

SPECIAL ARTICLE

Cost-Effectiveness of HIV Treatment in Resource-Poor Settings — The Case of Côte d'Ivoire

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ABSTRACT

BACKGROUND

As antiretroviral therapy is increasingly used in settings with limited resources, key questions about the timing of treatment and use of diagnostic tests to guide clinical decisions must be addressed.

METHODS

We assessed the cost-effectiveness of treatment strategies for a cohort of adults in Côte d'Ivoire who were infected with the human immunodeficiency virus (HIV) (mean age, 33 years; CD4 cell count, 331 per cubic millimeter; HIV RNA level, 5.3 log copies per milliliter). Using a computer-based simulation model that incorporates the CD4 cell count and HIV RNA level as predictors of disease progression, we compared the long-term clinical and economic outcomes associated with no treatment, trimethoprim–sulfamethoxazole prophylaxis alone, antiretroviral therapy alone, and prophylaxis with antiretroviral therapy.

RESULTS

Undiscounted gains in life expectancy ranged from 10.7 months with antiretroviral therapy and prophylaxis initiated on the basis of clinical criteria to 45.9 months with antiretroviral therapy and prophylaxis initiated on the basis of CD4 testing and clinical criteria, as compared with trimethoprim–sulfamethoxazole prophylaxis alone. The incremental cost per year of life gained was \$240 (in 2002 U.S. dollars) for prophylaxis alone, \$620 for antiretroviral therapy and prophylaxis without CD4 testing, and \$1,180 for antiretroviral therapy and prophylaxis with CD4 testing, each compared with the next least expensive strategy. None of the strategies that used antiretroviral therapy alone were as cost-effective as those that also used trimethoprim–sulfamethoxazole prophylaxis. Life expectancy was increased by 30% with use of a second line of antiretroviral therapy after failure of the first-line regimen.

CONCLUSIONS

A strategy of trimethoprim–sulfamethoxazole prophylaxis and antiretroviral therapy, with the use of clinical criteria alone or in combination with CD4 testing to guide the timing of treatment, is an economically attractive health investment in settings with limited resources.

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THE USE OF POTENT ANTIRETROVIRAL therapy has transformed the epidemic of the acquired immunodeficiency syndrome (AIDS) in populations with access to these drugs.¹ In settings with limited resources, where the provision of antiretroviral therapy was previously thought to be technically impossible, combination regimens have been found to have short-term efficacy similar to that in developed countries.²⁻⁸ The dramatic rise in global funding for the human immunodeficiency virus (HIV) and AIDS,^{9,10} together with reduced drug costs,¹¹⁻¹⁴ improves the feasibility of providing antiretroviral therapy in settings with limited resources.

As part of the “3 by 5” initiative to distribute antiretroviral treatment to 3 million people in 50 developing countries by the end of 2005, the World Health Organization (WHO) proposed guidelines that incorporate evidence from clinical trials and observational studies of the efficacy and toxicity of antiretroviral therapy.¹⁵ In addition to the relative efficacy, feasibility, and affordability of various treatment regimens, clinical guidance for treating patients with HIV infection requires consideration of criteria for initiating antiretroviral therapy, the relative performance and costs of diagnostic tests, and coordination with other treatment options, such as prophylaxis against opportunistic disease.

When the complexity of a clinical problem involves competing choices and the information required for some components of the decision is incomplete, decision-analysis methods offer a systematic approach to synthesizing existing data and quantifying the trade-offs for alternative options. Capitalizing on the availability of primary data from Côte d’Ivoire² and a recent analysis of the costs of trimethoprim–sulfamethoxazole prophylaxis,¹⁶ we conducted a decision analysis to estimate the clinical and economic outcomes associated with different treatment strategies in adults infected with HIV type 1 (HIV-1) in Côte d’Ivoire, a setting with limited resources.

METHODS

OVERVIEW

We modified a previously published model¹⁷ to simulate the natural history of HIV infection in patients in Côte d’Ivoire and to project the short- and long-term outcomes associated with trimethoprim–sulfamethoxazole prophylaxis alone,

antiretroviral therapy alone, and trimethoprim–sulfamethoxazole prophylaxis with antiretroviral therapy. We compared 22 strategies in which thresholds for initiating and discontinuing a single line of antiretroviral therapy were based on clinical criteria alone or on both the CD4 cell count and clinical criteria. The comparative performance of various strategies was assessed with the use of incremental cost-effectiveness ratios, in 2002 U.S. dollars per year of life gained. We calculated the incremental cost-effectiveness ratio, defined as the additional cost of a strategy, divided by its additional clinical benefit, as compared with the next least expensive strategy. We excluded strategies with higher costs and lower benefits than other options and those with higher incremental cost-effectiveness ratios than other more effective options.¹⁸ We adopted a modified societal perspective, in that the costs of patients’ time and travel were not included, and future costs and benefits were discounted at 3% per year.¹⁸

MODEL

We used first-order Monte Carlo simulation in which disease progression in an individual patient is characterized as a sequence of monthly transitions between health states.¹⁹ Health states in the model, descriptive of each patient’s underlying true health, were defined by current and maximum HIV RNA levels, current and nadir CD4 cell counts, and current and prior opportunistic diseases. Individual characteristics (age, sex, CD4 cell count, and HIV RNA level) were randomly drawn from a specified distribution of patients similar to those enrolled in the placebo group of the Agence Nationale de Recherches sur le SIDA (ANRS) 059 trial, a randomized, controlled trial of trimethoprim–sulfamethoxazole prophylaxis in Abidjan, Côte d’Ivoire²⁰: median age, 33 years; 40% men; and baseline CD4 cell count, 331 cells per cubic millimeter. Each patient’s lifetime clinical course was tracked, with all clinical events and accrued costs tallied. One million patients were simulated, one at a time, in order to provide stable estimates of long-term outcomes for each strategy.

