The Cost-effectiveness of Pre-Exposure Prophylaxis for HIV Infection in South African Women

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Methods. We linked data from recent trials to a computer model of HIV acquisition, screening, and care to project lifetime HIV risk, life expectancy (LE), costs, and cost-effectiveness, using 2 PrEP-related strategies among heterosexual South African women: (1) women receiving no PrEP and (2) women not receiving PrEP (a tenofovir-based vaginal microbicide). We used a South African clinical cohort and published data to estimate population demographic characteristics, age-adjusted incidence of HIV infection, and HIV natural history and treatment parameters. Baseline PrEP efficacy (percentage reduction in HIV transmission) was 39% at a monthly cost of $5 per woman. Alternative parameter values were examined in sensitivity analyses.

Results. Among South African women, PrEP reduced mean lifetime HIV risk from 40% to 27% and increased population discounted (undiscounted) LE from 22.51 (41.66) to 23.48 (44.48) years. Lifetime costs of care increased from $7280 to $9890 per woman, resulting in an incremental cost-effectiveness ratio of $2700/year of life saved, and may, under optimistic assumptions, achieve cost savings. Under baseline HIV infection incidence assumptions, PrEP was not cost saving, even assuming an efficacy >60% and a cost <$1. At an HIV infection incidence of 9.1%/year, PrEP achieved cost savings at efficacies ≥50%.

Conclusions. PrEP in South African women is very cost-effective by South African standards, conferring excellent value under virtually all plausible data scenarios. Although optimistic assumptions would be required to achieve cost savings, these represent important benchmarks for future PrEP study design.

Studies suggest that pre-exposure prophylaxis (PrEP) for human immunodeficiency (HIV) infection could make an important contribution to changing the trajectory of the HIV epidemic. Over the past 2 years, 4 trials—CAPRISA 004, Pre-Exposure Prophylaxis Initiative (iPrEx), CDC Botswana (TDF2), and Partners PrEP—demonstrated the efficacy of tenofovir-based PrEP for HIV infection, using alternative methods of PrEP delivery in different populations [1–4]. Reported HIV protective efficacy ranged from 39% (CAPRISA 004, vaginal gel) [1] to 44% (iPrEx, oral), [2] 63% (TDF2, oral) [3], and 73% (Partners PrEP, oral) [4] with effectiveness estimates ranging as high as 72%–97% among the most adherent patients. Populations studied include heterosexual women, men who have sex with
men, and heterosexual serodiscordant couples. More recently, PrEP studies have led to cause for more-measured enthusiasm. Both the phase-III FEM-PrEP trial of oral chemoprophylaxis in women and the oral tenofovir-only arm of the VOICE trial failed to demonstrate protective effects and were terminated early [5–7]. One possible explanation for differences in oral versus vaginal efficacy is that vaginal concentration of orally administered drug may be very sensitive to levels of adherence [8]. However, optimism was again tempered with the termination of the vaginal gel arm of the VOICE trial when interim results demonstrated no efficacy, compared with placebo [9]. Though the gel-related VOICE results conflict with those seen in CAPRISA, differences in dosing regimens may be a contributing factor, and data from the South African FACTS 001 trial, duplicating the CAPRISA dosing, are anxiously anticipated [10].

Because of the complexity of the evidence base, with different trials demonstrating different degrees of efficacy in different populations using different dosing regimens, we sought to provide threshold benchmarks to practitioners and funders in resource-limited settings when considering PrEP (either vaginal or oral) as a potential intervention in a population of South African women at high risk of infection. To do so, we also considered many critical implementation parameters not evaluable in the trials, such as the long-term impact of PrEP on transmission and costs, and how these parameters are influenced by target population risk, behavioral changes, acquired viral resistance, and toxicity.

