Journal of Infectious Diseases Advance Access published April 9, 2013

Antiretroviral Therapy and Pre-exposure Prophylaxis: Combined Impact on HIV-1 Transmission and Drug Resistance in South Africa

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ABSTRACT

Background: The potential impact of antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) with overlapping and non-overlapping antiretrovirals (ARVs) on HIV-1 transmission and drug resistance is unknown.

Methods: A detailed mathematical model was used to simulate the epidemiological impact of ART-alone, PrEP-alone, and combined ART+PrEP in South Africa.

Results: ART-alone initiated at CD4 < 200 cells/mm^3 (80% coverage and 96% effectiveness) prevents 20% of HIV-1 infections over 10 years but increases drug resistance prevalence to 6.6%. PrEP-alone (30% coverage and 75% effectiveness) also prevents 21% of infections but with lower resistance prevalence of 0.5%. The ratio of cumulative infections prevented to prevalent drug-resistant cases after 10 years is 7-fold higher for PrEP than for ART. Combined ART+PrEP with overlapping ARVs prevents 35% of infections but increases resistance prevalence to 8.2%, whereas ART+PrEP with non-overlapping ARVs prevents slightly more infections (37%) and reduces resistance prevalence to 7.2%.

Conclusions: Combined ART+PrEP is likely to prevent more HIV-1 infections than either strategy alone, but with higher prevalence of drug resistance. ART is predicted to contribute more to resistance than is PrEP. Optimizing both ART and PrEP effectiveness and delivery are the keys to preventing HIV-1 transmission and drug resistance.

INTRODUCTION

Oral antiretroviral (ARV) pre-exposure prophylaxis (PrEP) is a new biomedical intervention against HIV-1 transmission with proven efficacy [1-3]. There is concern, however, about the potential emergence and spread of HIV-1 drug resistance arising from rollout of PrEP, particularly in resource-constrained settings, where antiretroviral treatment (ART) options are limited [4]. This concern is amplified by the possibility that the same ARVs will be used for both ART and PrEP. The combination of two nucleoside reverse transcriptase inhibitors, tenofovir (TDF) and lamivudine or emtricitabine (3TC or FTC), with one non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz or nevirapine, is the WHO-recommended first-line ART regimen in several countries worldwide including South Africa [4], and TDF or TDF+FTC have shown efficacy in HIV-1 prevention trials [1-3]. Thus far, only nine drug-resistant cases have been observed among clinical trial participants on PrEP, most of whom had unrecognized acute infection at enrollment. However, clinical trials of PrEP are not designed to address the population-level and/or long-term epidemiological impact of PrEP including consequences of drug resistance. We therefore used a mathematical model [5] to examine the potential impact of orally administered overlapping and non-overlapping PrEP and ART on HIV-1 transmission and drug resistance in South Africa.

METHODS

Model Structure

We developed and analyzed a detailed mathematical model to assess the impact of PrEP and ART implementation on the adult population (15-49 year-olds) of South Africa, using deterministic and stochastic modeling techniques and the programming language C/C++. The

model describes population and epidemiological stratifications based on gender (male; female), sexual activity (high; medium; low; lowest), PrEP and ART use status (on; not-on), infection status (susceptible; infected), stage of HIV-1 infection (acute pre-seroconversion; acute post-seroconversion; early chronic; late chronic; AIDS), and HIV-1 drug susceptibility (drug-sensitive; drug-resistant). Model parameter assignments are made using recent results from PrEP trials [1-3, 6, 7] and data mainly from South/sub-Saharan Africa on HIV-1 disease progression [8], infectivity [9], sexual behavior [10], ART rollout [4, 11-18], and HIV-1 drug resistance [19-33]. The model is calibrated to simulate the HIV-1 epidemic in South Africa with adult HIV-1 prevalence (Figure S1) reaching 17% at the end of 2003, having female to male prevalence ratio of 1.6 and HIV-1 incidence near 2.4% [34]. Simplified model structure is shown in Figure S2 and model input parameters are shown in Tables 1, 2 and S1. Model equations and details are provided in the supplementary Text S1.

