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Potential Clinical and Economic Value of Long-Acting Preexposure Prophylaxis for South African Women at High-Risk for HIV Infection

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(See the editorial commentary by Landovitz and Grinsztejn on pages 1519–20.)

Background. For young South African women at risk for human immunodeficiency virus (HIV) infection, preexposure prophylaxis (PrEP) is one of the few effective prevention options available. Long-acting injectable PrEP, which is in development, may be associated with greater adherence, compared with that for existing standard oral PrEP formulations, but its likely clinical benefits and additional costs are unknown.

Methods. Using a computer simulation, we compared the following 3 PrEP strategies: no PrEP, standard PrEP (effectiveness, 62%; cost per patient, $150/year), and long-acting PrEP (effectiveness, 75%; cost per patient, $220/year) in South African women at high risk for HIV infection (incidence of HIV infection, 5%/year). We examined the sensitivity of the strategies to changes in key input parameters among several outcome measures, including deaths averted and program cost over a 5-year period; lifetime HIV infection risk, survival rate, and program cost and cost-effectiveness; and budget impact.

Results. Compared with no PrEP, standard PrEP and long-acting PrEP cost $580 and $870 more per woman, respectively, and averted 15 and 16 deaths per 1000 women at high risk for infection, respectively, over 5 years. Measured on a lifetime basis, both standard PrEP and long-acting PrEP were cost saving, compared with no PrEP. Compared with standard PrEP, long-acting PrEP was very cost-effective ($150/life-year saved) except under the most pessimistic assumptions. Over 5 years, long-acting PrEP cost $1.6 billion when provided to 50% of eligible women.

Conclusions. Currently available standard PrEP is a cost-saving intervention whose delivery should be expanded and optimized. Long-acting PrEP will likely be a very cost-effective improvement over standard PrEP but may require novel financing mechanisms that bring short-term fiscal planning efforts into closer alignment with longer-term societal objectives.

Keywords. HIV; preexposure prophylaxis; cost-effectiveness; South Africa; long-acting agents.

Human immunodeficiency virus (HIV) infection continues to be a major cause of mortality in sub-Saharan Africa [1]. Despite growth in antiretroviral therapy (ART) coverage, the incidence of HIV infection among South African female teenagers continues to grow, with the prevalence of infection increasing from 2.4% to 17.4% between ages 14 and 24 years [2]. Preexposure prophylaxis (PrEP) has proven effective at preventing HIV infection [3, 4] and is being considered for low-income and middle-income countries where the incidence of infection is high [5, 6]. However, the success of current standard oral PrEP (Std-PrEP) hinges on daily adherence, with overall effectiveness of Std-PrEP in trials ranging from 0% to 94% [3, 4, 7–12]. Novel long-acting formulas of PrEP (LA-PrEP) provide sustained drug levels when administered bimonthly or quarterly and could help improve adherence [13, 14]. These formulations would, however, require a brief (approximately 1-month) period of short-term adherence, to rule out acute toxicity with a short-acting formulation, prior to long-acting dosing. Phase II clinical trials (the HIV Prevention Trials Network [HPTN] 077 study, the Centre for the AIDS Programme of Research in South Africa [CAPRISA] 014 study, the ÉCLAIR study, and the HPTN 076 study) are planned or ongoing for 2 LA-PrEP formulas, cabotegravir/ GS K1265744 and rilpivirine/TMC278LA [15–17]. In animal studies, prophylaxis efficacies of rectal and vaginal formulations of these agents have reached 75%–100% [14, 18, 19].
Although modeling studies have already projected the cost-effectiveness and substantial clinical benefits of properly used Std-PrEP, the comparative cost and effectiveness of alternative PrEP formulations are unknown [20–23]. Our objective was to anticipate the development of newer PrEP formulations, to investigate effectiveness thresholds that would justify the additional cost over existing PrEP alternatives in a population of high-risk young women in South Africa, and to identify the key drivers and uncertainties behind that assessment.

