The Cost-effectiveness of Human Immunodeficiency Virus (HIV) Preexposure Prophylaxis and HIV Testing Strategies in High-risk Groups in India

Pooyan Kazemian,^{1,2,3} Sydney Costantini,¹ Nagalingeswaran Kumarasamy,⁴ A. David Paltiel,⁵ Kenneth H. Mayer,^{3,6,7} Nomita Chandhiok,⁸ Rochelle P. Walensky,^{1,2,3,9,10} and Kenneth A. Freedberg^{1,2,3,9,10,11}

¹Medical Practice Evaluation Center, and ²Division of General Internal Medicine, Massachusetts General Hospital, and ³Harvard Medical School, Boston, Massachusetts; ⁴CART Clinical Research Site, Infectious Diseases Medical Centre, Voluntary Health Services, Chennai, India; ⁵Department of Health Policy and Management, Yale School of Public Health, New Haven, Connecticut; ⁶Fenway Institute, Fenway Health, and ⁷Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts; ⁸Indian Council of Medical Research, Ansari Nagar, New Delhi, India; and ⁹Division of Infectious Diseases, Massachusetts General Hospital, ¹⁰Harvard University Center for AIDS Research, and ¹¹Department of Health Policy and Management, Harvard T. H. Chan School of Public Health, Boston, Massachusetts

Background. The human immunodeficiency virus (HIV) epidemic in India is concentrated among 3.1 million men who have sex with men (MSM) and 1.1 million people who inject drugs (PWID), with a mean incidence of 0.9–1.4 per 100 person-years. We examined the cost-effectiveness of both preexposure prophylaxis (PrEP) and HIV testing strategies for MSM and PWID in India.

Methods. We populated an HIV microsimulation model with India-specific data and projected clinical and economic outcomes of 7 strategies for MSM/PWID, including status quo; a 1-time HIV test; routine HIV testing every 3, 6, or 12 months; and PrEP with HIV testing every 3 or 6 months. We used a willingness-to-pay threshold of US\$1950, the 2017 Indian per capita gross domestic product, to define cost-effectiveness.

Results. HIV testing alone increased life expectancy by 0.07–0.30 years in MSM; PrEP added approximately 0.90 life-years to status quo. Results were similar in PWID. PrEP with 6-month testing was cost-effective for both MSM (incremental cost-effectiveness ratio [ICER], \$1000/year of life saved [YLS]) and PWID (ICER, \$500/YLS). Results were most sensitive to HIV incidence. PrEP with 6-month testing would increase HIV-related expenditures by US\$708 million (MSM) and US\$218 million (PWID) over 5 years compared to status quo.

Conclusions. While the World Health Organization recommends PrEP with quarterly HIV testing, our analysis identifies PrEP with semiannual testing as the cost-effective HIV prevention strategy for Indian MSM and PWID. Since nationwide scale-up would require a substantial fiscal investment, areas of highest HIV incidence may be the appropriate initial targets for PrEP scale-up.

Keywords. HIV; India; PrEP; testing; cost-effectiveness.

India is home to 2.2 million people living with human immunodeficiency virus (HIV), one of the largest populations of people living with HIV in the world [1]. The epidemic is concentrated in specific high-risk groups (HRGs), notably men who have sex with men (MSM) and people who inject drugs (PWID). HIV incidence within these groups varies widely regionally, with reported interquartile ranges between 0.4% and 1.2% per year for MSM and 0.6%–4.0% per year for PWID [2]. Continued high incidence suggests the need for focused prevention interventions such as preexposure prophylaxis (PrEP).

PrEP is a highly effective, evidence-based approach to preventing new HIV infections. For those at high risk of

acquiring HIV, PrEP using tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) can reduce HIV infection risk in MSM by >85% [3, 4]. However, PrEP effectiveness is highly dependent on medication adherence. International guidelines recommend that individuals continue PrEP as long as risk of infection persists [4]. For those on PrEP, routine HIV testing to screen for HIV acquisition and serum creatinine testing to screen for drug-related toxicity are recommended. Routine HIV testing in HRGs (without PrEP) can also enhance detection of newly infected individuals, decrease the number of individuals who present with advanced HIV disease, and reduce transmission if infected individuals are linked to care [5].

Although HIV incidence in MSM and PWID is high in India and PrEP is an effective prevention strategy, the costs, cost-effectiveness, and affordability of a nationwide PrEP scale-up for MSM and PWID in India have not been well described. Moreover, although the World Health Organization (WHO) currently recommends routine HIV testing every 3 months for persons taking PrEP, the optimal frequency of HIV testing has not been established [6]. Our goals were to examine and

Received 29 November 2018; editorial decision 16 March 2019; accepted 21 March 2019; published online March 28, 2019.

Correspondence: P. Kazemian, Massachusetts General Hospital, 100 Cambridge St, Suite 1600, Boston, MA 02114 (pooyan.kazemian@mgh.harvard.edu).

Clinical Infectious Diseases® 2020;70(4):633–42

© The Author(s) 2019. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/ciz249

compare the clinical and economic outcomes of implementing a PrEP program and HIV testing strategies alone at different frequencies, to assess (i) the cost-effectiveness of a PrEP program compared to HIV testing alone; (ii) the optimal testing frequency of a PrEP program; and (iii) the budget impact of PrEP scale-up for MSM and PWID in India.

