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HIV drug resistance surveillance for prioritizing treatment in resource-limited settings

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Abstract

Background—Sentinel testing programs for HIV drug resistance in resource-limited settings can inform policy on antiretroviral therapy (ART) and drug sequencing.

Objective—To examine the value of resistance surveillance in influencing recommendations toward effective and cost-effective sequencing of ART regimens.

Methods—A state-transition model of HIV infection was adapted to simulate clinical care in Côte d'Ivoire and evaluate the incremental cost-effectiveness of (1) no ART; (2) ART beginning with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen followed by a boosted protease inhibitor (PI)-based regimen; and (3) ART beginning with a boosted PI-based regimen followed by an NNRTI-based regimen.

Results—At a 5% prevalence of NNRTI resistance, a strategy that started with a PI-based regimen had a smaller health benefit and higher cost-effectiveness ratio than a strategy that started with an NNRTI-based regimen (cost-effectiveness ratio \$910/year of life saved). Results consistently favored

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initiation with an NNRTI-based regimen, regardless of the population prevalence of NNRTI resistance (up to 76%) and the efficacy of an NNRTI-based regimen in the setting of resistance. The most influential parameters on the cost-effectiveness of sequencing strategies were boosted PI-based regimen costs and the efficacy of this regimen when used as second-line therapy.

Conclusions—Drug costs and treatment efficacies, but not NNRTI resistance levels, were most influential in determining optimal HIV drug sequencing in Côte d’Ivoire. Results of surveillance for NNRTI resistance should not be used as a major guide to treatment policy in resource-limited settings.

Keywords

HIV/AIDS; sentinel resistance; Africa

Introduction

As antiretroviral treatment (ART) for HIV infection becomes increasingly available in resource-limited settings, concerns regarding the development of drug resistance are mounting [1]. While there is general agreement that potential drug resistance should not deter treatment efforts, monitoring the development and prevalence of drug resistance, especially in newly infected patients (primary resistance), has remained a public health priority [2]. Though CD4 cell count is available in many settings and HIV RNA in some, the more expensive individual genotype tests are rarely performed [2]. Resistance monitoring strategies, therefore, rely on surveillance resistance testing, where levels of resistance in a population are measured by a systematic sampling of clinical cohorts [2].

The World Health Organization (WHO) and the International AIDS Society (IAS) have worked collaboratively to establish the HIVResNet, a Global HIV Drug Resistance Surveillance Network with the stated purpose, among others, of providing information to guide effective treatment strategies [3]. Surveillance of resistance may inform the selection of country-wide first- as well as second-line regimens [4]. For example, in a country with a primary resistance rate of 10% to non-nucleoside reverse transcriptase inhibitors (NNRTI), it may seem sensible to change the first-line treatment regimen from an NNRTI-based regimen to a more expensive boosted protease inhibitor (PI)-based regimen [4]. Generally, NNRTI resistance threshold rates of 5% have been chosen to trigger concern and a more aggressive sentinel surveillance approach [2]. This 5% resistance threshold is similar to the antimicrobial resistance thresholds that have been used to generate policy changes in treatment of other infectious agents such as *Neisseria gonorrhoeae* [5].

The objective of the current study was to examine the value of surveillance resistance testing in guiding countrywide policies toward effective and cost-effective ART sequencing strategies in resource-limited settings. Specifically, information was sought regarding the following question facing decision makers. How should the data provided by surveillance testing be used and what resistance threshold would be appropriate to trigger population-wide changes in clinical policy?