Disease progression was modeled as a function of both the HIV RNA level and the CD4 cell count.^{17,21,22} Opportunistic diseases were divided into 11 groups and categorized as severe or mild.^{16,23} Incidence rates of opportunistic diseases and AIDS-related death were modeled as a

Table 1. Baseline Estimates for Selected Model Variables.*

Variable	Base Case	Source of Data
Distribution of initial HIV RNA		Seyler et al. ²
>100,000 copies/ml	0.6921	
30,001–100,000 copies/ml	0.2227	
10,001–30,000 copies/ml	0.0706	
3001–10,000 copies/ml	0.0135	
501–3000 copies/ml	0.0011	
0–500 copies/ml	0	
Mean monthly decrease in CD4 cell count according to HIV RNA (cells/mm ³)		Mellors et al., ²¹ Multicenter AIDS Cohort Study ²²
>30,000 copies/ml	6.375	
10,001–30,000 copies/ml	5.400	
3001–10,000 copies/ml	4.600	
501–3000 copies/ml	3.733	
0–500 copies/ml	3.025	
Efficacy of trimethoprim–sulfamethoxazole (% reduction in probability of infection)		Yazdanpanah et al., ¹⁶ Anglaret et al. ²⁰
Mild bacterial infection	48.4	
Severe bacterial infection	49.8	
Severe malaria	88.4	
Isosporiasis	81.8	
Toxoplasmic encephalitis	83.2	
Acute unexplained fever	59.1	
Mild fungal infection	–46.4	
Efficacy of first-line ART (% HIV RNA suppression at 52 wk)†	51.0	Seyler et al. ²
Efficacy of second-line ART (% HIV RNA suppression at 48 wk)†	43.2	Ivers et al. ³⁰
Drug toxicity (no. of events per 100 person-months)‡		
Minor, with trimethoprim–sulfamethoxazole prophylaxis	1.9	Landman et al., ³ Laurent et al., ^{5,6} Coetzee et al., ⁷ Djomand et al., ⁸ Anglaret et al. ²⁰
Major, with trimethoprim–sulfamethoxazole prophylaxis	0.7	Landman et al., ³ Laurent et al., ^{5,6} Coetzee et al., ⁷ Djomand et al., ⁸ Anglaret et al. ²⁰
Minor, with ART	1.47	Seyler et al., ² Landman et al., ³ Laurent et al., ^{5,6} Coetzee et al., ⁷ Djomand et al. ⁸
Major, with ART	0.54	Seyler et al., ² Landman et al., ³ Laurent et al., ^{5,6} Coetzee et al., ⁷ Djomand et al. ⁸

function of the CD4 cell count and the presence or absence of a history of opportunistic infection. Successful HIV RNA suppression after antiretroviral therapy resulted in a rise in the CD4 cell count and a corresponding reduction in the risks of opportunistic disease and death. Virologic failure was defined in the model as a 0.5-log increase in the HIV RNA level in 2 consecutive months

while the patient was receiving antiretroviral therapy, after which the CD4 cell count stayed constant for 1 year before declining at a monthly rate that depended on the viral load. Although the model updated CD4 cell counts and HIV RNA levels monthly and determined disease progression on the basis of these values, we assumed that clinical decisions were based on less frequent

Table 1. (Continued.)

Variable	Base Case	Source of Data
Annual costs of treatment (\$)§		
Trimethoprim–sulfamethoxazole prophylaxis	14.72	Yazdanpanah et al. ¹⁶
First-line ART	292	WHO, ^{11,12,14} Médecins sans Frontières ¹³
Second-line ART	682	Médecins sans Frontières ³¹
Laboratory tests at treatment initiation	7.91	Yazdanpanah et al., ¹⁶ WHO-CHOICE ³²
Minor drug toxicity¶	8.67	Yazdanpanah et al. ¹⁶
Major drug toxicity¶	151.64	Yazdanpanah et al. ¹⁶
Cost of tests (\$)		
CD4 cell count, per test	25	Médecins sans Frontières ¹³
Costs of treatment for OD (\$)		
		Yazdanpanah et al. ¹⁶
Severe bacterial infection	89.79	
Severe fungal infection	109.74	
Severe malaria	62.85	
Tuberculosis	215.49	
Isosporiasis	59.86	
Cerebral toxoplasmosis	87.79	
NTM	62.85	
Other severe OD	61.85	
Mild bacterial infection	34.92	
Mild fungal infection	30.93	
Other mild infection	34.92	
Costs of long-term care (\$)		
		Yazdanpanah et al., ¹⁶ WHO-CHOICE ³²
CD4 $\geq 200/\text{mm}^3$	19.40	
CD4 $< 200/\text{mm}^3$	14.18	
Terminal care	33.92	
Other unit costs of care (\$)		
Clinic visit	5.11	Yazdanpanah et al., ¹⁶ WHO-CHOICE ³²
Hospital day	15.22	Yazdanpanah et al. ¹⁶
Day care	7.56	Yazdanpanah et al. ¹⁶