METHODS

Analytic Overview

We used the Cost-effectiveness of Preventing AIDS Complications–International (CEPAC-I) model to project the clinical impact and cost-effectiveness of various PrEP and HIV testing interventions for MSM and PWID in India who are currently HIV uninfected or HIV infected but unaware of their infection. We modeled 7 strategies, targeted to MSM and PWID in India: (i) no PrEP or additional HIV testing (“StatusQuo”); (ii) a 1-time HIV test at model entry, around age 30 (“1timeTest”); routine HIV testing every (iii) 3 months, (iv) 6 months, or (v) 12 months (“3mTesting,” “6mTesting,” and “12mTesting,” respectively); and daily TDF/FTC-based PrEP with annual creatinine testing and routine HIV testing every (vi) 3 months or (vii) 6 months (“PrEP+3mTesting” and “PrEP+6mTesting,” respectively). HIV testing every 3 months with PrEP is the current monitoring frequency suggested by both the WHO and the US Centers for Disease Control and Prevention [6, 7].

Clinical outcomes included lifetime HIV infection risk, life expectancy, and number of HIV transmissions averted to members of each HRG and to those outside the HRGs. Economic outcomes include costs of HIV testing, PrEP (drug and laboratory monitoring), antiretroviral therapy (ART), and other HIV care costs, as well as cost savings from averting transmissions. We assessed these outcomes at 15-year and lifetime horizons.

We measured comparative value using incremental cost-effectiveness ratios (ICERs), defined as the additional cost per year of life saved (YLS), discounting both costs and life expectancy at 3% per year [8]. We defined the “cost-effective strategy” to be that single strategy that achieves the highest ICER not exceeding the willingness-to-pay (WTP) threshold for an additional year of life. We used a WTP threshold of US\$1950, the 2017 Indian per capita gross domestic product (GDP).

Microsimulation Model

CEPAC-I is a Monte Carlo state–transition microsimulation model of HIV prevention, infection, detection, progression, and treatment. The model advances monthly and tracks all individuals from model entry until death. Different model components, such as PrEP, HIV testing and detection, natural history of HIV disease, ART regimens, toxicities, adherence, and loss to follow-up, are parameterized with published data. The model has been validated in prior studies [9, 10].

PrEP and HIV Testing

We modeled PrEP as a reduction in the monthly probability of HIV infection, with added drug, HIV testing, and creatinine monitoring costs. PrEP is discontinued if an individual is infected with HIV and detected. In the base case, all routine testing and PrEP programs start at model entry and continue until age 45. For additional information, see the [Supplementary Appendix](#).

HIV Transmissions

In the model, MSM can acquire HIV from either other MSM or transgender women (TGW) [11]. PWID can acquire the disease from other PWID from either drug use or sexual activity [12]. At the beginning of the simulation, incidence for MSM and PWID is set to current epidemiological estimates. For strategies involving PrEP, incidence at time 0 accounts for the individual protection of PrEP for those who take the drug, accounting for both adherence and efficacy. Over time, incidence in all strategies decreases according to an estimated reduction in transmission within the HRG due to the “community benefit” of the intervention (ie, fewer transmitters with high HIV viral loads [VLs] transmitting to others). Incidence declines in the form of an exponential decay for the approximate 15-year duration of the intervention, after which it remains at a constant, lower value.

We also account for HIV transmissions from MSM and PWID to persons outside the HRGs, specifically from MSM to female partners and TGW [11], and PWID to their sexual partners, mostly non–drug users in India [13]. We project HIV transmissions averted in each strategy over 15 years from MSM and PWID to outside the risk group, compared to the baseline rate of transmission. The benefits of averting transmissions, in terms of life-years gained and cost savings, are estimated by simulating 2 cohorts, an HIV-infected and an HIV-uninfected cohort, starting from the year of the averted transmission. The difference in life-years and costs between a simulated individual living with HIV vs without HIV are used as inputs for life-years gained and HIV care costs saved per transmission averted.

Overall ICERs are calculated by combining projected life-years and costs associated with the HRG and life-years gained and cost savings related to averted transmissions to outside the HRG.

Model Input Parameters

Cohort Characteristics and Natural History

There are an estimated 3.1 million and 1.1 million total MSM and PWID in India [14, 15]. All individuals, whether HIV uninfected or HIV infected, were characterized by demographics based on Indian data. Mean age at model start was 29.4 years (MSM) and 34.3 years (PWID) [15, 16]. Of PWID, 92.8% were male [17]. All individuals experienced non-HIV natural history probabilities of mortality, with PWID facing an 8-fold higher risk of mortality via drug overdose during a 5 year high-drug-use period [18]. HIV

prevalence at model start was 4.3% for MSM and 9.9% for PWID [19]; 70.0% of infected MSM and 59.0% of PWID were undetected (Table 1) [20, 21]. Those who were HIV infected had either acute or chronic HIV at model start and a corresponding CD4 cell count and plasma HIV RNA based on India-specific distributions [22].

Those HIV-uninfected at model entry faced age-dependent monthly probabilities of HIV infection. Weighted average HIV incidence rates by age at model start (without PrEP) were 0.9/100 person-years (PY) (MSM) and 1.4/100 PY (PWID) [2]. Incidence varied by age based on published risk ratios fit to a

Gaussian curve; those aged 26–30 possessed the highest infection risk.

Intervention

Intervention uptake was 63.2% for routine testing and 55.7% for PrEP strategies in the base case [25, 26]. We defined PrEP effectiveness as the product of drug efficacy in a highly adherent, trial-based setting and the expected population adherence. PrEP efficacy was estimated at 96.0% [3, 27]. We assumed adherence was 68.0% [28]; this resulted in a combined effectiveness parameter of 65.0% (Table 1).

