Cost-Effectiveness of PrEP in HIV/AIDS Control in Zambia: A Stochastic League Approach

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Background: Earlier antiretroviral therapy initiation and pre-exposure prophylaxis (PrEP) prevent HIV, although at a substantial cost. We use mathematical modeling to compare the cost-effectiveness and economic affordability of antiretroviral-based prevention strategies in rural Macha, Zambia.

Methods: We compare the epidemiological impact and cost-effectiveness over 40 years of a baseline scenario (treatment initiation at CD4 <350 cells/μL) with treatment initiation at CD4 <500 cells per microliter, and PrEP (prioritized to the most sexually active, or nonprioritized). A strategy is cost effective when the incremental cost-effectiveness ratio (ICER) is <$3480 (<3 times Zambian per capita GDP). Stochastic league tables then predict the optimal intervention per budget level.

Results: All scenarios will reduce the prevalence from 6.2% (interquartile range, 5.8%–6.6%) in 2014 to about 1% after 40 years. Compared with the baseline, 16% of infections will be averted with prioritized PrEP plus treatment at CD4 <350, 34% with treatment at CD4 <500, and 59% with nonprioritized PrEP plus treatment at CD4 <500. Only treating at CD4 <500 is cost effective: ICER of $62 ($46–$75). Nonprioritized PrEP plus treating at CD4 <500 is borderline cost effective: ICER of $5861 ($3959–$8483). Initiating treatment at CD4 <500 requires a budget increase from $20 million to $25 million over 40 years, with a 96.7% probability of being the optimal intervention. PrEP should only be considered when the budget exceeds $180 million.

Conclusions: Treatment initiation at CD4 <500 is a cost-effective HIV prevention approach that will require a modest increase in budget. Although adding PrEP will avert more infections, it is not economically feasible, as it requires a 10-fold increase in budget.

Key Words: treatment as prevention, pre-exposure prophylaxis, cost-effectiveness, stochastic league tables

(*J Acquir Immune Defic Syndr* 2014;66:221–228)

INTRODUCTION

In 2011, 2.5 million individuals became newly infected with HIV.[1] Every person who becomes infected will need costly lifelong treatment. The treatment of currently infected individuals is already very costly, so ways in which to prevent new infections are important to keep costs under control.

It has been shown that daily oral antiretroviral drugs can prevent sexual transmission of HIV-1 in two ways.[2,3] One strategy is to give daily pre-exposure prophylaxis (PrEP) with the antiretroviral drugs tenofovir and emtricitabine to uninfected individuals to prevent HIV infection. Daily PrEP efficacy has been shown to be as high as 44%–75% when adherence is high.[4–6] Some studies, however, failed to show an impact of PrEP, likely due to suboptimal adherence.[7] Another strategy is earlier initiation of antiretroviral treatment among individuals who are infected with HIV-1 as prevention. As compared with delayed antiretroviral treatment at a CD4 cell count of <250 cells per microliter, initiating antiretroviral treatment between CD4 350 and 550 cells per microliter led to a 96% reduction in HIV transmission from a patient to their uninfected partner.[3] Importantly, this approach of "treatment-as-prevention" also provides clinical benefits as patients starting treatment at higher CD4 counts have a reduced risk for opportunistic infections and death.[3,8,9] Based on these benefits of earlier antiretroviral therapy (ART) initiation, the WHO has now moved from recommending treatment at CD4 <350 cells per microliter to treating earlier in infection at CD4 <500 cells per microliter.[10] The resources needed to implement treatment at CD4 <500 cells per microliter, however, are substantial. In many resource-limited settings, not all HIV patients eligible for treatment under the former guidelines receive care due to late diagnosis of HIV infection and poor linkage to- and retention in- care.[11–13] Thus, the resources needed to fully implement treatment at the earlier immunologic threshold of CD4 <500 cells per microliter are substantial.

Received for publication March 11, 2014; accepted March 11, 2014.

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Supported by the AIDS Fonds Netherlands (2010-035) and partially funded by the European Union FP7 grants CHAIN (No. 223131) and DynaNets (No. 233847).

Presented in part at the 7th Netherlands Conference on HIV Pathogensis, Epidemiology, Prevention and Treatment, November 19, 2013, Amsterdam, the Netherlands, and will be presented at the 2014 Conference on Retroviruses and Opportunistic Infections, March 3–6, Boston, MA.