CD4 testing and clinical assessments (every 6 to 12 months) (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

Several assumptions were necessary because of uncertainty about the efficacy of antiretroviral therapy; the rationale for our choices for the base case is described in the Supplementary Appendix.²⁴⁻²⁷ We conservatively assumed that after 10 years, patients no longer had virologic improvement; that after virologic failure, there

was a delay of 12 months before the CD4 cell count started to decline; and that in patients with a CD4 cell count of 50 per cubic millimeter or higher, antiretroviral therapy had an independent effect in reducing the incidence of opportunistic disease and mortality from AIDS.^{23,28}

SIMULATED STRATEGIES

Antiretroviral therapy was initiated on the basis of a defined number of specific opportunistic diseases, the results of a CD4 test, or both. When CD4

Table 1. (Continued.)					
Variable	Base Case				Source of Data
	0–50/mm ³	51–200/mm ³	201–500/mm ³	>500/mm ³	
Mean monthly risk of severe OD (%, by CD4 stratum) †					Anglaret et al., ^{20,33} Losina et al. ²³
Bacterial infection	3.36	3.04	1.73	1.08	
Fungal infection	0.50	0.33	0.17	0	
Malaria	0	0.50	0.42	0.50	
Tuberculosis	1.08	1.16	0.58	0.50	
Isosporiasis	0.50	0.75	0.25	0.17	
Cerebral toxoplasmosis	0.50	0.33	0.17	0	
NTM	2.06	0.25	0	0	
Other severe infection	7.07	6.37	3.28	1.24	
Mean monthly risk of mild OD (%, by CD4 stratum) †					Anglaret et al., ^{20,33} Losina et al. ²³
Bacterial infection	8.23	4.40	3.36	1.57	
Fungal infection	3.68	3.84	1.49	1.08	
Other mild infection	3.52	1.16	1.57	1.24	
	0–50/mm ³	51–200/mm ³	>200/mm ³		
Mean monthly risk of death (%, by CD4 stratum)					Anglaret et al., ^{20,33} Losina et al., ²³ Cole et al. ²⁸
Without prior opportunistic disease	8.99	0.91	0.33		
With prior opportunistic disease	7.69	4.48	0.66		

- * Costs are in 2002 U.S. dollars. ART denotes antiretroviral therapy, OD opportunistic disease, and NTM nontuberculous mycobacteriosis.
- † First-line ART efficacy and toxicity were derived from the ANRS 1203 cohort,² in which 73% of patients received two nucleoside reverse-transcriptase inhibitors and one protease inhibitor, 16% received two nucleoside reverse-transcriptase inhibitors and one nonnucleoside reverse-transcriptase inhibitor, and 11% received two nucleoside reverse-transcriptase inhibitors. For second-line ART, we used the suppression rate from the lower bound of the 95% confidence interval reported for 12-month suppression rates in a meta-analysis on ART in resource-poor settings.³⁰ Virologic improvement was limited to 10 years in the base case.³⁴ To model the independent effect of ART in patients with a CD4 count of 50 per cubic millimeter or higher,³ a rate ratio of 0.24 was applied to mortality rates, and rate ratios of 0.62 to 0.66 were applied to the incidence of severe ODs during treatment.²³
- ‡ Minor toxicity included events reported as probably or definitely attributable to the drug that did not require discontinuation of therapy; major toxicity included events that required discontinuation of therapy or, in the case of ART, a switch in drugs. Rates of toxic events with trimethoprim–sulfamethoxazole were derived from the ANRS 059 trial with the use of methods described elsewhere.^{16,20} The rates of major toxic events with ART were derived from the ANRS 1203 cohort in Côte d'Ivoire.² Since rates of minor toxicity were not reported in this cohort, we assumed that the proportion of minor to major events would be similar to that for trimethoprim–sulfamethoxazole in the ANRS 059 trial (approximately 2.5 to 1.0).²⁰ On the basis of the literature, we established the lower and upper bounds for major ART toxicity as 2% and 18%.^{3,5–8}
- § The costs of first-line ART reflect the most recently negotiated prices for generic fixed-dose combinations (e.g., two nucleoside reverse-transcriptase inhibitors and one nonnucleoside reverse-transcriptase inhibitor) for developing countries. We assumed that first-line therapy cost approximately \$24.33 per person per month (\$292 per year) and used approximately \$12.17 per month (\$146 per year) for the lower bound in the sensitivity analysis, on the basis of the price negotiated by the Clinton Foundation.¹¹ The estimated cost of second-line therapy was based on costs quoted by Médecins sans Frontières for a boosted protease-inhibitor regimen: lopinavir and ritonavir (133.3 mg and 33.3 mg, respectively), \$500 per year, and zidovudine and lamivudine (300 mg and 150 mg, respectively), \$182 per year. Also see the Supplementary Appendix.
- ¶ Estimated costs of minor trimethoprim–sulfamethoxazole toxicity were based on one outpatient visit and laboratory tests. Costs of major toxicity were based on 10 days of inpatient hospitalization, as previously described.¹⁶
- || Severe bacterial infections included pneumonia, bacterial enteritis, isolated bacteremia, and invasive urogenital infections. Mild bacterial infections included otitis–sinusitis, noninvasive urogenital infections, and skin abscess, erysipelas, or any cutaneous bacterial infection. Severe fungal infections included cryptococcal infection and esophageal candidiasis. Mild fungal infections included oral candidiasis, vaginal candidiasis, angular stomatitis, and onychomycosis. Other severe illnesses included other WHO clinical stage 3 and 4 defining events and other events requiring hospital admission or leading to death.^{16,20,23}