Methods

Analytic framework

A first-order Monte Carlo state-transition simulation model of HIV natural history and treatment applied to resource-limited settings was used to evaluate how an increasing prevalence of primary NNRTI resistance might influence optimal population-based choices for ART [6,7]. In the base case where the prevalence of NNRTI resistance was set at 5%, the clinical and economic consequences associated with three strategies were considered: (1) no

ART (co-trimoxazole prophylaxis alone); (2) ART beginning with an NNRTI-based regimen followed by a boosted PI-based regimen after clinical or immunological failure; and (3) ART beginning with a boosted PI-based regimen followed by an NNRTI-based regimen after failure. The same strategies were examined in settings where the rates of primary NNRTI resistance were varied. It was assumed that only two sequential ART regimens were available, and that the second regimen would be started after clinical failure of, or major toxicity from, the first regimen. To the extent possible, data were derived from Côte d'Ivoire to simulate a representative clinical cohort of chronically infected HIV patients in that country. Projected model-based outcomes included mean per person life expectancy (years) and lifetime costs (2005 US\$) as well as cost-effectiveness, expressed in incremental US\$/year of life saved. The time horizon of the analysis was patient lifetime. Consistent with guidelines for the reporting of cost-effectiveness analyses, a societal perspective was adopted (with the exclusion of patient time and travel costs); future costs and clinical benefits were discounted at 3% per year [8–10]. Sensitivity analyses were performed to examine the stability of the results in the face of alternative assumptions regarding ART efficacy, drug costs and ART starting, stopping and switching criteria. Based on a report by the Commission on Macroeconomics and Health, the WHO has suggested that interventions in a country are 'very cost-effective' if they have cost-effectiveness ratios less than the gross domestic product (GDP) per capita of that country and 'cost-effective' if they have ratios less than three times the per capita GDP of the country [9, 11]. Three times the inflation-adjusted GDP per capita in Côte d'Ivoire is \$2409 (2005 US\$) [12]. In sensitivity analyses, interventions with incremental cost-effectiveness ratios less than \$2409 were considered cost-effective and potentially worthy of a policy recommendation.

The model

The CEPAC International Policy model is a simulation of the natural history and treatment of HIV disease in resource-limited settings and was developed for these settings from the US-based Cost-Effectiveness of Preventing AIDS Complications model [6,7,13–16]. Details of both models have been published elsewhere and are presented in a technical appendix (available from the corresponding author) [6,7,13–16]. Health states in the Policy model are stratified by CD4 cell count, HIV RNA and history of prior opportunistic infections. In a single monthly cycle, patients are susceptible to a change in CD4 cell count and CD4 cell count-determined risks of opportunistic infections and death. As applicable to data reported from Côte d'Ivoire, opportunistic infections were divided into eight severe and three mild categories (Table 1). Death could occur from an acute opportunistic infection, CD4 cell count-adjusted AIDS-related causes (stratified by opportunistic infection history but not within 30 days of an opportunistic infection) and background non-AIDS causes from country-specific age- and sex-adjusted life tables for Côte d'Ivoire [17].

Clinical decision making in the model

While the model tracked the underlying CD4 cell count and HIV RNA level for purposes of disease progression, these data are not available for clinical decision-making unless a laboratory test is performed. Based on the lack of accessibility of laboratory data in many resource-limited settings, clinical decision-making in the model is based upon clinical history and presentation (e.g., the development of an opportunistic infection) in conjunction with an actual 'observed' CD4 cell count test obtained every 6 months. The clinical decisions included to begin prophylaxis with co-trimoxazole at an observed CD4 cell count ≤ 500 cells/ μ l, as well as ART starting, stopping and switching criteria [18]. ART decisions were based on WHO guidelines; the impact of alternative treatment decision was confirmed in sensitivity analyses. In the base case, the following three sets of ART criteria were defined. First, ART was initiated when there was a natural decline in the observed CD4 cell count (starting mean of 331 cells/ μ l) to < 200 cells/ μ l or when the patient developed one severe late-stage opportunistic infection (including severe fungal infection, isosporiasis, cerebral toxoplasmosis, non-tuberculous

mycobacteriosis or other severe illness; Table 1) [19]. Second, ART switched (if a second-line regimen was available) when the observed CD4 cell count fell to below 50% of its on-treatment peak *or* when the patient developed one severe late-stage opportunistic infection on therapy (after a time lag of 6 months after starting ART). Third, ART discontinued when (a) there were no further treatment options *and* (b) the observed CD4 cell count fell below 90% of its on-treatment peak *or* (c) when the patient developed one severe late-stage opportunistic infection on therapy (after a time lag of 6 months after starting ART) with no further treatment options available.

