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Laboratory Monitoring to Guide Switching Antiretroviral Therapy in Resource-Limited Settings: Clinical Benefits and Cost-Effectiveness

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Abstract

Background—As 2nd-line antiretroviral therapy (ART) availability increases in resource-limited settings, questions about the value of laboratory monitoring remain. We assessed the outcomes and cost-effectiveness (CE) of laboratory monitoring to guide switching ART.

Methods—We used a computer model to project life expectancy and costs of different strategies to guide ART switching in patients in Côte d'Ivoire. Strategies included clinical assessment, CD4 count, and HIV RNA testing. Data were from clinical trials and cohort studies from Côte d'Ivoire and the literature. Outcomes were compared using the incremental CE ratio. We conducted multiple sensitivity analyses to assess uncertainty in model parameters.

Results—Compared with 1st-line ART only, 2nd-line ART increased life expectancy by 24% with clinical monitoring only, 46% with CD4 monitoring, and 61% with HIV RNA monitoring. The incremental CE ratio of switching based on clinical monitoring was \$1,670/year of life gained (YLS) compared to 1st-line ART only; biannual CD4 monitoring was \$2,120/YLS. The CE ratio of biannual HIV RNA testing ranged from \$2,920 (\$87/test) to \$1,990/YLS (\$25/test). If 2nd-line ART costs were reduced, the CE of HIV RNA monitoring improved.

Conclusions—In resource-limited settings, CD4 count and HIV RNA monitoring to guide switching to 2nd-line ART improve survival and under most conditions are cost-effective.

Keywords

Laboratory monitoring; diagnostic tests; HIV RNA; viral load; HIV/AIDS; antiretroviral therapy

The past decade has seen unprecedented increases in access to and delivery of HIV treatment and care. Affordable and effective 1st-line antiretroviral regimens are now widely available and an estimated 3 million people have started antiretroviral therapy (ART) in

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resource-limited settings.¹ For those who need it, 2nd-line ART is becoming increasingly affordable and accessible.^{1, 2}

While access to and delivery of HIV treatment have improved, resource constraints have curbed use of laboratory-based diagnostic tests in many developing countries and led to shifting attitudes towards what should be recommended in terms of patient monitoring. In 2006, the World Health Organization's (WHO's) public health response to HIV led to guidelines emphasizing a tiered patient monitoring structure, with CD4 count at the district level and CD4 count and HIV RNA quantification at the regional level, but with neither considered compulsory for patient management.^{3, 4} In 2008, based on results from a study by Phillips et al. suggesting only modest clinical benefit from CD4 count or HIV RNA monitoring to guide switching to 2nd-line ART, WHO emphasized the use of clinical monitoring.^{5, 6} While HIV RNA testing has been available in only limited settings, the decreasing costs and simplification of CD4 count technologies have allowed scale-up of immunologic monitoring in many developing countries.⁶ This led the WHO to reaffirm the importance of CD4 counts and to recommend in 2009 that clinical failure should be confirmed at least by immunological criteria when HIV RNA is not available.⁷

In keeping with this recent recommendation, most current national guidelines consider CD4 counts along with clinical criteria as the standard of care for monitoring patients receiving antiretroviral therapy, while virologic monitoring in these settings is still generally considered optional.⁸⁻¹⁵ In the context of a country like Côte d'Ivoire, a low-income West African country with adult HIV prevalence of approximately 3.9%,^{17, 18} our objective was to examine the clinical benefits, costs, and cost-effectiveness of CD4 count and/or HIV RNA monitoring in guiding switching to 2nd-line ART.

Methods

Analytic Overview

We utilized a previously published simulation model of the natural history and treatment of chronic HIV disease.¹⁹⁻²¹ Clinical and cost data were derived from clinical trials and cohort studies conducted in Côte d'Ivoire, as well as publicly available fee schedules and cost databases.^{2, 22-25} Monitoring strategies to guide switching to 2nd-line ART were based on different criteria for detecting 1st-line antiretroviral failure (clinical, immunologic, or virologic). The performance of alternative strategies was evaluated using the incremental cost-effectiveness ratio, expressed as 2006 US dollars per year of life gained, and defined as the additional cost of a specific strategy, divided by its additional clinical benefit, compared with the next less expensive strategy.²⁶ We adopted a modified societal perspective (meaning that patient time and transportation costs were not included), with future benefits and costs discounted 3% annually.²⁶⁻²⁹ Sensitivity analyses were conducted to evaluate the impact of uncertain parameters and assumptions on the results. Additional information on the methods is available in the Appendix and in previous publications.^{19-21, 30-32}

Strategies

To quantify the benefit from the availability of 2nd-line therapy, we included two relevant comparators among the base case strategies: cotrimoxazole prophylaxis only and 1st-line ART only plus cotrimoxazole prophylaxis. In the base case, we evaluated three main monitoring approaches to diagnose 1st-line ART failure, thereby prompting a switch to 2nd-line ART. These included: (1) clinical monitoring, with failure defined as a single WHO stage III-IV event other than tuberculosis (TB) and invasive bacterial diseases; (2) immunologic monitoring, with failure defined as a 50% decrease from peak regimen-specific CD4 count (consistent with WHO recommendations); and (3) virologic monitoring,

with failure defined as a 1- $\log_{10}$ increase in HIV RNA and/or return to pre-treatment HIV RNA level (Table 1).

In a secondary analysis, we assessed variations of the three main monitoring strategies, including: (1) alternative clinical criteria for 1st-line failure (e.g., WHO stage III-IV event, including TB and/or invasive bacterial diseases); (2) alternative immunologic criteria for 1st line failure (e.g., 25% decrease in CD4 count); (3) combined clinical and immunologic/virologic monitoring (e.g., WHO stage III-IV event or a 1- $\log_{10}$ increase in HIV RNA and/or return to pre-treatment HIV RNA level); and (4) a 6-month delay in initiation of 2nd-line ART following observation of virologic failure.

Model

We employed the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) International model, an individual-level Monte Carlo simulation model of HIV disease progression and treatment.^{19-21, 30-32} Drawing from an initial distribution of country-specific demographic (age, sex) and clinical characteristics (CD4 count, HIV RNA level, history of opportunistic infection), the model draws upon monthly transition probabilities to simulate a cohort of individual patients whose clinical course is tracked from model entry until death. The model projects intermediate outcomes (e.g., longitudinal CD4 count, number and type of opportunistic infection) and long-term aggregate outcomes (e.g., life expectancy and lifetime costs).

Disease Progression in the Absence of Antiretroviral Therapy—HIV disease progression is modeled as a function of HIV RNA level and CD4 count³³. In the model, virologic and immunologic status are represented using six HIV RNA strata and six CD4 count strata.^{19, 20} Progression in the absence of therapy is based on a patient's true HIV RNA level, which determines the rate of CD4 count decline and in turn, the risk of specific opportunistic infections and death.^{33, 34} The model tracks this information throughout an individual's lifetime and distinguishes between underlying disease progression and observed measures of clinical, immunologic, and virologic status. Opportunistic infection rates are based on primary data from Côte d'Ivoire and are classified broadly as HIV-related severe events (severe malaria, TB, invasive bacterial diseases, and other WHO stage III-IV events), mild events (non-invasive bacterial diseases and WHO stage II events), and unexplained severe events (acute unexplained fever or acute unexplained diarrhea with hospitalization).^{19, 20} Cotrimoxazole prophylaxis—administered to all patients upon entry into care—results in a reduced risk of bacterial infections, malaria, other WHO stage III-IV events (toxoplasmosis, isosporosis, pneumocystosis, and nocardiosis), and unexplained severe events.^{20, 22, 35}

Disease Progression in the Presence of Antiretroviral Therapy—Simulated patients can either achieve HIV RNA suppression or not on a particular ART regimen. For patients who achieve HIV RNA suppression, disease progression is modeled based on decreases in HIV RNA level and increases in CD4 count. Virologically suppressed patients face a monthly risk of “late” failure, defined as a 0.5- $\log_{10}$ increase in HIV RNA over at least 2 consecutive months.³³ Late virologic failure is followed by a 12-month delay before CD4 count decline³⁶. Patients who either do not achieve HIV RNA suppression or who experience late virologic failure have CD4 declines similar to those not receiving ART. Regardless of an individual's virologic status, patients receiving ART experience an independent reduction in incidence of opportunistic infections and AIDS-related mortality.^{37, 38}

Patients experiencing undetected virologic failure and who continue on ART accumulate resistance.³⁹ Rather than model the accumulation of individual resistance mutations, we modeled the effects of incremental resistance accumulation on the efficacy of subsequent ART regimens. This was accomplished by specifying a relative percent decrease in the baseline 24-week virologic suppression of subsequent ART regimens for each month that a patient remains on a virologically failed regimen.⁴⁰⁻⁴² This relative percent decrease is hereafter referred to as the *resistance penalty*.

We specify the resistance penalty in Equation 1, below:

$$pnetSuccess_i = \min\{1, pSuccess_i\} * \left[(1 - respensuccess_i)^{cumVTime} \right] \quad (1)$$

In this equation, “*pnetSuccess*” represents the efficacy of current ART regimen *i* after virologic failure due to accumulated resistance from prior regimens; “*pSuccess_i*” represents the efficacy of ART regimen *i* after virologic failure in the absence of resistance from prior ART regimens; “*respensuccess_i*” represents the fractional reduction in the initial probability of success of regimen *i*, per month spent on prior regimens; “*cumVTime*” represents the cumulative number of months spent, across all ART regimens, after having virologically failed ART; and *i* represents the current ART regimen *i*, in which *i* is an integer value beginning with 1 and continuing toward the maximum number of sequential lines of ART available.

We assume that the resistance penalty does not affect CD4 response to subsequent regimens, conditional upon virologic response. We also assume that the penalty applies only to the initial 24-week efficacy of a subsequent regimen and not to an individual's probability of virologic failure at later time points. Derivation of the baseline value for the resistance penalty is shown in the Data section.