Table 1. Base Case Model Input Parameters for an Analysis of Human Immunodeficiency Virus (HIV) Testing and Preexposure Prophylaxis (PrEP) in Men Who Have Sex With Men and People Who Inject Drugs in India

Parameter	Value		Reference
Characteristics of initial cohort			
	MSM	PWID	
Age, y, mean (SD)	29.4 (5.7)	34.3 (6.5)	[15, 16]
Estimated size of population, millions	3.1	1.1	[14, 15]
HIV prevalence, %	4.3	9.9	[19]
HIV incidence, infections/100 PY (IQR)	0.9 (0.4–1.2)	1.4 (0.6–4.0)	[2]
Background testing rate, % per year	11.6	17.0	[20, 21]
% of HIV-infected persons detected (aware of their status)	30.0	41.0	[20, 21]
Linkage to care, %	87.5	79.6	[19]
Characteristics of sexual network members			
	Women	TGW	Sexual Partners
Age, y, mean (SD)	24.1 (5.7)	29.4 (5.7)	29.8 (6.5)
Background testing rate, % per year	3.2	11.5	3.2
Linkage to care, %	80.0	91.5	80.0
Intervention parameters			
PrEP uptake, % willing to participate	55.7		[25]
Testing uptake, % willing to participate	63.2		[25, 26]
PrEP effectiveness, % incidence reduction	65.0		[27, 28]
Transmission dynamics			
	MSM	PWID	
Transmission inside the risk group, rate/100 PY, off PrEP	17.6	13.0	[2]
Transmission outside the risk group, rate/100 PY	6.2 (to TGW); 0.6 (to women)	2.5	[12, 13, 29, 30]
Acute, off-ART transmission RR	5.3	5.3	[31]
Clinical characteristics post-HIV infection			
Acute CD4 count, cells/μL, mean (SD)	553 (230)	...	[22]
First-line overall suppression at 48 weeks, %	82.1	...	[32]
Monthly CD4 increase on ART			[32]
First month, mean (SD)	83 (38)	...	
After first month, mean (SD)	4 (2)	...	
Costs			
PrEP-associated costs			
PrEP drug cost (\$/month)	5.55	...	[33]
HIV test cost (\$/test) ^a	4.39	...	[22]
Clinic visit cost (\$/visit)	5.99	...	[34]
Creatinine testing cost (\$/test)	3.00	...	Assumption
ART costs			
First-line ART, \$/month	9.10	...	[33]
Second-line ART, PI-based regimen, \$/month	22.74	...	[33]
Monitoring and care costs			
HIV viral load test (\$/test)	22.08	...	[35]
CD4 cell count test (\$/test)	3.69	...	[35]
Routine care cost (conditional on CD4 count, \$/month)	7.48–25.83	...	[34]

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; PI, protease inhibitor; PrEP, preexposure prophylaxis; PWID, people who inject drugs; PY, person-years; RR, risk ratio; SD, standard deviation; TGW, transgender women.

^aThose who receive a positive result will take an additional confirmatory test and incur double the cost.

Transmission

The weighted average transmission rates to those outside the HRG, across VL strata at model start, were 0.6/100 PY (MSM to female partners), 6.2/100 PY (MSM to TGW), and 2.5/100 PY (PWID to sexual partners) (Table 1). Those in the highest VL stratum (>100 000 copies/mL) were 56 times more likely to transmit HIV than those in the lowest stratum (<500 copies/mL) [36]. Those with acute HIV infection were 5.3 times more likely to transmit HIV than those with chronic HIV [31].

Costs

PrEP drug costs were \$ US 5.55/month [33]. HIV test costs were \$ US 4.39/test, and associated clinic visits were \$ US 5.99/visit [34]. ART regimen costs were \$ US 9.10/month for nonnucleoside reverse transcriptase inhibitor–based first-line regimens and \$ US 22.74/month for protease inhibitor–based second-line regimens [33].

Sensitivity Analysis

We conducted 1-way sensitivity analysis on HIV incidence, PrEP efficacy, intervention stopping age, cohort age at initiation, PrEP and HIV testing uptake, PrEP costs, and HIV test costs, varying parameters across literature-derived or plausible ranges to reflect uncertainty and potential heterogeneity among MSM

and PWID in India. We identified the most critical parameters, which we then subjected to 2-way sensitivity analyses. Finally, we conducted a probabilistic sensitivity analysis (PSA), drawing from appropriate distributions to simultaneously vary key input parameters. In sensitivity analyses, we compared PrEP+6mTesting to 12mTesting, as well as PrEP+3mTesting to PrEP+6mTesting, to illuminate the differences between routine HIV testing alone, routine HIV testing with PrEP, and increased HIV testing with PrEP.

In an additional scenario analysis, we evaluated an alternative strategy to daily PrEP, where PrEP is taken on an event-driven basis, OnDemandPrEP (Supplementary Appendix).

Budget Impact Analysis

We conducted a budget impact analysis of key strategies over a 5- and 15-year horizon (undiscounted per convention) [37]. We considered all HIV-related expenditures, such as the costs of HIV clinic visits, testing, ART, and PrEP, from a modified country-wide, societal perspective.

