Clinical Benefits and Cost-Effectiveness of Laboratory Monitoring Strategies to Guide Antiretroviral Treatment Switching in India

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Abstract

Current Indian guidelines recommend twice-annual CD4 testing to monitor first-line antiretroviral therapy (ART), with a plasma HIV RNA test to confirm failure if CD4 declines, which would prompt a switch to second-line ART. We used a mathematical model to assess the clinical benefits and cost-effectiveness of alternative laboratory monitoring strategies in India. We simulated a cohort of HIV-infected patients initiating first-line ART and compared 11 strategies with combinations of CD4 and HIV RNA testing at varying frequencies. We included adaptive strategies that reduce the frequency of tests after 1 year from 6 to 12 months for virologically suppressed patients. We projected life expectancy, time on failed first-line ART, cumulative 10-year HIV transmissions, lifetime cost (2014 US dollars), and incremental cost-effectiveness ratios (ICERs). We defined strategies as cost-effective if their ICER was $<1 \times$ the Indian per capita gross domestic product (GDP, \$1,600). We found that the current Indian guidelines resulted in a per person life expectancy (from mean age 37) of 150.2 months and a per person cost of \$2,680. Adding annual HIV RNA testing increased survival by ~ 8 months; adaptive strategies were less expensive than similar nonadaptive strategies with similar life expectancy. The most effective strategy with an ICER $<1 \times$ GDP was the adaptive HIV RNA strategy (ICER \$840/year). Cumulative 10-year transmissions decreased from 27.2/1,000 person-years with standard-of-care to 20.9/1,000 person-years with adaptive HIV RNA testing. In India, routine HIV RNA monitoring of patients on first-line ART would increase life expectancy, decrease transmissions, be cost-effective, and should be implemented.

Keywords: HIV, India, laboratory monitoring, cost-effectiveness

Introduction

OVER 2 MILLION PEOPLE in India are living with HIV, the third largest national epidemic.¹ In 2004, the Indian National AIDS Control Organization (NACO) began providing antiretroviral therapy (ART) to patients free of charge

at eight government hospitals.² Second-line ART was introduced to the program in 2008. Subsequently, the number of ART centers providing treatment increased substantially—by late 2016, around 900,000 people were receiving first-line ART and around 16,000 were on second-line ART.³ With new guidelines to treat all regardless of CD4

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count, and the continued increase in rollout, identifying the best monitoring strategy for patients on first-line ART to determine when to switch treatment to second-line is critical.^{4,5}

Current World Health Organization (WHO) guidelines recommend CD4 counts to assess baseline risk and at 6 and 12 months in persons with stable viral suppression, or continued every 6 months if viral load is not available. If available, viral load monitoring is recommended at 6 and 12 months, and then every 12 months.⁴ In many resource-limited settings, however, the high cost of routine viral load monitoring has limited its use.^{6,7} National guidelines in India now recommend 6-monthly CD4 monitoring to identify suspected first-line failure, followed by an HIV RNA test to confirm virologic failure and trigger a switch to second-line ART.^{8,9} There is currently a plan to move to routine HIV RNA monitoring as recommended by the WHO, scaling-up throughout the next few years.¹⁰

Essential to achieving the UNAIDS 90-90-90 global HIV virologic suppression treatment target is the accurate detection of ART failure and switching to effective therapy.¹¹ Immunologic failure criteria using CD4 monitoring have been shown, however, to have poor accuracy for detecting virologic failure and can result in switching patients to second-line ART either too early or too late.^{8,12} Individuals who switch early, without virologic failure, spend more time on costly second-line ART.¹³ Those who switch late, months or years after virologic failure, spend more time at increased risk of HIV-related morbidity and mortality, may develop resistance mutations necessitating either more expensive salvage therapies or inevitable disease progression, and will have longer periods with viremia and risk of transmission.¹³⁻¹⁶ Our objective was to estimate the long-term clinical impact and cost-effectiveness of alternative monitoring strategies to detect virologic failure and guide switching to second-line ART for HIV-infected patients in India.