Patient-Level Monitoring of Clinical, Immunologic, and Virologic Status—

Patient-level HIV disease progression and treatment efficacy are monitored through clinical, immunologic (via CD4 counts), and/or virologic (via HIV RNA tests) assessments. Clinical assessments occur upon entry into care, presentation with any acute event, and at 3-month intervals. CD4 and HIV RNA tests, if available, occur upon entry into care and at 6-month intervals thereafter.⁴ Treatment-related decisions (i.e., starting, switching, or stopping ART regimens) are made based on information from clinical assessments and, if available, CD4 counts and/or HIV RNA tests.

Clinical and Cost Data

Cohort Characteristics and Natural History—Data were derived mainly from trials and cohort studies conducted in Côte d'Ivoire by the Programme PAC-CI. Initial distributions of age, sex, and CD4 count were derived from the ACONDA cohort, an observational cohort of HIV-infected adults and a continuation of the ANRS 1203 Cotrame cohort study in Abidjan, Côte d'Ivoire (Table 2).^{43, 44} Incidence of opportunistic infections (a function of CD4 count), HIV-related mortality (a function of both CD4 count and history of opportunistic infection), and efficacy and toxicity of cotrimoxazole prophylaxis were estimated from ANRS 059 trial data, as well as data from the ANRS 1203 and 1220 study cohorts.^{23, 24, 45} Risk of non-HIV-related mortality was derived from country-specific life tables for Côte d'Ivoire.⁴⁶

Antiretroviral Therapy—Effectiveness of non-nucleoside reverse transcriptase inhibitor-(NNRTI-) based 1st-line ART was derived from a prospective cohort study of treatment-

naïve patients in Abidjan.⁴⁴ At 24 weeks, 80.2% of patients experienced HIV RNA suppression to ≤ 300 copies/mL and a median CD4 count increase of 127 cells/ μ L (IQR 64, 201).⁴⁴ We assumed that, in the absence of resistance, the effectiveness of protease inhibitor- (PI-) based 2nd-line ART was similar to that for 1st-line ART (at 24 weeks, 77.0% suppressed to < 400 copies/mL and a mean CD4 count increase of 186 cells/ μ L).⁴⁷ Incidence of ART-related severe adverse events was 10.8 (95% CI: 5.4–12.0) per 100 person-years;⁴⁸ these events led to a switch in drug of similar cost, effectiveness, and drug class.

To derive the baseline value for the resistance penalty, we used 3 pieces of information: PI-based ART efficacy in the absence of resistance, PI-based ART efficacy in the presence of resistance (i.e., thymidine analogue mutations resulting from failure of 1st-line nucleoside reverse transcriptase inhibitors), and time spent on virologically failed ART. For PI-based ART efficacy in the absence of resistance, 24-week virologic suppression (< 400 copies/mL) was 77.0%.⁴⁷ In the presence of resistance, 24-week virologic suppression (< 400 copies/mL) was 73.3% for patients on a 2nd-line, PI-based regimen.⁴⁹ For time spent on virologically failed ART, we estimated that mean time spent on a virologically failed 1st-line ART regimen was 10.8 months.⁵⁰ We assumed that this estimate reflected the difference between higher HIV RNA suppression (i.e., 77.0%) in the absence of resistance and lower HIV RNA suppression (i.e., 73.3%) in the presence of resistance. We substituted these three estimates into Equation 1 to solve for the baseline value for the resistance penalty:

$$respensuccess_2 = 1 - \left[\left(pnetSuccess_2 * \frac{1}{pSuccess_2} \right)^{\frac{1}{cumVTime}} \right] = 1 - \left[\left(0.733 * \frac{1}{0.77} \right)^{\frac{1}{10.8}} \right]$$

These data resulted in an overall estimate of a 0.45% relative decrease in baseline 24-week HIV RNA suppression per month on virologically failed 1st-line ART. We evaluated a wide range (0%–1.63%) of values for the resistance penalty, reflecting overlap in both the 95% confidence intervals of the ART efficacy data and uncertainty in the variables informing the resistance penalty.

Costs—We estimated direct medical costs for HIV-related care (e.g., inpatient care, outpatient visits, treatment of acute clinical events, other routine care, medications, and laboratory costs) from the placebo arm of ANRS 059, a trial evaluating cotrimoxazole prophylaxis in Abidjan, as well as from the literature.^{2, 22, 51} These costs were adjusted to 2006 price levels and converted, when necessary, from local currency to US dollars using official exchange rates. Costs of antiretroviral therapy came from a publicly available pricing guide for developing countries.² Reflecting 1st-line ART in the ACONDA cohort,⁴⁴ we calculated a cost of 1st-line ART of \$121/year. This was the weighted average of several regimens — 52% stavudine, lamivudine, nevirapine (\$100 annually), 22% stavudine, lamivudine, efavirenz (\$120 annually), 20% zidovudine, lamivudine, efavirenz (\$177 annually), and 6% other (\$120 annually). We assumed that 2nd-line ART costs included tenofovir/emtricitabine (\$199 annually) plus lopinavir/ritonavir (\$550 annually), for a total cost of \$749 per year. We assumed all drug costs reflected a WHO-recommended dosing schedule. For each cost estimate, we established plausible upper and lower bounds to evaluate real-world cost differences (e.g., due to projected decreases or realistic variation in 2nd-line ART costs^{2, 53}) as well as to assess uncertainty.

Results

Base-Case Analysis

Undiscounted life expectancy was 2.2 years for cotrimoxazole prophylaxis only and 12.0 years for 1st-line ART only plus cotrimoxazole prophylaxis, with projected undiscounted life expectancies ranging from 14.9 years for clinical monitoring to 17.5 years for biannual CD4 monitoring to 19.3 years for biannual HIV RNA monitoring to guide switching to 2nd-line ART. Compared with only one line of ART, the incremental benefits from the availability of 2nd-line ART ranged from a 24.3% increase in undiscounted life expectancy with clinical monitoring to a 46.4% increase with CD4-based monitoring, to a 61.3% increase with HIV RNA monitoring (Table 3). Given the availability of 2nd-line ART, CD4-based monitoring increased undiscounted life expectancy 17.6% compared to clinical monitoring; HIV RNA monitoring resulted in a further 10.2% increase in undiscounted life expectancy compared to CD4-based monitoring.

Mean CD4 counts at 1st-line observed failure ranged from 129 to 467 cells/ μ L, with earlier detection of failure (as occurred with the HIV RNA monitoring strategy) associated with a higher CD4 count at time of failure detection and switching.

Table 3 also shows the incremental cost-effectiveness ratios (ICERs) for each strategy assuming three potential costs for HIV RNA monitoring (\$87, \$50, and \$25). Compared to clinical monitoring, CD4-based monitoring (switching to 2nd-line ART when a 50% decrease in peak CD4 count is observed on 1st-line ART) had an incremental cost-effectiveness ratio of \$2,120 per year of life gained (YLS). In comparison, virologic monitoring (with a failure criterion of 1-log₁₀ increase in HIV RNA or return to pre-treatment HIV RNA level) had an incremental cost-effectiveness ratio ranging from \$2,920 (\$87 per HIV RNA test) to \$1,990 (\$25 per HIV RNA test) per YLS. Complete results for the base case analysis are shown in the Appendix.

While no consensus exists on a universal threshold below which an intervention would be considered “cost-effective”, benchmarks can be useful to compare the relative value provided by different interventions to improve health. For example, the Commission on Macroeconomics and Health has suggested that an incremental cost-effectiveness ratio of less than 3 times a country’s annual per capita gross domestic product (GDP) represents a cost-effective intervention.^{54, 55} Based on three sources for the annual GDP per capita at nominal values for Côte d’Ivoire (US\$1,016 to US\$1,178), an approximate cost-effectiveness threshold of three times that would range from approximately US\$3,000 to US\$3,500.⁵⁶⁻⁵⁸

Sensitivity Analysis

Figure 1 shows the results of sensitivity analyses in which parameters were varied to assess their impact on the incremental cost-effectiveness ratio of virologic monitoring to detect 1st-line ART failure. The analysis was conducted using baseline HIV RNA test costs of both \$50 (Upper Panel) and \$87 (Lower Panel). In addition to HIV RNA test costs, cost-effectiveness results were most sensitive to the cost of 2nd-line ART and the relative decrease in 2nd-line ART efficacy per month on virologically failed 1st-line ART (i.e., the “resistance penalty”). Cost-effectiveness results were less sensitive to chronic care costs, the cost of CD4 count tests, the efficacy of 2nd-line ART, the discount rate, and the probability of late failure.

As the cost of 2nd-line therapy was reduced, the cost-effectiveness of virologic monitoring became more attractive. If the cost of 2nd-line ART approximated that of 1st-line ART (~\$121 per year) the incremental cost-effectiveness ratio of virologic monitoring improved to

less than \$1,000 per YLS (HIV RNA test cost of \$50) and to less than \$1,200 per YLS (HIV RNA test cost of \$87). Decreasing the “resistance penalty” influenced both life expectancy and cost-effectiveness for the HIV RNA monitoring strategy. If the baseline resistance penalty was increased from 0.45% (base case) per month to 1.5% per month— as might occur in 3rd-line and subsequent ART regimens — HIV RNA monitoring was both more effective and more cost-effective than all other strategies.

An influential assumption on the cost-effectiveness of virologic monitoring was the duration of 2nd-line ART following detected failure. Consistent with clinical care in many countries, we assumed that 2nd-line ART was continued until death, in spite of clinical, immunologic, and/or virologic failure;⁴ the increase in life expectancy associated with this base case assumption was approximately 8 months, compared with stopping 2nd-line ART after virologic failure. Given the disproportionate increase in costs across these two extreme assumptions, reduction in the cost of 2nd-line ART and/or stopping 2nd-line ART at some point after virologic failure, had a major influence on the cost-effectiveness of HIV RNA monitoring.

