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Genotype assays and third-line ART in resource-limited settings: A simulation and cost-effectiveness analysis of a planned clinical trial

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Abstract

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CONFLICTS OF INTEREST

SBL: None

MDH: Dr. Hughes is a paid member of data monitoring committees for Boehringer Ingelheim, Medicines Development, Pfizer and Tibotec.

BG: Dr. Grinsztejn has received honoraria to participate in advisory boards from Merck and Tibotec and for lectures from Merck, Tibotec and GSK.

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Objectives—To project the clinical and economic outcomes of a genotype assay for selection of third-line antiretroviral therapy (ART) in resource-limited settings, as per the planned international A5288 trial (MULTI-OCTAVE).

Methods—We used the Cost-effectiveness of Preventing AIDS Complications (CEPAC)-International Model to compare three strategies for subjects who have failed second-line ART in South Africa: (1) Sustained second-line: no genotype assay, all subjects remain on second-line ART; (2) A5288: genotype to determine the resistance profile and assign an appropriate regimen; or (3) Population-based third-line: no genotype, all subjects switch to a potent third-line regimen. Model inputs are from published data in South Africa. Resistance profiles, ART regimens, and efficacy data were those used for trial planning.

Results—Projected life expectancy for sustained second-line, A5288, and population-based third-line are 61.1, 103.8, and 104.2 months. Compared to sustained second-line (\$12,460), per person lifetime costs increase for the A5288 (\$39,250) and population-based (\$44,120) strategies. The incremental cost-effectiveness ratio of A5288, compared to sustained second-line, is \$7,500/year of life saved (YLS), and for population-based third-line, compared to A5288, is \$154,500/YLS. In the A5288 strategy, very late presentation to care, coupled with lengthy delays to obtain the genotype, dramatically reduces 5-yr survival, making the population-based third-line strategy more attractive.

Conclusions—We project that, while the public health approach to third-line therapy is unaffordable, genotype assays and third-line ART in resource-limited settings will increase survival and be cost-effective compared to the population-based approach, supporting the value of an efficacy study.

Keywords

Resource-limited setting; antiretroviral therapy; ART; ACTG; A5288; genotype; third-line ART; cost-effectiveness; HIV

INTRODUCTION

The World Health Organization (WHO) estimates that over 100,000 adults are on second-line antiretroviral therapy (ART) in resource-limited settings [1]. Studies in these settings have documented first-line ART failure rates of 10–51% after 6–12 months on ART [2–5], indicating that an increasing number of HIV-infected subjects will require second- and then third-line treatment. Without HIV RNA monitoring [6], many subjects may spend extended periods of time on failing regimens, accumulating drug resistance mutations [7–10] that likely decrease future ART efficacy [11–13]. Given the limitations in health resources, infrastructure, and number of experienced HIV providers, genotype tests – used in developed nations – have seemed impractical in resource-limited settings thus far. Given the increasing frequency of first-line and now second-line ART failure with a variety of emerging resistance patterns [8, 9, 14–18], questions remain about how best to provide third-line therapy.

To evaluate the use of genotype assays and third-line ART in resource-limited settings, the AIDS Clinical Trials Group (ACTG) is planning a prospective interventional study. The Management Using the Latest Technologies in Resource-limited Settings to Optimize Combination Therapy After Viral Failure (MULTI-OCTAVE) Study (A5288) will examine appropriately-tailored ART. Eligible subjects with triple-class drug experience (nucleoside reverse-transcriptase inhibitors [NRTI], non-nucleoside reverse-transcriptase inhibitors [NNRTI] and protease inhibitors [PI]) and detectable viral load will have a genotype assay that is used to assign each subject to one of four ART groups based upon the resistance

mutations detected. The primary study objective is to demonstrate 48-week virologic suppression rates of 65%.

While the study results will determine the efficacy of a genotype assay and tailored third-line therapy, this intervention will require additional resources [19–21]. The objective of the current study is to project the long-term clinical benefits, costs and cost-effectiveness of the A5288 intervention, compared to the current standard of care.

METHODS

Analytic Overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International model, a widely-published model of HIV disease [22–24], to evaluate the clinical impact and cost-effectiveness of genotype testing and tailored third-line ART for subjects in resource-limited settings. In a simulation of triple-drug-class experienced subjects, we examined the following strategies: (1) Sustained second-line: no genotype assay, all subjects remain on or restart second-line ART; (2) A5288: genotype assay used to determine the resistance profile, subjects assigned an appropriate ART regimen for their profile; or (3) Population-based third-line: no genotype assay, all subjects begin a potent third-line ART regimen. We assumed NRTIs, NNRTIs and PIs are available for strategy 1, but that third-line therapy is unavailable. Strategy 3 simulates an empiric “public health approach” where a new potent regimen might be available—raltegravir (RAL), ritonavir-boosted darunavir (DRV/RTV), and etravirine (ETR)—regardless of and without information regarding resistance; this strategy is used as a likely most effective and most expensive comparator. Strategy 2 simulates the A5288 study, in which all drug classes of strategies 1 and 3 are available along with individual genotype resistance patterns.