RESULTS

Clinical Outcomes

In MSM, the 4 HIV testing strategies decreased lifetime HIV infection risk from 12.3% in StatusQuo to 10.8%–12.0%; PrEP had a

Table 2. Base Case Clinical and Economic Model Outcomes for Preexposure Prophylaxis and Human Immunodeficiency Virus Testing Strategies for Men Who Have Sex With Men and People Who Inject Drugs in India

Strategy ^a	Lifetime Infection Risk, %	Transmissions Averted/15 y, Inside the Risk Group	Transmissions Averted/15 y, Outside the Risk Group		LY, Primary Cohort (Undiscounted)	LY, Primary Cohort (Discounted)	Cost, Primary Cohort (Discounted, \$)	ICER, 15 y (\$/YLS)	ICER, lifetime (\$/YLS)
			Women	TGW					
MSM									
StatusQuo	12.3	...	...	...	38.77	21.65	380	...	...
1timeTest	12.0	3730	350	3940	38.85	21.69	400	900	400
12mTesting	11.4	14 290	1030	11 440	38.96	21.74	460	3300	800
6mTesting	11.1	18 660	1350	15 020	39.02	21.77	530	Dom	Dom
3mTesting	10.8	25 010	1750	19 530	39.07	21.79	670	Dom	Dom
PrEP+6mTesting	5.4	145 340	4440	49 570	39.67	22.02	830	6300	1000
PrEP+3mTesting	5.3	147 720	4570	51 000	39.68	22.03	950	41 100	14 100
PWID									
StatusQuo	16.1	...	...	...	32.02	18.92	460	...	...
1timeTest	15.8	1570	650	...	32.09	18.96	480	1000	400
12mTesting	15.3	4510	1550	...	32.17	19.00	510	2700	Dom
6mTesting	14.9	6440	2170	...	32.23	19.02	560	Dom	Dom
3mTesting	14.5	8690	2900	...	32.29	19.05	650	Dom	Dom
PrEP+6mTesting	7.6	62 560	8530	...	32.93	19.31	700	3400	500
PrEP+3mTesting	7.4	63 450	8780	...	32.95	19.32	780	21 000	7600

All costs and life-years are reported over a lifetime horizon; costs are in 2017 US dollars. Discounted costs and life-years are reported using a rate of 3% per year. Transmissions averted and costs are rounded to the nearest 10; ICERs are rounded to the nearest \$100. A strategy is labeled “dominated” if it is more costly and less effective than another strategy or some combination of other strategies. A strategy is labeled “cost-effective” if it is not dominated by any other strategy and it has the largest ICER not exceeding the willingness-to-pay (WTP) for an additional year of life. In this analysis, we use a WTP threshold of US\$1950, equal to the 2017 Indian per capita gross domestic product. The cost-effective strategy is shown in bold (2 right-hand columns).

Abbreviations: Dom, dominated; ICER, incremental cost-effectiveness ratio; LY, life-years; MSM, men who have sex with men; PrEP, preexposure prophylaxis; PWID, people who inject drugs; TGW, transgender women; YLS, year of life saved.

^aStrategies are as follows: StatusQuo, no preexposure prophylaxis or additional human immunodeficiency virus testing; 1timeTest, 1-time human immunodeficiency virus test; 3mTesting, 6mTesting, and 12mTesting, routine human immunodeficiency virus testing every 3, 6, or 12 months, respectively; PrEP+3mTesting and PrEP+6mTesting, daily tenofovir disoproxil fumarate/emtricitabine–based preexposure prophylaxis with annual creatinine testing and routine human immunodeficiency virus testing every 3 or 6 months, respectively.

Figure 1. Comparison of different strategies for human immunodeficiency virus testing and preexposure prophylaxis in terms of life expectancy and costs for men who have sex with men (A) and people who inject drugs (B). This figure portrays all 7 strategies in a 2-dimensional cost-effectiveness plane, with lifetime costs on the horizontal axis and life expectancy on the vertical axis. The gray line is the “efficiency frontier,” a boundary that traces out the maximum benefit that can be obtained for any given level of investment. The efficiency frontier forms the outer envelope of the “efficient programs” (ie, programs that deliver a given level of benefit at a lower cost than any alternative program or collection of programs). Strategies that lie below the frontier are labeled “dominated.” Shapes and colors represent testing frequencies: the orange circle represents a 1-time test, the purple diamond represents yearly testing, and the blue square and green triangle represent 6- and 3-month testing, respectively. All outcomes are discounted 3% per year and include the benefits of transmissions averted. Abbreviations: 1timeTest, 1-time human immunodeficiency virus test; 3mTesting, routine human immunodeficiency virus testing every 3 months; 6mTesting, routine human immunodeficiency virus testing every 6 months; 12mTesting, routine human immunodeficiency virus testing every 12 months; MSM, men who have sex with men; PrEP+3mTesting, daily tenofovir disoproxil fumarate/emtricitabine-based preexposure prophylaxis with annual creatinine testing and routine human immunodeficiency virus testing every 3 months; PrEP+6mTesting, daily tenofovir disoproxil fumarate/emtricitabine-based preexposure prophylaxis with annual creatinine testing and routine human immunodeficiency virus testing every 6 months; PWID, people who inject drugs; StatusQuo, no preexposure prophylaxis or additional human immunodeficiency virus testing.

much greater impact, with lifetime infection risk declining to 5.3% in PrEP+3mTesting. Over 15 years, transmissions averted from MSM ranged from 8020 with 1timeTest to 203 290 with PrEP+3mTesting (Table 2). In PWID, results were similar; PrEP+3mTesting decreased lifetime HIV infection risk from 16.1% to 7.4%, and transmissions averted ranging from 2220 with 1timeTest to 72 230 with PrEP+3mTesting (Table 2 and Supplementary Tables 1–5).