Alternative criteria for detecting 1st-line ART failure

Figure 2 shows the relationship between lifetime costs and life expectancy for the three main base case monitoring strategies and variations of these strategies that alter the criteria for 1st-line ART failure. Strategies that rely on laboratory monitoring — either CD4 count or HIV RNA — to guide switching always resulted in higher life expectancy than strategies relying on clinical monitoring alone. Expanding the clinical failure criterion to include both TB and invasive bacterial diseases was more costly and less cost-effective than the base-case criterion of WHO Stage III-IV events, excluding TB and invasive bacterial diseases, or WHO Stage III-IV, including TB but not invasive bacterial diseases. Changing the CD4 monitoring criterion for 1st-line ART failure from a 50% to a 25% decline in peak CD4 also was an efficient strategy; it was more costly and more effective than the base case strategy, although it was less effective than HIV RNA monitoring. None of the strategies that combined clinical and immunologic or virologic monitoring was more effective, less costly, or more cost-effective, than the base case strategies.

We also assessed the impact of a 6-month delay in initiation of 2nd-line ART following observed failure of 1st-line ART for all HIV RNA monitoring strategies. This strategy generally was not more effective or more cost-effective than virologic monitoring strategies that did not employ a delay. Results for these sensitivity analyses are shown in the Appendix.

Discussion

In resource-limited settings, the role of CD4 count and HIV RNA monitoring in ART management remains an area of widespread debate, despite being standard clinical practice in most developed countries.^{5, 16, 59-65} We addressed the impact of using CD4 count and/or HIV RNA monitoring to guide switching to 2nd-line ART in Côte d'Ivoire. We found that earlier detection of 1st-line ART failure (via immunologic or virologic monitoring) resulted in higher CD4 counts upon observed 1st-line ART failure, shorter duration on virologically failed 1st-line ART, and earlier switching to 2nd-line ART. Accordingly, while the incremental life-expectancy gains associated with providing 2nd-line ART (compared with 1st-line ART only) was 24.3% with clinical monitoring, laboratory monitoring substantially increased these survival gains: 46.4% with CD4 count monitoring and 61.3% with HIV RNA monitoring.

This analysis suggests that the cost-effectiveness of laboratory monitoring is influenced most by the cost of 2nd-line ART, the impact of resistance on 2nd-line ART efficacy, and the duration of 2nd-line ART following virologic failure. We found that virologic monitoring would be cost-effective, according to the criteria of the Commission on Macroeconomics and Health, in all of the following instances: the decrease in 2nd-line efficacy due to time spent on virologically failed 1st-line ART is greater than 1% per month, cost of 2nd line ART is less than \$300, or if the HIV RNA test cost is less than \$90. With the exception of situations where virologic monitoring dominates (i.e., is more effective and less costly, or more effective and more cost-effective) CD4-based monitoring — for example, at very low HIV RNA test costs of \$25 — switching to 2nd-line ART based on a 50% decline in CD4 cell counts is consistently cost-effective. At very low HIV RNA test costs, we found that if the CD4 count costs were decreased to less than \$15 per test, CD4-based monitoring was no longer dominated. In this case, HIV RNA testing had a cost-effectiveness ratio of \$2,030 per life year gained compared to CD4 monitoring, and CD4 count monitoring had a cost-effectiveness ratio of \$1,970 per life year gained compared to clinical monitoring.

Due to the high cost of 2nd-line ART, one of the most influential assumptions on the cost-effectiveness of virologic monitoring was the duration of time that 2nd-line ART was continued following failure. Importantly, there is a substantial life expectancy gain associated with continuing ART following virologic failure; however, this clinical benefit is accompanied by an even greater increase in costs. We found that a reduction in 2nd-line ART costs or discontinuing ART after 2nd-line failure – at some point before the end of life – improved the cost-effectiveness of HIV RNA monitoring. It is likely that as HIV-infected individuals in Côte d'Ivoire and other resource-limited settings begin to fail 2nd-line therapy, further downward pressure on drug prices will also provide the opportunity for 3rd-line therapy, including newer drugs. If that is the case, and there is ongoing development of resistance with continuation of 2nd-line therapy after virologic failure of those regimens, then it will also improve long-term outcomes to switch from 2nd- to 3rd-line therapy at the time of virologic failure. This would further support the use of HIV RNA monitoring in the future.

We also assessed several variations of the three main monitoring strategies using alternative clinical criteria for 1st-line failure. Expanding the clinical failure criterion to include TB or invasive bacterial diseases was more costly and less cost-effective than a criterion of WHO Stage III-IV events, excluding TB and invasive bacterial diseases (base case), or WHO Stage III-IV events, including TB but not invasive bacterial diseases. Changing the CD4 monitoring criterion for 1st-line ART failure to a 25% decline in peak CD4 count was an efficient strategy. Although less effective than HIV RNA monitoring, it was both more effective (and more costly) than a criterion of a 50% decline in peak CD4 count (base case). None of the strategies that combined clinical and immunologic or virologic monitoring was more effective or less costly, or more cost-effective, than the base case strategies.

These results have important implications for clinical and budgetary planning. While the results provide information about the value of different laboratory monitoring techniques to detect the timing of 1st-line antiretroviral failure, they can also inform issues related to affordability and budget planning. For example, for a clinic of 10,000 patients — similar to the CePRef clinic in Abidjan⁴⁴ — the percent of patients alive at ten years with CD4-guided switching of antiretroviral therapy would be 66% compared to 60% without CD4 monitoring. Total per person costs of care would increase to \$6,120 from \$5,040, with the additional costs attributable primarily to earlier switching from 1st-line to more expensive 2nd-line ART.

Several modeling studies have sought to address the debate on laboratory monitoring to guide HIV treatment management in resource-limited settings.^{5, 19, 61, 64, 66, 67} While results from this analysis correspond with those found in some — but not all — existing studies^{61, 64}, the current analysis differs from the literature in several ways. First, the underlying model structure varies across studies. For example, Bishai et al. did not explicitly model resistance and used US input data in their model. Bendavid et al. also did not model resistance, and used data from Southern Africa. Both of these studies examined initiation and switching of antiretroviral therapy, not just switching as in the current study.

The different findings in the current study compared to that by Phillips *et al.* are primarily due to changes in model input parameters. The Phillips study assumed that all patients had a WHO stage 4 event before starting ART, and the mean CD4 count of the cohort at the time of ART initiation was 66/ μ L. In the current study, only 0.5–20% of the cohort had a prior Stage 3/4 event, and the mean CD4 count was 140/ μ L. Because the cohort had less severe illness at initiation and experienced lower mortality, the potential benefits of earlier switching using CD4 or HIV RNA testing were greater, leading to lower cost-effectiveness ratios for all monitoring tests.

This study has several limitations. First, we assumed that results from CD4 count and HIV RNA tests accurately reflect underlying patient-level disease status and that laboratories used to analyze test measurements yield accurate and consistent results.^{68–70} Second, we did not assess different CD4 count and HIV RNA test technologies, nor did we consider alternative delivery mechanisms. Third, limited data were available to inform the “resistance penalty”. Although an emerging literature exists on drug- and/or regimen-specific mutation accumulation,⁴⁰ little information exists on the impact of regimen-specific mutations on subsequent antiretroviral efficacy. Therefore, we believe the method used to characterize the impact of resistance as a function of time on virologically failed ART most accurately reflects the evidence base.^{41, 42} To that end, we used the most current data available to inform the resistance penalty and performed extensive sensitivity analysis on this parameter. Fourth, we did not account for the fact that CD4 count decline may be discordant with virologic failure; therefore, without HIV RNA monitoring some people will be unnecessarily switched to 2nd-line therapy.^{71, 72} Accounting for this discordant response would make HIV RNA monitoring even more favorable. Finally, we did not factor into the analysis the impact of resistance on HIV transmission dynamics. Specifically, we did not account for any population-level benefit of decreased HIV transmission of wild type or resistant virus due to earlier switching from a virologically failed 1st-line regimen to an effective 2nd-line regimen. Inclusion of these effects likely would result in HIV RNA monitoring appearing even more favorable.

As ART becomes increasingly available for HIV-infected individuals in Côte d'Ivoire and in other resource-limited settings, it is critical to understand both the clinical and economic value of laboratory monitoring for HIV management. This analysis suggests that CD4 count and HIV RNA monitoring to guide switching to 2nd-line ART in resource-limited settings improves survival and under most conditions is cost-effective. These results support the value of investing in low-cost HIV RNA tests, reducing prices for 2nd-line ART, and developing a better understanding of the relationships between delayed switching, development of resistance mutations, and subsequent antiretroviral efficacy.

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Technical Appendix

The text below provides additional detail on the methods informing this paper, as well as supplementary results and sensitivity analysis.

Appendix Methods

Strategies

To quantify the benefit from the availability of 2nd-line therapy, we included two relevant comparators among the base case strategies: cotrimoxazole prophylaxis only and 1st-line ART only plus cotrimoxazole prophylaxis. In the base case, we assessed three main monitoring approaches: (1) clinical monitoring, with failure defined as a WHO stage III-IV event; (2) immunologic monitoring, with failure defined as a 50% decrease from peak regimen-specific CD4 count (consistent with WHO recommendations); and (3) virologic monitoring, with failure defined as a minimum 1-log₁₀ increase in HIV RNA and/or return to pre-treatment HIV RNA level. In a secondary analysis, we evaluated variations of the three main monitoring strategies. These included: (1) alternative clinical criteria for 1st line failure (WHO stage III-IV event or TB, WHO stage III-IV event or TB or invasive bacterial diseases); (2) alternative immunologic criteria for 1st line failure (25% decrease from peak regimen-specific CD4 count); (3) combined clinical and immunologic / virologic monitoring (e.g., WHO stage III-IV event or a minimum 1-log₁₀ increase in HIV RNA and/or return to pre-treatment HIV RNA level); (4) delayed initiation of second-line ART following virologic failure. A complete list of strategies is shown in Appendix Table A1.