Methods

Analytic overview

We used a mathematical microsimulation model of HIV disease progression and treatment to project outcomes associated with alternative monitoring strategies for HIV-infected patients on first-line ART in India.¹⁷⁻²¹ We simulated a cohort of patients initiating first-line ART and compared different potential monitoring strategies for diagnosing ART failure and guiding switch to a second-line protease inhibitor-based regimen. Model outcomes included projected life expectancy, 10-year primary transmissions per 1,000 HIV-infected person-years, lifetime costs, incremental cost-effectiveness ratios (ICERs) measured in 2014 U.S. dollars per year of life saved (\$/YLS), and 5-year budgetary impact from an all payer perspective. Costs and life expectancy were discounted at 3% annually for cost-effectiveness results. Costs were reported undiscounted for budgetary impact.²² We categorized strategies with an ICER less than $1 \times$ India's annual per capita gross domestic product (GDP) (\$1,600 in 2014) as cost-effective.^{23,24} To assess the impact of uncertainty around parameter estimates as they relate to the ICER threshold, we conducted sensitivity analysis on model parameters in multiple domains.²⁵

The Cost-Effectiveness of Preventing AIDS Complications International (CEPAC-I) Model

The Cost-Effectiveness of Preventing AIDS Complications International (CEPAC-I) model is a widely published and validated microsimulation of HIV disease and treatment in multiple countries.^{17-20,26} Briefly, the model simulates a cohort of HIV-infected individuals based on distributions of demographic (age, gender) and clinical (CD4 count, HIV RNA) characteristics. In the absence of suppressive ART, patients experience a monthly decline in CD4 count; higher set point HIV RNA is associated with more rapid CD4 decline.^{27,28} CD4 count, in turn, determines the monthly risk of HIV-related morbidity and mortality.²⁹⁻³² Co-trimoxazole prophylaxis reduces the risk of certain HIV-related diseases.^{30,33}

Upon starting an ART regimen, each patient has an initial probability of achieving HIV RNA suppression. This probability is correlated with a patient's adherence level, with highly-adherent patients more likely to achieve suppression.³⁴ Patients who achieve virologic suppression experience a monthly increase in CD4 count (with an upper bound defined by the average CD4 count of an HIV-uninfected person), reducing their risk of morbidity and mortality. Patients on suppressive ART are subject to a monthly probability of later virologic failure that is inversely correlated with adherence (i.e., highly adherent patients have a lower probability of later failure). Upon virologic failure, and in the absence of additional suppressive ART, HIV RNA returns to set-point and CD4 counts begin to decline.

Regimen failure is defined by the 2016 WHO antiretroviral guidelines, 6 months after ART initiation: CD4 count below pre-ART baseline or less than 100 cells/ μ l (immunologic failure), HIV RNA above 1,000 copies/ml (virologic failure), or WHO stage 3/4 clinical event (clinical failure).⁴ When available, HIV RNA test results (either routine or confirmatory) are used to make final treatment decisions. Strategies without HIV RNA confirmation of failure require consistent CD4 tests (routine and confirmatory) to result in a failure diagnosis. We assumed that patients remain on second-line ART until death or loss to follow-up. On second-line ART, patients receive 6-monthly CD4 monitoring for the purposes of prescribing prophylaxis.

The model tracks each simulated patient's "true" underlying CD4 count and HIV RNA. Treatment decisions, however, such as ART failure diagnosis and switching to next line ART regimen, are based on CD4 count and/or HIV RNA "observed" through laboratory monitoring. For patients on ART, CD4 count and HIV RNA testing can be performed either on a routine, adaptive, or confirmatory basis. With routine laboratory monitoring, tests occur at ART initiation and regular intervals thereafter. Adaptive strategies include switching the frequency of HIV RNA and CD4 monitoring, if part of the strategy, from twice-annual to annual testing after 12 months of virologic suppression. For strategies with confirmatory laboratory monitoring, HIV RNA tests are performed to confirm a diagnosis of regimen failure (based on a routine CD4 count, routine HIV RNA test, or a clinical finding) and trigger regimen switches. Upon diagnosis of regimen failure, all patients restart their previous regimen (in case of nonadherence), with a chance for resuppression with CD4 increase or virologic suppression. The monitoring strategy for the resuppression regimen is as defined by the strategy, and observed failure on this restart prompts a switch to second-line ART.

Patients also experience a monthly, adherence-stratified risk of loss to follow-up. Once lost, patients can return to care at a defined monthly rate, or by presenting with an opportunistic infection. Additional model structure details are both published and online (<http://web2.research.partners.org/cepac>).^{17,18,20,26,35}

Transmissions

To project 10-year primary HIV transmissions originating from the modeled cohort, we used model-reported monthly HIV RNA output and meta-analysis based transmission rates.^{16,36} We reported transmissions per 1,000 HIV-infected person-years over 10 years. We excluded higher-order transmissions (i.e., those originating from these primary transmissions). To maintain conservative cost-effectiveness projections, we did not include the impact of monitoring strategies on transmission in our cost-effectiveness analysis.