METHODS

Analytic Overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)–International model [11–14], a mathematical simulation of HIV screening and disease, to project clinical, epidemiologic, and economic outcomes associated with tenofovir-based PrEP gel in heterosexual women in South Africa. We simulated a cohort of HIV-uninfected South African women under 2 strategies: (1) No PrEP, which included HIV screening every 5 years, and (2) PrEP, which included tenofovir-based, pericoitally delivered, vaginal gel, with monthly HIV screening. Under both strategies, patients identified as HIV-infected received the current South African HIV treatment standard of care [15, 16]. Although CAPRISA 004 provided estimates for base case PrEP efficacy and program costs, sensitivity analyses were intentionally conducted to encompass the spectrum of costs and efficacies from all the reported successful orally and vaginally dosed PrEP trials [1–4]. CAPRISA 004 trial–based estimates were first applied to baseline South African incidence values; we then used sensitivity analyses to widely vary incidence, HIV screening frequency, PrEP efficacy, acquired nucleoside reverse-transcriptase resistance, and costs. Model-based outcomes included projected lifetime HIV infection risk, life expectancy, costs, and incremental cost-effectiveness.

We measured cost-effectiveness in 2010 US dollars per year of life saved (YLS), reporting economic outcomes from a modified societal perspective (excluding patient time and travel costs), using a 3% annual discount rate [17]. We applied the recommendations of the World Health Organization (WHO) Commission on Macroeconomics and Health to denote strategies with incremental cost-effectiveness ratios less than the per capita gross domestic product (GDP; $7200 for South Africa) as very cost-effective and ratios <3 times the per capita GDP as cost-effective ($21 600) [18–20].

Model Overview

The CEPAC-International Model is a state-transition, Monte Carlo simulation of HIV acquisition, detection, and clinical care [11–14]. Model users define cohort attributes (eg, mean age, sex, CD4 cell count, HIV RNA distributions, and other demographic and/or clinical characteristics) and therapeutic alternatives (eg, number, sequencing, and efficacy of antiretroviral [ART] regimens). Two components of the model were used: the PrEP Module, which incorporates the mechanics of PrEP administration and monitoring, the incidence of HIV infection in the initially uninfected cohort, and the components of HIV screening; and the Disease Model, which includes details of those who become HIV infected, including the natural history, clinical management, and costs of HIV disease.

PrEP Module

The PrEP Module captures the attributes of a PrEP program, including target population characteristics (eg, age and sex distributions and HIV infection incidence) and intervention characteristics (eg, efficacy, behavioral changes, HIV screening frequency, and toxicity) [11–14]. In the No PrEP strategy, population- and age-based incidence rates determined the risk of HIV infection. In the PrEP strategy, the background HIV infection incidence was attenuated by the efficacy of the PrEP intervention (39% in the base case), defined as a reduction in primary HIV infection incidence. To remain conservative, we assumed that after initiation, PrEP was continued until HIV infection or death and examined this assumption in sensitivity analyses. For persons receiving PrEP, a defined proportion of the cohort experienced PrEP-related adverse events (eg, tenofovir-related nephrotoxicity) [21–23].

Infection was detected using an HIV test, either through current testing availability (No PrEP: mean, every 5 years) [14] or through the increased screening frequency accompanying the PrEP program. HIV screening (and other laboratory monitoring) in the PrEP program were in concordance with the study protocols of CAPRISA 004 and other trials; HIV-uninfected women receiving PrEP were followed up with monthly HIV tests.
and had biannual chemistry panels performed [1]. Although we adhered strictly to the trial protocols for purposes of modeling the study, we understand that monthly testing is neither practical nor feasible in a country-wide PrEP program. We considered HIV testing at alternative frequencies, as seldom as biannually, to examine this assumption in sensitivity analyses. We assumed a point-of-care rapid HIV test, with 99.6% sensitivity and 98.0% specificity, without the ability to detect primary HIV infection during the window period [24]. After HIV detection, PrEP was discontinued and treatment was provided according to details in the Disease Model. To produce conservative cost-effectiveness estimates, we assumed that PrEP continued lifelong; we relaxed this assumption in sensitivity analyses and examined the impact of stopping PrEP at different ages.