HIV-1 Drug Resistance

We stratify HIV-1-infected individuals based on their ARV status, HIV-1 drug susceptibility, type of drug resistance, and virus population dynamics of drug-resistant HIV-1 including persistence and reversion of resistance [35]. The model tracks individuals infected with different viral variants over time, either untreated, on PrEP, or on ART. We do not explicitly represent different drug-resistant mutants but assume the emergence and transmission of 184V with PrEP use [1, 2, 6]; and although several different mutations may arise with ART use (such as 103N, 106M, 181C, 184V, 65R), 184V is the most common. *Transmitted resistance* may occur from a donor either on PrEP, not-on PrEP, on ART, or not-on ART, having a majority population of drug-resistant virus, to a recipient either on or not-on PrEP. *Acquired resistance* may occur due to de-novo selection on PrEP or ART in persons with wild-type infection; re-

emerge from archived drug-resistant variants on PrEP or ART; or persist/accumulate on ART. Upon removal of drug pressure, either by discontinuation of ART or PrEP or transmission to a recipient not-on PrEP or ART, the drug-resistant virus may revert to drug-sensitive virus after a period of persistence. Prior to reversion, drug-resistant variants comprise the majority population, whereas following reversion they become a minority population [35].

ARV Interventions, Base-Case Scenarios and Model Analyses

We simulate three different rollout strategies for ARV-mediated HIV-1 prevention: ART-alone, PrEP-alone (a hypothetical illustration), and ART+PrEP; and compare the epidemiological outcomes with an ARV-naïve epidemic. For each strategy, we first construct and analyze a reference-case (base-case) scenario using a defined set of input parameters including estimates of the effectiveness of ART and PrEP for prevention of HIV-1 from the HPTN 052 [36] and the Partners PrEP Study [1], respectively; followed by uncertainty and sensitivity analyses [37].

Base-Case Analyses

ART Rollout and Effectiveness

In our model, individuals become treatment eligible at CD4 counts < 200 cells/mm^3[11]. Treatment scale-up starts at the end of 2003 [17] and the proportion of eligible persons on ART (i.e. coverage) reaches 55% by the end of 2009 [18] and 80% by the end of 2011[11]. Coverage is then maintained at 80% throughout the simulation [11]. To represent the current situation in South Africa, we simulate two additional scenarios of expanded ART rollout in which treatment eligibility threshold changes at the end of 2009 to include individuals with CD4 between 200 and 350 cells/mm^3 [4], reaching 66% coverage at CD4 < 350 cells/mm^3 threshold by the end of 2011 [15]; Coverage is then: i) maintained at the 66% level (termed status-quo coverage) or ii)

increased to reach 80% at the end of 2016 [12] and maintained thereafter (termed optimized coverage). We model only first-line ART with conservative coverage to focus on the interplay between first-line ART and PrEP, assuming that access to second-line regimens [38] and drug resistance testing [39] is limited. In base-case analyses we assume ART reduces HIV-1 transmission by 96% [36]. Our model represents virologic suppression and failure (with/without drug resistance), dropout, survival and HIV-1 transmission during the first and subsequent years of ART.

PrEP Rollout and Effectiveness

The effectiveness of PrEP against HIV-1 acquisition is a composite of efficacy and adherence [40]. The Partners PrEP Study showed the effectiveness of oral TDF+FTC PrEP to be 75% (95% CI 55 to 87); with 90% efficacy of PrEP in those with near-perfect adherence, and only 12% of subjects having less than 80% adherence [1].

We therefore stratify individuals into two groups based on their level of adherence to PrEP: high or low. For base-case analyses we assume that close to 90% of individuals have 95% adherence and about 10% have low (near-zero) adherence. However, given the conflicting results from different PrEP trials (TDF+FTC was ineffective in the Fem-PrEP trial [6] and oral TDF was ineffective in the VOICE trial [7]), for uncertainty and sensitivity analyses we use a wide range of input estimates for PrEP efficacy and adherence and the proportion of individuals in the two (high/low) adherence groups.

PrEP (TDF+FTC) scale-up starts in 2012 and achieves 30% coverage over a five-year period that is then maintained. We assume that PrEP is about 90% efficacious against wild-type

virus [1, 2] and that the average duration of PrEP use is five-years in susceptible individuals with HIV-1-testing every six months (and PrEP discontinuation if HIV-1 infection occurs). For the ART+PrEP strategy, in addition to our base-case scenario with overlapping drugs (i.e. cross-resistance) between PrEP (TDF+FTC) and ART (TDF+FTC+NNRTI), we simulate an alternate scenario with identical model input and structural assumptions except for there being no overlap/cross-resistance between ART and PrEP.