Model Structure

We employed a 1st-order Monte Carlo simulation model — the CEPAC-International model — of HIV disease progression and treatment. The model is characterized by three main health states — Chronic HIV, Acute Events, and Death — which are further defined by current and setpoint HIV RNA, current and nadir CD4 count, and current and prior opportunistic infections. Using a random number generator to draw from an initial distribution of country-specific demographic (age, sex) and clinical characteristics (CD4 count, HIV RNA level, history of opportunistic infection), the model simulates individual patients whose clinical course is tracked from model entry until death. A sequence of monthly transition probabilities determines each individual patient's chance of transitioning to or remaining in a particular health state.

The model projects state-specific intermediate outcomes (e.g., mechanism of detection for antiretroviral failure, mean CD4 cell count upon observed antiretroviral therapy failure, mean time between virologic failure and observed failure) associated with each health state and long-term aggregate outcomes (e.g., mean life expectancy and lifetime costs). To obtain stable estimates for each strategy, one million simulations are conducted, one at a time, with

summary statistics calculated across the simulated cohort. The model is coded in the C programming language and compiled in VC++ 6.0 (Microsoft, Redmond, WA).

The Resistance Penalty

In the presence of ineffective antiretroviral therapy (ART) (i.e., upon true, but not yet detected, virologic failure), we hypothesize that individuals faced consequences for time on ineffective treatment. Specifically, upon virologic failure, we assume patients receiving antiretroviral therapy while not fully suppressed virologically are at greater risk of developing resistance to subsequent drug regimens.¹ The *resistance penalty* characterizes resistance based on an individual's cumulative time spent on failed antiretroviral therapy^{2, 3} and yields a reduction in the efficacy of subsequent antiretroviral regimens containing drugs in the same class from which resistance arose. Please see the main text for the detailed information regarding specification of the resistance penalty.

Antiretroviral Therapy Initiation

In the base case, HIV-infected individuals received 1st-line antiretroviral therapy when a patient's pre-treatment CD4 cell count fell below 200 cells/mm³; a patient experienced any one severe opportunistic infection (bacterial enteritis, other invasive bacterial diseases, tuberculosis, other WHO stage III–IV events, malaria, or other non-specific severe events); or when a patient presented with CD4 cell count above 200 cells/mm³ but below 350 cells/mm³ along with a primary or secondary opportunistic infection.⁴ In settings in which laboratory tests were not routinely available (see Secondary Analysis), patients started 1st-line antiretroviral therapy after experiencing any one of severe opportunistic infections (bacterial enteritis, other severe bacterial diseases, tuberculosis, other WHO stage III–IV events, malaria, or other non-specific severe events).

Assumptions

We made a number of assumptions in the model: First, HIV-infected individuals initiated 1st-line ART in accordance with current WHO guidelines.⁴ We also assumed that CD4 counts were used to initiate 1st-line ART no matter the monitoring strategy; however, CD4 tests after antiretroviral initiation were administered only if specified by the monitoring strategy. Second, due to possible initial patient adherence issues, detection of 1st-line ART failure could not occur until at least 12 months after initiation of the 1st-line regimen. Third, we assumed that all opportunistic infections were detected and treated. Fourth, we assumed that variations in immunologic measurements (due to individual biologic variation or test measurement error) and virologic measurements (due to individual biologic variation, test measurement errors, or virologic “blips”) were captured in CD4 cell count and HIV RNA strata. Fifth, laboratory tests were repeated to verify immunologic or virologic failure of antiretroviral therapy. Sixth, diagnostic tests were discontinued after observed failure of the last ART regimen and patients remained on the 2nd-line regimen for the duration of his or her lifetime.⁴ Finally, regimen-specific virologic suppression on antiretroviral therapy was limited to ≤15 years. Model assumptions were evaluated in sensitivity analysis.

Clinical Data

Additional data not shown in Manuscript Table 2 are shown in Appendix Table A2. Information on the derivation of select estimates is discussed in the text that follows.

The Resistance Penalty

For the resistance penalty (i.e., the decrease in subsequent antiretroviral efficacy due to accumulated resistance mutations), we drew upon data from the literature and assumptions

to determine a conservative baseline value and plausible range. Antiretroviral efficacy estimates for a 2nd-line, PI-based regimen in the absence of resistance were derived from the MONARK trial, which evaluated lopinavir/ritonavir plus zidovudine and lamivudine in 53 treatment naïve patients (77% HIV RNA suppressed <400 copies/mL at 24 weeks).⁵ Second-line, PI-based antiretroviral efficacy in the presence of resistance was derived from 80 treatment-experienced patients receiving atazanavir plus ritonavir, tenofovir, and 1 nucleoside reverse transcriptase inhibitor (didanosine, stavudine, lamivudine, zidovudine, or abacavir); HIV RNA suppression <400 copies/mL was estimated as 73.3% at 24 weeks.⁶

We assumed the cumulative time on virologically failed 1st-line ART was 10.8 months, which reflects median duration of ART prior to study enrollment in 124 subjects experiencing virologic failure after 24 weeks on their 1st ART regimen.⁷ While some study subjects enrolled were receiving a PI-based regimen at the time of enrollment, over 90% were receiving an NNRTI-based regimen. We assumed a range for time on virologically failed 1st-line ART of 3 months (for patients observed to have failed via virologic criterion) to 58 months (for patients observed to have failed via immunologic criterion (25% decrease in peak CD4)). These data yielded an estimate of a 0.45% (range: 0.00%–1.63%) relative monthly decrease in 2nd-line HIV RNA suppression at 24 weeks due to time on virologically failed 1st-line ART.

For a secondary analysis in which we assumed treatment expansion to 3rd-line ART, we estimated a resistance penalty of 0.45% per month on virologically failed 1st-line ART (as in the base case) and 1.00% per month on virologically failed 2nd-line ART. The latter estimate was obtained by calibrating the value of the resistance penalty until aggregate outcomes across all simulated patients reflected 61.3% HIV RNA suppression (24 weeks)⁶ in patients receiving 3rd-line ART.

Appendix Results

Base Case and Modified Base Case Strategies

Complete results for all 19 monitoring strategies (base case strategies and variations of these strategies), along with cotrimoxazole prophylaxis and 1st-line ART only plus cotrimoxazole prophylaxis, are shown in Appendix Table A3. Undiscounted life expectancy was 2.2 years for cotrimoxazole prophylaxis only and 12.0 years for 1st-line ART only plus cotrimoxazole prophylaxis. In the base case, undiscounted life expectancy associated with the availability of 2nd-line ART ranged from 14.9 years for clinical monitoring (1st-line ART failure criterion of 1 WHO stage III-IV event, excluding tuberculosis and invasive bacterial diseases) to 17.5 years for biannual CD4 monitoring (50% decrease in peak CD4) to 19.3 years for biannual HIV RNA monitoring to guide switching to 2nd-line ART (immediate switch). Compared with only 1 line of ART, the incremental benefits from the availability of 2nd-line ART ranged from a 24.3% increase in undiscounted life expectancy to a 46.4% increase to a 61.3% increase, respectively. Mean CD4 counts at 1st-line observed failure ranged from 129 to 467 cells/μL, with earlier detection of failure (as occurred with HIV RNA monitoring strategies) associated with a higher CD4 count at time of failure detection and switching.

Appendix Table A3 shows the discounted costs and incremental cost-effectiveness ratios for each strategy assuming an HIV RNA test cost of \$87 per test. Compared to clinical monitoring, CD4-based monitoring (switching to 2nd-line ART when a 50% decrease in peak CD4 count is observed on 1st-line ART) had an incremental cost-effectiveness ratio of \$2,120 per year of life gained (YLS). In comparison, virologic monitoring (with a failure

criterion of 1-log₁₀ increase in HIV RNA or return to pre-treatment HIV RNA level) had an incremental cost-effectiveness ratio of \$3,750 per YLS.

Appendix Table A3 also shows complete results of the modified base case strategies with alternative 1st-line ART failure criteria. None of the strategies that combined clinical and immunologic or virologic monitoring were more effective, less costly, or more cost-effective, than the base case strategies. These modified base case strategies are presented pictorially in Figure 2 of the main text.

In the base case, we examined the impact of different monitoring strategies on the timing of ART (Appendix Figure A1). For HIV RNA monitoring (immediate switch), mean duration on virologically failed 1st-line ART was 1.1 years, representing approximately 5.5% of total life expectancy. In contrast, mean time on virologically failed ART for a CD4-based monitoring strategy (50% decrease in peak CD4) was 5.1 years, or 28.9% of total life expectancy. Detecting ART failure earlier — as occurs when using HIV RNA monitoring — resulted in a shorter duration on virologically failed 1st-line ART and longer total duration on 2nd-line ART.

We also evaluated the influence of different monitoring strategies on survivorship (Appendix Figure A2). Median survivals were 12.79 years for a clinical switching strategy, 16.13 years for a CD4-based switching strategy, and 18.96 years for an HIV RNA-based switching strategy. By approximately 2 years, the proportion of the initial cohort surviving when relying on HIV RNA-based switching criteria always exceeded the proportion surviving when relying on CD4-based criteria. By approximately 5 years, the proportion of the initial cohort surviving when relying on CD4-based criteria always exceeded the proportion surviving when relying on clinical criteria.

Secondary Analyses

Settings in Which No Laboratory Monitoring is Available

In this secondary analysis, we assumed that no CD4 and/or HIV RNA tests were available and that all treatment-related decisions, including antiretroviral therapy initiation, relied solely on clinical information. First-line ART only resulted in discounted life expectancy of 9.39 years and discounted lifetime costs of \$5,290. With the availability of 2nd-line ART, mean CD4 count at 1st-line observed failure ranged from 129 to 243 cells/μL using failure criteria of 1 WHO stage III-IV event, excluding tuberculosis but not invasive bacterial diseases, and 1 WHO stage III-IV event, including both tuberculosis and invasive bacterial diseases, respectively. Using 1 WHO stage III-IV event, excluding both tuberculosis and severe bacterial diseases, to guide switching increased discounted life expectancy by 1.62 years and lifetime costs by \$2,700, for an incremental cost-effectiveness ratio of \$1,670 per year of life gained compared to 1st-line ART only. The addition of tuberculosis to the clinical failure criterion increased life expectancy 0.23 years for an additional \$650. Including both tuberculosis and invasive bacterial diseases resulted in an additional 0.35 years and \$1,170, for an incremental cost-effectiveness ratio of \$3,340 compared to clinical monitoring with a failure criterion of 1 WHO stage III-IV event, including tuberculosis only.