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

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Treatment as prevention has been estimated to eliminate the epidemic when all patients are diagnosed early in infection and placed immediately on treatment.[14,15] In practice, however, approximately 70% of patients in studies from Zambia are diagnosed with a CD4 count below 350 cells per microliter[16] and thus would not be able to initiate treatment early (CD4 350–550 cells/μL).[3] Even if individuals are diagnosed in time, there are still problems with linkage to- and retention in- pre-ART care, resulting in individuals not initiating treatment on time.[17] Although PrEP is less effective than treatment as prevention, PrEP can still play a role in preventing infections, particularly among high-risk individuals.[18]

Stochastic league tables (SLT) are an innovative approach to report on the cost-effectiveness of HIV/AIDS interventions in the context of uncertainty around the costs and effects estimates, and especially future funding. Previous cost-effectiveness analyses typically identify whether interventions are cost effective compared with some international threshold.[17,19] In this article, we improve on this approach by using SLT. First, we identify the optimal mix of interventions by reference to an explicit budget level, and thereby avoid the use of cost-effectiveness thresholds. Second, we move away from deterministic approaches to cost-effectiveness analyses that report uncertainty ranges around a mean—instead, we use a bootstrapping procedure in which we calculate the probability that an intervention is included in this optimal mix. Third, given the uncertainty about HIV funding, we determine the optimal mix of interventions for different budget levels. Given that international funding has stagnated or declined in recent years while the absolute number of HIV-infected individuals increases,[20] this type of analysis is essential as costs will have to be taken on by country health systems.

We aim to evaluate the epidemic impact and cost-effectiveness of PrEP and treatment as prevention, and their combinations in the context of a previously described mathematical model of the HIV epidemic in the rural setting of Macha, Zambia. We aim to introduce SLT to the HIV field and use it to assess what mix of interventions is most efficient at different budget levels.[17] We also report standard cost-effectiveness ratios to indicate the differences between the two scenarios.

METHODS

Setting and Population

Our model is based on the rural population of Macha, Zambia, and uses data from the HIV Clinic at Macha Mission Hospital in the Southern Province of Zambia.[17,21] The hospital serves as a district-level referral hospital for rural health centers within an 80 km radius, with approximately 90,000 persons who are aged 12 years and older in the Macha Mission Hospital catchment area as of 2011.[21] The antenatal prevalence between 2002[22] and 2009 was stable around 7.7%, and declined to below 5% in 2010 (local data). Since the start of the ART clinic in 2005, treatment is implemented according to WHO guidelines, initially at CD4 <200 cells per microliter and at CD4 <350 cells per microliter since 2010.

Mathematical Model

A previously described deterministic mathematical model was constructed and parameters were chosen to represent Macha.[17,23] Compared with the published model, the current model has now been adapted to incorporate population growth, updated HIV prevalence data from Macha, and treatment rollout in line with the treatment rollout experienced in Macha. Using Monte Carlo filtering techniques,[24] we accepted 539 of 85,000 simulations that were associated with an HIV prevalence of 7.7% (6.7%–8.7%) from 2002 until 2009 and a decreasing prevalence between 2009 and 2010 in accordance with Macha data (where a prevalence of <5% were observed for 2010 and 2011). The accepted simulations also had to have an adult population (aged 12 and older) of 90,000 (80,000–100,000) in 2007, and an extrapolated adult population of 96,000 (86,000–106,000) in 2012. After 40 years, the population is predicted to be 197,000 [interquartile range (IQR), 186,000–208,000]. The model calibration to the population and HIV prevalence is shown in **Supplemental Digital Content 1 and 2,** http://links.lww.com/QAI/A513, respectively.

Baseline Scenario

Our baseline scenario is the current practice in Macha, with an annual population HIV test rate of 10%–20%, which leads to approximately 50% of patients initiating ART with a CD4 <200 cells per microliter.[17] Therefore, not all individuals are diagnosed before their CD4 count reaches the treatment initiation threshold. After a positive HIV test, 70% of individuals are retained in care.[17] Treatment is then started at CD4 <350 cells per microliter. Patients who then initiate treatment have a reduced infectivity between 90% and 100%.[2,3,25] We assumed that all these variables remained constant over the 40-year period.

Intervention Scenarios

In this analysis, we evaluated the costs and effects associated with a change in treatment guidelines to initiate treatment at CD4 <500 cells per microliter (in line with the new WHO guidelines[10]). We also evaluated the costs and effects of two hypothetical PrEP scenarios. Both PrEP scenarios assumed that treatment would continue at CD4 <350 cells per microliter. We also evaluated both PrEP scenarios combined with a treatment initiation threshold of CD4 <500 cells per microliter. All interventions are implemented in 2014, scale up linearly over 1–2 years, and are implemented until 2054.

Nonprioritized Versus Prioritized PrEP Distribution

It is not known how PrEP will be implemented in daily practice. We therefore examined the impact of two hypothetical scenarios where PrEP is perfectly and imperfectly prioritized to represent both ends of the prioritization spectrum.[17] In the first hypothetical scenario, we examined the impact of perfect prioritization by assigning approximately half of the individuals in the two highest sexual activity groups, 5%–15% of the population, to receive PrEP. We

assigned PrEP to just half of the highest sexual activity groups, as identifying those groups completely would not be feasible. In the second hypothetical scenario where PrEP is imperfectly prioritized, PrEP is assigned to 40%–60% of the population at random. For these analyses, we assumed moderate population-level PrEP adherence, where effectiveness ranged from 20% to 60%.[6]

Early Treatment Initiation

For this scenario, the treatment initiation threshold is CD4 <500 cells per microliter. The test rate and retention in care remain the same as in the baseline scenario,[17] thus, individuals may still be diagnosed and initiate treatment late in infection. With these test and retention rates, there will still be approximately 20% of patients who are diagnosed with a CD4 cell count between 350 and 500 and therefore initiate treatment early in this scenario.