Uncertainty Analyses

We perform uncertainty analyses to estimate the extent of variation in our projections across a broad range of input parameter estimates that include the following assumptions (Tables 1-2): ART effectiveness is 73-99%; PrEP efficacy against wild-type virus is 70-99%; PrEP adherence among individuals highly adherent is 80-99% and among poorly adherent is 1-79% ; the proportion of individuals highly adherent is 10-90%; PrEP coverage is 15-45% ; average duration of PrEP use is 2.5-7.5 years; the frequency of HIV-1 testing under the PrEP program is 3-9 months; and the time by which about 100% of wild-type virus recipients acquire PrEP resistance from inappropriate PrEP use with perfect adherence is 3-9 months with the median time to acquired resistance of about 1 month [41]. We perform 50,000 simulations using Latin hypercube sampling (LHS) for each ARV-based strategy, and compute the epidemiological outcomes (median and interquartile range [IQR]) in comparison with an ARV-naïve baseline epidemic. We also calculate the outcomes for the overlapping and non-overlapping ART+PrEP strategies in comparison with ART-alone as baseline.

Sensitivity Analyses

We conduct sensitivity analyses to identify those parameters that exert the greatest influence on the predicted model outcomes for each strategy. For these time-dependent multivariate analyses, we use the input and output data from our uncertainty analyses to derive standardized regression coefficients (SRCs). In addition, we examine the sensitivity of model's predictions to the modeling technique by comparative analyses of our stochastic and deterministic model simulations.

Inappropriate PrEP Use

We simulate two contexts of inappropriate PrEP initiation and use by previously infected individuals by extending our PrEP-alone and ART+PrEP base-case scenarios. In the first, individuals in the pre-seroconversion phase of acute HIV-1 infection are started on PrEP ("window-use"). In the second, individuals with undiagnosed established HIV-1 infection start PrEP inappropriately at a rate of 2.5% per year ("general-use"). The duration of inappropriate PrEP-use following seroconversion is determined by the HIV-1 testing interval assumed for the PrEP program (6 months for base-case; LHS range: 3-9 months). For general-use, the duration is determined by the frequency of population surveillance (one year for base-case).

RESULTS

Prevention of HIV-1 Transmission

Base-Case Scenarios

Figure 1A shows the impact of different ARV-based strategies on HIV-1 prevention after 10 years compared with an ARV-naïve epidemic. ART-alone is projected to prevent 20% of HIV-1 infections (0.92 million). Similarly, PrEP-alone prevents 21% (0.96 million) of HIV-1 infections. The combined strategy of ART+PrEP is predicted to be most effective, reducing infections by 35% (>1.6 million) with overlapping regimens and 37% (> 1.7 million) with non-overlapping ARV regimens.

Expanded ART Rollout

The scenarios which expand treatment rollout to include coverage at CD4 < 350 cells/mm^3, result in modest increase in infections prevented when measured against the base-case scenarios of ART-alone and overlapping ART+PrEP (Figure 1B). Coverage at 66% (status-quo coverage) respectively prevents 23% and 38% infections while 80% coverage (optimized coverage) prevents 28% and 41% infections versus 20% and 35% for the base-case ART-alone and ART+PrEP scenarios.

Prediction Uncertainty of HIV-1 Prevention

Figure 2A shows the results of uncertainty analyses for the three ARV-based strategies. The median decrease in HIV-1 infections with ART-alone after 10 years is 15% (IQR: 12%-

19%), PrEP-alone is 14% (IQR: 10%-18%), overlapping ART+PrEP is 27% (IQR: 22%-31%) and non-overlapping PrEP is 28% (IQR: 23%-33%).

Overlapping ART+PrEP (Figure 2C) prevents a median of 12.7% (IQR: 9.1%-17.2%) more infections than ART-alone. Results are similar for non-overlapping ART+PrEP (median: 14%; IQR: 10-18.9%).

HIV-1 Drug Resistance

Base-Case Scenarios

Figure 3A shows the impact of different ARV-based strategies on HIV-1 drug resistance prevalence compared with an ARV-naïve epidemic. After 10 years of PrEP-alone, the prevalence of overall resistance is low at 0.5% (20,090 cases). Drug resistance prevalence is higher from the ART-alone strategy at 6.6% overall (307, 254 cases) with 4.2% acquired (195,758 cases) and 2.4% transmitted resistance (111,497 cases). The prevalence of resistance increases further from overlapping ART+PrEP to 8.2% (339, 895 cases) with the prevalence of acquired and transmitted ART resistance increasing to 4.6% and 3.3%, respectively. With non-overlapping ART+PrEP, drug resistance prevalence falls modestly to 7.2% due to a lower prevalence of transmitted ART resistance (2.2%). In terms of the number of prevalent cases of drug resistance (data not shown), acquired ART resistance falls modestly from both overlapping and non-overlapping ART+PrEP, when measured against ART-alone, however transmitted ART resistance rises with overlapping but falls with non-overlapping ART+PrEP. Both acquired and transmitted cases of PrEP resistance fall from ART+PrEP, when measured against PrEP-alone.