testing was available, we assumed that antiretroviral therapy was started in patients with a CD4 count of less than 200 per cubic millimeter; a CD4 count of 200 to 350 per cubic millimeter with severe malaria, a severe bacterial infection, a severe fungal infection, tuberculosis, isosporiasis, cerebral toxoplasmosis, nontuberculous mycobacteriosis, or another severe illness; or a CD4 cell count of more than 350 per cubic millimeter and a severe opportunistic disease other than malaria, bacterial infection, or tuberculosis. Antiretroviral therapy was discontinued, or second-line therapy was instituted, on the basis of an observed 50% or 90% decrease from the peak CD4 cell count during treatment. When CD4 testing was unavailable, we assumed that antiretroviral therapy was initiated if either one or two severe opportunistic diseases developed and was discontinued (or switched to second-line therapy) if there was clinical failure, defined as a specified number of severe opportunistic diseases (one, three, or five). To ensure adequate time for the immunologic benefits of antiretroviral therapy to be realized,²⁹ opportunistic diseases diagnosed during the first 6 months of antiretroviral therapy were not considered as criteria for discontinuation of treatment.

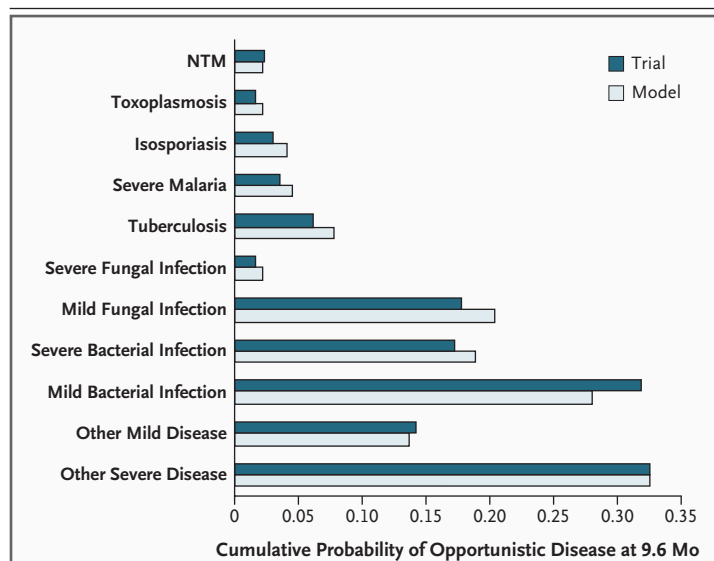


Figure 1. Internal Validity of the Model.

Model-based estimates of the probability of specific opportunistic infections at 9.6 months, the median duration of follow-up for patients in the ANRS 059 trial, are compared with data obtained from the trial. Outcomes projected by the model are within 10 to 15% of reported trial results. NTM denotes nontuberculous mycobacteriosis.

We conservatively assumed that only a single antiretroviral regimen was available, although second-line therapy was evaluated in a secondary analysis. We also made the following six assumptions: trimethoprim–sulfamethoxazole prophylaxis was initiated when the CD4 cell count was less than 500 per cubic millimeter or after any opportunistic disease; if CD4 testing was not available, routine clinic visits occurred every 12 months; after an opportunistic disease or during treatment with trimethoprim–sulfamethoxazole and antiretroviral therapy, visits occurred every 6 months; if CD4 testing was available, clinic visits and CD4 testing occurred every 6 months; treatment was provided for opportunistic diseases, with the exception of Kaposi’s sarcoma, lymphoma, invasive herpesvirus infection, and cytomegalovirus infection; and lifelong maintenance therapy was provided for pneumocystis pneumonia and isosporiasis but not for toxoplasmosis or nontuberculous mycobacteriosis.