PrEP also had a much greater impact than routine HIV testing on life expectancy. In MSM, 3mTesting increased

life-years (undiscounted) by 0.30 years, while PrEP+3mTesting increased life-years by 0.91 years. In PWID, life expectancy also increased substantially with PrEP compared to testing strategies alone; routine testing every 3 months increased life expectancy by 0.27 years, whereas PrEP+3mTesting increased life expectancy by 0.93 years.

Cost and Cost-effectiveness

For MSM, discounted per-person lifetime costs were \$380 for StatusQuo and \$830 for PrEP+6mTesting (Table 2). Over a 15-year time horizon, 1timeTest was the cost-effective strategy, with an ICER of \$900/YLS. Because the benefits of PrEP accrue over time, at a lifetime horizon, 1timeTest and 12mTesting were economically efficient, though PrEP+6mTesting was the cost-effective strategy, with an ICER of \$1000/YLS (Table 2 and Figure 1).

For PWID, discounted per-person lifetime costs were \$460 for StatusQuo and \$700 for PrEP+6mTesting. 1timeTest was the cost-effective strategy over a 15-year horizon, with an ICER of \$1000/YLS (Table 2). At a lifetime horizon, 1timeTest was still efficient, with an ICER of \$400/YLS; no other routine testing strategies were economically efficient. Similarly, PrEP+6mTesting was the cost-effective strategy for PWID at a lifetime horizon, with an ICER of \$500/YLS. For both HRGs, there is a relatively large incremental survival benefit to PrEP, but a diminishing incremental benefit to more frequent testing (Figure 1).

Sensitivity Analysis

In 1-way sensitivity analysis, for both MSM and PWID, ICERs were most sensitive to HIV incidence, PrEP costs, and intervention stopping age (Figure 2). The ICER for PrEP+6mTesting for both HRGs increased to above the WTP threshold only if incidence was below 0.6/100 PY. We also considered simultaneous variation of HIV incidence and PrEP costs (Figure 3) as well as HIV incidence and intervention stopping age (Supplementary Figure 1). If MSM incidence was 1.2/100 PY, as is the case in specific regions in India, PrEP+6mTesting was cost-saving if PrEP costs decreased to \$1/month (Figure 3). If PWID incidence was 2.8/100 PY, also the case in specific regions, PrEP+6mTesting was cost-saving compared to 12mTesting for PrEP costs up to \$5/month. PrEP+6mTesting ceased to be cost-effective when the intervention continued until age 55 and incidence was below 0.8/100 PY in MSM or 1.2/100 PY in PWID (Supplementary Figure 1).

As the WHO guidelines currently suggest every 3-month HIV testing with PrEP, we also considered whether PrEP+3mTesting, compared to PrEP+6mTesting, could be cost-effective (Supplementary Figure 3). Across a plausible range of HIV incidence (0.4–2.4/100 PY) and test costs (\$1–\$7/test), PrEP+3mTesting was never cost-effective for MSM. PrEP+3mTesting became cost-effective for PWID only with HIV incidence $\geq 3.6/100$ PY and test costs of \$1/test.

Figure 2. One-way sensitivity analysis on the cost-effectiveness of daily tenofovir disoproxil fumarate/emtricitabine-based preexposure prophylaxis with annual creatinine testing and routine human immunodeficiency virus testing every 6 months (PrEP+6mTesting) compared to routine human immunodeficiency virus testing every 12 months (12mTesting) among men who have sex with men (A) and people who inject drugs (B). This “tornado” diagram portrays the results of a series of 1-way sensitivity analyses. Each horizontal bar represents the range of incremental cost-effectiveness ratio (ICERs) for PrEP+6mTesting compared to 12mTesting when a given model parameter is varied across its plausible range. Ranges examined are presented next to the parameter label as (base case value: parameter input corresponding to the lowest ICER/parameter input corresponding to the highest ICER). Uptake refers to varying 12mTesting and PrEP+6mTesting uptake simultaneously, keeping the uptake ratio constant. Parameters are arranged along the vertical axis in order of their impact on the ICER, with the most influential parameters at the top of the figure. The dashed line represents the 2017 Indian per capita gross domestic product of US\$1950. ICERs to the left of the dashed line are “cost-effective.” Abbreviations: GDP, gross domestic product; HIV, human immunodeficiency virus; ICER, incremental cost-effectiveness ratio; MSM, men who have sex with men; PrEP, preexposure prophylaxis; PWID, people who inject drugs; PY, person-years; YLS, years of life saved.

When HIV incidence, PrEP efficacy, and intervention uptake were simultaneously varied in PSA, the ICER for PrEP+6mTesting had a 70% chance of being cost-effective for MSM at the base case WTP threshold. The PSA further demonstrated that under plausible distributions for the 3 variables, PrEP+6mTesting remained cost-effective for PWID with high certainty at the same WTP threshold (Supplementary Figure 4).

Budget Impact Analysis

We estimated the budget impact if HIV testing and PrEP were available to the estimated 3.1 million MSM and 1.1 million PWID in India, with a program participation rate (uptake) of 55.7% (PrEP strategies) and 63.2% (testing strategies). Over a 5-year horizon, 1timeTest increased expenditures for MSM from \$151 million to \$206 million, or by \$55 million

compared to StatusQuo (36%, Figure 4). PrEP+6mTesting, while cost-effective by the GDP criterion, increased outlays to \$859 million, or by \$708 million (469%). This budget impact includes \$30 million in offsets (over the same 5-year horizon) from transmissions averted to those outside the HRG in the PrEP+6mTesting strategy. For PWID, 1timeTest increased spending from \$74 million to \$96 million, or by \$21 million compared to StatusQuo (28%). PrEP+6mTesting increased expenditures to \$292 million, or by \$218 million (293%). These expenditures include \$6 million in offsets from transmissions averted from PWID to those outside the HRG in PrEP+6mTesting. Over a 15-year horizon, making PrEP with 6-month testing available to MSM and PWID in India would increase the HIV care budget by US\$1.67 billion (MSM) and US\$387 million (PWID) compared to the status quo (Supplementary Figure 2).