Expanded ART Rollout

The scenarios of expanded ART rollout result in modest increase in drug resistance prevalence when measured against the base-case scenarios of ART-alone and overlapping ART+PrEP strategies (Figure 3B). Drug resistance prevalence respectively increases to 8.3% and 10.1% in status-quo coverage scenarios and 11.4% and 13.4% in optimized coverage scenarios, versus 6.6% and 8.2% in the base-case scenarios of ART-alone and ART+PrEP.

Ratio of cumulative infections prevented to prevalent and incident drug resistant cases

To compare the resistance consequences of different ARV-based strategies we calculated ratios of cumulative infections prevented to resistance over 10 years, either defined as prevalent cases (prevailing cases with majority drug-resistant variants; Figure 4A) or incident (new cases of transmitted or acquired drug resistance; Figure 4B). PrEP-alone prevents about 48 infections for each prevalent drug resistant case and more than 5 infections for each incident drug resistant case. Inappropriate window-use in the PrEP-alone strategy decreases these ratios modestly to 46 and 4.8 respectively. By contrast, inappropriate general-use PrEP markedly reduces the ratios to 10 and 1, respectively. ART-alone prevents about 7 infections for each prevalent drug resistant case and about 1 infection for each incident drug resistant case, which is 6 to 7 fold lower than for PrEP. The prevention-resistance ratios for prevalent and incident cases are 9.8 and 1.4 for overlapping ART+PrEP and 14.7 and 1.7 for non-overlapping ART+PrEP.

Prediction Uncertainty of HIV-1 Drug Resistance

Figure 2B shows the results of uncertainty analyses for HIV-1 drug resistance outcomes from different ARV-based strategies. After 10 years, the median overall prevalence of drug resistance from ART-alone is 5.9% (IQR: 4.6%-7.4%), from PrEP-alone is 0.5% (IQR: 0.3%-

0.7%), from overlapping ART+PrEP is 7% (IQR: 5.6%-8.8%) and non-overlapping ART+PrEP is 6.5% (IQR: 5.2-8.1%). These finding are consistent with our base-case scenarios.

Overlapping ART+PrEP compared to ART-alone (Figure 2C), increases the number of prevalent overall and transmitted ART resistant cases after 10 years by a median 8.8% (IQR: 5.8%-13.1%) and 15.9% (IQR: 11.4%-21.9%), respectively, while modestly decreasing the number of acquired ART resistant cases (median: -0.9%; IQR: -1.8%-0%). Non-overlapping ART+PrEP decreases the overall drug resistance prevalence at 20 years (median: -4%; IQR: -7.5%-0.7%).

Inappropriate PrEP Use

Inappropriate PrEP use by persons infected at baseline increases HIV-1 drug resistance from PrEP. When measured against the overlapping ART+PrEP base-case, an overlapping ART+PrEP strategy that includes inappropriate window-use PrEP prevents almost the same number infections (1.63 million), with a modest increase (8.3% vs. 8.2%) in the prevalence of resistance (data not-shown). In contrast, overlapping ART+PrEP with inappropriate general-use PrEP leads to an increase in the overall resistance prevalence from 8.2% to over 10%, with acquired PrEP resistance rising to 1.3% from 0.2% and transmitted PrEP resistance to 0.4% from 0.1% (data not-shown). Non-overlapping ART+PrEP with inappropriate general-use PrEP raises the overall resistance prevalence to 8.5% (data not-shown).

Sensitivity Analyses

The results of sensitivity analyses are described in detail in Text S1 and summarized in Table 3.

DISCUSSION

The important insights derived from our study are several. First, an ART strategy of treatment initiation at CD4 < 200 cells/mm^3 combined with PrEP prevents more infections than either ART-alone or PrEP-alone; however, the incremental benefit of PrEP critically depends on PrEP efficacy, adherence and coverage. Second, the prevalence of HIV-1 drug resistance is largely driven by ART in both ART-alone and ART+PrEP strategies. Third, PrEP-alone results in low prevalence of drug resistance; high PrEP adherence leads to fewer infections and less opportunity for acquired resistance, while low adherence leads to predominantly wild-type breakthrough infections because of low drug pressure for emergence of acquired resistance. Fourth, use of overlapping ARVs for both ART and PrEP could increase drug resistance prevalence compared to ART-alone due to more frequent transmitted resistance. By contrast, resistance prevalence falls with non-overlapping ART+PrEP; however, this decrease is modest because the principal driver of resistance is ART, not PrEP. Fifth, inappropriate PrEP initiation among individuals with undetectable HIV-1 infection produces only a minor increase in the overall resistance prevalence; however, inappropriate PrEP use among persons with established HIV-1 infection could significantly increase drug resistance from PrEP. Lastly, PrEP prevents many more infections per case of resistance than ART does.