**METHODS**

**Analytic Overview**

We used the Cost-Effectiveness of Preventing AIDS Complications–International (CEPAC-I) model to project clinical benefits, estimate upfront investments, and establish cost-effectiveness performance benchmarks for LA-PrEP for high-risk South African women aged 18–25 years. Leveraging our prior work on Std-PrEP [22, 23], we examine 3 strategies: (1) no PrEP, (2) Std-PrEP with 62% effectiveness [10], and (3) LA-PrEP with 75% effectiveness [14, 18, 24]. We examined the sensitivity of our findings to uncertainty in LA-PrEP effectiveness, HIV infection incidence, duration of PrEP use, and LA-PrEP programmatic cost. Model outcomes included lifetime risk of HIV infection (per 1000 women at high risk), 5-year mortality and cost, cost per infection averted, lifetime survival and cost, and incremental cost-effectiveness ratios (ICERs) in 2014 US dollars per life-year saved. All outcomes used for economic evaluation are reported using a 3% annual discount rate. We labeled programs as “very cost-effective” if their ICERs were less than the South African annual per capita gross domestic product (GDP; ie, $7000) and as “cost-effective” if their ICERs were <3 times the GDP [25, 26]. We also examined the 1-year and 5-year budget impacts of an LA-PrEP strategy in this population. We conducted our analysis from the HIV program perspective and excluded later medical care costs for HIV-uninfected women.

**Model Overview**

CEPAC-I is a state-transition simulation of HIV prevention, case detection, and disease progression that is used to project clinical, epidemiologic, and economic outcomes of HIV prophylaxis and treatment programs. Model users define cohort characteristics, HIV screening policies, treatment regimens, and disease-monitoring policies, which all influence the natural history of HIV disease progression. For this analysis, all model entrants were PrEP-eligible, HIV-uninfected, high-risk South African women.

**PrEP Module**

HIV-negative women (mean age, 18 years) entered the module and were subjected to an age-dependent incidence of HIV infection. To simulate HIV screening that might occur in communities, all women underwent HIV testing every 3 years, on average [6].

We assumed that PrEP effectiveness, measured as a percentage reduction in HIV infection incidence, incorporated both intrinsic drug efficacy and anticipated client adherence. Women receiving one of the PrEP strategies underwent quarterly HIV screening to ensure that antiretroviral agents were not being prescribed suboptimally as prophylaxis to HIV-infected women [27]. In the base case, we assumed that women only received PrEP when their HIV infection risk was highest (ie, from the age at model entry through age 25 years) and relaxed this assumption in sensitivity analyses.

**Disease Module**

Women who became infected with HIV entered the disease module and traversed the natural history of HIV progression until they received a diagnosis of HIV infection via ongoing HIV screening efforts or via PrEP-associated HIV testing or until they developed a severe opportunistic infection [23]. Once HIV infection was detected, PrEP was discontinued, and the woman became eligible for guideline-concordant HIV care [28, 29], including ART initiation at a CD4+ T-cell count of <500 cells/μL. In the model, ART suppressed viral load, increased the CD4+ T-cell count, and decreased the risk of opportunistic infections and death [29, 30].

Per South African standards, we assumed 2 sequential lines of ART: first-line efavirenz-based therapy and second-line protease inhibitor–based therapy. For women receiving PrEP who became infected with HIV, we assumed in the base case that there was no resistance-related reduction in the efficacy of first-line ART, because LA-PrEP uses different antiretroviral agents than those used for treatment in South Africa [28]. We then conducted sensitivity analyses around this assumption, implementing a 10% absolute decrease in the rate of virologic suppression during first-line ART for those who were infected.

**Model Input Data**

**Demographic Parameters**

We simulated a cohort of 1 million high-risk South African women with a mean age (±SD) of 18 ± 2 years and an annual incidence of HIV infection of 5.0% until age 26 years, as reported in the Preexposure Prophylaxis Trial for HIV Prevention Among African Women (FEM-PrEP; 5.0%) [11], the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study (5.7%) [9], and the 2012 South African National Prevalence, Incidence, and Behaviour Survey (SANPibs; 4.5%) [2]. At age ≥26 years, the annual incidence of HIV infection was age adjusted to that for the average female in South Africa (ie, 2.1% for women aged 26–44 years and 0.85% for women aged ≥45 years), as derived from the SANPibs and the 2011 South African census (Table 1) [2, 31].