**Disease Model**

Details of the CEPAC-International model have been reported previously [11–14]. In brief, when women in the simulation acquired HIV infection, they transitioned to the Disease Model and progressed with the natural history of HIV infection. They were only eligible for HIV-related monitoring, care, and therapy after HIV detection. Their clinical course was represented by monthly transitions between health states, defined by CD4 cell count, HIV RNA level, and history of opportunistic infection. In the model, HIV RNA level determined the rate of monthly CD4 cell count decrease, whereas absolute CD4 cell count determined the probability of opportunistic infection and chronic HIV-related mortality [25, 26]. In accordance with current standards of care, patients who received a diagnosis of HIV infection attended biannual clinic visits for CD4 cell count assessment [15, 16, 27].

When laboratory and clinical monitoring revealed that criteria for ART initiation were met (CD4 cell count, <200 cells/µL; WHO stage IV disease; or CD4 cell count <350 cells/µL with tuberculosis), women received up to 2 sequential ART regimens (Table 1). During the first year of ART, patients were monitored biannually for CD4 cell count and HIV RNA level and yearly thereafter [15, 16, 27]. When ART resulted in HIV RNA suppression, CD4 cell count increased with a concomitant reduction in the risk of opportunistic infection and death [25, 30–33]. The Disease Model captures the impact of PrEP-associated resistance by allowing a user-defined proportion of the population who received PrEP (but became infected regardless) to have a decreased probability of virologic suppression during first-line ART. Patients with virologic suppression were also at monthly risk for treatment failure, resulting in virologic rebound and CD4 cell count decrease [30–33]. ART failure was defined as a 1-log increase in HIV RNA level, as observed by standard laboratory monitoring [15, 16]. Detection of failure of a first-line regimen resulted in an immediate switch to the second-line regimen, which the patient received until death [15, 16, 27].

The clinical trajectory of each person’s condition was tracked from entry into the simulation until death, regardless of HIV status. Multiple individual simulations were then aggregated to achieve stable estimates of survival and costs.

**Model Input Data**

**Demographic Parameters**

Data on the demographic and clinical characteristics of the simulated cohort were derived from South African studies [1, 28, 40–42]. The target population was South African women (mean age, 23.9 years) [1]. The incidence of HIV infection was age adjusted for the female South African population. In the base case, for women aged <25 years, annual incidence was 2.2% (Table 1) [28].

**PrEP Input Parameters**

In the base case, we used the trial-based PrEP efficacy estimate of 39% [1]. Although trials have not demonstrated significant PrEP-related toxicity, we conservatively assumed that PrEP recipients have toxicity at a frequency of 0.02% per month (derived from the CAPRISA trial upper confidence limit) [1], with a resultant risk of death of 1 in 10 000. Similarly, the trials provided little evidence of later ART resistance in those who experienced PrEP failure [1, 2, 43]. We remain >1000-fold in excess of the upper confidence limit and assumed in the base case that 5% of the PrEP-receiving cohort became infected with ART-resistant virus; we further assumed that those infected with resistant virus have a resultant 10% absolute decrease in the rate of virologic suppression of the first-line ART regimen.

**Costs**

Costs of vaginal gel were estimated by multiplying the reported $0.32/dose (applicator and gel) by the recommended 2 doses per sex act (once before and once after sex) by 7.2 acts (the mean number of acts per woman per month). Thus, the mean PrEP gel and applicator cost was $5 per woman per month [35]. Because this cost estimate accounts for all reported sex acts, it is higher than the gel costs from CAPRISA 004 ($0.32/dose [44] × 6 applicators returned per month [1] = $1.92/month) and is likely to be a higher estimate than costs that may materialize for a widely available vaginal gel (approximately $0.32/dose) [45]. In the context of a PrEP program, monthly HIV tests and biannual chemistry panels added annual costs of $70 and $63 [46, 47]. Total yearly PrEP program-related costs (the cost of PrEP, HIV tests, and chemistry panels) were approximately $188. Annual ART costs were $105–504 [35]. Direct medical care costs for HIV care (clinic visits, inpatient days, and monitoring tests) were derived using health care utilization and unit costs from the Cape Town AIDS Cohort (Table 1) [37, 39].