Input data

Opportunistic infections—Selected input data for the model are summarized in Table 1 [6,11,20–35]. The incidence of opportunistic infections and their related mortality estimates were derived from results of the placebo arm of ANRS 059, a randomized controlled trial of co-trimoxazole prophylaxis in Abidjan, Côte d'Ivoire [6]. Results of the intervention arm from this trial provided estimates for co-trimoxazole prophylaxis efficacy [6]. Initial cohort characteristics, including mean CD4 cell count, were also obtained from ANRS 059 [20,21]; the initial viral load distribution was obtained from the ANRS 1203 study in Abidjan, a continuation of ANRS 059 with available HIV RNA data [20,21].

Antiretroviral treatment efficacy—Efficacies of alternative ART options were derived from a literature review of ART use in Africa and were supplemented with US data only if no data from Africa were available [21,24–33]. All regimens included two nucleoside reverse transcriptase inhibitors (NRTI) and either an NNRTI or a boosted PI. The model incorporated separate estimates of efficacy for both NNRTI-containing and PI-containing regimens, when each was used as either first- or second-line therapy, as well as an estimate of NNRTI efficacy in the presence of resistance (Table 1, see also the Technical appendix available from the authors).

Since the data were similar and other experiences have not documented an efficacy advantage of initiating treatment using either an NNRTI- or a boosted PI-based regimen [21,24–29,31], an efficacy of 75% at 48 weeks was applied to both initial regimens in order to avoid conferring an initial advantage to either treatment regimen. Because of limited options for NRTI drugs in Côte d'Ivoire and other resource-limited settings, it was assumed that when two lines of therapy were available these drugs would be largely 'recycled' in the second regimen (so the NNRTI to PI and PI to NNRTI strategies would contain two NRTI plus an NNRTI or a boosted PI, respectively). In this case, boosted PI-based therapy following an initial NNRTI-based regimen would have similar efficacy to boosted-PI treatment alone: 58% viral load suppression at 48 weeks [32]. Similarly, NNRTI-based therapy following an initial PI-based regimen would have similar efficacy to NNRTI treatment alone: 30% viral load suppression at 48 weeks [33].

Resource use and costs—Data from the ANRS 059 trial were used to estimate resource use related to HIV care. Costs were estimated independently for three economically relevant HIV disease stages: acute clinical illness (within 30 days of an opportunistic infection); no acute clinical illness, stratified by CD4 cell count; and terminal care (final month of life). Direct medical costs included inpatient admissions (their associated length of stay, laboratory tests, clinical procedures, and drugs dispensed) and outpatient visits. Costs associated with this resource use were from Youpougnon University Hospital in Abidjan, Côte d'Ivoire, urban community clinics in Abidjan and the CeDReS laboratory of the Treichville University Hospital cost database; they were updated to 2005 US\$ when appropriate [6,36].

ART costs were taken from the 2005 negotiated prices of generic fixed dose combinations for developing countries [34]. An NNRTI-based regimen cost \$427/year and a boosted PI-based

regimen cost \$580/year. These costs were estimated for stavudine, lamivudine, and lopinavir/ritonavir. Because in different clinical circumstances, there are sometimes reasons to prefer nevirapine and other times to prefer efavirenz, the more costly efavirenz was the conservative choice as the NNRTI in the analysis. This decision would bias results in favor of choosing the more expensive boosted-PI regimen. Other medication costs were derived from pharmacy records of Médecins Sans Frontières-Logistique (Bordeaux, France) and public and private drug suppliers in Côte d'Ivoire [6].