**PrEP Effectiveness**

Animal studies of LA-PrEP demonstrated prevention efficacies ranging from 75% to 100% (Table 1) [14, 18, 24]. We used an LA-PrEP effectiveness of 75% in the base case, to approximate 1 missed LA-PrEP dose per year. Trial-based effectiveness estimates for Std-PrEP have varied from 0% (in the FEM-PrEP and
VOICE study) in nonadherent populations to 94% (in the Partners PrEP study) in fully adherent populations [4, 9, 11, 12]. Acknowledging this wide range, we set a relatively high effectiveness estimate of 62% (from the TDF2 study [10]) for Std-PrEP in the base case (the effectiveness among heterosexual women ranges from 49% to 75%). We intentionally used 62% instead of a lower reported effectiveness because this sets a reasonable yet high standard against which we could compare the value of LA-PrEP (data in Supplementary Figure 4 compare LA-PrEP to Std-PrEP with 49% effectiveness). We chose the TDF2 study specifically because it was conducted with a target study population similar to that used in our analysis. PrEP toxicity was excluded from the base case because the majority of PrEP trials have reported no difference in the rate of serious adverse events across study groups [3, 4, 7, 9, 10] and because a study on the safety and tolerability of LA-PrEP reported no severe adverse events [32].

**PrEP Costs**

We estimated the monthly drug cost of Std-PrEP (tenofovir-emtricitabine) as $6.25 [33]. Although the cost of LA-PrEP is unknown, pricing of long-acting versus short-acting contraceptives showed that long-acting injectables cost nearly the same as or less than daily pills [34]. However, we conservatively approximated the LA-PrEP drug cost to be double that of Std-PrEP (ie, $12.50 monthly). The programmatic cost of both LA-PrEP and Std-PrEP incorporated the cost of drug, biannual chemistry panels, and clinic visits. Each biannual chemistry panel costs $15.50 [35], and a quarterly routine clinic visit costs $10.40. Thus, in our model the base case total monthly programmatic
cost for patients receiving Std-PrEP was $12.30 and that for LA-PrEP was $18.60. We conducted sensitivity analyses examining variations in overall programmatic cost, noting that, for LA-PrEP, only 70% of the overall cost was related to the cost of the drug itself (Table 1).

**Other Inputs**
Other key inputs are provided in Table 1 [2, 8–11, 14, 18, 24, 27, 29, 31, 33, 35–41].

**Sensitivity Analyses**
In sensitivity analyses, we varied LA-PrEP effectiveness, HIV infection incidence, age at PrEP discontinuation, and LA-PrEP programmatic cost. We then chose extreme values within realistic ranges of key PrEP-related parameters and combined them to create plausibly optimistic and pessimistic scenarios for LA-PrEP, compared with no PrEP and Std-PrEP.

**Budget Impact**
To inform financial planning, we conducted 1-year and 5-year budget impact assessments of alternative PrEP strategies. We adopted the perspective of the South African HIV prevention program, restricting our attention to undiscounted PrEP program cost (including drug, clinic visit, and chemistry panel cost) and assumed a 50% uptake. We estimated the number of PrEP-eligible South African women aged 18–25 years [31] by deducting the percentage of women with prevalent HIV infection (range, 2.4%–28.4%) from age-stratified population estimates [2]. Beyond the first year, we introduced women aged 18 years who were newly eligible for PrEP and removed the expected number of women with incident cases, given Std-PrEP or LA-PrEP effectiveness. We then multiplied this figure by the annual Std-PrEP or LA-PrEP program cost and subtracted the annual ART-associated cost savings resulting from PrEP-averted infections.

**RESULTS**

**Base Case**

**Clinical Outcomes**
The lifetime risk of HIV infection in high-risk South African women with no PrEP was 630 cases/1000. With an average of 8 years of PrEP use, the risk of infection declined, ranging from 540 cases/1000 with Std-PrEP (effectiveness, 62%) to 510 cases/1000 with LA-PrEP (effectiveness, 75%). The undiscounted per-person life expectancy starting from model entry (mean age, 18 years)—including women with and those without HIV infection—was shortest with the no PrEP strategy (47.7 years). Life expectancy for the PrEP strategies extended from 50.1 years (for Std-PrEP) to 50.4 years (for LA-PrEP). As a point of validation, this range of life expectancy was consistent with reports for South African HIV-infected adults receiving ART [42, 43]. PrEP also averted HIV-related deaths: over a 5-year period, LA-PrEP averted 16 HIV-related deaths per 1000 high-risk women, compared with no PrEP (Table 2).