**Sensitivity Analyses**

We examined the impact of assuming a wide range of values for many individual parameters, including but not limited to annual incidence of HIV infection, PrEP efficacy, frequency of HIV
Table 1. Model Inputs for Select Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base Case Value</th>
<th>Range in Sensitivity Analysis</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline cohort characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean years (SD)</td>
<td>23.9 (3)</td>
<td>17.9–29.9</td>
<td>[1]</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual HIV infection incidence by age, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25 years</td>
<td>2.2</td>
<td>1.1–44</td>
<td>[28]</td>
</tr>
<tr>
<td>≥26 years</td>
<td>1.0</td>
<td>0.5–20</td>
<td>[28]</td>
</tr>
<tr>
<td><strong>PrEP characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PrEP efficacy, a %</td>
<td>39</td>
<td>10–90</td>
<td>[1]</td>
</tr>
<tr>
<td>PrEP toxicity, b %/month</td>
<td>0.02</td>
<td>0.01–2</td>
<td></td>
</tr>
<tr>
<td>Probability of PrEP resistance among those infected on PrEP</td>
<td>0.05</td>
<td>0.05–1.0</td>
<td>Assumption</td>
</tr>
<tr>
<td><strong>HIV test characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average background HIV test frequency</td>
<td></td>
<td>Every 5 years</td>
<td>[14]</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>99.6</td>
<td></td>
<td>[24]</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>98.0</td>
<td>98–100</td>
<td>[24]</td>
</tr>
<tr>
<td>Initial CD4 cell count, mean cells/µL (SD)</td>
<td>664 (294)</td>
<td></td>
<td>[25]</td>
</tr>
<tr>
<td>HIV RNA distribution after acute infection, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;100 000 copies/mL</td>
<td>42</td>
<td></td>
<td>[29]</td>
</tr>
<tr>
<td>30 001–100 000 copies/mL</td>
<td>28</td>
<td></td>
<td>[29]</td>
</tr>
<tr>
<td>10 001–30 000 copies/mL</td>
<td>18</td>
<td></td>
<td>[29]</td>
</tr>
<tr>
<td>3001–10 000 copies/mL</td>
<td>8</td>
<td></td>
<td>[29]</td>
</tr>
<tr>
<td>501–3000 copies/mL</td>
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<td></td>
<td>[29]</td>
</tr>
<tr>
<td>21–500 copies/mL</td>
<td>1</td>
<td></td>
<td>[29]</td>
</tr>
<tr>
<td><strong>Efficacy of antiretroviral therapy, first- and second-line regimens</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA suppressed at 6 months, %</td>
<td>74.7</td>
<td>10% decrease for 0–100% of cohort</td>
<td>[30]</td>
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<tr>
<td>ART failure rate after 6 months, %/month</td>
<td>1.59</td>
<td></td>
<td>[31, 32]</td>
</tr>
<tr>
<td>CD4 increase at 6 months, mean cells/µL</td>
<td>148</td>
<td></td>
<td>[33]</td>
</tr>
<tr>
<td>Discount rate, %/year</td>
<td>3</td>
<td>1–5</td>
<td>[34]</td>
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<tr>
<td><strong>Costs, 2010 US$</strong></td>
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<td></td>
<td></td>
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<tr>
<td>PrEP program costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir-based PrEP, monthly (annual)</td>
<td>5 (55)</td>
<td>2.31–23.05</td>
<td>[35]</td>
</tr>
<tr>
<td>HIV test, c per test (annual)</td>
<td>6 (70)</td>
<td>2.33–4.67</td>
<td>[35]</td>
</tr>
<tr>
<td>Chemistry panel, d per test (annual)</td>
<td>32 (63)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiretroviral therapy, annual</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF/3TC/EFV</td>
<td>169</td>
<td></td>
<td>[35]</td>
</tr>
<tr>
<td>d4T/3TC/EFV</td>
<td>105</td>
<td>120–200</td>
<td>[35]</td>
</tr>
<tr>
<td>AZT/3TC/LPV/r</td>
<td>504</td>
<td></td>
<td>[35]</td>
</tr>
<tr>
<td>Minor drug toxicity</td>
<td>14</td>
<td></td>
<td>[36]</td>
</tr>
<tr>
<td>Major drug toxicity</td>
<td>1948</td>
<td></td>
<td>[36]</td>
</tr>
<tr>
<td>Cotrimoxazole prophylaxis, monthly</td>
<td>1</td>
<td></td>
<td>[35]</td>
</tr>
<tr>
<td>Minor drug toxicity</td>
<td>14</td>
<td></td>
<td>[25, 37, 38]</td>
</tr>
<tr>
<td>Major drug toxicity</td>
<td>1948</td>
<td></td>
<td>[25, 37, 38]</td>
</tr>
<tr>
<td>CD4 test, per test</td>
<td>12</td>
<td></td>
<td>[38]</td>
</tr>
<tr>
<td>HIV RNA test, per test</td>
<td>62</td>
<td></td>
<td>[38]</td>
</tr>
<tr>
<td>Routine care, monthly (ranges by CD4 cell count)</td>
<td>55–782</td>
<td></td>
<td>[25, 37, 39]</td>
</tr>
<tr>
<td>Inpatient hospital care, per day</td>
<td>278</td>
<td></td>
<td>[37]</td>
</tr>
<tr>
<td>Outpatient hospital care, per visit</td>
<td>14</td>
<td></td>
<td>[37]</td>
</tr>
</tbody>
</table>