Simulated strategies

We simulated 11 potential monitoring strategies that varied in the frequency of CD4 monitoring (twice-annual and annual) and the frequency of HIV RNA monitoring (none, confirmation only, twice-annual, and annual) (Appendix Table A1). Adaptive strategies all included HIV RNA monitoring. In adaptive strategies, testing frequencies decrease from twice-annual testing to annual testing after patients were observed to have been virologically suppressed for at least 12 months post ART-initiation. For the adaptive HIV RNA test strategy and the adaptive CD4 and HIV RNA test strategy, both HIV RNA and CD4 tests were implemented in an adaptive manner. For the twice-annual CD4 and adaptive HIV RNA (WHO) strategy, only the HIV RNA test was implemented in an adaptive manner (Appendix Table A1). In every strategy that includes both routine CD4 and routine HIV RNA monitoring, all routine

TABLE 1. SELECTED MODEL INPUTS FOR AN ANALYSIS OF LABORATORY MONITORING FOR HIV-INFECTED PERSONS IN INDIA

Parameter	Base case value	Range evaluated	Reference
Initial cohort characteristics			
CD4 count, mean (SD) cells/ μ l	192 (109)	83–301	37 ^a
Age, mean (SD) years	37 (10)		38 ^a
Gender, % male	48		38 ^a
HIV RNA set point, median (IQR) log ₁₀ copies/ml	4.8 (4.3–5.2)		29 ^b
Baseline ART adherence, % of cohort			40 ^b
Adherence <50%	6		
Adherence 50%–95%	57		
Adherence $\geq$ 95%	37		
ART efficacy			37,40 ^b
HIV RNA suppression at 6 months, overall, % ^c	84	74–94	
HIV RNA resuppression at 6 months, overall, %	19	10–50	
Virologic failure rate after 6 months, %/month	0.54		
Mean CD4 gain while suppressed, cells/ μ l/month			
Months 1–2	76		
Months 3 and after	4		
Delay to second-line therapy initiation after observed failure, month(s)	1	1–24	Assumption
Loss to follow-up, %/month			40,44
Adherence <50%	1.6		
Adherence >95%	0.2		
Transmission, rate/100PY			16
Late-stage disease (CD4 cell count <200 cells/ μ l)	9.03		
HIV RNA level			
>100,000 copies/ml	9.03		
10,001–100,000 copies/ml	8.12		
3,001–10,000 copies/ml	4.17		
501–3,000 copies/ml	2.06		
$\leq$ 500 copies/ml	0.16		
Costs (2014 USD)			
First-line ART, annually	95.5	47.8–191.0	45
Second-line ART, annually	260.4	95.5–425.3	45
Third-line ART, annually	1,693		71
CD4 test, per test	3.4		45
HIV RNA test, per test	20.5	3.4–37.5	45
Number of persons in care with a CD4 count of 350–500 cells/ μ l	120,000		45
Number of persons in care with a CD4 count >500 cells/ μ l	170,000		45

^aDistributions are truncated normal distributions calculated to fit stratified distributions in referenced sources.

^bModel input values derived from primary data described in referenced source.

^cOverall suppression will be lower for second-line ART, as poorly-adherent patients are more likely to fail first-line ART and initiate second-line ART.

ART, antiretroviral therapy; IQR, interquartile range; NACO, National AIDS Control Organization; PY, person-year; SD, standard deviation; USD, United States dollars.

CD4 monitoring was stopped after the patients' observed CD4 rose above 200 cells/ μ l and they had been on ART for at least 6 months.

Base case model inputs

Model inputs were derived primarily from Indian cohorts (Table 1). Mean [standard deviation (SD)] CD4 count at ART initiation was 192 (109) cells/ μ l and ART was initiated at all CD4 counts.³⁷ Mean (SD) age was 37 (10) years, and 48% of patients were male.³⁸ The HIV RNA set point distribution was derived from a cohort of HIV-infected patients entering care at the Y.R. Gaitonde Centre for AIDS Research and Education (YRG CARE) in Chennai.²⁹ ART efficacy for first- and second-line, stratified by the adherence distribution, resulted in an overall 84% HIV RNA suppression rate, consistent with data from Indian studies.^{37,39–43} Patients had a 19% chance of HIV RNA resuppression at 6 months when restarting a failed regimen.³⁷ Adherence-dependent loss to follow-up rates ranged from 0.2%/month to 1.6%/month.⁴⁴ The CD4-stratified incidence of HIV-related diseases was taken from patients in the YRG CARE cohort.²⁹

Transmission rates ranged from 0.16/100 to 9.03/100 person-years, stratified by HIV RNA (Table 1).¹⁶ Late-stage infection transmission rate was assumed to be the same as in the highest viral load stratum (9.03/100 person-years).