**Cost and Cost-effectiveness Outcomes**
Over a 5-year horizon, the per-person costs of PrEP were substantially higher ($840 for Std-PrEP and $1130 for LA-PrEP) than for no PrEP ($260). The cost of averting 1 HIV infection over a lifetime was estimated as $10 100 for Std-PrEP and $12 400 for LA-PrEP. When all 3 strategies were compared over a lifetime, including the cost of ART, the Std-PrEP strategy was the least expensive ($5270). Compared with no PrEP, both Std-PrEP and LA-PrEP were less expensive and more effective, and therefore cost saving. Compared with Std-PrEP, the ICER of LA-PrEP was $150/life-year saved (Table 2).

The 3 strategies differed in terms of the components of their costs. Increasingly aggressive PrEP approaches required a greater investment in PrEP-related program cost (Figure 1). However, these investments were offset by savings in HIV-related cost (Figure 1). Compared with no PrEP, spending an average of $1530 per person on LA-PrEP resulted in $1960 less spent per person on total HIV care.

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**Table 2. Base Case Results**

|Variable| No PrEP | Std-PrEP | LA-PrEP |
|---|---|---|---|
|Lifetime HIV infection risk, a cases/1000 high-risk women| 630| 540| 510|
|Undiscounted per-person life expectancy, b y| 47.7| 50.1| 50.4|
|5-y HIV infections averted, compared with no PrEP, no./1000 high-risk women| . . .| 127| 156|
|5-y HIV-related deaths averted, compared with no PrEP, no./1000 high-risk women| . . .| 15| 16|
|Discounted 5-y cost per high-risk woman, c $| 260| 840| 1130|
|Discounted PrEP cost per lifetime HIV infection averted, $| . . .| 10 100| 12 400|
|Discounted life expectancy, y| 23.9| 24.8| 25.0|
|Discounted per person lifetime cost, d $| 5730| 5270| 5300|
|ICER vs no PrEP, $/life-year saved| . . .| Cost saving e| Cost saving e |
|ICER vs Std-PrEP, $/life-year saved| NA| . . .| 150|

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; LA-PrEP, long-acting preexposure prophylaxis; NA, not applicable; PrEP, preexposure prophylaxis; Std-PrEP, standard preexposure prophylaxis.

a Lifetime HIV infection risk was projected from the cohort starting age of 18 years.

b Per-person life expectancy was projected from the cohort starting age of 18 years. A per-person undiscounted life expectancy of 50 years corresponds here to an overall life expectancy of 69 years.

c Costs were measured in 2014 $ and discounted at a rate of 3%.

d PrEP was more effective and less expensive than the comparator strategy.
Strategies also differed in terms of their cost and benefit trajectories over time. When we focused on the first 5 years after program implementation, increasingly aggressive PrEP strategies were costlier (Table 2). Viewed over a longer horizon, however, PrEP interventions were less costly. The LA-PrEP strategy required a higher initial investment (Figure 2A); its discounted cost greatly exceeded that of the no PrEP strategy and slightly exceeded that of the Std-PrEP strategy over the first 5–15 years. However, the higher eventual cost related to increased numbers of HIV infections and treatment with the no PrEP strategy caused the cumulative discounted cost curves to converge (the curves crossed at approximately year 29; data not shown). Beyond that point, the LA-PrEP strategy had lower cumulative cost. LA-PrEP also reduced the number and delayed the occurrence of HIV-related deaths (Figure 2A) and the number of women requiring ART (Figure 2B).

Sensitivity Analyses
We summarize our extensive sensitivity analyses in the section below, reporting on key instances variation in the input data assumptions had a material impact on our policy findings or were clinically important. A fuller report is provided in the Supplementary Materials.

LA-PrEP Effectiveness
Clinical benefits increased with increases in LA-PrEP effectiveness (Table 3). Lifetime risk of HIV infection decreased from 510 cases/1000 high-risk women (base case effectiveness, 75%) to 490 and 470 cases/1000 high-risk women (effectiveness, 85% and 95%, respectively); similarly, more HIV-related deaths were averted as effectiveness increased. Average lifetime cost also decreased, dropping as low as $4530 per woman at 95% effectiveness; as total lifetime cost decreased, PrEP accounted for a greater proportion of total cost.