Figure 3. Multiway sensitivity analysis on the cost-effectiveness of daily tenofovir disoproxil fumarate/emtricitabine-based preexposure prophylaxis (PrEP) with annual creatinine testing and routine human immunodeficiency virus testing every 6 months (PrEP+6mTesting) compared to routine human immunodeficiency virus (HIV) testing every 12 months (12mTesting) for men who have sex with men (A) and people who inject drugs (B). This figure shows the incremental cost-effectiveness ratio (ICERs) of PrEP+6mTesting compared to 12mTesting when HIV incidence and PrEP costs are varied simultaneously. PrEP costs are varied from the base case value of \$5.55 along the horizontal axis. Incidence is varied along the vertical axis across a plausible range for each high-risk group. Green indicates cost-savings (ie, PrEP+6mTesting costs less and confers greater life-years than 12mTesting); blue demonstrates that the ICER is less than half the Indian annual per capita gross domestic product (GDP) in 2017, (US\$1950); yellow suggests that the ICER is between 0.5 and 1 times the 2017 per capita GDP; red indicates that the ICER is above the 2017 per capita GDP. The "X" marks where the base case value lies. We labeled ICERs below the annual Indian per capita GDP as "cost-effective" (see Methods). Abbreviations: GDP, gross domestic product; HIV, human immunodeficiency virus; MSM, men who have sex with men; PrEP, preexposure prophylaxis; PWID, people who inject drugs; PY, person-years.

DISCUSSION

The concentration of HIV in HRGs in India is a major concern of the Indian National AIDS Control Organization (NACO), with voluntary counseling and testing centers focused on these populations continuing to expand throughout the country. However, the percentage of HIV-infected HRG members aware of their status remains relatively low, incidence is high, and transmission from HRG members to the general population is a major concern for the spread of HIV infection [1, 13]. Determining the impact of focused intervention efforts for HRGs is a critical consideration in India.

Using a validated simulation model of HIV disease and treatment, we demonstrated that at a lifetime horizon, PrEP with 6-month HIV testing is the cost-effective strategy for both MSM and PWID in India. Offering 3-month testing with PrEP—the current recommended testing frequency by WHO [6]—is not a cost-effective strategy in India. PrEP was more economically

efficient (ICER <0.5 times GDP) for PWID, reflecting higher HIV incidence in this population.

Both 1- and 2-way sensitivity analysis, as well as PSA, suggest that results are highly sensitive to HIV incidence, with PrEP not being cost-effective with incidence <0.6/100 PY. As the HIV epidemic in India is concentrated in particular regions (eg, major urban areas in the south for MSM, and in the northeast for PWID), where the incidence across cities reaches as high as 1.2/100 PY for MSM and 4.0/100 PY for PWID [2], PrEP for these risk groups will be more economically efficient on a city-specific basis. Our results demonstrated that the value of routine HIV testing and PrEP accrues over time, as neither the routine testing strategies nor the PrEP strategies were cost-effective at 15 years but became so over a lifetime. This is because a primary benefit of both testing and PrEP is in averting HIV transmissions, which result in life-years gained and cost savings years later.

Figure 4. Five-year budget impact of 4 strategies for human immunodeficiency virus (HIV) testing and preexposure prophylaxis (PrEP) in India. This shows the total undiscounted expenditures over 5 years for men who have sex with men (MSM) (A) and people who inject drugs (PWID) (B), based on an estimated 3.1 million MSM and 1.1 PWID currently living in India. Strategies considered include no preexposure prophylaxis or additional HIV testing; 1-time HIV test; routine HIV testing every 12 months; and daily tenofovir disoproxil fumarate/emtricitabine–based preexposure prophylaxis with annual creatinine testing and routine HIV testing every 6 months. Expenditures attributable to the primary cohort are stratified into 4 categories: (i) expenditures directly attributed to the intervention, including increased HIV testing, clinic visits, and PrEP drug costs; (ii) direct antiretroviral therapy (ART) expenditures, which include the cost of ART drugs for those who acquire HIV; (iii) other HIV care expenditures that include all other associated HIV medical costs, such as CD4 testing, HIV viral load testing, clinic visits, and opportunistic disease costs; and (iv) background testing, which includes HIV testing associated with current levels of screening in India. Outlays for the primary cohort incorporate savings from reduced transmission within the primary cohort itself. Savings from reduced transmission outside the primary cohort are accounted for separately (green bars). Total expenditures are calculated by subtracting the savings from transmissions averted from HIV care outlays associated with the primary cohort. Abbreviations: 1timeTest, 1-time human immunodeficiency virus test; 12mTesting, routine human immunodeficiency virus testing every 12 months; ART, antiretroviral therapy; HIV, human immunodeficiency virus; HVL, human immunodeficiency virus viral load test; M, millions; MSM, men who have sex with men; PrEP, preexposure prophylaxis; PrEP+6mTesting, daily tenofovir disoproxil fumarate/emtricitabine–based preexposure prophylaxis with annual creatinine testing and routine human immunodeficiency virus testing every 6 months; PWID, people who inject drugs; StatusQuo, no preexposure prophylaxis or additional human immunodeficiency virus testing; USD, US dollars.