The extent of coverage and the degree of effectiveness against HIV-1 transmission are the principal determinants of the infections prevented with ART. Similarly, PrEP coverage and effectiveness against HIV-1 acquisition are the key determinants of the additional preventive benefit of ART+PrEP. The paradigm of test and treat [42] has gained considerable momentum,

and the HPTN 052 trial [36] has provided the needed proof of concept for ART-based prevention, though its population-level impact may be limited by potential reluctance of asymptomatic HIV-infected persons for ART initiation. Notwithstanding scale-up efforts, there is considerable unmet need for ART in resource-constrained settings; about 60% of those eligible did not have access to ART at the end of 2010 [43]. Moreover, the population-level effect of treatment as prevention could be limited by the actual proportion of infected individuals optimally and durably suppressed on ART. In 2010, of the 1.2 million infected persons in the US, 80% were aware of their status, but 41% were retained in care, and only 28% had virologic suppression [44]. The situation is much worse in sub-Saharan Africa, where about two-thirds of HIV-infected persons are unaware of their seropositive status [45]. In a systematic review [46], fewer than one-third of HIV-positive persons were retained in care between HIV-1 testing and ART initiation. Furthermore, studies show high rates of loss to follow-up among patients starting ART [16]. Thus, PrEP could play an important additional role in controlling the HIV-1 pandemic. Prioritized coverage with effective PrEP of individuals at highest risk of HIV-1 acquisition and spread could potentially yield the optimal public health and cost benefits [40].

ART rollout is also limited by infrequent [18] access to second-line regimens and CD4 cell count, rather than virological monitoring [4]. As a result, there are high levels of drug resistance mutations among individuals with prolonged virological failure [22, 32], which may compromise both first [29, 47] and the limited second-line [48] ART regimens available. Our model shows that ART drives the prevalence of HIV-1 drug resistance in both ART-alone and ART+PrEP strategies. The principal determinants of the prevalence of acquired resistance include ART coverage, survival on ART with acquired resistance and the rate of treatment failure. For the prevalence of transmitted resistance, determinants include the infectiousness of

persons with acquired ART resistance and the persistence time of transmitted resistance. We find that PrEP is about 6 to 7 fold more efficient in HIV-1 prevention than ART in terms of ratios of infections prevented to incident/prevalent drug-resistant cases generated. Thus, improving the effectiveness of first- and second-line ART is critical for preventing HIV-1 infection and controlling drug resistance.

Our model projects low prevalence of drug resistance from PrEP. Highly effective PrEP results in few breakthrough infections and chance for emergence of acquired resistance. By contrast, poorly effective PrEP fails to protect from acquisition of wild-type HIV-1 but also fails to exert selective pressure for emergence of acquired resistance. Both of these phenomena have been observed in recent PrEP trials [1, 2]. However, drug resistance from PrEP at the population-level could rise with inappropriate PrEP use among those with undiagnosed HIV-1 infection. While this increase is modest from inappropriate PrEP use during the pre-seroconversion phase of acute infection, it becomes more pronounced with inappropriate use among persons with established HIV-1. The latter may be of concern in potential situations of unsupervised PrEP use (e.g. black marketing and drug sharing [49]) or inaccurate HIV-1 testing [50].

There are some important limitations of our model. The accuracy of our predictions will be affected by variations in the model structure and sexual activity details, for which data are very limited. We therefore employed a well-established template of sexual behavior [40] with robust epidemiological and demographic parameterization, broadly applicable to South Africa. Nevertheless, the HIV-1 epidemic in South Africa is heterogeneous and incompletely understood; with significant differences between the demographic and HIV-1/AIDS epidemiological estimates predicted by different agencies. HIV-1 incidence is also not precisely known even when measured directly at the population level. Although there is uncertainty

regarding ARV-related parameters, we employed ranges (within plausible bounds) and performed extensive sensitivity and uncertainty analyses. We excluded population stratification by age and analysis of prioritized ARV implementation, as this was addressed in previous work [40]. Because of limited access to both second-line regimens [38] and drug-resistance testing [39] in resource-limited settings, we chose not to represent specific drug-resistance mutations or second- or third-line ART regimens, nor do we consider HIV-1 subtype polymorphism. We also did not explicitly include other influences on transmission. These and other refinements will be included in future work although including such parameters greatly increases model complexity.