BASELINE ESTIMATES FOR MODEL VARIABLES

Baseline estimates for selected variables, as derived from published studies, are shown in Table 1.^{2,3,5-8,11-14,16,20-23,28,30-34} Additional details are provided in the Supplementary Appendix. Estimates of the initial HIV RNA distribution, efficacy of antiretroviral therapy, and drug toxicity were obtained from the ANRS 1203 study, a continuation of the ANRS 059 study of trimethoprim–sulfamethoxazole prophylaxis in Abidjan, Côte d’Ivoire.² Estimates of the efficacy of antiretroviral therapy implicitly reflect the rate of adherence in the trial from which the data are drawn; we therefore conducted a sensitivity analysis based on estimates from a literature review.^{3,5-8,35} Estimates for the incidence of opportunistic diseases and death were based on data from the placebo group in the ANRS 059 study and estimated as functions of four CD4 strata (≤ 50 , 51 to 200, 201 to 500, and >500 cells per cubic millimeter) as previously described.^{17,20,23,33} Mortality rates from causes other than HIV infection were based on data specific for Côte d’Ivoire.³⁶

Direct medical costs of HIV-related care included the costs of hospitalizations, outpatient consultations, laboratory tests, clinical procedures, and medications.²⁰ Costs were estimated for the treatment of opportunistic diseases and for long-term care (termed “routine care costs”) in patients with different CD4 cell counts, as pre-

viously described (see the Supplementary Appendix).¹⁶ Costs were inflated to 2002 price levels with adjustment according to the gross domestic product (GDP) for Côte d'Ivoire, and costs in local currency were converted to U.S. dollars on the basis of prevailing exchange rates.^{37,38}

The study was approved by the institutional review boards at the participating institutions. The requirement for informed consent was waived because our study involved analysis of secondary data.

RESULTS

MODEL VALIDATION

Figure 1 shows the model-based estimates of opportunistic diseases as compared with data from the ANRS 059 trial.²⁰ Projected model outcomes were generally within 10 to 15% of reported trial results.

BASE-CASE ANALYSIS

Figure 2 shows the relationship between the total lifetime costs and discounted life expectancy

for all 22 treatment strategies assessed. Strategies involving both antiretroviral therapy and trimethoprim-sulfamethoxazole prophylaxis were consistently more effective and more cost-effective than those involving antiretroviral therapy alone. Strategies based on CD4 measurements and clinical criteria for initiating and discontinuing antiretroviral therapy were always more effective than strategies based on clinical criteria alone.

Table 2 shows the costs, life expectancy, and incremental cost-effectiveness ratios associated with the six most efficient strategies. Trimethoprim-sulfamethoxazole alone increased undiscounted life expectancy by 1.6 months and cost \$240 per year of life gained, as compared with no treatment. The incremental benefit of using antiretroviral therapy in addition to prophylaxis ranged from 10.7 to 45.9 undiscounted months, depending on the criteria for initiating and discontinuing antiretroviral therapy. The most effective strategy used CD4 testing and provided a gain of 14.0 months in life expectancy, at a cost of \$1,180 per year of life gained, as compared with strategies relying on clinical information alone.

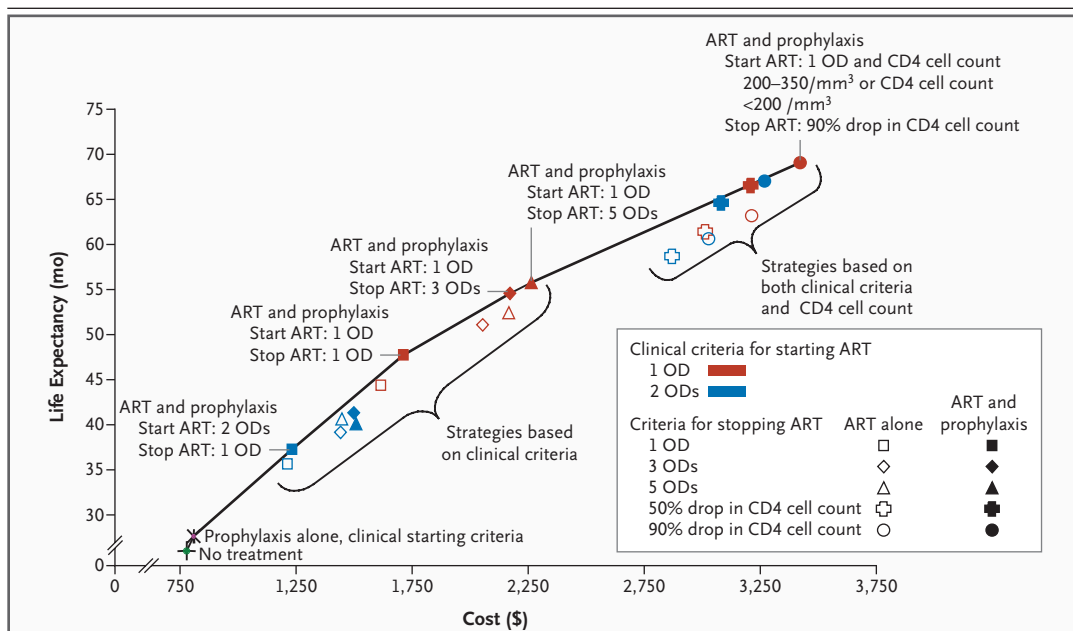


Figure 2. Cost-Effectiveness of Treatment Strategies.

Strategies lying on the curve were more efficient than those lying to the right of the curve because they were more effective and either cost less or had a lower cost-effectiveness ratio, as compared with the next least expensive strategy. Strategies that relied on clinical criteria alone for starting and stopping antiretroviral therapy (ART), which are clustered in the lower left portion of the curve, were always less effective than strategies that included CD4 testing (clustered in the upper right portion of the curve). Strategies that involved ART alone (open symbols) were always more costly and less cost-effective than those that involved both ART and trimethoprim-sulfamethoxazole prophylaxis (solid symbols). All costs are in 2002 U.S. dollars. OD denotes opportunistic disease.