Treatment Expansion to 3rd-line ART

Because 3rd-line and subsequent regimens are becoming increasingly available in settings like Côte d'Ivoire, we assessed the impact of available downstream regimens in sensitivity analysis. Compared to a clinical monitoring strategy, a CD4-based strategy with failure defined as at least a 50% decrease in peak on-treatment CD4 increased discounted life expectancy by 1.90 years and lifetime costs by \$3,590. Using a 1-log₁₀ increase in HIV RNA or return to pre-treatment HIV RNA level provided the greatest clinical benefit of all

monitoring strategies assessed (discounted life expectancy of 14.7 years) for an additional \$3,920 compared to CD4-based monitoring.

Sensitivity Analysis

We assessed the robustness of results through clinically plausible variations in assumptions and parameter values. In the text that follows and in Appendix Table A4, we present select results not discussed in the main text.

Select One-way Sensitivity Analyses

CD4 at Presentation (Table A4-a)—We considered three cohorts entering care with CD4 counts of 100 (standard deviation (SD) 25), 250 (SD 25), and 425 (SD 25) cells/ μ L (versus CD4 count 140 (SD 116) cells/ μ L in the base case). No matter the stage at which patients entered care, we found that life expectancy for HIV RNA monitoring strategies exceeded CD4 monitoring strategies, which in turn exceeded clinical monitoring strategies. When patients entered care later (i.e., initial CD4 count 100 (SD 25) cells/ μ L), monitoring strategies resulting in earlier detection of 1st-line ART failure (as occurred with HIV RNA monitoring) became increasingly cost-effective compared to monitoring strategies detecting 1st-line ART failure later (as occurred with CD4-based monitoring strategies).

Effectiveness of Antiretroviral Therapy (Table A4-b)—Decreasing 2nd-line HIV RNA suppression in the absence of resistance from 80.4% to 64.0% (24 weeks) diminished both discounted life expectancy and discounted lifetime costs for all monitoring strategies. When we assumed that 2nd-line HIV RNA suppression increased (88% suppressed at 24 weeks), both life expectancy and lifetime costs for all monitoring increased. However, in both cases, the relative ranking of the monitoring strategies did not change and our policy conclusions remained consistent.

We also assessed the delay in CD4 decline after virologic failure. When we assumed a delay in CD4 decline >18 months after virologic failure (versus 12 months in the base case), we found that an HIV RNA temporal strategy (i.e., relying on HIV RNA to identify failure and postponing the switch to 2nd-line ART by 6 months) became an efficient strategy (results not shown). However, variations in our assumptions regarding the delay in CD4 decline after virologic failure did not change overall policy conclusions.

Monitoring Frequency (Table A4-c)—We explored the implications of using different CD4 and HIV RNA monitoring frequencies. Monitoring HIV RNA every 12 months (rather than every 6 months, as in the base case) followed by an immediate switch decreased both lifetime costs and life expectancy; however, lifetime costs decreased at a rate faster than life expectancy, thereby decreasing the incremental cost-effectiveness ratio compared to CD4 monitoring. While discounted life expectancy for this strategy decreased by about 1% compared to the base case (13.36 years vs. 13.52 years), discounted lifetime costs decreased by over 10.3% (\$12,860 vs. \$14,190).

Appendix

Table A1
Monitoring Strategies to Guide Switching to 2nd-line ART

Strategy [*]	Test Modality	Criteria for 1 st -line ART Failure
Clinical Monitoring (Stage III-IV) [†]	Clinical	WHO stage III-IV event

Strategy*	Test Modality	Criteria for 1 st -line ART Failure
Stage III-IV & TB	Clinical	WHO stage III-IV event or TB
Stage III-IV & TB, Bacterial	Clinical	WHO stage III-IV event or TB or severe bacterial infection
Immunologic Monitoring (50% ↓ CD4)[‡]	CD4	50% ↓ in peak CD4
25% ↓ in peak CD4	CD4	25% ↓ in peak CD4
Stage III-IV/CD4	Clinical/CD4	WHO stage III-IV event or 50% ↓ in peak CD4
Stage III-IV & TB/CD4 50%	Clinical/CD4	WHO stage III-IV event or TB or 50% ↓ in peak CD4
Stage III-IV & TB, Bacterial/CD4 50%	Clinical/CD4	WHO stage III-IV event or TB or severe bacterial infection or 50% ↓ in peak CD4
Stage III-IV/CD4 25%	Clinical/CD4	WHO stage III-IV or 25% ↓ in peak CD4
Stage III-IV & TB/CD4 25%	Clinical/CD4	WHO stage III-IV event or TB or 25% ↓ in peak CD4
Stage III-IV & TB, Bacterial/CD4 25%	Clinical/CD4	WHO stage III-IV event or TB or severe bacterial infection or 25% ↓ in peak CD4
Virologic Monitoring (1-log ↑/pre-tx)	HIV RNA	1-log₁₀ ↑ or return to pre-treatment HIV RNA
Delayed switch to 2 nd -line (6 months)	HIV RNA	WHO stage III-IV event or 1-log ₁₀ ↑ or return to pre-treatment level
Stage III-IV/HIV RNA	Clinical/HIV RNA	WHO stage III-IV event or 1-log ₁₀ ↑ or return to pre-treatment HIV RNA
Stage III-IV & TB/HIV RNA	Clinical/HIV RNA	WHO stage III-IV event or TB or 1-log ₁₀ ↑ or return to pre-treatment HIV RNA
Stage III-IV & TB, Bacterial/HIV RNA	Clinical/HIV RNA	WHO stage III-IV event or TB or severe bacterial infection or 1-log ₁₀ ↑ or return to pre-treatment HIV RNA
Stage III-IV/HIV RNA (6 months)	Clinical/HIV RNA	WHO stage III-IV or 1-log ₁₀ ↑ or return to pre-treatment HIV RNA
Stage III-IV & TB/HIV RNA (6 months)	Clinical/HIV RNA	WHO stage III-IV event or TB or 1-log ₁₀ ↑ or return to pre-treatment HIV RNA
Stage III-IV & TB, Bacterial/HIV RNA (6 months)	Clinical/HIV RNA	WHO stage III-IV event or TB or severe bacterial infection or 1-log ₁₀ ↑ or return to pre-treatment HIV RNA

Abbreviations: ART = antiretroviral therapy; WHO = World Health Organization; and TB = tuberculosis.

* Shaded rows indicate the 3 general base case strategies. Strategies evaluated in secondary analyses are shown without shading. In the strategies, clinical, immunologic, and virologic observed failure criteria for 1st-line ART were not mutually exclusive. For example, observed 1st-line ART failure could occur based on either clinical criteria (i.e., 1 WHO stage III-IV event excluding TB and bacterial infections) or immunologic criteria (i.e., 25% decrease in peak, regimen-specific CD4).

[‡] Clinical events categorized as WHO stage III-IV events did not include invasive bacterial diseases or tuberculosis unless otherwise specified. In the model, WHO stage III-IV events consisted of severe visceral events, non-visceral events, and non-specific events. We defined visceral events as the occurrence of toxoplasmosis, isosporosis, cryptococcosis, Kaposi's sarcoma, lymphoma, cryptosporidiosis, microsporidiosis, non-tuberculosis mycobacteriosis, invasive herpes simplex virus, or cytomegalovirus infection. Non-visceral events included chronic genital herpes simplex virus and oesophageal candidiasis. Non-specific events consisted of unexplained diarrhea for >30 days and fever of unexplained origin (no focus, non-specific pneumonia, and non-specific neurologia). Other severe opportunistic infections included tuberculosis and severe bacterial events (pneumonia, isolated bacteremia, invasive uro-genital events, and severe bacterial infections from

other causes). Estimates assumed no administration of cotrimoxazole to the study population. In sensitivity analysis, we varied incidence of opportunistic events by $\pm 50\%$.

[‡]Immunologic failure occurred based on a percent decrease in peak observed, regimen-specific CD4 count.

Table A2

Additional Model Input Variables

Variable	Base Case Value					Reference(s)
Clinical characteristics in the absence of antiretroviral therapy						
Mean monthly CD4 count decline (SD) by HIV RNA stratum (cells/ μ L)						
> 30,000 copies/mL				6.4 (0.3)		Mellors et al. ⁸
10,001–30,000 copies/mL				5.4 (0.2)		
3,001–10,000 copies/mL				4.6 (0.2)		
500–3,000 copies/mL				3.0 (0.3)		
<500 copies/mL				3.0 (0.3)		
Rate of clinical events, by CD4 count (events per 100 person-years)*						
	≤ 50 cells/mL	51–100 cells/mL	101–200 cells/mL	201–350 cells/mL	350–500 cells/mL	>500 cells/mL
HIV-related, severe						
WHO stage III–IV						
Visceral	35.54	17.32	4.21	2.45	0.65	0.43
Non-visceral	33.42	15.99	5.55	1.44	0.71	0.27
Non-specific	25.23	11.80	5.72	1.72	1.07	0.54
Bacterial enteritis	16.10	15.60	10.24	5.78	3.91	2.19
Bacterial infections	15.66	40.81	17.67	9.11	6.34	4.96
Malaria	36.27	34.28	22.62	14.94	20.64	17.01
Tuberculosis	4.21	8.03	7.96	3.09	1.70	0.28
HIV-related, mild						
Fungal infections	119.28	56.43	31.58	13.94	12.41	8.10
Bacterial infections	24.37	22.95	21.71	16.19	12.93	12.07
Other	50.79	35.21	31.80	18.93	12.51	10.60
Other severe events [†]	5.10	4.10	3.10	2.10	1.00	0.70
% acute mortality, by CD4 count stratum						
	≤ 50 cells/mL	51–100 cells/mL	101–200 cells/mL	201–350 cells/mL	350–500 cells/mL	>500 cells/mL
HIV-related, severe						
WHO stage III–IV						