Abbreviations: AZT, zidovudine; d4T, stavudine; EFV, efavirenz; HIV, human immunodeficiency virus; LPV/r, ritonavir-boosted lopinavir; PrEP, pre-exposure prophylaxis; SD, standard deviation; TDF, tenofovir; 3TC, lamivudine.

a PrEP efficacy is defined as a percentage reduction in the monthly incidence of HIV infection.
b Derived from the estimated upper confidence limit in the CAPRISA 004 trial.
c The cost of the HIV test assumes a rapid test with pretest counseling. Reactive tests are confirmed with a second rapid test, with a cost of $2.
d The cost of the chemistry panel assumes the costs of urea, creatinine, bilirubin, aspartate aminotransferase, and alanine aminotransferase testing, as well as the costs of reagents, staff salary, equipment, overhead, and facilities.
testing, age, age-based discontinuation of PrEP, and costs. We simulated the important interplay between behavioral risk, adherence, and costs in the model with use of multiway sensitivity analyses on the annual incidence (reflecting risk), PrEP efficacy (reflecting potency and adherence), and costs (reflecting adherence, programmatic differences, and drug pricing). We also varied the probability of fatal toxicity, the proportion of the cohort with PrEP-related resistance, and its associated decrement in virologic suppression. The most influential parameters were then simultaneously varied.

RESULTS

Base Case
In a South African female population, with mean age of 23.9 years and an annual incidence of HIV infection of 2.2% for persons ≥25 years (annual incidence of 1% for persons ≥26 years), lifetime projected HIV infection risk was 40%. Discounted (undiscounted) population life expectancy was 22.51 (41.66) years, and the per-person lifetime cost was $7280 (Table 2). PrEP, with 39% efficacy, decreased the lifetime risk of HIV infection to 27% and increased discounted (undiscounted) life expectancy to 23.48 (44.48) years. Mean discounted lifetime costs also increased to $9890 per person, resulting in an incremental cost-effectiveness ratio of $2700/YLS, compared with the No PrEP strategy.