Table 2. Clinical Benefits and Cost-Effectiveness of Alternative Treatment Strategies.*

Strategy	CD4 Testing	ART Starting Criteria†	ART Stopping Criteria	Undiscounted	Discounted	Discounted	Incremental Cost-Effectiveness Ratio
				Life Expectancy	Life Expectancy	Lifetime Costs	
				<i>mo</i>		<i>\$</i>	<i>\$/yr of life gained</i>
No treatment	—	—	—	33.6399	31.4086	783	—
Trimethoprim–sulfamethoxazole alone	No	—	—	35.2454	32.8148	811	240
Trimethoprim–sulfamethoxazole and ART	No	2 ODs from subgroup	1 OD	45.9814	41.3731	1,233	590
Trimethoprim–sulfamethoxazole and ART	No	1 OD from subgroup	1 OD	57.2883	50.6996	1,716	620
Trimethoprim–sulfamethoxazole and ART	No	1 OD from subgroup	3 ODs	65.5831	56.8151	2,171	890
Trimethoprim–sulfamethoxazole and ART	No	1 OD from subgroup	5 ODs	67.1231	57.8712	2,264	1,060
Trimethoprim–sulfamethoxazole and ART	Yes	CD4 cell count <200/mm ³ , CD4 cell count <350/mm ³ and 1 severe OD or 1 OD from subgroup	90% decrease in CD4 cell count	81.1667	69.6337	3,423	1,180

*ART denotes antiretroviral therapy, and OD opportunistic disease.

†ODs included in the base case for ART starting criteria were severe fungal infection, isosporiasis, toxoplasmosis, nontuberculous mycobacteriosis, and other severe illness.

SENSITIVITY ANALYSIS

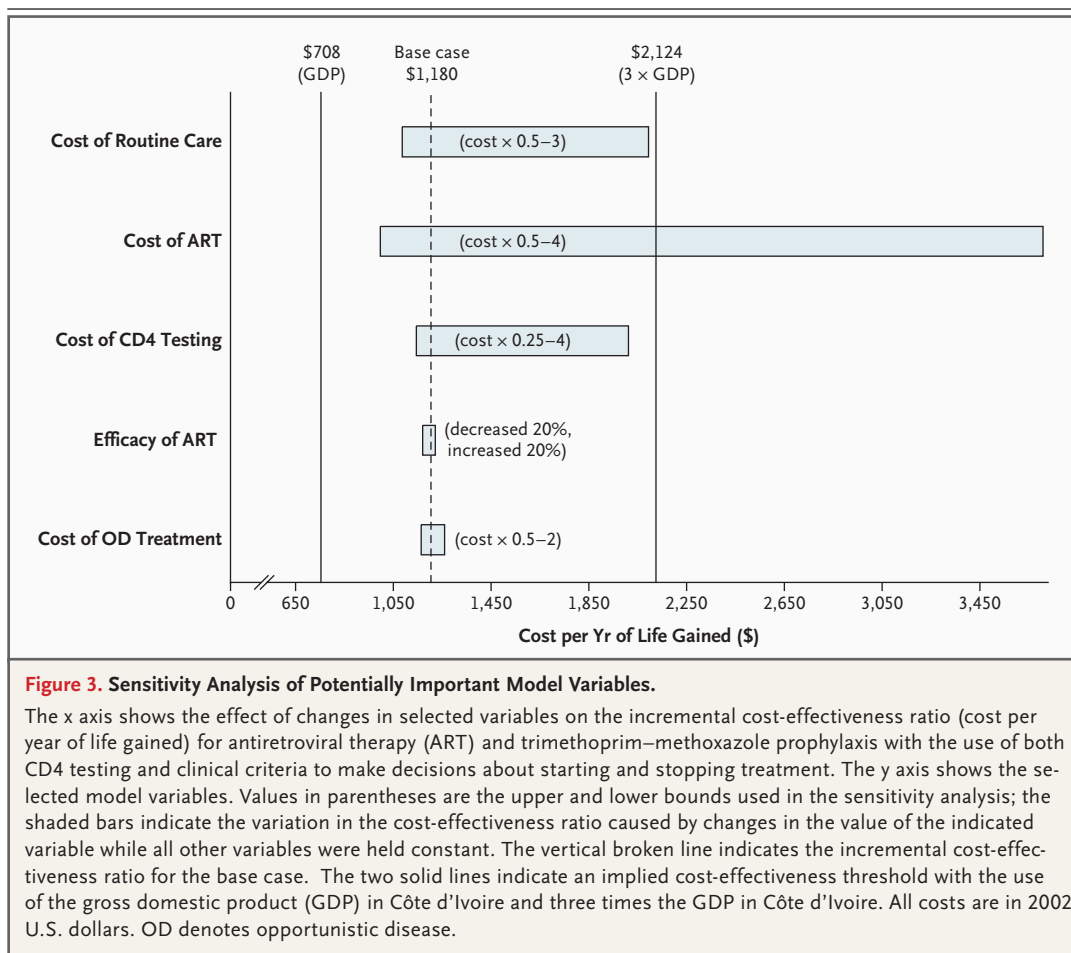
Figure 3 shows how the incremental cost-effectiveness ratio for the most effective strategy, antiretroviral therapy and prophylaxis with the use of CD4 testing, varied with changes in selected variables. The results were most sensitive to changes in the costs of routine care, antiretroviral therapy, and CD4 tests and were less sensitive to plausible changes in the efficacy of antiretroviral therapy and in the costs of treatment for opportunistic diseases.