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Results

Base case

In a cohort with a starting mean CD4 cell count of 331 cells/ μ l (SD, 268) receiving no ART (co-trimoxazole prophylaxis alone), the mean per person discounted survival was 2.78 years (2.98 years undiscounted), and the mean discounted per person lifetime cost was \$1090 (Table 2). In the same cohort with an NNRTI resistance prevalence of 5%, a strategy that started with a boosted PI-based regimen and followed with an NNRTI-based regimen upon immunologic failure (PI to NNRTI, in addition to co-trimoxazole prophylaxis) more than doubled the mean discounted per person life expectancy to 6.71 years (7.99 years undiscounted) and increased mean discounted per person cost to \$4970 (Table 2). A strategy that began with an NNRTI-based regimen followed by a PI-based regimen increased mean per person life expectancy to 7.30 years (8.89 years undiscounted) and mean discounted per person cost to \$5210. Compared with co-trimoxazole alone, starting with a PI-based regimen yielded less health benefit and had a higher incremental cost-effectiveness ratio (weakly dominated) than a strategy starting with an NNRTI-based regimen (cost-effectiveness ratio \$910/year of life saved) [8,37].

Sensitivity analyses

Table 3 (and the technical appendix available from the authors) provides results of sensitivity analyses for key model input parameters. Under all reported scenarios, initiating with an NNRTI-based regimen weakly dominated strategies of initiation with a boosted PI-based regimen. Changes in the rate of CD4 cell count decline ($\pm 25\%$) resulted in the largest changes in overall life expectancy. The incremental cost-effectiveness ratio for starting with an NNRTI-based regimen ranged from \$880/year of life saved (0% discount rate) to \$1040/year of life saved (50% increase in routine care costs). Despite ranges reported in Table 3, the prevalence of NNRTI resistance at which the optimal treatment strategy changed fluctuated only from 65% to 79%.

Although results were relatively insensitive to the parameters reported in Table 3, results of other sensitivity analyses were more influenced by changes in drug costs and the efficacy of a second-line ART regimen. Figure 1 displays a multi-way sensitivity analysis of three variables: the population prevalence of NNRTI resistance, the efficacy of a boosted-PI regimen when used as second-line therapy, and the cost of a PI-based regimen. The figure indicates the most cost-effective strategy based on a cost-per-year-of-life-saved threshold of three times the inflation-adjusted GDP (2005) of Côte d'Ivoire.

Population prevalence of non-nucleoside reverse transcriptase inhibitor resistance—In the base case, the prevalence of resistance would have to exceed 76% before the sequencing choice would favor a PI-based regimen first (Fig. 1, straight solid arrow). From

32–60% NNRTI resistance, the PI-based initiation strategy was more expensive and less clinically effective (strongly dominated). The PI-based initiation strategy was less effective and had a higher cost-effectiveness ratio (weakly dominated) than using the NNRTI-based regimen first as long as the prevalence of NNRTI resistance was $< 31\%$.

Efficacy of a boosted protease inhibitor-based regimen used as second-line therapy—Because of the concern surrounding NRTI resistance and the reduced efficacy of a PI-based regimen when used as second-line therapy, this sensitivity analysis examined how poorly a boosted PI-based regimen could function yet still warrant its use as first-line treatment (Fig. 1). At the base case costs and a 5% prevalence of NNRTI resistance, a boosted PI-based regimen could have a 48-week HIV RNA suppression rate as low as 26% (straight hollow arrow) for the incremental cost-effectiveness ratio to remain below the cost-effectiveness threshold of three times the GDP of Côte d'Ivoire. As the efficacy of a second-line boosted PI-based regimen increases, the tolerable threshold prevalence of NNRTI resistance to prefer initiating with an NNRTI-based regimen also would increase.