One-way Sensitivity Analysis
Three parameters had the largest impact on cost-effectiveness: PrEP efficacy, PrEP drug costs, and annual incidence of HIV infection in the target population (Figure 1). PrEP remained very cost-effective (<$7200/YLS) even with varying tenofovir resistance (proportion of population ranging from 0% to 100%) or increasing frequency of fatal PrEP-associated toxicity (0.5 times to 100 times). The Centers for Disease Control and Prevention suggests that HIV testing in a PrEP program be conducted every 3 months [48]; this testing frequency (compared with monthly testing in the base case) produced a similar life expectancy but at reduced cost, resulting in a more attractive incremental cost-effectiveness ratio of $1600/YLS. Results also remained very cost-effective when PrEP was discontinued at ages 35–45 years. No single input parameter change, within the ranges considered, rendered PrEP cost saving.

Multiway Sensitivity Analysis: The Impact of Incidence, Efficacy, and Cost
Simultaneously varying the aforementioned most influential parameters produced results ranging from not cost-effective to cost saving (Figure 2). However, at values represented by all of the reported trials, results were robust; PrEP was very cost-effective and bordered on cost saving (Figure 2). Decreasing PrEP drug costs alone by 50% produced moderately more favorable results, and reducing total PrEP program costs by 50% resulted in cost savings at 3 of the incidence and efficacy combinations represented by the trials.

Budgetary Impact of PrEP for HIV-Uninfected Women in South Africa
Under base case assumptions, the savings from reduced HIV care costs with PrEP programs (compared with the HIV care costs without PrEP programs) will not offset the additional costs associated with the provision of PrEP (Figure 3). At 5 years, cumulative discounted costs will be $1075 per person in the PrEP program. Of these costs, 24% will be attributable to PrEP medications, 27% to PrEP laboratory monitoring costs, 31% to HIV testing costs, and 19% to HIV care costs for persons who become newly infected. By 20 years, HIV care costs for persons who become newly infected will account for 41% of total costs. To achieve coverage for half the 11.1 million women in South Africa aged 15–44 years who are HIV uninfected and potentially PrEP eligible, the discounted PrEP budget over the next 5 years would be $6.0 billion [49].

DISCUSSION

Among South African women, vaginal PrEP would be a highly cost-effective intervention. At $2700/YLS, PrEP remained below

<table>
<thead>
<tr>
<th>Table 2. Base Case Results and Select Scenario Analyses</th>
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<tbody>
<tr>
<td><strong>Strategy</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>No PrEP</td>
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<tr>
<td>PrEP</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; PrEP, pre-exposure prophylaxis; YLS, year of life saved.

a Incidence 2.2%.

b Lifetime infection risk is projected from the cohort starting age of 23.9 years.
the WHO-suggested very cost-effective threshold in South Africa, under a range of model parameter values chosen to capture the performance of both vaginal and oral alternatives. Cost savings could only be achieved under optimistic assumptions, in which PrEP was targeted to populations in which the incidence of HIV infection is high (≥5%/year), with high efficacy (≥50%) and at lower PrEP drug costs (<$40/year). The cost-effectiveness results compare very favorably with those that have been published for ART and CD4 cell count laboratory monitoring for HIV in South Africa [12, 50, 51].

Improvements in adherence—whether through easier regimens, such as a vaginal ring, targeting populations likely to be most receptive, or training providers to encourage compliance—are crucial to maximizing the effectiveness of a PrEP program. The results from FEM-PrEP and the early termination of the TDF-only arm in VOICE might suggest that efficacy of oral chemoprophylaxis is exquisitely sensitive to suboptimal adherence, because vaginal levels are marginal for protection even with the best adherence [5–8]. The more recent termination of the vaginal gel arm of VOICE, with no statistical benefit over placebo, results in more confusion in light of the earlier CAPRISA findings [9]. It is still not known whether daily gel administration, as in VOICE, may provide inferior protection than the before and after pericoital regimen studied in CAPRISA 004 [1].

