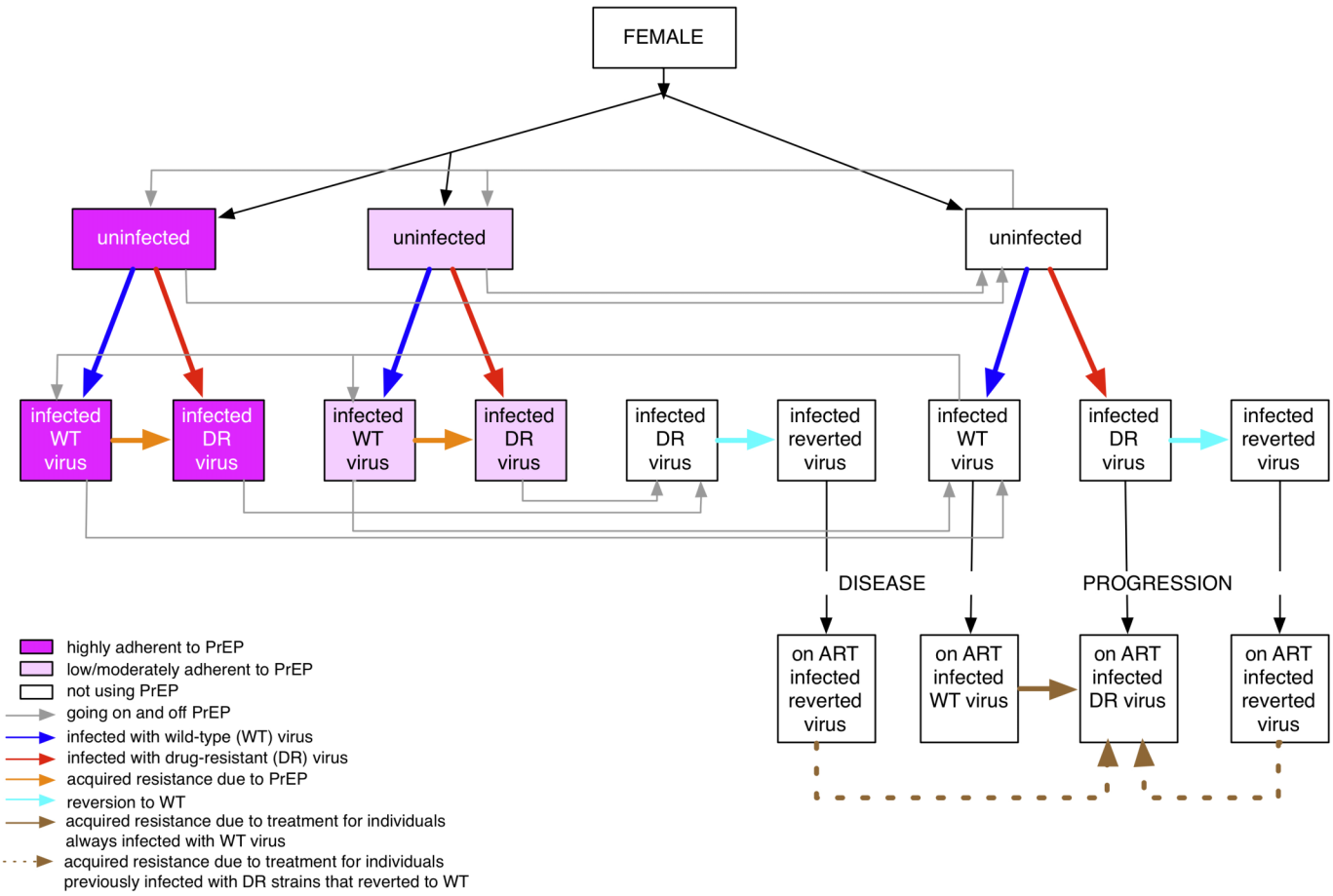

Figure 5 | Simplified flow diagram of the PrEP model for women. The model includes both current treatment programs and the implementation of potential PrEP interventions. A full description of the flow-diagram is given in the Methods section. The equations that specify the model are given in Section 1 of the Supplementary Material.

Mathematical Model. The model is described by 66 ordinary differential equations: 33 for women and 33 for men; equations are given in Section 1a in the SM. A simplified schema of the model is shown in Figure 5 for women; the corresponding schema for men is shown in Figure S1 in the SM. In Figure 5 women with high adherence to PrEP are represented by the dark purple rectangle and the two dark purple squares, women with low/moderate adherence to PrEP are represented by the light purple rectangle and the two light purple squares, and women not taking PrEP are represented by the white rectangle and white squares. The four rectangles represent uninfected women, and squares represent HIV-infected women. Uninfected women can go on or off PrEP, as shown by the grey arrows. We assume PrEP will reduce, but not eliminate, the risk of infection. Consequently, whether or not a woman is taking PrEP she can become infected with wild-type strains (shown by blue arrows) or resistant strains (shown by red arrows). HIV-infected women who are taking PrEP are at risk of developing resistance (shown by the orange arrows) until they either give up PrEP (shown by the grey arrows) or are retested when they try to renew their prescription, whichever occurs first. Resistant strains that are selected when on PrEP can revert to wild-type strains when off PrEP, reversion can also occur in individuals with transmitted resistance (shown by the turquoise arrows). These resistant strains remain as minority strains and can reemerge when the infected individual goes on treatment (shown by the brown arrow). The model also allows for the development of resistance in treated individuals infected with wild-type strains (shown by brown arrow). The model is described in greater technical detail in Section 1 of the SM.