Cost of a boosted protease inhibitor-based regimen—At lower PI-based regimen costs, starting with a boosted PI-based regimen becomes cost-effective at lower prevalence rates of NNRTI resistance. For example, at 80% of PI-regimen base case costs and a second-line viral suppression rate of 58%, it is cost-effective to start with a PI-based regimen at a prevalence of NNRTI resistance of 68% (Fig. 1, curved solid arrow). At 90% of PI-based regimen base case costs and the same 58% suppression rate, the prevalence of NNRTI resistance must increase to $> 72\%$ before meeting the three times GDP threshold to start with a PI-based regimen (Fig. 1, curved hollow arrow).

Using one antiretroviral drug regimen only

Scenarios were also examined that assumed access to only a single regimen of therapy. With a prevalence of 5% NNRTI resistance, the incremental cost-effectiveness ratio of an NNRTI-based regimen compared with co-trimoxazole alone was \$800/year of life saved; a boosted PI-based regimen instead incrementally increased discounted life expectancy by 0.075 years (0.9 months) and undiscounted life expectancy by 0.92 years (1.1 months), with an incremental cost-effectiveness ratio of \$7500/year of life saved. A boosted PI-based regimen became cost-effective (meeting the three times GDP threshold) at a 5% NNRTI-resistance prevalence only if its annual cost were reduced to \$464, or 80% of its current cost (Fig. 2, solid arrow). A boosted PI-based regimen weakly dominated a NNRTI-based regimen only when the NNRTI-resistance prevalence was $> 39\%$ (Fig. 2, hollow arrow).

Discussion

As ART use increases in resource-limited settings and drug resistance follows, questions will arise regarding how to apply results from resistance surveillance programs. We used a simulation model of HIV infection to examine the role of sentinel resistance programs in informing national ART policies. The prevalence of primary resistance to NNRTI, within reasonably expected ranges, is not an important criterion in the selection of an optimal treatment regimen, when either one or two ART regimens are available in a country like Côte d'Ivoire. Even if PI costs decrease, we found that the increased efficacy of a boosted PI-based regimen in the face of NNRTI resistance is not enough to make it cost-effective to use initially, according to criteria described by the WHO and the Commission on Macroeconomics and Health.

In the absence of resistance, boosted PI- and NNRTI-based regimens have similar efficacy as initial regimens [21,24–29,31]. When only a single regimen is available, the boosted PI-based regimen was preferable only at a fraction of its current cost (80%) or at very high rates (39%)

of NNRTI resistance. In the case of two available regimens, the model inherently favors initiating with an NNRTI-based regimen and using a boosted PI-regimen subsequently. We assumed that, because NRTI options are currently limited in countries like Côte d'Ivoire, they would be 'recycled' in a second line of therapy. When immunological and clinical criteria are used to make ART decisions, rather than earlier switching based on HIV RNA testing, increased NRTI resistance may occur owing to ongoing viral replication and the development of thymidine analogue mutations [38]. Therefore, when used as second line, the PI- or NNRTI-based regimen would likely have an efficacy similar to the addition of a single drug to an already resistant NRTI backbone. Since boosted PI monotherapy has greater efficacy than NNRTI monotherapy, the efficacy of a second-line boosted PI-based regimen would likely be superior to and more durable than that of an NNRTI-based regimen [32,33]. Data are beginning to emerge suggesting that the efficacy of boosted PI monotherapy may, in fact, be greater than assumed in this analysis [39]. This would move the sequencing decision toward starting with the NNRTI-based regimen followed by the PI-based regimen, regardless of the prevalence of resistance in the population. For this reason, following a boosted PI-based regimen with an NNRTI-based regimen may not seem clinically sensible; clinicians may prefer to maintain the partial suppressive benefit of the boosted PI-based regimen [32]. If a switch is not made to the less expensive NNRTI-based regimen at the time of clinical failure of an initial boosted-PI based regimen, the results favoring starting with an NNRTI-based regimen would be further reinforced.