Costs of first-line (\$96/year) and second-line (\$260/year) ART in addition to CD4 count (\$3) and HIV RNA (\$21) tests were from NACO.⁴⁵ CD4-stratified inpatient and outpatient utilization estimates for HIV-related morbidity and mortality were from YRG CARE.⁴⁶ To estimate treatment status- and CD4-stratified costs incurred, including the costs of opportunistic infections, these utilization estimates were multiplied by average costs per inpatient day and per outpatient visit derived from an economic analysis of YRG CARE services.⁴⁷

Sensitivity analyses

We performed sensitivity analyses on key input parameters. We varied CD4 count at ART initiation, first-line ART efficacy, 1-year retention rates, delay to second-line ART after detection of failure, availability of third-line ART, first-line ART cost, HIV RNA test cost, and second-line ART cost. We varied annual per person second-line ART cost from \$96 (~the cost of first-line ART) to \$425 (the difference between first- and second-line ART added to the second-line base case cost). We varied HIV RNA test cost in a similar manner, from \$3 to \$38. In analyses that included third-line ART, patients moved to third-line therapy after observed second-line failure. We defined the efficacy of third-line ART as equal to that of first- and second-line therapy. Once patients were observed to fail third-line ART, they switched back to first-line therapy (with only twice-annual CD4 monitoring) to avoid the unnecessary, high cost of third-line therapy. In accordance with Indian guidelines, we did not move patients failing second-line ART back to first-line in the base-case.⁹ In one-way sensitivity analysis we compared all strategies with each other; we then directly compared the economically efficient strategies with each other to determine which parameters had the greatest impact on the results. In multi-way sensitivity analysis, we varied several parameters at once to determine how those changes might influence the policy conclusions.

Budget impact analysis

To estimate the 5-year budgetary impact of the monitoring strategy defined as cost-effective on the Indian national program, we scaled model-projected undiscounted costs over 5 years to the current number of persons in each of three cohorts of people living with HIV (PLWH) in the Indian national program: (1) persons currently in care and on ART with CD4 counts <350/ μ l (n = 893,000, with scale-up of lab

TABLE 2. CLINICAL AND ECONOMIC OUTCOMES OF IMPLEMENTING MONITORING STRATEGIES FOR HIV-INFECTED PATIENTS IN INDIA

Monitoring strategy	Discounted LE (months)	Time on failed first-line ART	10-Year transmissions (per 1000 person-years)	Discounted lifetime cost (USD)	ICER (USD/YLS)
Annual CD4 with HIV RNA confirmation	148.9	47.0	27.3	2,600	—
Twice-annual CD4	146.3	50.9	28.5	2,610	Dominated
Twice-annual CD4 with HIV RNA confirmation (NACO, SOC)	150.2	46.5	27.2	2,680	740
Annual HIV RNA	158.2	12.0	21.6	3,270	Dominated
Annual CD4 and HIV RNA tests	158.4	12.0	21.5	3,270	Dominated
Twice-annual CD4 and annual HIV RNA	158.6	11.7	21.5	3,300	Dominated
Adaptive HIV RNA	160.0	9.2	20.9	3,360	840
Adaptive CD4 and HIV RNA ^a	160.0	9.2	20.8	3,370	Dominated
Twice-annual CD4 and adaptive HIV RNA (WHO)	160.0	9.2	20.8	3,370	Dominated
Twice-annual HIV RNA	159.8	7.9	20.4	3,560	Dominated
Twice-annual CD4 and HIV RNA	159.6	7.9	20.4	3,570	Dominated

Strategies in *bold* are nondominated (see Results section and Fig. 1). All strategies that include both routine CD4 testing and HIV RNA testing stop CD4 testing when observed CD4 counts are >200 cells/ μ l and ART was initiated at least 12 months earlier (see Methods section).

^aBoth CD4 and HIV RNA are done every 6 months for 1 year, then every 12 months.