A key conclusion of this study is that combined ART+ PrEP can have a greater public health impact than ART alone; however, overlapping ARVs for both can increase drug resistance in resource-limited settings. Drug resistance prevalence is predominantly driven by ART and not PrEP; consequently, non-overlapping strategies will produce only modest declines in resistance. Thus it is critical to consider the impact of ARVs not only on prevention but also drug resistance. Improved efficacy of first-line therapy and timely switching of ART to effective second-line regimens are critical for controlling HIV-1 drug resistance. In addition, frequent and accurate HIV-1 testing could minimize resistance consequences of PrEP. Our study also highlights that poor adherence to PrEP will undermine its potential impact on HIV-1 prevention. Thus, prioritization of PrEP to groups at most risk of HIV-1 acquisition and counseling about PrEP adherence are likely to maximize efficiency of PrEP and minimize drug resistance.

FIGURE LEGENDS

Figure 1 Panel A: Cumulative new HIV-1 infections prevented after 10 years (2012-2022) compared to a naïve epidemic assuming base-case scenarios. **Panel B:** Cumulative new HIV-1 infections prevented after 10 years (2012-2022) compared to naïve epidemic assuming scenarios with different treatment eligibility thresholds and levels of coverage.

Figure 2 Uncertainty Analyses: Results of 50,000 simulations are shown as columns representing the median values and bars representing the interquartile range. **Panel A:** Cumulative new HIV-1 infections prevented after 10 years (2012-2022), compared to a naïve epidemic. **Panel B:** Prevalence of drug resistance after 10 years (2012-2022). Panel C: Cumulative new HIV-1 infections prevented and prevalence of drug resistance from ART+PrEP after 10 years (2012-2022), compared to an epidemic with ART-alone.

Figure 3 Panel A: Prevalence of drug resistance after 10 years (2012-2022) assuming base-case scenarios. **Panel B:** Prevalence of drug resistance after 10 years (2012-2022) assuming scenarios with different treatment eligibility thresholds and levels of coverage. Columns of different colors represent the prevalence of overall drug resistance and acquired and transmitted drug resistance from ART and PrEP.

Figure 4 Panel A: The ratio of cumulative infections prevented to prevalent drug resistant cases (2012-2022). **Panel B:** The ratio of cumulative infections prevented to incident drug resistant cases (2012-2022). Window use refers to inappropriate PrEP initiation by persons in the pre-seroconversion phase of acute HIV-1. General use refers to inappropriate PrEP initiation by persons with established HIV-1 infection at a per capita rate of 2.5/year**.**

FUNDING
This work was supported by the Bill & Melinda Gates Foundation (OPP1005974)

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

FOOTNOTE

(1) Conflict of Interest:

Ume L. Abbas acknowledges grant support from the Bill and Melinda Gates Foundation (OPP1005974).

John W. Mellors is a member of the scientific advisory board of Gilead Sciences, has share options of RFS Pharmaceuticals, and acknowledges grant support from the AIDS Clinical Trials Group (NIAID U01AI38858), the Microbicide Trials Network (NIAIDU01AI068633), the National Cancer Institute (SAIC contract 20XS190A), and the Bill and Melinda Gates Foundation (OPP1005974).

Other authors do not report any conflict of interest.

(2) Sources of Financial Support:

Bill & Melinda Gates Foundation (OPP1005974)

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

(3) Presented in Part at:

18th Conference on Retroviruses and Opportunistic Infections. Boston, MA, February 27 - March 2, 2011 (Abstract # 98LB)

6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Rome, Italy from 17-20 July 2011 (Abstract # TUPE364)

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Table 1. Model ART-Related Input Parameters

PARAMETER	SYMBOL	BASE CASE	Uncertainty LHS* RANGE	UNIT	REFERENCE
ART Coverage					
Start of ART Rollout		2004			[17]
% of eligible individuals enrolled in ART at 2010		55%			[18]
% of eligible individuals enrolled in ART at 2012	Θ	80%	65%–95%		[11]
Coverage beyond 2012		80%	65%–95%	per year	
ART Dropout					
During the first year of ART	$1/\eta^H$	0.10	0.05–0.15	per year	[13, 16]
During subsequent years of ART	$1/\eta^T$	0.05	0.025–0.075	per year	[13, 16]
Infectivity relative to wild-type (WT) virus					
On suppressive ART		4%	1%–27%		[36]
With acquired ART resistance		75%	37.5%–100%		[19, 22, 25, 27]
With transmitted ART resistance		100%	50%–100%		[24, 27]
Disease Progression					
Mortality in first year of suppressive ART	ϖ^H	0.1	0.05–0.15	per year	[13, 14, 16]
Mortality in subsequent years of suppressive ART	ϖ^T	0.05	0.025–0.075	per year	[13, 14, 16]
Relative to WT disease progression with acquired majority ART resistance, on or off ART		75%	37.5%–100%		[19, 22, 25]
Relative to WT disease progression while non-adherent to ART		100%	100%		