Despite the findings that information on the prevalence of NNRTI resistance from routine surveillance is unlikely to affect specific policies in settings similar to those in Côte d'Ivoire, there is clear value in continuing this resistance monitoring effort. The emergence of resistance is one quality measure of the ability of a public health infrastructure to deliver, and monitor adherence to, effective ART. Furthermore, the population prevalence of resistance may be helpful in developing strategies for the prevention of mother-to-child transmission [2]. Finally, there is value in the knowledge of baseline resistance patterns in terms of HIV transmission and other population and epidemiological trends that are otherwise difficult to quantify.

This study should be interpreted within the context of its limitations. As is standard in model-based analyses, we compiled data from numerous sources to inform model input parameters. When data were not specifically from Côte d'Ivoire, we believe that they were from sources that were similar to those in Côte d'Ivoire. Because we found that the prevalence of NNRTI resistance should have little effect on treatment sequencing decisions, we anticipate that these results could be generalized to other resource-limited settings, although this would depend on the relative efficacy and cost of the particular regimens in a given setting. While the model included tuberculosis incidence and treatment costs, the advantages of using NNRTI-based therapy emerged even without considering the advantages of NNRTI therapy in the presence of concomitant tuberculosis therapy (i.e. rifampin) [40].

Because of lack of available data in the general population, efficacy of the NNRTI-based regimen in the setting of nevirapine resistance was derived from women who had previously received nevirapine as part of a program to prevent mother-to-child transmission. While adherence may be better in these women than in the general population, the policy conclusions remained stable with regard to changes in this model variable. The calculation of resource use was based on clinical trial data, which may lead to an increase in follow-up visits and more detailed diagnostic work-ups, thereby overestimating true costs. Study results, however, were also robust to changes in resource use parameters. We also did not include quality adjustment, which weights years of life in proportion to their health-related quality; as such, all regimens will be even less cost-effective because more total life years are saved than quality-adjusted life years.

We restricted the analysis to the initial treatment decision, which is the most pressing question concerning primary NNRTI resistance and health outcomes for patients. While transmission of resistance and emergence of resistance to NRTI and PI will likely occur over time, we chose to focus on the challenging question of single-class resistance and its implications for drug sequencing. As data from sentinel resistance programs continue to emerge, future analyses should address the additional complexity of the possible resistance pattern combinations as well as transmitted resistance. While cost-effectiveness is only one of many criteria that help to inform policy decisions, costs remain a critical and often determining factor in settings where resources are scarce [9,10]. Notably, the results of this analysis are presented with the intention of maximizing population-based health without an explicit consideration of equity. Patients with NNRTI resistance will have poorer treatment outcomes in a country where NNRTI drugs are favored. The importance of equitably distributing more costly therapies should not be understated; results of cost-effectiveness analyses may nonetheless help to inform these decisions [8].

The emergence of drug resistance, both at the individual and the population level, is a complication of the life-sustaining benefits of ART. In resource-limited settings with few treatment options, among the biggest concerns is the development of resistance to the NNRTI class, especially with the widespread use of single-dose nevirapine to prevent mother-to-child HIV transmission [30]. One of the stated goals for surveillance of resistance prevalence is to inform the rational use of ART and the revision of treatment guidelines. However, when cost-effectiveness criteria are used to inform guidelines, we found that sequencing strategies should be most influenced by other criteria, including drug costs and efficacy, rather than the prevalence of resistance.

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Fig. 1. Multi-way sensitivity analysis examining scenario when two regimens of antiretroviral therapy are available

Lines represent the different costs of a boosted protease inhibitor (PI) regimen with the base case indicated by the lower right line and 80% base case costs with the upper left line. The region to the left of the applicable cost line represents the scenarios for which it is preferable to start with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based therapy, followed by a PI-based therapy upon immunological failure (NNRTI to PI). The region to the right of the applicable cost line represents the scenarios for which it is preferable to start with a PI-based therapy, followed by an NNRTI-based therapy (PI to NNRTI). The base case scenario is indicated by the line with the open circles. The horizontal dotted line represents the base case boosted PI-based regimen efficacy when used as second line.