Minga et al.,⁹ Seyler et al.¹⁰

Variable	Base Case Value					Reference(s)
Visceral and non-specific events	40.00	32.3	9.72	4.65	1.50	0.00
Bacterial infections and malaria	14.29	14.29	5.77	3.25	0.00	0.00
Tuberculosis	50.00	50.00	22.22	4.17	1.50	0.00
Non-HIV-related [†]	14.29	14.29	5.77	3.25	0.00	0.00
<i>Rate of chronic HIV/AIDS mortality in the absence of antiretroviral therapy, by CD4 count stratum (events per 100 person-years)*</i>						
	≤50 cells/mL	51–100 cells/mL	101–200 cells/mL	201–350 cells/mL	350–500 cells/mL	>500 cells/mL
WHO stage III–IV events, excluding TB and invasive bacterial diseases	63.95	63.95	34.79	18.11	1.58	0.00
HIV-related TB and invasive bacterial diseases, malaria, and other severe events	13.25	13.25	5.96	3.30	1.58	0.00
Efficacy and toxicity of cotrimoxazole[‡]						
<i>Efficacy (% reduction in risk of opportunistic infection)</i>						
Mild bacterial infection				48.8		
Bacterial enteritis and other severe bacterial infection				49.8		
Malaria				88.4		
Isosporiasis				81.8		
Toxoplasmic encephalitis				83.3		
Acute unexplained fever				17.9		
<i>Toxicity (per 100 person-months)</i>						
Minor events				1.9		
Major events				0.7		
Antiretroviral efficacy						
<i>3rd-line antiretroviral therapy in the absence of resistance</i>						
HIV RNA suppression [§]				77.0% at 24 weeks		
CD4 count increase [¶]				+105 cells/μL at 24 weeks		
Resistance penalty (monthly relative decrease) [§]				-1.00% in 3 rd -line HIV RNA suppression at 24 weeks per month on virologically failed 1 st - and 2 nd -line ART		

Minga et al.,⁹ Seyler et al.,¹⁰

Anglaret et al.,¹¹
Yazdanpanah et al.¹²

Delfraissy et al.,⁵ Johnson et al.,⁶ Marconi et al.⁷

Variable	Base Case Value	Reference(s)
Costs (2006 US\$)[¶]		
<i>Opportunistic infection treatment (per event)</i>		
HIV-related, severe *		Yazdanpanah et al. ¹²
WHO stage III-IV		
Visceral	98.16	
Non-visceral	98.16	
Non-specific	93.69	
Bacterial enteritis	137.39	
Bacterial infections	137.39	
Malaria	96.17	
Tuberculosis	329.74	
HIV-related, mild		
Fungal infections	47.32	
Bacterial infections	53.43	
Other	53.43	
Non-HIV-related [‡]	94.65	Médecins sans Frontières, ¹³ Yazdanpanah et al. ¹²
<i>Antiretroviral therapy (annual)</i>		
3 rd -line ART (PI-based)**	749.00	

Abbreviations: WHO = World Health Organization; PY = person-year; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; and IQR = interquartile range.

Note: Unless otherwise indicated, model variables were varied +/-50% to assess the impact of clinically plausible variations in assumptions and parameter values.

* Clinical events categorized as WHO stage III-IV events did not include invasive bacterial diseases or tuberculosis unless otherwise specified. In the model, WHO stage III-IV events consisted of severe visceral events, non-visceral events, and non-specific events. We defined visceral events as the occurrence of toxoplasmosis, isosporosis, cryptococcosis, Kaposi's sarcoma, lymphoma, cryptosporidiosis, microsporidiosis, non-tuberculosis mycobacteriosis, invasive herpes simplex virus, or cytomegalovirus infection. Non-visceral events included chronic genital herpes simplex virus and oesophageal candidiasis. Non-specific events consisted of unexplained diarrhea for >30 days and fever of unexplained origin (no focus, non-specific pneumonia, and non-specific neurologia). Other severe opportunistic infections included tuberculosis and severe bacterial events (pneumonia, isolated bacteremia, invasive uro-genital events, and severe bacterial infections from other causes). Estimates assumed no administration of cotrimoxazole to the study population. In sensitivity analysis, we varied incidence of opportunistic events by +/-50%.

[‡] Other severe events were defined as severe events requiring hospitalization (e.g., acute unexplained fever or acute unexplained diarrhea with hospitalization).

[§] In accordance with WHO guidelines, patients received 960 mg of cotrimoxazole daily (800 mg sulfamethoxazole plus 160 mg trimethoprim).¹⁴

[¶] We assumed 3rd-line HIV RNA suppression in the presence of resistance was 61.3% at 24 weeks;⁶ in the absence of resistance, we assumed a value of 77.0% suppressed at 24 weeks.⁵ In the absence of data on time on virologically failed 2nd-line ART, we derived the value for the resistance penalty as applied to 3rd-line ART by calibrating the value of the resistance penalty (1.0% per month) until aggregate outcomes across all simulated patients reflected 61.3% HIV RNA suppression (24 weeks)⁶ in patients receiving 3rd-line ART.

^{**} For 3rd-line ART (assessed in a secondary analysis), we estimated 24-week CD4 count increases from baseline of 105 cells/ μ L, which reflects adjustments for loss to follow-up and reporting time.

Cost estimates did not include direct non-medical costs, patient time costs, or the opportunity cost of foregone earnings due to illness. All costs were adjusted to 2006 price levels and converted, when necessary, from local currency to US dollars using official exchange rates.

** ART costs were derived based on Clinton Foundation negotiated ceiling prices.¹³ Costs of 3rd-line ART (assessed in a secondary analysis) were assumed to be equivalent to 2nd-line ART costs. We assumed all negotiated costs reflected 2006 price levels. See main text, Table 2 for details.

Table A3
Clinical Benefits, Costs, and Cost-effectiveness of
Monitoring Strategies to Guide Switching to 2nd-line
Antiretroviral Therapy: Base Case and Modified Base
Case Strategies (HIV RNA Test Cost = \$87)

Strategy*	Mean CD4 at Observed ART Failure (cells/mL)	Undiscounted Life Expectancy (years)	Discounted Life Expectancy (years)	Discounted Lifetime Costs (\$)†	ICER (\$/years of life gained)‡
Cotrimoxazole only	N/A	2.21	2.11	1,060	--
1 st -line ART only plus cotrimoxazole	N/A	11.95	9.39	5,290	580
1 st - & 2 nd -line ART plus cotrimoxazole					
1 WHO stage III-IV event§	129	14.85	11.01	7,990	1,670
1 WHO stage III-IV event, including TB	173	15.29	11.24	8,640	dominated
1 WHO stage III-IV event, including TB or invasive bacterial diseases	243	15.90	11.59	9,810	dominated
50% decrease in peak CD4¶	189	17.49	12.42	10,980	2,120
50% decrease in peak CD4 or 1 WHO stage III-IV event	214	17.50	12.47	11,410	dominated
50% decrease in peak CD4 or 1 WHO stage III-IV event, including TB	230	17.40	12.41	11,600	dominated
50% decrease in peak CD4 or 1 WHO stage III-IV event, including TB or invasive bacterial infections	265	17.18	12.32	12,030	dominated
25% decrease in peak CD4	308	18.48	13.00	12,240	2,170
25% decrease in peak CD4 or 1 WHO stage III-IV event	310	18.31	12.93	12,440	dominated
25% decrease in peak CD4 or 1 WHO stage III-IV event, including TB	312	18.12	12.83	12,540	dominated
HIV RNA temporal (Switch 6 months after observed failure) or 1 WHO stage III-IV event, including TB or invasive bacterial diseases¶	418	17.62	12.61	12,610	dominated
25% decrease in peak CD4 or 1 WHO stage III-IV event, including TB or invasive bacterial diseases	321	17.71	12.63	12,710	dominated
HIV RNA temporal (Switch 6 months after observed failure) or 1 WHO stage III-IV event, including TB	440	18.30	12.95	13,170	dominated
HIV RNA temporal (Switch 6 months after observed failure) or 1 WHO stage III-IV event	452	18.64	13.14	13,450	dominated

Strategy*	Mean CD4 at Observed ART Failure (cells/mL)	Undiscounted Life Expectancy (years)	Discounted Life Expectancy (years)	Discounted Lifetime Costs (\$)†	ICER (\$/years of life gained)‡
HIV RNA temporal (Switch 6 months after observed failure)	467	19.13	13.38	13,830	dominated
HIV RNA (Switch immediately) or 1 WHO stage III-IV event, including TB or invasive bacterial diseases	418	18.22	12.97	13,950	dominated
HIV RNA (Switch immediately) or 1 WHO stage III-IV event, including TB	440	18.71	13.22	14,070	dominated
HIV RNA (Switch immediately) or 1 WHO stage III-IV event	452	18.97	13.34	14,110	dominated
¶ HIV RNA (Switch immediately)	467	19.28	13.52	14,190	3,750

Abbreviations: ICER = incremental cost-effectiveness ratio; N/A = not applicable; ART = antiretroviral therapy; WHO = World Health Organization; and TB = tuberculosis.

* Shaded rows indicate the 3 general base case strategies. Strategies evaluated in secondary analyses are shown without shading. In the strategies, clinical, immunologic, and virologic observed failure criteria for 1st-line ART were not mutually exclusive. For example, observed 1st-line ART failure could occur based on either clinical criteria (i.e., 1 WHO stage III-IV event excluding TB and bacterial infections) or immunologic criteria (i.e., 25% decrease in peak, regimen-specific CD4). All ART strategies included cotrimoxazole prophylaxis. In accordance with WHO guidelines, patients received 960 mg of cotrimoxazole daily (800 mg sulfamethoxazole plus 160 mg trimethoprim).¹⁴

† Costs are reported in 2006 US\$.