HIV Infection Incidence
When annual incidence was reduced from 5.0% to 2.5% (the population average risk in South Africa), LA-PrEP no longer achieved cost savings, and the PrEP cost per averted infection increased to $21 800; however, LA-PrEP was very cost-effective as compared to no PrEP, with an ICER of $680/life-year saved (<10% annual per capita GDP). Among very high-risk women—similar to those observed in the CAPRISA 004 study (HIV infection incidence, 9.0%/year) [8]—LA-PrEP averted 27 deaths/1000 women over 5 years and cost $8200 per averted infection. Supplementary Figures 3 and 4 provide 2-way sensitivity analyses of LA-PrEP as compared to Std-PrEP at alternative Std-PrEP efficacies (62% and 49%) and in average-risk, high-risk, and very high-risk populations.

Duration of LA-PrEP Use
In the base case analysis, we assumed that LA-PrEP was administered from model entry (ie, at a mean age of 18 years) through age 25 years. If LA-PrEP was administered for longer durations—through age 35 or 45 years—a greater cumulative per-person investment (from $5300 to $5840 or $6240) would be required, LA-PrEP program cost would account for a larger fraction of total outlay (48%–60%), and lifetime risk of HIV would...
decrease from 510 to 430 or 340 cases per 1000 high-risk women (Supplementary Figure 1). Alternatively, if PrEP “fatigue” resulted in its use only through age 19 years, lifetime cost for LA-PrEP would be higher than in the base case, despite reduced PrEP expenditure, because 2 years of PrEP use would not avert enough infections to decrease lifetime cost substantially as compared to the no PrEP strategy.

**LA-PrEP Cost**

When the overall LA-PrEP program cost decreased by 50% of the base case value to $9/month, cost savings were achieved as early as 13 years after program implementation, per-person lifetime cost was $4540, and the PrEP cost per infection averted was $6200. If LA-PrEP overall program cost was 150% of the base case ($28/month)—as might occur if the dosing frequency were every 2 months—the ICER for LA-PrEP as compared to no PrEP was very cost-effective, at $280/life-year saved (4% of GDP), and was cost-effective as compared to Std-PrEP, at $7870/life-year saved (112% of GDP; Supplementary Figures 2 and 3); at 150% of cost, LA-PrEP cost $18 400 per infection averted. At a monthly cost exceeding $45 and $310, LA-PrEP ceased to be cost-effective as compared to Std-PrEP and no PrEP, respectively.

**Resistance-Related Reduction in ART Efficacy**

A sensitivity analysis adding a 10% absolute reduction in virologic suppression due to resistance among persons who experience breakthrough HIV infections during LA-PrEP produced no material impact on any major outcome or on the resultant policy recommendation.

**Optimistic and Pessimistic LA-PrEP Scenarios**

In a best-case scenario for LA-PrEP use, highly effective LA-PrEP (effectiveness, 85%) was administered at low cost ($9 monthly) and successfully targeted to very high-risk (annual incidence, 9%) women. Use of LA-PrEP in this optimistic scenario (Table 3), averted 29 deaths/1000 women in the first 5 years, cost $4620 per woman over her lifetime, and cost $3600 per infection averted as compared to no PrEP. In a pessimistic scenario, less effective LA-PrEP (effectiveness, 65%) was administered at higher cost ($28 monthly) to the general population of women with average risk of HIV infection (annual incidence, 2.5%). Even under this pessimistic scenario, less effective LA-PrEP (effectiveness, 65%) was administered at higher cost ($28 monthly) to the general population of women with average risk of HIV infection (annual incidence, 2.5%). Even under this pessimistic scenario, LA-PrEP had an ICER of $2420/life-year saved as compared to no PrEP (very cost-effective, 35% of GDP) but it was not cost-effective as compared to Std-PrEP ($165 360/life-year saved). LA-PrEP reduced the lifetime risk of HIV infection to 500 cases/1000 high-risk women and cost $37 500 per infection averted, compared with no PrEP.

**Budget Impact Analysis**

An estimated 3 million South African women ages 18–25 years are eligible for PrEP each year [31]. Providing LA-PrEP to half this population, at an average per-person programmatic cost of $220 annually, would cost $327 million in the first year (Std-PrEP cost, $217 million) and $1.6 billion over 5 years (Std-PrEP cost, $1.1 billion).