PrEP Combined With Early Treatment

For the combination scenarios, we looked at the impact of expanding the treatment initiation threshold to CD4 <500 cells per microliter combined with prioritized and nonprioritized PrEP, respectively.

Cost-Effectiveness Analysis

Standard cost-effectiveness analysis typically identifies a single cost-effectiveness ratio for an intervention (with an uncertainty range), which is then compared with a cost-effectiveness threshold. The World Health Organization suggests that interventions are cost effective if they cost less than three times the gross national income per capita (three times gross national income in Zambia is $3480)[26] per quality-adjusted life year (QALY) gained. Decisions are then made on the incremental cost-effectiveness ratio (ICER) where each scenario is compared with the next least-costly scenario.[27] The SLT method is preferable, however, as the analysis calculates the probability of selection of an intervention, and then calculates this probability for different budget levels. This probability reflects the likelihood that an intervention is the most economically attractive option. Using this method, no comparison of results to an arbitrary cost-effectiveness threshold is required, and thus could be more suitable tool for resource prioritization in diverse settings.

The construction of SLT requires four steps.[28] First, using Monte Carlo simulations, random draws are taken from estimated distributions of total costs and effects for all interventions, defined a priori. The distribution of effects is taken directly from the output of the 539 model simulations. To reflect uncertainty, costs are here assumed to be log-normally distributed,[29] with an SD of ±10% of the cost values collected in Macha to represent small potential variations in price. We defined uncertainty around 11 variables of quantities and prices (for a table of full ranges and distributions of costs and effects used, see **Supplemental Digital Content 3 and 4**, http://links.lww.com/QAI/A513). The covariance is assumed to be zero. The conclusions are not dependent on these assumptions. Random draws are then taken from these distributions for all interventions. We then determine the average cost of the baseline scenario to treat HIV and opportunistic infections in Macha. We estimate this based on current HIV treatment costs collected from Macha combined with the results from our mathematical model.

The second step is to determine the optimal mix of interventions for given levels of resource availability (at increments of $100,000 in this analysis) for mutually exclusive interventions.[28,30] The baseline intervention is then evaluated according to its average cost-effectiveness ratio (vs. doing nothing), while the cost-effectiveness of others in the mutually exclusive set is evaluated incremental to the baseline intervention.[28]

Third, this process is repeated 10,000 times to provide 10,000 estimates of the optimal mix of interventions.[28] *P* represents the number of times an intervention is included in the optimal mix, and *P*/10,000 is the probability that the intervention is included. Thus, *P* is the proportion of samples for which the intervention is estimated to be optimal based on the sample average and ICERs.[28]

Fourth, the procedure is repeated for varying levels of resource availability to reveal the "resource expansion path," showing the probability that each intervention will be included at different levels of resource availability (in increments of $100,000).[28] Decision makers can use this information to prioritize interventions should more resources become available for HIV prevention. The probability that a more expensive alternative will be included increases with resource availability.[28] We present results from the current budget up to a 12-fold increase of the current budget for illustrative purposes.

To evaluate the long-term effects of treatment and PrEP interventions, we conducted the analysis over a 40-year time horizon. Each scenario was run in our mathematical model. All model outputs used to populate the stochastic league analysis can be found in **Supplemental Digital Content 3**, http://links.lww.com/QAI/A513. Costs have been discounted appropriately to implement interventions beginning in 2014, and discounted at an annual rate of 3% thereafter (a table of cost used for this analysis can be found in **Supplemental Digital Content 4**, http://links.lww.com/QAI/A513). QALY estimates were then multiplied by the number of people in each disease state at each time point and were discounted at an annual rate of 3% to get a total number of QALYs expected in the population over the 40-year time period (a table of QALY estimates can be found in **Supplemental Digital Content 5**, http://links.lww.com/QAI/A513).[27,31] SLT were generated with MCLeague Software (Version 1.1.1, World Health Organization, Geneva, Switzerland).

RESULTS

Impact of Baseline Scenario, Treating at CD4 <350 Cells per Microliter

Treating patients at a CD4 <350 cells per microliter alone is predicted to strongly reduce the epidemic over the coming 40 years and is predicted to reduce prevalence from 6.2% (IQR, 5.8%–6.6%) in 2014, down to 1.3% (IQR, 0.9%–1.9%) in 2054 (Fig. 1). In line with prevalence reduction, incidence is predicted to decline from 5 per 1000 susceptible