‡ Dominated strategies were either more expensive and less effective or less cost-effective, compared to the next least expensive strategy.

§ In clinical switching strategies, clinical events categorized as “WHO stage III-IV” did not include TB or invasive bacterial diseases unless otherwise specified.

¶ Strategy recommended in current WHO guidelines.⁴

// In strategies labeled “HIV RNA”, failure was defined as a 1-log₁₀ increase in or a return to pre-treatment HIV RNA level.

Table A4

Table A4-a. Sensitivity Analysis on CD4 count at Presentation

Strategy*	Discounted Life Expectancy (years)	Discounted Lifetime Costs (\$)†	ICER (\$/years of life gained)‡
<u>CD4 count at Presentation = 100 (SD 25) cells/μL (Base Case = 140 (SD 116) cells/uL)</u>			
Cotrimoxazole only	1.65	900	--
1 st -line ART plus cotrimoxazole	9.09	4,870	530
1 st - & 2 nd -line ART plus cotrimoxazole			
1 WHO stage III-IV event§	10.81	7,660	1,630
50% decrease in peak CD4¶	12.18	10,840	2,310
HIV RNA (Switch immediately)	13.32	13,600	2,420
<u>CD4 count at Presentation = 250 (SD 25) cells/μL (Base Case = 140 (SD 116) cells/uL)</u>			
Cotrimoxazole only	2.90	1,340	--
1 st -line ART plus cotrimoxazole	10.64	6,510	670

Table A4-a. Sensitivity Analysis on CD4 count at Presentation

Strategy*	Discounted Life Expectancy (years)	Discounted Lifetime Costs (\$)†	ICER (\$/years of life gained)‡
1 st - & 2 nd -line ART plus cotrimoxazole			
1 WHO stage III-IV event§	12.27	9,290	1,700
50% decrease in peak CD4¶	13.95	12,380	1,840
HIV RNA (Switch immediately)	14.97	16,630	4,150
CD4 count at Presentation = 425 (SD 25) cells/μL (Base Case = 140 (SD 116) cells/uL)			
Cotrimoxazole only	4.57	1,880	--
1 st -line ART plus cotrimoxazole	11.58	6,900	720
1 st - & 2 nd -line ART plus cotrimoxazole			
1 WHO stage III-IV event§	12.94	9,270	1,740
50% decrease in peak CD4¶	14.48	12,270	1,950
HIV RNA (Switch immediately)	15.28	16,210	4,930

Abbreviations: ICER = incremental cost-effectiveness ratio; ART = antiretroviral therapy; and WHO = World Health Organization.

* All ART strategies included cotrimoxazole prophylaxis. In accordance with WHO guidelines, patients received 960 mg of cotrimoxazole daily (800 mg sulfamethoxazole plus 160 mg trimethoprim).¹⁴ No matter the stage at which patients entered care, patients received antiretroviral therapy in accordance with WHO recommendations.⁴

† Costs are reported in 2006 US\$.

‡ Dominated strategies were either more expensive and less effective or less cost-effective, compared to the next least expensive strategy.

§ In clinical switching strategies, clinical events categorized as WHO stage III–IV did not include invasive bacterial diseases or tuberculosis.

¶ Strategy recommended in current WHO guidelines.⁴

|| In strategies labeled “HIV RNA”, failure was defined as a 1-log₁₀ increase in HIV RNA or a return to pre-treatment HIV RNA level.

Table A4-b. Sensitivity Analysis on ART effectiveness

Strategy*	Discounted Life Expectancy (years)	Discounted Lifetime Costs (\$)†	ICER (\$/years of life gained)‡
2 nd -line ART HIV RNA suppression at 24 weeks = 64.0% (Base Case = 77.0%)			
Cotrimoxazole only	2.11	1,060	--
1 st -line ART plus cotrimoxazole	9.39	5,290	580
1 st - & 2 nd -line ART plus cotrimoxazole			
1 WHO stage III-IV event§	10.69	7,640	1,810
50% decrease in peak CD4¶	11.95	10,400	2,190
HIV RNA (Switch immediately)	12.88	13,380	3,210
2 nd -line ART HIV RNA suppression at 24 weeks = 88.0% (Base Case = 77.0%)			
Cotrimoxazole only	2.11	1,060	--
1 st -line ART plus cotrimoxazole	9.40	5,290	580
1 st - & 2 nd -line ART plus cotrimoxazole			
1 WHO stage III-IV event§	11.27	8,280	1,600

Table A4-b. Sensitivity Analysis on ART effectiveness

Strategy*	Discounted Life Expectancy (years)	Discounted Lifetime Costs (\$)†	ICER (\$/years of life gained)‡
50% decrease in peak CD4¶	12.80	11,460	2,070
HIV RNA (Switch immediately)¶	14.05	14,870	2,730
<u>Delay in CD4 decline after virologic failure = 6 months (Base Case = 12 months)</u>			
Cotrimoxazole only	2.11	1,060	--
1 st -line ART plus cotrimoxazole	9.16	5,170	580
1 st - & 2 nd -line ART plus cotrimoxazole			
1 WHO stage III-IV event§	10.78	7,860	1,660
50% decrease in peak CD4¶	12.24	10,950	2,110
HIV RNA (Switch immediately)¶	13.24	13,870	2,920
<u>Delay in CD4 decline after virologic failure = 18 months (Base Case = 12 months)</u>			
Cotrimoxazole only	2.11	1,060	--
1 st -line ART plus cotrimoxazole	9.63	5,410	580
1 st - & 2 nd -line ART plus cotrimoxazole			
1 WHO stage III-IV event§	11.23	8,100	1,680
50% decrease in peak CD4¶	12.57	10,990	2,150
HIV RNA (Switch immediately)	13.73	14,430	2,980

Abbreviations: ART = antiretroviral therapy; ICER = incremental cost-effectiveness ratio; and WHO = World Health Organization.

* All ART strategies included cotrimoxazole prophylaxis. In accordance with WHO guidelines, patients received 960 mg of cotrimoxazole daily (800 mg sulfamethoxazole plus 160 mg trimethoprim).¹⁴

† Costs are reported in 2006 US\$.

‡ Dominated strategies were either more expensive and less effective or less cost-effective, compared to the next least expensive strategy.

§ In clinical switching strategies, clinical events categorized as WHO stage III–IV did not include invasive bacterial diseases or tuberculosis.

¶ Strategy recommended in current WHO guidelines.⁴

|| In strategies labeled “HIV RNA”, failure was defined as a 1-log₁₀ increase in HIV RNA or a return to pre-treatment HIV RNA level.

Table A4-c. Sensitivity Analysis on Monitoring Frequency

Strategy*	Discounted Life Expectancy (years)	Discounted Lifetime Costs (\$)†	ICER (\$/years of life gained)‡
<u>Monitor CD4 count every 12 months (Base Case = every 6 months)</u>			
Cotrimoxazole only	2.11	1,060	--
1 st -line ART plus cotrimoxazole	9.39	5,290	580
1 st - & 2 nd -line ART plus cotrimoxazole			
1 WHO stage III-IV event§	11.01	7,990	1,670
50% decrease in peak CD4¶	11.79	9,670	2,150
HIV RNA (Switch immediately)	13.52	14,190	2,610
<u>Monitor HIV RNA every 12 months (Base Case = every 6 months)</u>			
Cotrimoxazole only	2.11	1,060	--
1 st -line ART plus cotrimoxazole	9.39	5,290	580

Table A4-c. Sensitivity Analysis on Monitoring Frequency

Strategy*	Discounted Life Expectancy (years)	Discounted Lifetime Costs (\$)†	ICER (\$/years of life gained)‡
1 st - & 2 nd -line ART plus cotrimoxazole			
1 WHO stage III-IV event§	11.01	7,990	1,670
50% decrease in peak CD4¶	12.42	10,980	dominated
HIV RNA (Switch immediately)	13.36	12,860	2,010

Abbreviations: ICER = incremental cost-effectiveness ratio; ART = antiretroviral therapy; and WHO = World Health Organization.

* All ART strategies included cotrimoxazole prophylaxis. In accordance with WHO guidelines, patients received 960 mg of cotrimoxazole daily (800 mg sulfamethoxazole plus 160 mg trimethoprim).¹⁴

† Costs are reported in 2006 US\$.

‡ Dominated strategies were either more expensive and less effective or less cost-effective, compared to the next least expensive strategy.

§ In clinical switching strategies, clinical events categorized as WHO stage III-IV did not include bacterial infections or tuberculosis.

¶ Strategy recommended in current WHO guidelines.⁴

// In strategies labeled "HIV RNA", failure was defined as a 1-log₁₀ increase in HIV RNA or a return to pre-treatment HIV RNA level.

Figure A1. Percent time on antiretroviral therapy, by virologic suppression status and type of monitoring strategy

This figure depicts the percent of undiscounted life expectancy on 1st- and 2nd-line ART, by virologic suppression status and type of monitoring. Each bar reflects a representative clinical (failure criterion: 1 WHO stage III-IV event, excluding tuberculosis and invasive bacterial diseases), immunologic (failure criterion: 50% decrease in peak on-treatment CD4), or virologic (failure criterion: 1 log₁₀ increase in or return to pre-treatment HIV RNA level, immediate switch) monitoring strategy. Time on suppressed and virologically failed 1st-line ART is shown dark red (■) and dark purple (■), respectively. Time on suppressed and virologically failed 2nd-line ART is shown in lighter red (■) and lighter purple (■),

respectively. Detecting ART failure earlier — as occurs when using HIV RNA monitoring — resulted in a shorter duration on virologically failed 1st-line ART and longer total duration on 2nd-line ART. ART: antiretroviral therapy.