Quantifying the need for Second-Line Therapies. To determine whether introducing PrEP could change the need for SLT we calculated a ratio: the number of individuals that would need SLT if PrEP was made available divided by the number of individuals that would need SLT if PrEP was not available. A ratio > 1 indicates the introduction of PrEP interventions would increase the number of individuals needing SLT and a ratio < 1 indicates that it would decrease the number of individuals needing SLT. The SLT need ratio was calculated both for TDF-based PrEP and Truvada-based PrEP; for each regimen the ratio was calculated separately for treatment-naïve individuals and treatment-experienced individuals. Treatment-naive individuals who need SLT are either individuals who were infected with resistant strains through transmission or individuals who acquired resistance when taking PrEP. Treatment-experienced individuals in need of SLT are individuals that acquired resistance during treatment with first-line regimens.

Parameterization. We parameterized our model using demographic and behavioral data from Botswana (Table S1 in the SM). We used data from the Demographic Health Survey conducted in Botswana[34,42]; in this survey they collected demographic and behavioral data in a two stage stratified sampling scheme and then weighted these data to ensure that the survey participants adequately represented the general population in Botswana. We also used data from Botswana to model their current treatment programs and treatment regimens in terms of viral suppression rates and rates of acquiring resistance on treatment; see Section 1h in the SM, parameter values are given in Table S2. The parameter values that we used to define the "quality" of PrEP interventions are given in Table S6 and Table S7.

In the model, all individuals who become infected with HIV pass through the following stages: (i) acute infection, (ii) infected but not yet eligible for treatment (i.e., CD4 count $>$ 200 cells/microL) and (iii) eligible for treatment (i.e., CD4 count $\leq$200 cells/microL). After passing through these three stages individuals can go on treatment; parameters specifying time spent in each stage is given in Table S3 in the SM. In the different stages of infection, and when on treatment, we assume different viral loads; see Table S4 in the SM. We use viral loads to calculate infectivity; see Section 1d and Table S5 in the SM. We assume that a reduced viral load translates into reduced infectiousness[43] and hence reduces the transmissibility of HIV[44–48].

We discuss our assumptions in modeling TDF-based and Truvada-based PrEP regimens with respect to M184V and K65R in Section 1g in the SM; regimen-specific parameter values are given in Table S7 in the SM.

Model Calibration/validation. Before modeling the interaction between treatment programs and PrEP interventions we calibrated/validated the model using Monte Carlo filtering and fitted the model to empirical data from Botswana; see Section 2 in the SM for details, and Table S9 and Figure S8. This procedure resulted in reducing an initial sample of 10,000 simulations, obtained through Latin Hypercube Sampling[49], to 937 simulations. We used these 937 simulations to conduct a series of uncertainty and sensitivity analyses[41,49].

Uncertainty Analyses. To conduct uncertainty and sensitivity analyses we treated all of the PrEP-related parameters in the model as experimental variables. Experimental variables were either PrEP program-level parameters (Table S6) or parameters that define the biological characteristics of PrEP regimens (Table S7). Together these parameters characterize the "quality" of a PrEP intervention. We also used parameters specifying the "quality" of treatment parameters as experimental variables. We modeled both TDF-based and Truvada-based PrEP interventions; differences between the two regimens are discussed in Section 1g and regimen-specific parameter values are given in Table S7.

We conducted three uncertainty analyses, each based on the 937 simulations obtained after calibrating the model to current epidemiological data from Botswana. In the first we modeled current treatment programs in Botswana without introducing PrEP interventions. In the second we modeled current treatment programs and TDF-based PrEP interventions. In the third we modeled current treatment programs and Truvada-based PrEP interventions. We used the results from these analyses to compare the epidemiological impact of TDF-based PrEP versus Truvada-based PrEP.

See Section 3 in the SM for further details of these uncertainty analyses.

Sensitivity analyses. We conducted two types of sensitivity analyses: one based on calculating PRCCs and the other based on calculating SRC and response hypersurface modeling[41]; see Section 3 in the SM for details of methods and a description of the differences between these two methods. Each type of sensitivity analysis enabled us to identify the model parameters that had the greatest influence on the predicted outcomes (i.e., the key parameters). Both analyses identified the same parameters as being important (see Table 2 and S10 in the SM). Once the key parameters had been identified, we constructed nonlinear response hypersurfaces based on linear and interaction terms; we calculated SRCs with their 95% confidence intervals as a measure of sensitivity (see Table S10 in the SM). Each response hypersurface shows the quantitative effect of two of the key parameters on the epidemiologic outcome variable of interest.

Since we wanted to assess the effects of PrEP interventions for both TDF-based and Truvada-based PrEP we conducted four sensitivity analyses: PRCCs for TDF-based PrEP, response hypersurface modeling for TDF-based PrEP, PRCCs for Truvada-based PrEP and response hypersurface modeling for Truvada-based PrEP.

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Author contributions

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Additional information

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