Adaptive, testing every 6 months for 1 year, then every 12 months thereafter; dominated, strategy is more expensive and less effective than another strategy or less cost-effective than a combination of other strategies, and therefore not an efficient use of resources; ICER, incremental cost-effectiveness ratio; LE, life expectancy; LM, life month; SOC, standard of care; USD, United States dollars; WHO, World Health Organization recommended strategy; YLS, year of life saved.

monitoring over 3 years), (2) persons currently in care with CD4 counts $>350/\mu\text{L}$ expected to initiate ART over the next 3 years ($n=97,000/\text{year}$), and (3) persons expected to enter care and initiate ART each year at any CD4 count, reflective of the recent test and treat policy in India ($n=125,000/\text{year}$).^{5,45} All transmitted cases expected to present to care within the next 5 years in India are included in this budget impact analysis. We did not account for differences in transmission between the strategies. We assumed that these persons would initiate ART with similar clinical characteristics to those in our base case analysis (see Appendix Fig. A1 for a detailed schema of the budget impact analysis). Cost categories were divided into (1) care costs (opportunistic infection treatment and routine care costs), (2) ART costs, (3) CD4 test costs, and (4) HIV RNA test costs.

Results

Base case results

Twice-annual CD4 monitoring, without HIV RNA testing, resulted in the lowest discounted life expectancy (146.3 months, Table 2). With addition of an HIV RNA test to confirm CD4-defined immunologic failure, life expectancy increased to 148.9 months with annual CD4 monitoring and 150.2 months with twice-annual CD4 monitoring. Strategies that included routine and adaptive HIV RNA testing further improved life expectancies, to between 158.2 and 160.0 months. In general, for each monitoring strategy, increasing the frequency of both CD4 and HIV RNA testing from annual to twice-annual resulted in an increase in life expectancy. The three strategies that included adaptive HIV RNA monitoring

resulted in the greatest life expectancy (and similar life expectancy of 160.0 months for each).

Time spent on failed first-line ART and transmission estimate outcomes

Time on failed first-line ART ranged from as high as 50.9 months for twice-annual CD4 monitoring to as low as 7.9 months for twice-annual HIV RNA monitoring. Adding routine HIV RNA monitoring substantially reduced time spent on failed first-line therapy (from 46.5 to 12.0 months). Cumulative 10-year transmissions followed the same trend as time on failed first-line ART, with the most transmissions in the twice-annual CD4 monitoring strategy (28.5/1,000 person-years) and the least transmissions in the twice-annual HIV RNA monitoring strategy (20.4/1,000 person-years).

Costs and cost-effectiveness

Strategies without routine HIV RNA monitoring had the lowest per person discounted lifetime costs (\$2,600–2,680). Routine HIV RNA testing, with or without routine CD4 monitoring, increased lifetime costs (\$3,270–3,570). Adaptive strategies were always less costly than their nonadaptive counterparts. Adding a CD4 test (either twice-annual or annual) to the three strategies that included adaptive HIV RNA monitoring resulted in an increased cost, with no difference in life expectancy.

Two strategies were cost-effective by the GDP criterion, with annual CD4 with HIV RNA confirmation as the comparator strategy. These were (1) Twice-annual CD4 monitoring with confirmatory HIV RNA, the current NACO recommended strategy (ICER=\$740/YLS), and (2) Adaptive HIV RNA

FIG. 1. Projected costs and survival under alternative laboratory monitoring strategies for HIV disease in India. Efficiency frontier of 11 monitoring strategies; testing frequencies are represented by different shapes, annual ($\square$), twice-annual ($\triangle$), adaptive ($\circ$), twice-annual CD4 and annual HIV RNA ($\diamond$), and twice-annual CD4 and adaptive HIV RNA ($\times$). Types of tests included in each strategy are represented by different colors, CD4 testing only (blue), CD4 testing with HIV RNA confirmation (green), HIV RNA testing only (red), and CD4 and HIV RNA testing (purple). Sharp increases in the slope of the efficiency frontier can be observed with the addition of HIV RNA confirmation of CD4 testing. Life expectancy and costs both increase as adaptive HIV RNA monitoring is implemented. Increasing the frequency of HIV RNA monitoring to twice-annual incurs additional cost with no benefit in life expectancy. HVL, HIV viral load; LM, life months; NACO, National AIDS Control Organization; USD, U.S. dollars.