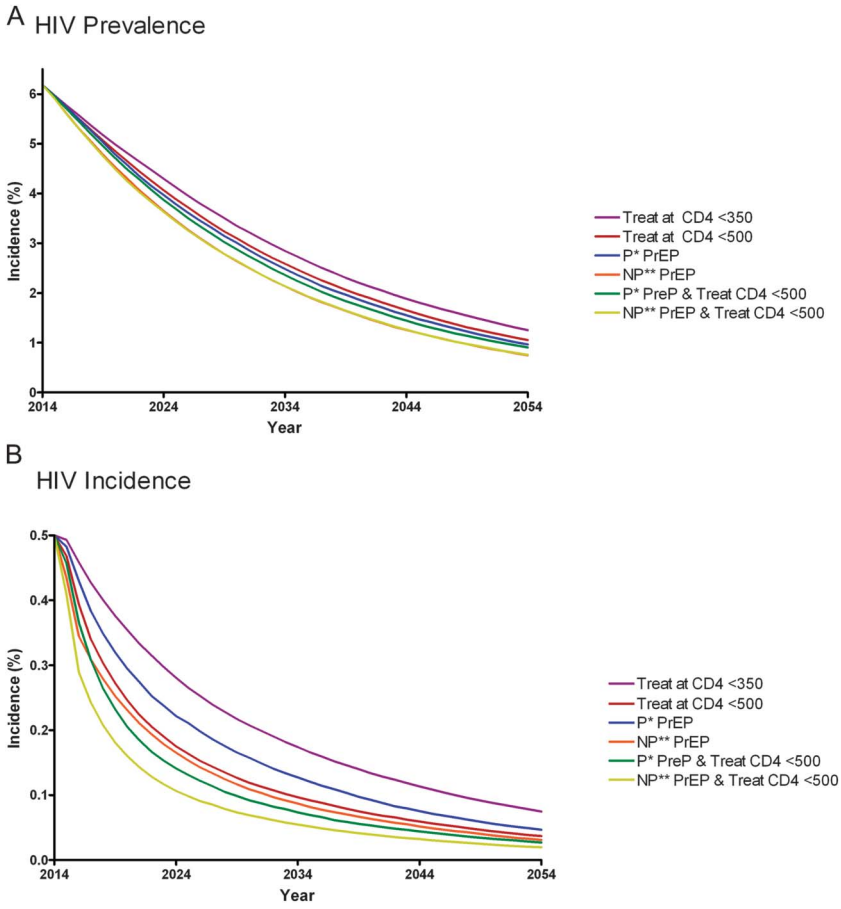

FIGURE 1. HIV prevalence (A) and incidence (B) over 40 years in Macha, Zambia. P*, prioritized PrEP to half of the most sexually active adult population; NP**, nonprioritized PrEP: PrEP to half of the adult population.

individuals (IQR, 4–5.9 per 1000 individuals) in 2014 down to 0.7 per 1000 individuals (IQR, 0.4–1.4 per 1000 susceptible individuals) after 40 years (Fig. 1).

Impact of Interventions

All interventions were predicted to reduce incidence even further as compared with the baseline scenario of treating at CD4 <350 cells per microliter. The hypothetical prioritized PrEP scenario, where PrEP is prioritized to half of the most sexually active had the smallest impact on new HIV infections of all interventions evaluated, averting 16% (IQR, 7.8%–28.0%) over 40 years, compared with treating at CD4 <350 cells per microliter alone (Fig. 2). The intervention with the greatest impact on new HIV infections was the hypothetical nonprioritized PrEP (giving PrEP to half of susceptible individuals) in combination with treatment initiation at CD4 <500 cells per microliter, averting 59% of new infections (IQR, 52.7%–65.2%) over 40 years compared with treating at CD4 <350 cells per microliter.

Standard Cost-Effectiveness Analysis

In the standard cost-effectiveness analysis, the only intervention that is cost effective is initiating treatment in those with a CD4 <500 cells per microliter at $62 per QALY gained (IQR, $46–$75) after 40 years (Table 1). There was 1 strategy, nonprioritized PrEP and initiating treatment at CD4 <500 cells per microliter, that straddled the standard cost-effectiveness threshold. The median ICER of this scenario is $5861 (IQR, $3959–$8483), which by definition is not cost effective. However, 20.0% of simulations were considered cost-effective by the standard threshold with an ICER of <$3480 per QALY gained.

Stochastic League Tables

We predict that it will cost on average $20,000,000 to treat HIV and opportunistic infections over the coming 40 years in Macha if treatment is continued at CD4 <350 cells per microliter. Therefore, this is also the most likely economically attractive prevention scenario for the $20,000,000 budget. This scenario had a 52.0% probability of being included in the optimum mix of interventions. Initiating treatment at CD4 <500 cells per microliter had a probability of being included of just 7.0%. In the remaining cases (41.0% of all random draws), costs of each possible option overrun the available resources and no intervention can be funded fully. This explains why the probabilities do not add up to 100% at low budget levels (Fig. 3).