Although they have not emerged as significant issues in clinical trials, PrEP-induced toxicity, resistance, and risk compensation remain an implementation concern. We found that the clinical benefits of PrEP at the population level overwhelmingly offset any plausible level of adverse reactions, resistant breakthrough infections, or behavioral disinhibition [11, 52]. Of note, risk-reduction effects have been demonstrated in microbicide, pre- and postexposure prophylaxis, and vaccine studies [1, 2, 53–59]. The challenge will be to sustain these effects if PrEP becomes a public health program with less frequent clinical monitoring.

Despite its excellent value, PrEP implementation will not pay for itself. This analysis suggests that the per-woman investment would be $1075/person, or $6.0 billion, for 50% coverage of all eligible women in South Africa over the next 5 years. This investment will pay substantial dividends both in HIV cases averted and in the associated care costs prevented. However, if a one-size-fits-all prevention approach proves to be infeasible,
targeting PrEP to women at highest risk and/or those most likely to adhere will pay the highest returns on investment and may even prove to be cost saving.

Although our findings offer very strong evidence of the cost-effectiveness of PrEP, they are more tempered than those that have been previously reported [60]. We believe that the following modeling choices explain and justify our more conservative conclusions: first, we accounted explicitly for the indirect costs of providing PrEP (including regular HIV testing and chemistry panels); second, we captured the possibility (and the

\[\text{Figure 2. Multiway sensitivity analyses: incremental cost-effectiveness of pre-exposure prophylaxis (PrEP). This figure reports the ranges of incremental cost-effectiveness ratios for PrEP as a function of the 3 most influential parameters identified in Figure 1: human immunodeficiency virus (HIV) infection incidence of 1%–11% annually (vertical axis), PrEP efficacy of 0%–95% (horizontal axis), and PrEP program cost (the 3 vertical panels). The color indicates the incremental cost-effectiveness ratio achieved by each combination of parameters, ranging from not cost-effective in red (ratio >$21,600 per year of life saved [YLS]), to cost-effective in yellow ($7200–21,600/YLS), to very cost-effective in orange (<$7200/YLS), to cost saving in green. A, Base PrEP program costs. B, Base PrEP program costs with 50% reduction in PrEP drug cost (from $55/year to $28/year). C, 50% reduction in base PrEP program costs (from $188/year to $94/year). The base case and CAPRISA 004, iPrEX, TDF2 and Partners PrEP trial point estimates are indicated in each panel by the (+).}\]
expected costs) of adverse outcomes, including PrEP-related toxicity and the potential for antiretroviral resistance attributable to prophylaxis failure; third, we recognized the time value of cost-effectiveness outcomes and that the costs of PrEP are incurred long before its prevention benefits are realized; fourth, in the absence of data demonstrating capacity to accurately target PrEP to those at the highest risk, we model it as a lifelong (or until infected) intervention.

This analysis has several limitations. We applied efficacies from short-term trials conducted in groups at high risk of HIV infection (heterosexual women, men, and men who have sex with men) at high risk to different populations and projected these results over longer periods [5, 6]. Until trials can confirm the durable efficacy of a tenofovir vaginal gel, the efficacy and optimal dosing of PrEP remain uncertain. Recognizing this uncertainty, we considered a wide range of efficacies and dosing strategies. Second, we considered only the first generation of HIV infections prevented, conservatively ignoring the additional benefit of later HIV infections averted. Last, we estimated and considered a wide range of PrEP program costs, because costs for a vaginal gel and for PrEP implementation are not yet available.

This analysis suggests that PrEP, when applied to South African women, will substantially reduce the lifetime risk of HIV infection and be very cost-effective. Given the long-awaited proof-of-concept of PrEP as an effective female-initiated prevention option, its implementation holds substantial potential for reducing the incidence of HIV infection in South Africa, where PrEP will provide excellent value for money.

**Notes**

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