Virilogic Failure

WT virus failure rate during first year of ART	$\hat{\Lambda}^{HW}$	20%	10%–30%	per year	[19, 30, 32]
WT virus failure rate during subsequent years of ART	$\hat{\Lambda}^{TW}$	5%	2.5%–7.5%	per year	[19, 30]
DR virus failure rate during first year of ART	$\hat{\Lambda}^{HV}$	50%	25%–75%	per year	[29]
DR virus failure rate during subsequent years of ART	$\hat{\Lambda}^{TV}$	15%	7.5%–22.5%	per year	[29]
% failing first year ART due to non-adherence (NA) (no acquired DR)	$\hat{\alpha}^{H}$	4%		per year	[32]
% failing in subsequent years of ART due to NA (no acquired DR)	$\hat{\alpha}^{T}$	2%		per year	[32]
Persistence time of transmitted ART resistance	ψ^{R1}	3	1.5 - 4.5	years	[23, 26, 33]
Persistence time of acquired ART resistance	ψ^{R2}	0.25	0.125–0.375	years	[20, 31]

* Latin Hypercube Sampling

Table 2. Model PrEP-Related Input Parameters

PARAMETER		BASE-CASE	Uncertainty LHS* RANGE	UNIT	REFERENCE
PrEP Program					
% of individuals enrolled into PrEP (coverage)	φ	30%	15%–45%		
% of inappropriate PrEP use among individuals with established infection	$\widetilde{\varphi}$	2.5%	-		
Initial year of PrEP deployment			2012		
Time to reach target coverage		5	2.5–7.5	years	
HIV testing frequency in the PrEP program	$1/\phi^P$	6	3–9	months	
HIV testing frequency in the general population	$1/\phi^{\widetilde{P}}$	1	-	years	
Average duration of PrEP use	$1/\sigma$	5	2.5–7.5	years	
Effects of PrEP					
Efficacy of PrEP for wild-type or reverted virus	ξ^W	90%	70%–99%		[1, 2]
Adherence when highly/poorly adherent	θ	95%/1%	80-99%/1-79%		[1]
Proportion highly/poorly adherent		88%/12%	10-90%/90-10%		[1]
Efficacy of PrEP against resistant virus	ξ^R, ξ^Q	0.25 ξ^W	0.125 ξ^W –0.375ξ^W		
Relative infectivity while on PrEP with wild-type or reverted virus		100%	50%–100%		[2]
Relative infectivity of acquired PrEP-resistant virus, on or off PrEP		75%	50%–100%		[2]
Relative infectivity of transmitted PrEP-resistant virus, on or off PrEP		100%	50%–100%		[2, 21, 27]
Time to acquisition of PrEP resistance with wild-type virus in an entire cohort	t_1	0.5	0.25–0.75	years	

Time to acquisition of PrEP resistance with reverted resistant virus in an entire cohort	t_2	$0.5t$	$0.25t_1$–$0.75t_1$	years	
Rate of PrEP resistance acquisition with wild-type virus	π^W	$-\ln(1-0.99\theta)/t_1$	$-\ln(1-0.99\theta)/t_1$	per year	
Rate of PrEP resistance acquisition with reverted resistant virus	π^{r1}, π^{a1}	$-\ln(1-0.99\theta)/t_2$	$-\ln(1-0.99\theta)/t_2$	per year	
Persistence time of transmitted PrEP resistance	ψ^{Q1}	2	1-3	years	[2, 26, 27, 33]
Persistence time of acquired PrEP resistance	ψ^{Q2}	0.125	0.0625-0.1875	years	[2]
Relative Disease Progression rates					
- while on PrEP with wild-type infection		100%	50%–100%		[2]
- with acquired resistance to PrEP, on or off PrEP		75%	50%–100%		[2]
- while on PrEP with transmitted or reverted resistant infection		100%	50%–100%		[2, 21, 27]
- with transmitted resistant virus and no ARV pressure		100%	50%–100%		[2, 21, 24, 27]

* Latin Hypercube Sampling

Table 3. Sensitivity Analysis of Outcomes with ARV strategies vs. Naïve Epidemic at 2022¶