For a $25,000,000 budget (25% increase in budget), changing the treatment initiation threshold to CD4 <500 cells per microliter is the best intervention to support, with a 96.7% probability of being included in the optimum mix of interventions. Keeping the treatment initiation threshold

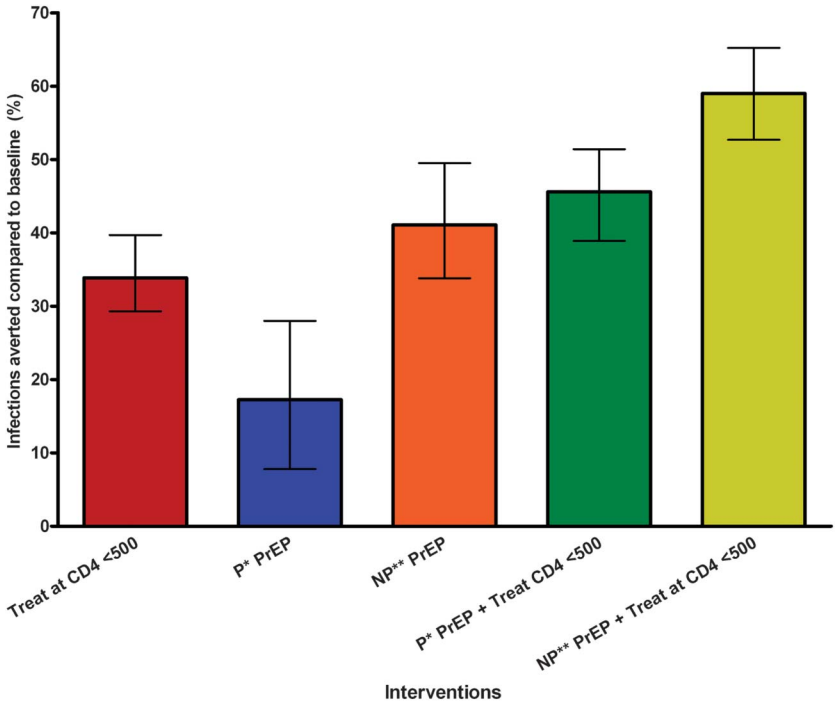

FIGURE 2. Cumulative median percentage of infections averted (and IQR) after 40 years of implementation by intervention, compared with the baseline of treating at CD4 <350 cells per microliter. P*, prioritized PrEP to half of the most sexually active adult population; NP**, nonprioritized PrEP: PrEP to half of the adult population.

at CD4 <350 cells per microliter has a 3.3% probability of inclusion in the optimum mix of interventions. For budgets between $25 and $80 million (25%–400% increase in budget), the probability of including treatment at CD4 <500 cells per microliter in the optimum mix of interventions is nearly 100%.

Only at much higher budget levels, greater than $110,000,000 (>550% increase in budget), is PrEP worth the economic investment. At a budget of $110,000,000 over 40 years, the most likely optimal HIV prevention mix includes prioritized PrEP in addition to initiating treatment at CD4 <500 cells per microliter, with a probability of inclusion of 59.6%. The probability of inclusion of treatment at CD4 <500 cells per microliter alone at this budget level is still 40.4%. At a budget of $200,000,000 (1000% increase in budget), the most likely optimal mix transitions to include nonprioritized PrEP in addition to initiating treatment at CD4 <500 cells per microliter, with a probability of being the optimal mix of interventions of 51.5%. At this budget level, the probability of including prioritized PrEP and treatment at CD4 <500 cells per microliter is also high at 45.8%.

Prioritized PrEP would never be included as an optimal prevention strategy without simultaneously treating individuals with CD4 <500 cells per microliter, as the probability of including prioritized PrEP in the absence of treating at CD4 <500 cells per microliter optimal mix is 0 at all budget levels. The probability of including nonprioritized PrEP in the absence of expanded HIV eligibility criteria is very low (0.1%–1.7%), at 40-year budgets between $130 and $260 million.

DISCUSSION

We predict that the optimal mix of HIV interventions for small budget increases (>$3,000,000 over 40 years, or a 15% increase in budget) is to change the treatment initiation threshold to CD4 <500 cells per microliter. Our analysis shows that PrEP should not be considered without also expanding the treatment eligibility criteria, as scenarios with PrEP in the absence of expanded treatment were never included in the optimal mix of interventions at any budget level. The PrEP scenarios that do include expanded HIV eligibility criteria of CD4 <500 cells per microliter should not be considered, however, unless the 40-year budget for HIV care and prevention in the setting is at least $110,000,000, or greater than a 550% increase in budget.

In our standard cost-effectiveness analysis, we found that nonprioritized PrEP in addition to changing the treatment initiation threshold to CD4 <500 cells per microliter was considered cost-effective in 20% of simulations. It is important to note that the budget level in which this combination is included in the optimal mix of interventions is $200,000,000, or 10-times the cost of treating at CD4 <350 cells per microliter alone. Thus, although nonprioritized PrEP and initiating treatment at CD4 <500 cells per microliter had borderline cost-effectiveness by standard cost-effectiveness analyses, the total cost to implement it would make it infeasible. This indicates the importance of explicitly referring to budget levels in economic analyses of health interventions.