**DISCUSSION**

New long-acting antiretroviral formulations may soon provide a PrEP option that does not require daily adherence to pills. Anticipating the development of long-acting options, we compared
the potential clinical benefits, additional cost, cost-effectiveness, and budget impact of existing and novel PrEP strategies. We found that, in high-risk populations (annual HIV infection incidence, 5.0% [9, 11]), currently available oral PrEP formulations, with an effectiveness of 62%, would avert deaths, extend life expectancy, reduce the lifetime risk of HIV infection, and save money in the long term, compared with no PrEP. LA-PrEP, with an effectiveness of 75%, could avert even more deaths, provide longer life expectancy, and result in an even lower lifetime risk of HIV infection. LA-PrEP would also be cost saving as compared to no PrEP in the long term. Compared with standard PrEP, it would have an attractive ICER ($150/life-year saved)—just 2% of South Africa’s GDP per capita. This is substantially less than reported cost-effectiveness ratios for ART in South Africa, ranging from $1240 to $2400/life-year saved (updated to 2014 US dollars) [29, 41, 44, 45].

Viewed on an individual basis, LA-PrEP would cost about $12 400 (discounted) per infection averted, more than twice the per-person lifetime discounted cost of care in the absence of PrEP ($5730). However, the upfront investment in LA-PrEP would be offset in the long term by reduced HIV transmission and a lower overall cost of HIV treatment.

Despite long-term cost savings, the scale-up of a PrEP program, even if successfully targeted, would be substantial. According to the South African National Strategic Plan, $2.8 billion is needed in the 2015–2016 fiscal year to meet the goals for prevention and treatment of sexually transmitted diseases, tuberculosis, and HIV infection, a value that already

| LA-PrEP Strategy                  | Lifetime Risk of HIV Infection, a Infections/1000 High-Risk Women | 5-y Averted HIV-Related Deaths, No./1000 High-Risk Women | Discounted Per-Person Lifetime Cost, a $ | PrEP Cost, % of Total Cost | Discounted PrEP Cost per Lifetime HIV Infection Averted, a $ | ICER, $/Life-Year Saved |
|-----------------------------------|---------------------------------------------------------------|--------------------------------------------------------|---------------------------------|---------------------|-------------------------------------------------|------------------------|
| Base case                         | 510                                                          | 16                                                    | 1                               | 5300                | 28                                             | 12 400                 | Cost saving           |
| Effectiveness, %                  |                                                               |                                                       |                                 |                     |                                                 |                        |                      |
| 65                                | 530                                                          | 15                                                    | 0                               | 5660                | 26                                             | 14 200                 | Cost saving           |
| 85                                | 490                                                          | 17                                                    | 2                               | 4920                | 31                                             | 10 800                 | Cost saving           |
| 95                                | 470                                                          | 18                                                    | 3                               | 4530                | 34                                             | 9 600                  | Cost saving           |
| HIV infection annual incidence until age 25 y, % |                                                               |                                                       |                                 |                     |                                                 |                        |                      |
| 2.5                               | 490                                                          | 8                                                     | 0                               | 4830                | 32                                             | 21 800                 | 680                  | 4790                 |
| 9.0                               | 550                                                          | 27                                                    | 2                               | 6000                | 24                                             | 8 200                  | 60                  | 1770                 |
| PrEP through age                  |                                                               |                                                       |                                 |                     |                                                 |                        |                      |
| 19 y                              | 600                                                          | 8                                                     | 0                               | 5640                | 8                                              | 15 000                 | 590                  |
| 35 y                              | 430                                                          | 16                                                    | 1                               | 5840                | 48                                             | 14 100                 | 60                  | 1770                 |
| 45 y                              | 340                                                          | 16                                                    | 1                               | 6240                | 60                                             | 13 000                 | 280                 | 2 490                |
| Program cost, % of basecase       |                                                               |                                                       |                                 |                     |                                                 |                        |                      |
| 50 ($9/mo)                        | 510                                                          | 16                                                    | 1                               | 4540                | 16                                             | 6200                   | 280                 | 7870                 |
| 150 ($28/mo)                      | 510                                                          | 16                                                    | 1                               | 6040                | 37                                             | 18 400                 | 280                 | 7870                 |
| Scenario                          |                                                               |                                                       |                                 |                     |                                                 |                        |                      |
| Optimistic (85% efficacy, 50% cost, 9.0% incidence) | 520                                                          | 29                                                    | 4                               | 4620                | 16                                             | 3600                   | 60                  | 1770                 |
| Pessimistic (65% efficacy, 150% cost, 2.5% incidence) | 500                                                          | 8                                                     | 0                               | 5780                | 39                                             | 37 500                 | 2420                | 165 360              |