PrEP with 6-month testing, while cost-effective by the GDP criterion, would require a substantial fiscal investment if offered to all MSM and PWID in India. The NACO of India reported an annual budget of approximately \$279 million for 2017, or \$1.40 billion over the next 5 years if the budget remains stable [38]. This suggests that either a major part of the budget would have to be redirected to provide PrEP to all MSM and PWID or additional resources would be needed. It may be more feasible in the near

term to offer PrEP to MSM and PWID in regions with the highest HIV incidence. If on-demand PrEP were proven effective in India, this could decrease the budget impact of a PrEP program [4].

Our analysis has several limitations. First, although our approach accounts for the individual benefit of an intervention (for HRG members) and the community benefit gained from preventing transmission, we included only the first “generation” of transmissions from inside to outside the HRG. We did

not account for the chain effect of subsequent generations of transmissions in the general population. Hence, the number of transmissions averted is somewhat underestimated. Second, although an oral TDF-based PrEP demonstration project for MSM/TGW is proposed and soon to be under way in India [39], we do not currently have India-specific data on PrEP effectiveness. We therefore relied on data from other countries and qualitative surveys to account for potential uptake [4]. Finally, we did not account for the potential non-HIV-related benefits of frequent HIV testing as part of a PrEP program, such as the opportunity to diagnose and treat other sexually transmitted infections at these visits.

In summary, in contrast to the WHO-recommended 3-month testing with PrEP, PrEP with 6-month testing is the cost-effective strategy for MSM and PWID in India. PrEP with every 6-month testing, however, would entail substantial healthcare expenditures. Given the country's HIV budget, other opportunity costs, and the fact that PrEP with 6-month testing is more economically efficient at higher incidence, PWID and MSM in regions with the highest HIV incidence may be appropriate initial targets for PrEP programs in India.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health (NIH), Massachusetts General Hospital (MGH), or Harvard University.

Financial support. This work was supported by the NIH (grant numbers R01 MH105203 and R01 DA015612 to A. D. P., 5UM1 AI069432 to N. K., and R37 AI058736 to P. K., K. H. M., and K. A. F.); the Harvard University Center for AIDS Research (grant number P30 AI060354 to K. H. M.); and the Steve and Deborah Gorlin MGH Research Scholar Award (to R. P. W.).