Similar to previous modeling studies,[32,33] we found that PrEP and earlier ART initiation thresholds both reduce incidence. In line with these studies, we predicted that the combination of PrEP and ART reduces incidence even further.[32,33] Many studies have recently looked into the cost-effectiveness of oral daily PrEP in generalized epidemics,[34–38] and approximately half have found that PrEP can be cost effective.[35–37] Of the two studies that found PrEP is not cost effective, one assumed that individuals on PrEP would increase their

TABLE 1. Cost-Effectiveness of Treatment at CD4 <500 Cells per Microliter, PrEP Interventions, and Combinations Thereof Over 40 Years

Intervention	Total Cost in $ Millions (IQR)	Infections Averted (IQR)	QALYs Gained (IQR)	Average Cost-Effectiveness Ratio (IQR)	Incremental Cost-Effectiveness Ratio (IQR)	Conclusions
Treatment available at CD4 <350 cells/μL, standard care, no PrEP	19.7 (17.5–22.0)	—	—	—	—	—
Treatment available at CD4 <500 cells/μL	22.0 (19.8–24.5)	3388 (2179–5329)	40,643 (29,353–53,676)	$62 ($46–$75)	$62 ($46–$75)	Very cost effective
Prioritized PrEP to most sexually active	75.9 (50.7–113.1)	1502 (740–2775)	13,611 (7032–24,305)	$4103 ($2890–$5803)	Dominated*	Dominated*
Prioritized PrEP to most sexually active and treatment available at CD4 <500 cells/μL	78.9 (53.8–117.6)	4494 (3003–6935)	50,936 (38,117–67,270)	$1153 ($686–$1756)	Weakly dominated†	Weakly dominated†
Nonprioritized PrEP, PrEP randomly distributed	170.1 (159.1–182.4)	4053 (2480–6708)	40,318 (26,512–61,199)	$3730 ($2454–$5691)	Dominated*	Dominated*
Nonprioritized PrEP, PrEP randomly distributed and treatment available at CD4 <500 cells/μL	173.6 (161.9–185.8)	5894 (3832–8876)	67,835 (48,809–89,899)	$2253 ($1672–$3188)	$5861 ($3959–$8483)	Not cost-effective

*Less effective and more costly than the next least-expensive scenario.
†ICER is higher than the next most effective program.

number of partners,[34] and the other assumed changes in condom use.[38] These reasons are thought to be key drivers of those two cost-effectiveness results.[39] Other than the differences in changes of risk behavior, the differences in cost-effectiveness depended largely on the assumptions regarding PrEP adherence, coverage, and prioritization strategy.[39] In our study, we assumed low-to-moderate PrEP adherence, as modeled by a 20%–60% efficacy, we predicted that PrEP-only scenarios were not cost effective. Given our assumption about relatively low efficacy, our PrEP-only scenarios fall in line with models by other groups.

Pretorius et al[38] used a population-based model to predict the cost-effectiveness of PrEP compared with and in combination with increasing treatment. This model examines PrEP in the context of ART scale-up in the context of the South African epidemic. They have predicted that PrEP and "universal access to testing and treatment" would have a similar impact on incidence after 10 years, and the combination of the two would have the strongest impact. They have also predicted, however, that universal access to testing and treatment was cost effective, while PrEP would need to cost more than five times less than treatment to be more cost effective than universal access to testing and treatment. Our model has shown similar results and has the added value of putting the cost-effectiveness in the context of a budget.

Because of tightening budgets worldwide, ways in which to maximize HIV prevention in an affordable way are crucial. In addition, studies evaluating the impact and cost-effectiveness on HIV prevention of PrEP in the context of expanding ART guidelines are needed. The SLT approach allows decision makers to see how to maximize effectiveness with potential budget increases and put PrEP and treatment as prevention in