Fig. 2. The incremental cost-effectiveness of non-nucleoside reverse transcriptase inhibitor (NNRTI)-based (versus cotrimoxazole prophylaxis only) and boosted protease inhibitor (PI)-based (versus NNRTI-based) regimens at various prevalence rates of NNRTI resistance and boosted PI regimen costs

Only one regimen of antiretroviral therapy is available in this analysis. The cost-effectiveness threshold of three times the gross domestic product in Côte d'Ivoire (\$2409) is indicated by the dotted horizontal line.

Table 1

Data for model input parameters.

Variable	Estimate	Reference
Initial cohort		
CD4 cell count [cells/ μ l (SD)]	331 (268)	[20]
Initial HIV RNA (copies/ml) distribution (%)		[21]
> 100 000	69.21	
30 001–100 000	22.27	
3001–10 000	7.06	
501–3000	1.35	
0–500	0.11	
Mean monthly CD4 cell decline (cells/ μ l) by HIV RNA strata (copies/ml)		[22]
> 30 000	6.375	
10 001–30 000	5.400	
3001–10 000	4.600	
501–3000	3.733	
$\leq$ 500	3.025	
Percentage monthly risk of severe opportunistic infections ^a		[23]
Bacterial	1.08–3.36	
Fungal	0.00–0.50	
Malaria	0.00–0.50	
Tuberculosis	0.50–1.16	
Isosporiasis	0.17–0.75	
Toxoplasmosis	0.00–0.50	
Non-tuberculosis mycobacteriosis	0.00–2.06	
Other	1.24–7.07	
Percentage monthly risk of mild opportunistic infections ^a		[23]
Bacterial	1.57–8.23	
Fungal	1.08–3.68	
Other mild infections	1.16–3.52	
Rates of virological suppression		
Two sequential regimens of ART available (% suppressed at 48 weeks)		
first line, 2NRTI + NNRTI; second line, 2NRTI + PI		
NNRTI + 2NRTI (no resistance)	75	[21,24–29]
NNRTI + 2NRTI (with resistance)	38	[30]
PI + 2NRTI (no resistance)	58	[32]
first line, 2NRTI + PI; second line, 2NRTI + NNRTI		
PI + 2NRTI (no resistance)	75	[31]
NNRTI + 2NRTI (no resistance)	30	[33]
NNRTI + 2NRTI (with resistance)	10	Assumption
One regimen of ART available		
NNRTI + 2NRTI (no resistance)	75	[21,24–29]
NNRTI + 2NRTI (with resistance)	38	[30]
PI + 2NRTI (no resistance)	75	[31]
Efficacy of co-trimoxazole (% reduction in probability of infection)		[6,20]
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 infections ^b	–46.4	
Annual costs of treatment (2005 US\$)		
2NRTI + NNRTI	427	[34]
2NRTI + PI	580	[34]
Co-trimoxazole prophylaxis	17	[6]
Test costs (\$US)		[35]
CD4 cell count (per test)	5	
Monthly costs of chronic care (2005 US\$) for CD4 cell count strata (cells/ μ l)		[6,11]
> 200	21.96	
$\geq$ 200	16.04	
Terminal care cost	38.38	
Costs of specific components of care (2005 US\$)		[6]
Clinic visit	5.79	
Hospital day	17.23	
Day care	8.55	

ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

^a Risk is stratified by CD4 cell count; in nearly all cases monthly risk increases with decreasing CD4 cell count. The following five severe opportunistic infections are considered late stage and are used to trigger initiation of ART: severe fungal infection, isosporiasis, cerebral toxoplasmosis, non-tuberculous mycobacteriosis, or other severe illness.

^b The risk of mild fungal infections is increased by 46.4% in the presence of co-trimoxazole [6].