Potential conflicts of interest. K. H. M. has received research grants from ViiV Healthcare and Gilead Sciences. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. National AIDS Control Organisation (NACO). India HIV estimations: 2015 technical report. Available at: <http://naco.gov.in/sites/default/files/India%20HIV%20Estimations%202015.pdf>. Accessed 2 November 2018.
2. Solomon SS, Mehta SH, McFall AM, et al. Community viral load, antiretroviral therapy coverage, and HIV incidence in India: a cross-sectional, comparative study. *Lancet HIV* **2016**; 3:e183–90.
3. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* **2016**; 387:53–60.
4. Molina JM, Capitant C, Spire B, et al; ANRS IPERGAY Study Group. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* **2015**; 373:2237–46.
5. National AIDS Control Organisation (NACO). National guidelines for HIV testing. **2015**. Available at: http://www.naco.gov.in/sites/default/files/National_Guidelines_for_HIV_Testing_21Apr2016.pdf. Accessed 2 November 2018.
6. World Health Organization. WHO implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. **2017**. Available at: <http://www.who.int/hiv/pub/prep/prep-implementation-tool/en/>. Accessed 19 November 2018.
7. Mullins TL, Lally M, Zimet G, Kahn JA; Adolescent Medicine Trials Network for HIV/AIDS Interventions. Clinician attitudes toward CDC interim pre-exposure prophylaxis (PrEP) guidance and operationalizing PrEP for adolescents. *AIDS Patient Care STDS* **2015**; 29:193–203.
8. Katz DA, Welch HG. Discounting in cost-effectiveness analysis of healthcare programmes. *Pharmacoeconomics* **1993**; 3:276–85.
9. Paltiel AD, Weinstein MC, Kimmel AD, Seage GR 3rd, Losina E, Zhang H, et al. Expanded screening for HIV in the United States—an analysis of cost-effectiveness. *N Engl J Med* **2005**; 352:586–95.
10. Walensky RP, Borre ED, Bekker LG, Resch SC, Hyle EP, Wood R, et al. The anticipated clinical and economic effects of 90–90–90 in South Africa. *Ann Intern Med* **2016**; 165:325–33.
11. Deshpande S, Bharat S. Sexual partner mixing and differentials in consistent condom use among men who have sex with men in Maharashtra, India. *Glob Public Health* **2015**; 10:103–18.
12. Kermode M, Armstrong G, Medhi GK, Humtsoe C, Langkham B, Mahanta J. Sexual behaviours of men who inject drugs in northeast India. *Harm Reduct J* **2015**; 12:4.
13. Solomon SS, Mehta SH, Latimore A, Srikrishnan AK, Celentano DD. The impact of HIV and high-risk behaviours on the wives of married men who have sex with men and injection drug users: implications for HIV prevention. *J Int AIDS Soc* **2010**; 13(Suppl 2):S7.
14. Thomas B, Mimiaga MJ, Kumar S, Swaminathan S, Safren SA, Mayer KH. HIV in Indian MSM: reasons for a concentrated epidemic and strategies for prevention. *Indian J Med Res* **2011**; 134:920–9.
15. Aceijas C, Friedman SR, Cooper HLE, Wiessing L, Stimson GV, Hickman M. Estimates of injecting drug users at the national and local level in developing and transitional countries, and gender and age distribution. *Sex Trans Infect* **2006**; 82(Suppl 3):iii10–7.
16. Saggurti N, Mishra RM, Proddutoor L, et al. Community collectivization and its association with consistent condom use and STI treatment-seeking behaviors among female sex workers and high-risk men who have sex with men/transgenders in Andhra Pradesh, India. *AIDS Care* **2013**; 25(Suppl 1):S55–66.
17. Lucas GM, Solomon SS, Srikrishnan AK, et al. High HIV burden among people who inject drugs in 15 Indian cities. *AIDS* **2015**; 29:619–28.
18. Solomon SS, Celentano DD, Srikrishnan AK, et al. Mortality among injection drug users in Chennai, India (2005–2008). *AIDS* **2009**; 23:997–1004.
19. National AIDS Control Organisation (NACO). Annual report 2015–2016. Available at: http://naco.gov.in/sites/default/files/Annual%20Report%202015-16_NACO.pdf. Accessed 2 November 2018.
20. Joint United Nations Programme on HIV/AIDS. India progress report. **2010**. Available at: http://data.unaids.org/pub/report/2010/india_2010_country_progress_report_en.pdf. Accessed 2 November 2018.
21. Mehta SH, Lucas GM, Solomon S, et al. HIV care continuum among men who have sex with men and persons who inject drugs in India: barriers to successful engagement. *Clin Infect Dis* **2015**; 61:1732–41.
22. Venkatesh KK, Becker JE, Kumarasamy N, et al. Clinical impact and cost-effectiveness of expanded voluntary HIV testing in India. *PLoS One* **2013**; 8:e64604.
23. Shekhawat BS, Jain S, Solanki HK. Caregiver burden on wives of substance-dependent husbands and its correlates at a tertiary care centre in northern India. *Indian J Public Health* **2017**; 61:274–7.
24. Alvarez-Uria G. Factors associated with delayed entry into HIV medical care after HIV diagnosis in a resource-limited setting: data from a cohort study in India. *PeerJ* **2013**; 1:e90.
25. Chakrapani V, Newman PA, Shunmugam M, et al. Acceptability of HIV pre-exposure prophylaxis (PrEP) and implementation challenges among men who have sex with men in India: a qualitative investigation. *AIDS Patient Care STDS* **2015**; 29:569–77.
26. Schneider J, Kumar R, Dandona R, et al. Social network and risk-taking behavior most associated with rapid HIV testing, circumcision, and preexposure prophylaxis acceptability among high-risk Indian men. *AIDS Patient Care STDS* **2012**; 26:631–40.
27. Anderson PL, Glidden DV, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci Transl Med* **2012**; 4:151ra25.
28. Grinsztejn B, Hoagland B, Moreira RI, et al; PrEP Brasil Study Team. Retention, engagement, and adherence to pre-exposure prophylaxis for men who have sex with men and transgender women in PrEP Brasil: 48 week results of a demonstration study. *Lancet HIV* **2018**; 5:e136–45.
29. UpToDate. Estimated per-act risk for acquisition of HIV, by exposure route. **2018**. Available at: https://www.uptodate.com/contents/image?imageKey=ID%2F60145&topicKey=ID%2F113426&rank=1~99&source=see_link&search=prep%20toxicities. Accessed 2 November 2018.

30. amfAR: The Foundation for AIDS Research. Addressing HIV among transgender individuals in Asia. **2015**. Available at: <http://amfar.org/Addressing-HIV-Among-Transgender-Individuals-in-Asia/>. Accessed 2 November 2018.
31. Bellan SE, Dushoff J, Galvani AP, Meyers LA. Reassessment of HIV-1 acute phase infectivity: accounting for heterogeneity and study design with simulated cohorts. *PLoS Med* **2015**; 12:e1001801.
32. Walmsley SL, Antela A, Clumeck N, et al; SINGLE Investigators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med* **2013**; 369:1807–18.
33. Clinton Health Access Initiative. 2016 CHAI ARV reference price list. **2016**. Available at: http://www.clintonhealthaccess.org/content/uploads/2016/11/2016-CHAI-ARV-Reference-Price-List_FINAL.pdf. Accessed 2 November 2018.
34. Homan RK, Ganesh AK, Duraisamy P, et al. Economic analyses of YRG CARE services: implications for program sustainability. Research Triangle Park, NC: Family Health International, **2000**.
35. Médecins Sans Frontières. Untangling the web of antiretroviral price reductions. Available at: http://www.msfaccess.org/sites/default/files/MSF_UTW_17th_Edition_4_b.pdf. Accessed 2 November 2018.
36. Attia S, Egger M, Müller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. *AIDS* **2009**; 23:1397–404.
37. US Department of Veterans Affairs. Budget impact analysis. Available at: <https://www.herc.research.va.gov/include/page.asp?id=budget-impact-analysis>. Accessed 2 November 2018.
38. The Asian Age. After 2016 cut, fund to fight AIDS receives 17.62 percent boost. **2017**. Available at: <http://www.asianage.com/india/all-india/020217/after-2016-cut-fund-to-fight-aids-receives-1765-per-cent-boost.html>. Accessed 2 November 2018.
39. Sahay S, Dhayarkar-Bangar S. To study feasibility of oral TDF-containing PrEP, administered, once daily orally to men having sex with men (MSM) and transgenders (TGs) in India. New Delhi: Indian Council of Medical Research, **2017**.