The most influential of the base-case assumptions was that of an independent effect of antiretroviral therapy on the incidence of opportunistic disease and mortality from AIDS among patients with a CD4 cell count of 50 per cubic millimeter or higher.^{17,20,23,33} For the most effective strategy (antiretroviral therapy and prophylaxis with the use of CD4 testing), gains in life expectancy over that associated with no treatment were approximately 50% lower and incremental cost-effectiveness ratios were twice those for the base case when we assumed no independent effect of antiretroviral therapy. Other assumptions (e.g., a delayed decline in the CD4 cell count after virologic failure and the enduring efficacy of antiretroviral therapy) similarly influ-

enced both life-expectancy gains and costs, and thus had minimal influence on cost-effectiveness (see the Supplementary Appendix).

With access to second-line antiretroviral therapy, life expectancy improved by 10 months (approximately 30%), lifetime costs increased by \$1,080, and the incremental cost-effectiveness ratio was \$1,300 per year of life gained as compared with the most effective first-line antiretroviral strategy. Results of sensitivity analyses that included first- and second-line treatment were similar to those in the base case (see the Supplementary Appendix).

Table 3 shows the average CD4 cell count at which antiretroviral therapy was initiated if CD4 testing was not available, as well as the incremental gains in life expectancy as compared with no treatment, for three strategies with different clinical criteria for initiating treatment. In the base case, the average CD4 cell count at the initiation of antiretroviral therapy was higher with the more lenient criterion of one opportunistic disease than with the stricter criterion of two opportunistic diseases (255 vs. 189 per cubic millimeter), when CD4 testing was not available. With the most effective strategy, involving the use of both clinical criteria and CD4 test information



to guide the initiation of antiretroviral therapy, the average CD4 cell count at which treatment was initiated was 231 per cubic millimeter, reflecting the most efficient targeting of patients likely to benefit from therapy.

For all three strategies, as the set of opportunistic diseases used as criteria for the initiation of antiretroviral therapy was expanded incrementally to include severe malaria, tuberculosis, and severe bacterial disease, the average CD4 cell count at which treatment was initiated increased (Table 3). With the most inclusive set of opportunistic diseases, the incremental increases in life expectancy were greatest for strategies that rely solely on clinical criteria.

DISCUSSION

Several studies have addressed economic issues related to the prevention and treatment of HIV infection in developing countries,³⁹⁻⁴⁵ but few

analyses have compared different strategies for initiating antiretroviral therapy by quantifying their clinical benefits for individual patients. When added to trimethoprim–sulfamethoxazole prophylaxis, antiretroviral therapy with the use of CD4 testing provided a gain in life expectancy of nearly 4 years. For strategies relying only on clinical criteria, the initiation of antiretroviral therapy after the first severe opportunistic disease provided nearly 1 year of additional life expectancy, as compared with initiation of treatment after two opportunistic diseases. Furthermore, if only a single antiretroviral regimen is available, delaying its discontinuation until three or more opportunistic diseases occur provides substantial clinical benefits. The added value of CD4 testing to guide decisions about the timing of treatment translated into a gain in life expectancy of more than 1 year, as compared with the most effective strategy relying solely on clinical information. These survival gains are similar to, or

Table 3. Sensitivity Analysis of Opportunistic Diseases (ODs) Included in the Clinical Criteria for Starting Antiretroviral Therapy (ART).

Variable and Strategy	ART Starting Criteria*	ODs Used as Clinical Criteria				
		Base-Case Subgroup	Base-Case Subgroup plus Severe Malaria	Base-Case Subgroup plus Tuberculosis	Base-Case Subgroup plus Severe Bacterial Infection	Base-Case Subgroup plus Severe Malaria, Tuberculosis, and Severe Bacterial Infection
Average CD4 cell count at initiation of ART (cells/mm ³)						
Trimethoprim-sulfamethoxazole and ART [†]	2 ODs from subgroup	189	196	206	213	230
Trimethoprim-sulfamethoxazole and ART [‡]	1 OD from subgroup	255	263	266	273	287
Trimethoprim-sulfamethoxazole and ART [§]	CD4 cell count <200/mm ³ , CD4 cell count <350/mm ³ , and 1 severe OD or 1 OD from subgroup	231	238	239	246	256
Incremental life-expectancy gain vs. no treatment (mo)						
Trimethoprim-sulfamethoxazole and ART [†]	2 ODs from subgroup	10.0	10.4	11.8	12.8	14.7
Trimethoprim-sulfamethoxazole and ART [‡]	1 OD from subgroup	26.5	27.3	28.8	30.5	32.8
Trimethoprim-sulfamethoxazole and ART [§]	CD4 cell count <200/mm ³ , CD4 cell count <350/mm ³ and 1 severe OD, or 1 OD from subgroup	38.2	38.6	38.6	39.0	39.5
Incremental cost-effectiveness ratio (\$/yr of life gained) [¶]						
Trimethoprim-sulfamethoxazole and ART [†]	2 ODs from subgroup	592	594	595	596	600
Trimethoprim-sulfamethoxazole and ART [‡]	1 OD from subgroup	1057	1092	1006	1058	1045
Trimethoprim-sulfamethoxazole and ART [§]	CD4 cell count <200/mm ³ , CD4 cell count <350/mm ³ and 1 severe OD, or 1 OD from subgroup	1182	1207	1283	1379	1572

* ODs included in the base-case subgroup for starting ART were severe fungal infection, isosporiasis, toxoplasmosis, nontuberculous mycobacteriosis, and other severe illness.