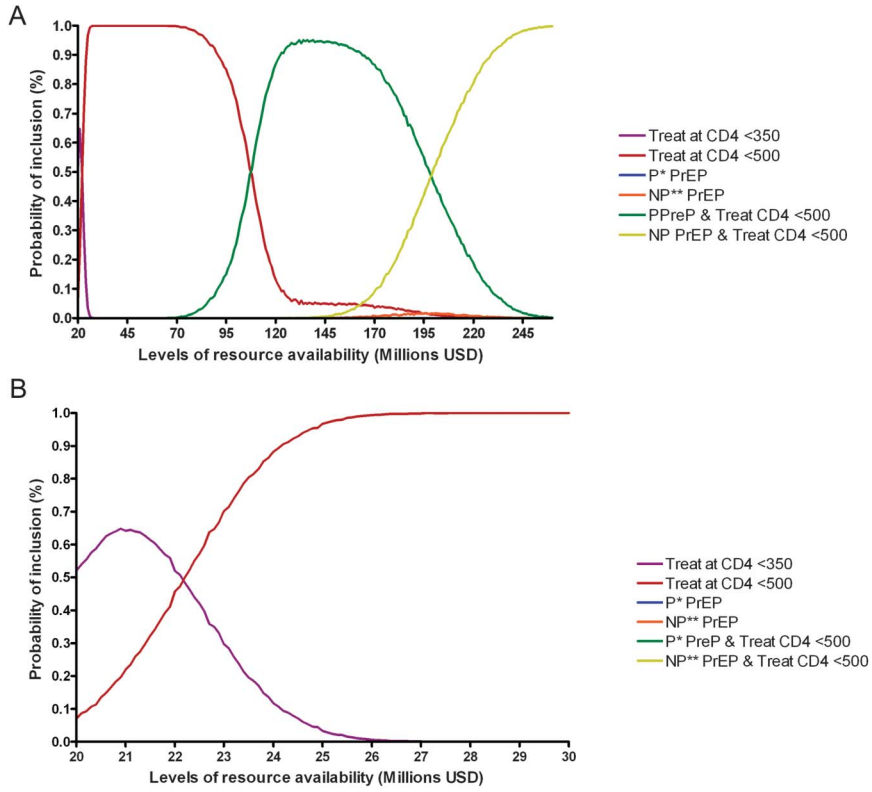

FIGURE 3. Stochastic league curves for 6 HIV prevention interventions: probability of inclusion (%) in the optimum package of HIV prevention techniques, by 40-year available budget (B zoomed in version of A). P*, prioritized PrEP to half of the most sexually active adult population; NP**, non-prioritized PrEP: PrEP to half of the adult population.

the context of budget constraints. This approach also enables us to simultaneously take into account uncertainty regarding costs, quantities, and effects, leading to comprehensive results. Another strength of our study is access to cost and epidemiologic data from Macha, Zambia, enabling us to make reliable predictions about the potential impact of expanded HIV eligibility criteria and PrEP implementation.

This study has some potential limitations. First, we have estimated what the cost of treating HIV and HIV-related conditions would be over 40 years based on current costs, although the true long-term costs are unknown. If the actual budget is lower than our calculation, it may be difficult to consider implementing any intervention other than treating at CD4 <350 cells per microliter, and it could be difficult to fully implement that treatment guideline. If the actual budget is higher, then other interventions may be more effective at comparatively lower budget increases. Second, we have not taken into account the health system capacity or the programmatic costs associated with implementing an intervention. Although there may be a budget to implement PrEP, there may not be the personnel available to implement the intervention. Third, programmatic costs could be substantial. We have left this out as it would depend on the specific plan of action chosen by decision makers for each intervention and would add further uncertainty into the model. Fourth, we have chosen the baseline scenario to initiate treatment at CD4 <350 cells per microliter. We do this as although the new WHO guidelines recommend initiating treatment between CD4 350 and 500 cells per microliter, the guidelines first recommend prioritizing to individuals with CD4 <350 cells per microliter.[10] Finally, more laboratory monitoring, such as regular viral load monitoring or resistance testing, could be implemented instead of or in addition to expanding the treatment eligibility criteria, but we have not incorporated different patient monitoring techniques into this analysis.[40] In the future, the stochastic league approach can be used to aid resource allocation decisions both between and within the realms of patient monitoring and HIV prevention. Our results should also be confirmed across settings in other validated mathematical models to allow for broader generalizability.

In conclusion, expanding treatment to treat those with CD4 <500 cells per microliter is the optimal strategy for reducing the HIV epidemic with modest budget increases in a generalized epidemic. If PrEP is being used, it should only be implemented in combination with increased access to antiretroviral treatment. Although strategies involving PrEP can be considered cost effective using standard cost-effectiveness analyses, it is important to consider if a budget exists to implement PrEP, at what scale, and whether or not those funds could be more effective if allocated elsewhere.

REFERENCES

1. UNAIDS. *World AIDS Day Report 2012*. Geneva, Switzerland: UNAIDS; 2012.
2. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet*. 2010;375:2092–2098.
3. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med*. 2011;365:493–505.
4. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367:399–410.

5. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med.* 2012;367:423–434.
6. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med.* 2010; 363:2587–2599.
7. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med.* 2012;367:411–422.
8. Thompson MA, Aberg JA, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. *JAMA*. 2010;304:321–333.
9. Johnson LF, Mossong J, Dorrington RE, et al. Life expectancies of South African adults starting antiretroviral treatment: collaborative analysis of cohort studies. *PLoS Med*. 2013;10:e1001418.
10. WHO. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: Recommendations for a Public Health Approach*. Geneva, Switzerland: World Health Organization; 2013.
11. UNAIDS. *Global Report: UNAIDS Report on the Global AIDS Epidemic 2013*. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS (UNAIDS); 2013.
12. Rosen S, Fox MP. Retention HIV care between testing treatment Sub-Saharan Africa: a systematic review. *PLoS Med*. 2011;8:e1001056.
13. Kranzer K, Govindasamy D, Ford N, et al. Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review. *J Int AIDS Soc.* 2012;15:17383.
14. Granich RM, Gilks CF, Dye C, et al. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009;373:48–57.
15. Eaton JW, Johnson LF, Salomon JA, et al. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Med*. 2012;9:e1001245.
16. Topp SM, Li MS, Chipukuma JM, et al. Does provider-initiated counselling and testing (PITC) strengthen early diagnosis and treatment initiation? Results from an analysis of an urban cohort of HIV-positive patients in Lusaka, Zambia. *J Int AIDS Soc.* 2012;15:17352.
17. Nichols BE, Boucher CA, van Dijk JH, et al. Cost-effectiveness preexposure prophylaxis (PrEP) preventing HIV-1 infections rural Zambia: a model study. *PloS One*. 2013;8:e59549.
18. Murnane PM, Celum C, Mugo N, et al. Efficacy of pre-exposure prophylaxis for HIV-1 prevention among high risk heterosexuals: subgroup analyses from the Partners PrEP Study. *AIDS*. 2013;27(13):2155–2160.
19. *CHOosing Interventions that are Cost Effective (WHO-CHOICE)*. Geneva, Switzerland: World Health Organization; 2011. Available at: http://www.who.int/choice/costs/en/. Accessed December 1, 2011.
20. PEPFAR. *Fiscal year 2011: PEPFAR operational plan*. Washington, DC: PEPFAR; 2011.
21. van Dijk JH, Sutcliffe CG, Munsanje B, et al. Barriers to the care of HIV-infected children in rural Zambia: a cross-sectional analysis. *BMC Infect Dis.* 2009;9:169.
22. UNAIDS/WHO. *Epidemiological Fact Sheet on HIV and AIDS. Core Data on Epidemiology and Response. Zambia*. Geneva, Switzerland: UNAIDS; 2008.
23. van de Vijver DA, Nichols BE, Abbas UL, et al. Preexposure prophylaxis will have a limited impact on HIV-1 drug resistance in sub-Saharan Africa: a comparison of mathematical models. *AIDS*. 2013;27(18):2942–2951.
24. Rose KA, Smith EP, Gardner RH, et al. Parameter sensitivities, Monte Carlo Filtering, and model forecasting under uncertainty. *J Forecast.* 1991;10:117–133.
25. Reynolds SJ, Makumbi F, Nakigozi G, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. *AIDS*. 2011;25:473–477.
26. The World Bank. *Zambia: World Development Indicators*. Washington, DC: The World Bank; 2013. Available at: http://data.worldbank.org/country/zambia. Accessed May 2, 2013.
27. Drummond MF. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. Oxford, New York: Oxford University Press; 2005.
28. Hutubessy RC, Baltussen RM, Evans DB, et al. Stochastic league tables: communicating cost-effectiveness results to decision-makers. *Health Econ.* 2001;10:473–477.
29. Lord J, Asante MA. Estimating uncertainty ranges for costs by the bootstrap procedure combined with probabilistic sensitivity analysis. *Health Econ.* 1999;8:323–333.
30. Murray CJ, Evans DB, Acharya A, et al. Development of WHO guidelines on generalized cost-effectiveness analysis. *Health Econ.* 2000;9: 235–251.
31. Rudmik L, Drummond M. Health economic evaluation: important principles and methodology. *Laryngoscope*. 2013;123(6):1341–1347.
32. Cremin I, Alsallaq R, Dybul M, et al. The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis. *AIDS*. 2013;27:447–458.
33. Abbas UL, Glaubius R, Mubayi A, et al: Combined impact on HIV-1 transmission and drug resistance in South Africa. *J Infect Dis*. 2013;208 (2):224–234.
34. Abbas UL, Anderson RM, Mellors JW. Potential impact of antiretroviral chemoprophylaxis on HIV-1 transmission in resource-limited settings. *PLos One*. 2007;2:e875.
35. Walensky RP, Park JE, Wood R, et al. The cost-effectiveness of preexposure prophylaxis for HIV infection in South African women. *Clin Infect Dis.* 2012;54:1504–1513.
36. Williams BG, Abdool Karim SS, Karim QA, et al. Epidemiological impact of tenofovir gel on the HIV epidemic in South Africa. *J Acquir Immune Defic Syndr*. 2011;58:207–210.
37. Hallett TB, Baeten JM, Heffron R, et al. Optimal uses antiretrovirals prevention HIV-1 serodiscordant heterosexual couples South Africa: a modelling study. *PLoS Med.* 2011;8:e1001123.
38. Pretorius C, Stover J, Bollinger L, et al. Evaluating the cost-effectiveness of pre-exposure prophylaxis (PrEP) and its impact on HIV-1 transmission in South Africa. *PLos One*. 2010;5:e13646.
39. Gomez GB, Borquez A, Case KK, et al. The cost and impact of scaling up pre-exposure prophylaxis for HIV prevention: a systematic review of cost-effectiveness modelling studies. *PLoS Med.* 2013;10:e1001401.
40. Nichols BE, Sigaloff KC, Kityo C, et al. Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: a modeling study. *AIDS*. 2014;28(1):73–83.