Model input*	**Standardized Regression Coefficients (% variance explained)**		
	ART-alone	**PrEP-alone**	**ART+PrEP**
	Infections Prevented (%)		
Reduction in WT Infectivity on ART	0.70 (0.49)		0.47 (0.22)
ART Coverage	0.59 (0.35)		0.37 (0.14)
Relative Infectivity of virus with acquired ART resistance	-0.24 (0.06)		
PrEP Coverage		0.67 (0.45)	0.50 (0.25)
PrEP Proportion highly adherent		0.45 (0.20)	0.33 (0.11)
PrEP Adherence (low)		0.40 (0.16)	0.30 (0.09)
PrEP Efficacy against wild-type virus		0.29 (0.08)	
	Prevalence of Overall Drug Resistance (%)†		
Survival time on ART with acquired resistance	0.57 (0.32)		0.56 (0.31)
ART Coverage	0.46 (0.22)		0.44 (0.19)
WT Virologic failure rate during 1st yr on ART	0.36 (0.13)		0.34 (0.11)
WT Virologic failure rate during subsequent yrs on ART	0.31 (0.09)		0.30 (0.09)
% failing subsequent yrs on ART due to non-adherence	-0.25 (0.06)		-0.25 (0.06)

Persistence of transmitted ART resistance	0.23 (0.06)	0.25 (0.06)
PrEP Coverage	0.55 (0.30)	
Frequency of HIV Testing	-0.50 (0.25)	
PrEP Adherence (low)	0.30 (0.09)	
PrEP Efficacy against wild-type virus	-0.26 (0.07)	
Development time for acquired PrEP resistance	-0.25 (0.06)	
	Prevalence of Transmitted ART Resistance (%)	
Persistence of transmitted ART resistance	0.57 (0.32)	0.55 (0.30)
Relative Infectivity of virus with acquired ART resistance	0.45 (0.20)	0.46 (0.21)
Survival time on ART with acquired resistance	0.35 (0.12)	0.35 (0.12)
ART Coverage	0.30 (0.09)	0.29 (0.08)
WT Virologic failure rate during 1st yr on ART	0.25 (0.06)	0.24 (0.06)
	Prevalence of Acquired ART Resistance (%)	
Survival time on ART with acquired resistance	0.61 (0.38)	0.62 (0.39)
ART Coverage	0.49 (0.24)	0.49 (0.24)
WT Virologic failure rate during 1st yr on ART	0.37 (0.14)	0.35 (0.12)
WT Virologic failure rate during subsequent yrs on ART	0.32 (0.10)	0.32 (0.10)
% failing subsequent yrs on ART due to non-adherence	-0.26 (0.07)	-0.26 (0.07)
	Prevalence of Transmitted PrEP Resistance (%)	

PrEP Coverage	0.51 (0.26)	0.48 (0.23)
Persistence of transmitted PrEP resistance	0.39 (0.15)	0.39 (0.15)
Frequency of HIV Testing	-0.29 (0.09)	-0.30 (0.09)
PrEP Adherence (low)	0.29 (0.09)	0.28 (0.08)
Development time for acquired PrEP resistance	-0.24 (0.06)	-0.25 (0.06)
	Prevalence of Acquired PrEP Resistance (%)	
Frequency of HIV Testing	-0.56 (0.32)	-0.56 (0.31)
PrEP Coverage	0.52 (0.27)	0.50 (0.25)
PrEP Adherence (low)	0.28 (0.08)	0.27 (0.07)
PrEP Efficacy against wild-type virus	-0.28 (0.08)	-0.29 (0.08)
Development time for acquired PrEP resistance	-0.24 (0.06)	-0.24 (0.06)

¶The results of sensitivity analyses are described in the Text S1. Briefly, the principal determinants of infections prevented by PrEP-alone and/or ART+PrEP include PrEP coverage, reduction in wild-type viral infectivity by ART, the proportion of persons highly adherent to PrEP and the level of PrEP adherence. Drug resistance prevalence from ART-alone and ART+PrEP is most influenced by the duration of survival on ART with acquired ART resistance and the wild-type virologic failure rate during the first year of ART. PrEP coverage and the frequency of HIV-1 testing are the key determinants of drug resistance from PrEP.

*Parameters that contribute 5% or more of the variance in the model outcome are shown ($SRC^2 \geq 0.05$). The reported coefficients were significant with a p-value ≤ 0.05.§Of the total variance in the predicted outcome explained by the regression model. The respective R^2 values were: 0.93 (cumulative infections prevented); 0.94 (overall prevalence of resistance); 0.90 (prevalence of transmitted ART resistance); 0.95 (prevalence of acquired ART resistance); 0.79 (prevalence of transmitted PrEP resistance); and 0.81 (prevalence of acquired PrEP resistance); for ART+PrEP scenario. †Proportion of cases with drug-resistant infection in the infected population.