[†] This strategy assumes that CD4 testing is unavailable and that ART starting and stopping decisions are guided by clinical information only. ART stops with the occurrence of 1 OD.

[‡] This strategy assumes that CD4 testing is unavailable and that ART starting and stopping decisions are guided by clinical information only. ART stops with the occurrence of 5 ODs.

[§] This strategy assumes that CD4 testing is available and that ART starting and stopping decisions are guided by both clinical and immunologic information. ART stops when the CD4 cell count drops by 90% from the peak value during treatment.

[¶] The incremental cost-effectiveness ratio (in 2002 U.S. dollars) was calculated by comparing the strategy in question with the next best strategy.

exceed, those associated with most other treatment interventions.⁴⁶

There is no universal definition of a threshold ratio above which an intervention would not be considered cost-effective. Some have suggested that interventions with cost-effectiveness ratios less than the per capita GDP for a given country (\$708 in Côte d'Ivoire) be considered "very cost-

effective," and less than three times the per capita GDP (\$2,124 in Côte d'Ivoire) be considered "cost-effective."^{47,48} In the absence of available CD4 testing, providing trimethoprim-sulfamethoxazole prophylaxis and antiretroviral therapy according to the earliest initiation and latest discontinuation criteria would be very cost-effective, and the most effective strategy — using both CD4

testing and clinical criteria to guide decisions about the timing of treatment — would also be cost-effective; these approaches are consistent with the WHO guidelines.

This analysis has several limitations. We focused on survival gains, since there are limited data on disability or quality-of-life weights that are suitable for health states in our model. In addition, data were combined from multiple sources. Some cost variables were extrapolated from a clinical trial, although we omitted costs of protocol-driven procedures that are unlikely to be available in low-income settings.³² We did not include lost productivity costs associated with AIDS, but if we had, antiretroviral therapy and trimethoprim-sulfamethoxazole prophylaxis would have been even more cost-effective. Since we allowed for variation in CD4 measurements but did not explicitly model errors in clinical information, we may have unfairly biased the analysis against CD4 testing.

To make the results most relevant to real-world decisions, we focused on a narrow subgroup of questions about the most effective strategies for using clinical criteria with or without CD4 testing to guide the initiation and discontinuation of antiretroviral therapy when only a single line of therapy is available. The results for two lines of therapy are similar. A dynamic transmission model would be needed to address questions at the population level about the relative cost-effectiveness of both prevention and treatment strategies. The growing consensus, however, is that both prevention and treatment are critical to the control of HIV infection in developing countries.^{44,45,49} Although the issue of HIV screening is beyond the scope of this report, improved screening and linkage to care would allow a larger segment of the HIV-infected population to benefit from antiretroviral therapy. The benefits of trimethoprim-sulfamethoxazole prophylaxis reported for HIV-infected patients in Côte d'Ivoire should be extrapolated with caution to sub-Saharan African countries with a high prevalence of resistance to trimethoprim-sulfamethoxazole,^{50,51} although benefits have been shown even in these areas.⁵²⁻⁵⁵

Finally, this analysis focuses on HIV-1, not HIV-2. In areas with high rates of HIV-2 infection, additional issues should be considered, such as the optimal choice of a first-line antiretroviral regimen in the setting of resistance to nonnucleoside reverse-transcriptase inhibitors.^{52,53}

Cost-effectiveness is only one consideration in

the allocation of scarce resources.^{49,56,57} There may be differences in the availability of strategies, and the selection of a strategy may be based on considerations of infrastructure, equity, qualitative attributes, nonmonetary constraints, or synergy with other high-priority initiatives.^{49,56-58} Strategies identified as cost-effective may be unaffordable in the poorest countries without assistance. The results of this analysis may be used, however, to motivate the global community to direct resources toward investments that have the greatest promise of providing gains in health. Better data from treatment-rollout programs — data on efficacy, toxicity, direct medical and programmatic costs (including costs of reducing wastage and scaling up) — should be incorporated when available.⁵⁹ This is particularly important because nonmedical costs have been found to account for a substantial proportion of the total costs of interventions in other diseases.⁶⁰

Our results show that a single regimen of antiretroviral therapy combined with trimethoprim-sulfamethoxazole prophylaxis affords major survival benefits. Adding second-line regimens will increase survival further. It is always more effective and cost-effective to use trimethoprim-sulfamethoxazole in combination with an antiretroviral regimen. Approaches guided by CD4 testing, although more costly than those based on clinical information alone, are substantially more effective in terms of survival and are a promising public health investment.

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