Table 2

Discounted mean per person lifetime costs (2005 US\$), life expectancy, and incremental cost-effectiveness of different strategies with 5% prevalence of non-nucleoside reverse transcriptase inhibitor resistance in the population.

Treatment strategy ^a	Discounted mean per person cost (2005 US\$)	Discounted life expectancy (years)	Cost-effectiveness (\$/year of life saved)
no ART (co-trimoxazole prophylaxis alone)	1090	2.78	—
Two sequential regimens of ART			
Boosted PI-based regimen then NNRTI-based regimen	4970	6.71	Dominated ^c
NNRTI-based regimen then boosted PI-based regimen ^b	5210	7.30	910

ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

^a All strategies with ART included co-trimoxazole prophylaxis starting at an observed CD4 cell count < 500/μl and contained two nucleoside reverse transcriptase inhibitors. ART was switched when the observed CD4 cell count fell to below 50% of the peak or at the development of one severe, late-stage opportunistic infection and was stopped when the observed CD4 cell count fell to 90% of peak or at the development of one severe, late-stage opportunistic infection.

^b Overall mean survival is greatest with this strategy, requiring the longest duration of therapy, and leading to the highest overall cost.

^c Though per person costs are less, this strategy has a higher cost-effectiveness ratio (\$987/year of life saved) than the 'NNRTI + 2NRTI → PI + 2NRTI' strategy. By convention, such strategies are 'dominated' and cost-effectiveness ratios are not reported [8,37].

Table 3Sensitivity analysis of key model input parameters and baseline assumptions^a.

Treatment strategy	Undiscounted life expectancy NNRTI → PI (years)	Undiscounted life expectancy PI → NNRTI (years)	Cost-effectiveness ratio (\$/year of life saved) ^a	NNRTI resistance prevalence (%) where cost-effective to use PI → NNRTI ^b
Base case	8.89	7.99	910	76
ART starting criteria: CD4 cell count < 350 cells/μl <i>or</i> one opportunistic infection ^c	9.42	8.49	930	76
ART starting criteria: CD4 cell count < 200 cells/ml <i>or</i> four opportunistic infection <i>or</i> CD4 cell count < 350 cells/μl and one opportunistic infection ^c	8.49	7.61	890	78
First-line ART failure criteria: CD4 cell count fall of 90% <i>or</i> one opportunistic infection ^c	8.76	7.92	920	65
Rate of CD4 cell count decline + 25%	8.43	7.54	910	74
– 25%	9.51	8.61	920	79
Routine care costs + 50%	8.89	7.99	1040	78
– 50%	8.89	7.99	950	75
CD4 cell count test costs + 50%	8.89	7.99	920	76
– 50%	8.89	7.99	910	76
Discount rate 5%	—	—	930	76
0%	8.89	7.99	880	77

ART, antiretroviral therapy; CE, cost-effectiveness; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

^a In all cases, the cost-effectiveness ratio of the sequence PI + 2NNRTI → NNRTI + 2NNRTI compared with co-trimoxazole alone is higher than the incremental cost-effectiveness ratio of the NNRTI + 2NNRTI → PI + 2NNRTI sequence compared with the PI + 2NNRTI → NNRTI + 2NNRTI. By accepted convention, when this occurs, the cost-effectiveness ratios are reported as 'dominated' [8,37]. Thus, the incremental cost-effectiveness ratio reported compares the NNRTI + 2NNRTI → PI + 2NNRTI sequence to no ART (co-trimoxazole alone).

^b Applying an incremental cost-effectiveness threshold criteria of three times the per capita gross domestic product for Côte d'Ivoire.

^c All strategies included co-trimoxazole prophylaxis starting at an observed CD4 cell count < 500/μl. Late-stage severe opportunistic infections included in the base case ART starting subset: severe fungal, isosporiasis, toxoplasmosis, non-tuberculosis mycobacterium, or other severe illnesses.