FIG. 2. One-way sensitivity analysis on the cost-effectiveness of adaptive HIV RNA testing in India to monitor first-line ART. This shows the ICER of the adaptive HIV RNA monitoring strategy compared to the NACO monitoring strategy as multiple parameters were varied across plausible ranges. The three parameters that affected the ICERs the most were second-line ART annual costs, HIV RNA test costs, and availability of third-line ART. Ranges are presented in the following format: (base case; value that yields lowest ICER—value that yields highest ICER). The *dashed line* represents 1 $\times$ the Indian per capita GDP of \$1,600, a value commonly used to denote cost-effectiveness in the Indian setting. When all 11 strategies were compared to each other in similar sensitivity analyses the ICER for the adaptive HIV monitoring strategy compared to any of the other strategies remained well below \$1,600/YLS. ART, antiretroviral therapy; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; YLS, year of life saved.

testing (ICER=\$840/YLS, Fig. 1). The adaptive HIV RNA strategy led to the higher life expectancy of these two.

Sensitivity analyses

In one-way sensitivity analyses, we found that the cost-effectiveness of adaptive HIV RNA monitoring compared to the Indian Standard of Care (SOC) (twice-annual CD4 monitoring with HIV RNA confirmation) was most sensitive to second-line ART cost, HIV RNA test cost, availability of third-line ART, and first-line ART cost (Fig. 2). If the cost of second-line ART decreased by 18%, then the ICER for the adaptive HIV RNA strategy dropped below 50% of per capita GDP. Only if the cost increased by 63% would the ICER approach the GDP threshold of \$1,600/YLS. If HIV RNA test costs decreased by 83%, equaling the cost of CD4 testing, then the ICER for the adaptive HIV RNA testing strategy also decreased, to below 50% of Indian per capita GDP. The availability of third-line ART increased the ICER for adaptive monitoring to \$1,270/YLS, due to the relatively high cost of this therapy (\$1,693/year).

We examined the three most important of these parameters in a multi-way sensitivity analysis (Fig. 3). With no third-line ART available, the ICER for the adaptive HIV RNA testing strategy compared to the Indian SOC did not exceed \$1,200/YLS across a plausible range of HIV RNA and second-line ART costs (Fig. 3A). With third-line ART available, the ICER for the adaptive HIV RNA testing strategy approached the Indian per capita GDP of \$1,600/YLS, and then only if second-line ART costs also increased (Fig. 3B).

Budget impact

The 5-year projected HIV-related costs for persons on ART or expected to initiate ART in the next 5 years under

recent test and treat guidelines in the government program in India with the current NACO strategy were \$1.486 billion, of which 57% were care costs, 38% were ART costs, 4% were CD4 test costs, and 1% were HIV RNA test costs (Table 1 and Fig. 4). Adding adaptive HIV RNA monitoring increased total care costs at 5 years by \$292 million (to \$1.778 billion) compared to the current NACO strategy, representing a 20% cost increase over 5 years. Of the total costs, 47% were care costs, 40% were ART costs, 1% were CD4 test costs, and 12% were HIV RNA test costs. If the cost of HIV RNA testing decreased to \$10.25/test (50% of base case cost), then the 5-year costs under current guidelines would decrease to \$1.478 billion and \$1.675 billion for the NACO and adaptive HIV RNA strategies, representing an increase of \$197 million (13%) over 5 years.

Discussion

We used a mathematical model of HIV disease progression and treatment to assess the clinical impact and cost-effectiveness of alternative monitoring strategies to guide switching from first- to second-line ART in India. We found that HIV RNA confirmation of CD4-defined ART failure, recommended by the National AIDS Control Organization in India, is a cost-effective strategy that improves life expectancy (~4 months) with a small increase in cost compared to CD4-only monitoring. Some HIV RNA costs are recouped by averting unnecessary switches to more expensive second-line ART.¹³ Further, we found that adaptive HIV RNA monitoring provides substantial additional survival benefits (~10 months) and was cost-effective (ICER: \$840/YLS) compared to the current SOC of RNA confirmation. This degree of survival benefit compares favorably with that shown for other clinical interventions in India, including tuberculosis

FIG. 3. Three-way sensitivity analysis on second-line ART cost, HIV RNA test cost, and first-line ART efficacy. This shows variations in the ICER for adaptive HIV RNA monitoring compared to the NACO monitoring strategy (twice-annual CD4 testing with HIV RNA confirmation) with changes in second-line ART cost, HIV RNA test cost, and first-line ART efficacy. Second-line ART cost increases along the horizontal axis and HIV RNA test cost increases along the vertical axis. (A) Third-line ART is not available and (B) third-line ART is available. The X represents the base case ICER. The O represents the base case ICER if third-line ART were available.