Figure A2. 20-year survival, by type of monitoring strategy

This figure depicts time (x-axis) and survivorship (y-axis) for a treatment-eligible cohort entering care with mean CD4 140 cells/ μ L (standard deviation 116 cells/ μ L) for patients relying on clinical- (small dashed line), CD4- (solid line), or HIV RNA- (large dashed line) based switching strategies. Median survivals, indicated by the dotted line, were 12.79, 16.13, and 18.96 years, respectively. At approximately 2 years, the proportion of the initial cohort surviving and receiving HIV RNA monitoring began to diverge from the proportion of the cohort surviving and receiving clinical and CD4 count monitoring. By 5 years, the proportion of the initial cohort surviving and receiving CD4 count monitoring diverged from the proportion of the initial cohort surviving and receiving clinical monitoring.

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Figure 1.

Sensitivity analysis: incremental cost-effectiveness of virologic monitoring. This figure depicts the results of sensitivity analyses on the incremental cost-effectiveness of virologic monitoring with HIV RNA test costs of \$50 (Upper Panel) and \$87 (Lower Panel). The horizontal axis shows variations in the incremental cost-effectiveness ratio (US\$ per YLS) due to changes in values of select model variables listed on the vertical axis. Late failure refers to the monthly risk of virological failure for virologically suppressed patients. “Resistance penalty” refers to the decrease in 2nd-line ART efficacy due to time on virologically failed 1st-line ART (see Methods for details). Values in parentheses specify the upper and lower bounds assessed for each variable. The vertical broken line indicates the incremental cost-effectiveness ratio of virologic monitoring at an HIV RNA test cost of

either \$50 (upper) or \$87 (lower). ICER: incremental cost-effectiveness ratio; ART: antiretroviral therapy; YLS: year of life gained.

Figure 2.

Cost-effectiveness of switching to 2nd-line antiretroviral therapy: the efficient frontier. This figure shows 4 strategies considered to be efficient, including Clinical A (clinical monitoring with a failure criterion of WHO Stage III-IV event (excluding tuberculosis and invasive bacterial diseases)), CD4 count (immunologic monitoring with 1st-line ART failure criteria based on CD4 declines of 50% or 25% from peak on-treatment CD4 count), and HIV RNA test (virologic monitoring with failure criteria based on a log₁₀ increase in or return to pre-treatment HIV RNA). All other strategies shown are more costly and less effective (i.e., strongly dominated), or more costly and less cost-effective (i.e., weakly dominated). Where applicable, an HIV RNA test cost of \$87 was assumed.

Table 1
Selected Monitoring Strategies to Guide Switching to Second-Line ART

Strategy*	Test Modality	Criteria for 1 st -line ART Failure
Clinical Monitoring (Stage III-IV) [†]	Clinical	WHO stage III-IV event
Stage III-IV or TB	Clinical	WHO stage III-IV event or TB
Stage III-IV or TB or Bacterial	Clinical	WHO stage III-IV event or TB or invasive bacterial diseases
Immunologic Monitoring (50%↓CD4)	CD4	50% ↓ in peak CD4
25% ↓ in peak CD4	CD4	25% ↓ in peak CD4
Stage III-IV/CD4	Clinical/CD4	WHO stage III-IV event or 50% ↓ in peak CD4
Virologic Monitoring (1-log ↑/pre-tx)	HIV RNA	1-log ₁₀ ↑ or return to pre-treatment HIV RNA
Delayed switch to 2 nd -line (6 months)	HIV RNA	WHO stage III-IV or 1-log ₁₀ ↑ or return to pre-treatment HIV RNA
Stage III-IV/HIV RNA	Clinical/HIV RNA	WHO stage III-IV or 1-log ₁₀ ↑ or return to pre-treatment HIV RNA

Abbreviations: ART = antiretroviral therapy; WHO = World Health Organization; and TB = tuberculosis.

* Shaded rows indicate the 3 general base case strategies. Selected strategies evaluated in secondary analyses are shown without shading. A complete set of strategies is available in the Appendix (Appendix Table A1).

[†] Detailed definitions of WHO stage III–IV events are provided in the Appendix.

Table 2
Selected Model Variables

Variable	Base Case Value	Reference(s)
Initial cohort characteristics		
Mean age (SD) (yrs)	36.9 (9.2)	Toure et al. ⁴⁴
Gender distribution	70% female	Toure et al. ⁴⁴
Mean CD4 count (SD) (cells/ μ L)	140 (116)	Toure et al. ⁴⁴
Median HIV RNA (IQR) ($\log_{10}$ copies/mL)	5.3 (4.8–5.8)	Seyler et al. ⁴³
Antiretroviral efficacy, drug toxicity, and resistance penalty		
1 st - and 2 nd -line antiretroviral therapy [*]		Toure et al., ⁴⁴ Delfraissy et al. ⁴⁷
HIV RNA suppression at 24 weeks	80.4% (1 st -line); 77.0% (2 nd -line) (range: 64%–88%)	
CD4 count increase at 24 weeks (cells/ μ L) [†]	+127 (1 st -line); +143 (2 nd -line)	
Toxicity (per 100 person-years)		Anglaret et al., ²² Seyler et al. ²⁴
Minor toxic events [‡]	29.3	
Major toxic events	10.8	
Resistance penalty (monthly relative decrease) [§]	-0.45% in 2nd-line HIV RNA suppression at 24 weeks per month on virologically failed 1 st -line ART (range: 0.00%–1.63%)	Delfraissy et al., ⁴⁷ Johnson et al., ⁴⁹ Marconi et al. ⁵⁰
Costs (2006 US\$)[¶]		
<i>Clinic visits and laboratory tests</i>		
Clinic visit (per visit)	3.05	Yazdanpanah et al., ²⁰ WHO-CHOICE ²⁵
CD4 count (per test)	25.00	Médecins sans Frontières ⁵¹
HIV RNA (per test)	87.00	Médecins sans Frontières ⁵¹
Laboratory tests at antiretroviral therapy initiation	14.35	Yazdanpanah et al. ²⁰
<i>Opportunistic infection prophylaxis (annual)</i>		
Cotrimoxazole	2.69	Yazdanpanah et al. ²⁰
<i>Antiretroviral therapy (annual)</i>		
1 st -line ART (NNRTI-based)	121.00	
2 nd -line ART (PI-based)	749.00	
Minor drug toxicity (per event)	2.33	
Major drug toxicity (per event)	23.27	
<i>Routine care costs (monthly)</i>		
CD4 count $\geq$ 200 cells/ μ L	29.69	Yazdanpanah et al. ²⁰
CD4 count <200 cells/ μ L	21.69	
Terminal care & mortality	51.90	

Abbreviations: SD = standard deviation; WHO = World Health Organization; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; and IQR = interquartile range.

Note: Unless otherwise indicated, model variables were varied $\pm 50\%$ to assess the impact of clinically plausible variations in assumptions and parameter values.

* First-line ART efficacy data were derived from the ACONDA cohort, in which 52% received an initial ART regimen of stavudine, lamivudine, and nevirapine; 22% received stavudine, lamivudine, and efavirenz; and 20% received zidovudine, lamivudine, and efavirenz (with the remaining 6% receiving other regimens). We assumed a dosing scheduled in accordance with WHO recommendations — 300 mg once daily (zidovudine), 150 mg twice daily (lamivudine), 30 mg twice daily (stavudine), 600 mg once daily (efavirenz), and 200 mg once daily (nevirapine).

[†] For 1st-line ART, CD4 count increases were 76 (standard deviation (SD) 19) cells/ μ L per month for months 1–2 and 4 (SD 1) cells/ μ L per month thereafter. For 2nd-line ART, CD4 count increases were 65 (SD 16) cells/ μ L per month for months 1–2 and 3 (SD 1) cells/ μ L per month thereafter.

[‡] In the absence of data, the ratio of minor to major ART-related toxic events was assumed to be similar to those occurring due to cotrimoxazole prophylaxis, or approximately 2.7 times as many minor as major toxic events ²².

[§] We defined the resistance penalty as the relative percent decrease in 2nd-line 24-week virologic suppression for each month that a patient remained on a virologically failed 1st-line regimen. The resistance penalty is based on PI-based 2nd-line ART efficacy in the absence of resistance (77.0% suppressed at 24 wks) and the presence of resistance (73.3% suppressed at 24 wks), as well as time between 1st-line ART virologic and observed failure (10.8 months, range: 0.3–4.8 yrs). The baseline value of the resistance penalty was varied between 0% and 1.63% in sensitivity analysis.

[¶] Cost estimates did not include direct non-medical costs, patient time costs, or the opportunity cost of foregone earnings due to illness. All costs were adjusted to 2006 price levels and converted, when necessary, from local currency to US dollars using official exchange rates. Antiretroviral drug costs were not adjusted for inflation since these costs typically represent negotiated costs governed by patents, political forces, and other externalities.

Table 3
Benefits and Cost-effectiveness of Select Monitoring Strategies to Guide Switching to 2nd-line ART

Strategy*	Relative Increase in LE versus 1st-line ART (%)	Mean CD4 at Observed ART failure (cells/ μ L)	Incremental Cost-effectiveness Ratio (\$/YLS)		
			HIV RNA test cost=\$87	HIV RNA test cost=\$50	HIV RNA test cost=\$25
Cotrimoxazole only	--	N/A	--	--	--
1 st -line ART only plus cotrimoxazole	--	N/A	580	580	580
1 st , & 2 nd -line ART, plus cotrimoxazole					
1 WHO stage III-IV event [†]	24.3	129	1,670	1,670	1,670
50% ↓ in peak CD4 count [§]	46.4	189	2,120	2,120	dominated [‡]
HIV RNA, 1 log ₁₀ ↑ or return to pre-treatment HIV RNA	61.3	467	2,920	2,280	1,990

Abbreviations: LE = life expectancy; ART = antiretroviral therapy; N/A = not applicable; and WHO = World Health Organization.

* ART strategies assume prophylaxis with 960 mg of cotrimoxazole daily (800 mg sulfamethoxazole plus 160 mg trimethoprim).^{3,5}

[†] This strategy is more costly and less cost-effective (i.e., dominated), compared to the next less expensive strategy.

[‡] In this strategy, clinical events to guide switching to 2nd-line ART did not include tuberculosis or invasive bacterial diseases.

[§] Strategy recommended in current (2006) WHO guidelines.⁴