Abbreviations: HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; LA-PrEP, long-acting preexposure prophylaxis; PrEP, preexposure prophylaxis; Std-PrEP, standard preexposure prophylaxis.

a Lifetime HIV infection risk was projected from the cohort starting mean age of 18 years.
b Averted deaths were rounded down to the nearest integer.
c Costs were measured in 2014 $.
d The base case used LA-PrEP with an effectiveness of 75% in a population of women with 5.0% annual HIV infection incidence at a monthly cost of $18.60. PrEP was provided through age 25 y.
e PrEP was more effective and less expensive than the comparator strategy.
results in a $460 million gap in available funding [46]. Approximately 20% ($560 million) is earmarked for HIV prevention and testing initiatives, likely primarily targeted to the 28 million individuals aged 10–40 years. Yet, our estimated annual budget for LA-PrEP, assuming 50% uptake in high-risk women aged 18–25 years, is $327 million for just 1.5 million women. Thus, for LA-PrEP to truly be sustainable and scalable, creative fiscal strategies will be required. Concessionary loans, which would spread the cost of a PrEP program over a long period, might be one avenue of financing [47].

Our study has several limitations. First, while the efficacy of oral PrEP has been well established in clinical trials, its effectiveness in real-world medical practice has not. Further, the effectiveness and cost of LA-PrEP are unknown. We conducted broad sensitivity analyses around potential target populations and LA-PrEP prophylactic efficacy and cost values, but the point estimates will remain uncertain until more data are available. We did not include the impact of potential fatigue associated with injectables or loss to follow up in the LA-PrEP (or Std-PrEP) program, as has been associated with long-acting contraceptives [48]. However, we examined shorter LA-PrEP horizons (through age 19 years); we believe that LA-PrEP, compared with Std-PrEP, would be less likely associated with disengagement, because LA-PrEP would require much less intensive maintenance and follow-up care. Nevertheless, the LA-PrEP safety profile has yet to be established. The prolonged pharmacokinetic tail of long-acting nanofORMulations bears careful monitoring for toxicities (eg, fulminant drug-related liver or cutaneous drug reactions) and their potential contribution to the need for discontinuation and for medical care.

We also accounted only for first-generation, age-dependent transmission to HIV-negative women; inclusion of later-generation infections, especially in young women, would serve to make LA-PrEP even more cost-effective, with negligible impact on the early required budget. Further, we restricted our attention to women >18 years in this analysis. Expanding our assessment to include sexually active adolescent girls—a group with a similarly high HIV infection incidence—would likely both strengthen our cost-effectiveness findings and heighten the budget impact concerns regarding LA-PrEP.

Taken as a whole, our findings suggest a 2-part policy response. First, the delivery of existing oral PrEP formulations, which are very cost-effective, should be expanded and optimized for young, high-risk South African women. Scale-up of PrEP should be accompanied by improved community education and adherence interventions to ensure its effectiveness in the population. Data from large cohorts of women still report annual HIV infection incidences as strikingly high as 9.0%. An immediate need for effective prevention will persist until the full scale-up of treatment to all ART-eligible persons can be achieved [49, 50]. For young women at high risk for HIV infection, oral PrEP is one of the very few effective and cost-saving HIV prevention alternatives available.

Second, the research and development effort should be expanded to bring a viable LA-PrEP formulation to market. The evidence currently at our disposal suggests that long-acting PrEP could be a very cost-effective alternative to standard formulations. Depending on cost, discontinuation rates, and toxicities that are as-yet unanticipated, it might offer a small but still acceptable improvement (as injectable contraception is to oral contraceptive pills). However, even under the most optimistic scenario, a long-acting PrEP formulation is still several years away from implementation; moreover, a long-acting PrEP formulation will place an even greater strain on existing HIV prevention budgets. For this reason, the research effort to confirm the clinical effectiveness of newer LA-PrEP formulations must go hand in hand with a development effort to identify novel financing mechanisms that bring short-term fiscal planning efforts into closer alignment with longer-term societal objectives.

Supplementary Data
Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyrighted and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes
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R. P. W. had access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.
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