FIG. 4. Five-year budgetary impact of HIV RNA monitoring strategies in India. We project the 5-year budgetary impact for the standard of care strategy (twice-annual CD4 monitoring with HIV RNA confirmation) and adaptive HIV RNA monitoring. We include both persons in care and on ART at all CD4 counts, and persons who are expected to present to care over the next 5 years. Please see the Methods section and Appendix Figure 1 for a description of all cohorts included in the budgetary impact analysis. Total 5-year costs for each strategy and population size are represented by the height of the bars. We break costs down into the following four categories: (1) care costs, including OI treatment and routine care, (2) ART costs, (3) CD4 test costs, and (4) HIV RNA test costs. OI, opportunistic infection; USD, U.S. dollars.

preventive therapy with isoniazid, HIV testing in high-risk individuals, and newer methods of diabetes treatment.^{19,48,49}

Adaptive strategies, which decrease the frequency of testing from every 6 to every 12 months after 1 year of virologic suppression, were more cost-effective than their nonadaptive counterparts for every strategy. Once patients are suppressed, the probability of virologic rebound is low enough that the frequency of monitoring can be decreased without a decrease in life expectancy. Further, both adaptive and nonadaptive HIV RNA monitoring substantially decreased 10-year transmissions compared with CD4-based monitoring. CD4 and HIV RNA strategies do not increase life expectancy compared with adaptive HIV RNA strategies alone.

Our results were most sensitive to variation in second-line ART costs, HIV RNA test costs, and the availability of third-line therapy. Nonetheless, across a broad range of HIV RNA test and second-line ART costs, the ICER for the adaptive HIV RNA monitoring strategy never exceeded the Indian per capita GDP. Sensitivity analyses highlighted that the cost of the HIV RNA test itself, while influential, is not important enough across a plausible range to bring the ICER of the HIV RNA testing strategy above the cost-effectiveness threshold of $1 \times$ Indian per capita GDP. With newer types of rapid HIV RNA tests, it is likely that costs will come down and testing will become even more cost-effective.⁵⁰

Several clinical trials have examined the impact of laboratory monitoring on mortality and disease progression in patients on ART.⁵¹ In general, these studies have found modest or no survival gains with more intensive laboratory monitoring

(CD4 count vs. clinical monitoring only, HIV RNA vs. CD4 count only) over 2-year trial horizons.^{51–54} Cost-effectiveness analyses using these trial data have found that, over the limited trial time horizon, more intensive laboratory monitoring is generally either not cost-effective or borderline cost-effective.^{55–57} Our model produced results consistent with these trials in the short term, but showed that HIV RNA monitoring produced a survival benefit in the long-term and was cost-effective (Table 2). This is predominantly due to the long-term clinical benefits of appropriate therapy and avoiding unnecessary and costly second- and third-line ART.

Mathematical modeling studies have also projected the long-term outcomes associated with alternative laboratory monitoring strategies in resource-limited settings.^{18,58–62} These studies vary widely in model structure, inputs, and strategies examined, and have reached differing conclusions about the cost-effectiveness of CD4 and HIV RNA monitoring strategies to guide ART switching.⁶³ Our analysis differs from these previous studies in several ways. This is the first analysis that quantifies the cost-effectiveness of HIV RNA monitoring in India. Further, this analysis includes adaptive strategies, which tailor the frequency of the monitoring strategy at the individual patient level. Despite substantial differences in costs of care and GDP per capita, the results of this study are consistent with our previously published results based in Côte d'Ivoire, with both studies demonstrating the cost-effectiveness of adaptive HIV RNA monitoring.⁶⁴

While adaptive HIV RNA monitoring is cost-effective by international standards, it would increase total costs of care

over time. Our results show that an additional \$58.5 million per year would be required to implement adaptive HIV RNA testing for those currently in care, and expected to be in care, over the next 5 years. This added cost is lower than it would otherwise be due to opportunistic diseases prevented with less time on failed ART. The cost savings from transmissions averted from implementing routine HIV RNA monitoring would also offset some of the additional cost.

This analysis has several limitations. We were conservative with regard to HIV RNA monitoring by not including certain potential benefits of HIV RNA monitoring, including the clinical and economic effects of the additional reductions in downstream HIV transmission or limiting the development of transmitted resistance.^{65,66} Incorporating these benefits would only improve the cost-effectiveness of HIV RNA monitoring. There are other approaches to lab monitoring, such as point-of-care CD4 count and HIV RNA monitoring, which we did not include in the analysis. While these may be valuable in some resource-limited settings, particularly in rural areas, in India there are 528 ART centers and the epidemic is primarily urban, suggesting that access to labs is not an important constraint.^{3,67,68} Additionally, as NACO considers implementing alternative first-line ART regimens (such as integrase strand inhibitor-based regimens) that have higher initial suppression rates and may become available at a cost as low as \$75 per person per year, the optimal frequency of monitoring may change.⁶⁹ Our cost-effectiveness results remained robust, however, across a wide range of first-line ART initial suppression rates and costs. Implementing adaptive monitoring would require some additional coordination to change testing frequencies after 12 months. Finally, we did not consider strategies of pooling plasma samples across several persons with HIV for HIV RNA testing, which could be a way to decrease testing costs.⁷⁰ These strategies have generally not been adopted due at least in part to laboratory logistical challenges and concerns about accuracy.

In conclusion, using a detailed microsimulation model with clinical and economic data from India, we found that adaptive HIV RNA monitoring every 6 months for 1 year, followed by every 12 months, would improve life expectancy and be a cost-effective addition to HIV care in India. Adaptive HIV RNA monitoring would not only increase the life expectancy of PLWH in India, but would substantially decrease the amount of time spent on a failing ART regimen, reducing transmissions and bringing India closer to meeting the UNAIDS 90-90-90 global treatment targets. Implementing adaptive HIV RNA testing for first-line ART monitoring is an important priority in India.

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Author Disclosure Statement

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Appendix

APPENDIX FIG. A1. Cohorts modeled in the budget impact analysis of laboratory monitoring strategies in India. Each year of the 5-year budget impact analysis is represented vertically, increasing from left to right. In year 1, the budget impact includes three cohorts of HIV-infected persons in India: (1) 893,000 persons currently in care and on ART with a CD4 < 350/μL, *teal*; (2) 97,000 persons (each year) in care with a CD4 between ≥350/μL expected to initiate ART over the next 3 years under the recent Indian test and treat guidelines, *green*; and (3) 125,000 persons presenting to care and initiating ART with a CD4 < 350/μL, *orange*. For the adaptive HIV RNA strategy, HIV RNA monitoring is incorporated over 3 years for the 893,000 persons currently in care and on ART with a CD4 < 350 μL as follows: 200,000 the first year, 300,000 the second year, and 393,000 the third year. Each year a new cohort of persons presenting to care and initiating ART is incorporated into the analysis. ART, antiretroviral therapy.

APPENDIX TABLE A1. ALTERNATIVE LABORATORY MONITORING STRATEGIES SIMULATED

Category	Monitoring strategy	Monitoring frequency (months)		Confirmatory RNA?	CD4 stop criterion? ^a
		CD4	RNA		
Routine CD4	Twice-annual CD4	12	—	No	No
Routine CD4, RNA confirmation	Twice-annual CD4 with HIV RNA confirmation (NACO, SOC)	6	—	Yes	No
	Annual CD4 with HIV RNA confirmation	12	—	Yes	No
Routine HIV RNA testing	Twice-annual HIV RNA tests	—	6	No	—
	Annual HIV RNA tests	—	12	No	—
Routine CD4 and HIV RNA testing	Twice-annual CD4 and HIV RNA tests	6	6	No	Yes
	Twice-annual CD4 and annual HIV RNA tests	6	12	Yes	Yes
	Annual CD4 and HIV RNA tests	12	12	No	Yes
Adaptive strategies ^b	Adaptive HIV RNA tests	—	6 to 12	No	—
	Adaptive CD4 and HIV RNA tests	6 to 12	6 to 12	No	Yes
	Twice-annual CD4 and Adaptive HIV RNA (WHO)	6	6 to 12	Yes	Yes

All strategies include an opportunity for virologic suppression, on the previous regimen after diagnosis of treatment failure (see Methods section).

^aIn every strategy that includes both routine (or adaptive) CD4 and routine (or adaptive) HIV RNA monitoring, all scheduled CD4 monitoring was stopped once the patients' observed CD4 rose above 200 cells/μL and they had been on ART for at least 6 months.

^bIn adaptive strategies, monitoring is reduced from every 6 months to every 12 months after virologic suppression for at least 1 year.

ART, antiretroviral therapy; NACO, National AIDS Control Organization; SOC, standard of care; WHO, World Health Organization.