Model outcomes include projected five-year survival, life expectancy, and lifetime cost. We ordered the strategies by increasing costs and computed the incremental cost-effectiveness ratios (ICERs) for each strategy, compared to the next less costly, non-dominated strategy [25]. Dominated strategies are those that are less effective and more costly than another strategy (strongly dominated) or less costly but incrementally less cost-effective than a more effective strategy (weakly dominated) [26]. All outcomes were discounted at an annual rate of 3% [25]. Guided by the recommendations of the World Health Organization (WHO) Commission on Macroeconomics and Health, we consider an intervention to be cost-effective if its incremental cost-effectiveness ratio is less than 3 times the annual *per capita* Gross Domestic Product (GDP, South African 2009 GDP = US \$5,800) [27, 28]. Sensitivity analyses were conducted to evaluate the impact of uncertain parameters and assumptions on the results.

The CEPAC-International Model

The CEPAC-International model is a mathematical simulation model that projects the clinical course of HIV disease and treatment [22–24]. Simulated subjects enter the model one at a time and are followed until death, transitioning monthly between health states. These states (defined by CD4 count and HIV RNA level) are descriptive and predictive of clinical and economic outcomes. [29]. Death results from opportunistic infections, chronic HIV, or non-HIV related events at probabilities derived from clinical trials and cohort studies in South Africa [30–32].

Without treatment, subjects experience an HIV RNA-dependent monthly CD4 decrease, resulting in an increased risk of opportunistic infections and chronic HIV-related mortality [29, 30]. Co-trimoxazole prophylaxis is administered according to guidelines to subjects upon entry into care [33, 34].

Upon ART initiation, there is a 24-week probability of HIV RNA suppression (ART efficacy). Virologic suppression on ART is defined as HIV RNA <200 copies/mL [35], and results in a decrease in HIV RNA level and is generally accompanied by a concomitant increase in CD4 count. After 24 weeks, suppressed subjects experience a monthly risk of “late” failure. When this occurs, virologic rebound ensues, resulting in a decrease in CD4 count after a twelve-month delay [36]. Subjects failing to achieve ART suppression initially, or who experience late virologic failure, have HIV RNA-dependent rates of CD4 decline similar to those not accessing ART. Regardless of suppression status, subjects on ART experience a CD4-dependent reduced risk of opportunistic infections and HIV-related chronic mortality [37, 38].

While clinical events occur based on “true” CD4 and HIV RNA status, clinical decisions, such as switching ART regimens, are made based upon available clinical, immunologic and virologic assessments. In this analysis, clinical monitoring occurs at 3-month intervals; acute events also precipitate clinic visits. Guided by WHO recommendations and current standards of care in most sub-Saharan African nations, CD4 tests are performed biannually but HIV RNA tests are not initially available. Treatment failure is defined as a 50% decrease from peak CD4 count, return to pre-ART CD4 nadir, a CD4 count <100/ μ l, or a new WHO stage III–IV event [6].

Clinical and Cost Input Parameters

ART-naïve Cohort for Model Initialization—To define the likely subjects for the A5288 trial, we “initialized” the cohort. We defined an ART-naïve cohort of subjects with HIV in South Africa, with mean age 32.8 years, and mean CD4 87/ μ l [30, 39, 40]. Over 40% of the cohort has HIV RNA >100,000 copies/ml [41]. Subjects initiate a first-line NNRTI-based ART regimen with CD4 <350/ μ l or with WHO stage III-IV disease, irrespective of CD4 [6]. First-line ART efficacy is 75% [42]. Those suppressed have a mean CD4 increase of 148/ μ l after 48 weeks [42, 43]. The monthly probability of “late” virologic failure is 1.3% [44, 45]. We assumed that second-line PI-based ART has the same efficacy and immunological benefits as first-line ART [42]. Per the A5288 protocol, once subjects are identified as failing second-line ART, an HIV RNA test is performed to confirm trial eligibility (although it would usually otherwise be unavailable) [35]. Subjects with confirmed HIV RNA levels >1,000 copies/mL are considered eligible. To ensure that an identical patient population initiates each of the three strategies, we assumed that HIV RNA tests were used to confirm ART failure before beginning any of the three strategies, after which it is again no longer available. The model simulation was stopped after confirmed second-line ART failure, and the characteristics of the “A5288-eligible cohort” were defined (Table 1).

Triple-class Experienced Subjects – the A5288-eligible Cohort—The model-simulated A5288 eligible subjects have mean age 45.4 years and mean CD4 189/ μ l. The model projected that 26% percent of subjects have a history of severe opportunistic infection, and 33% have a history of tuberculosis.

The A5288-eligible subjects initiate their next ART regimen according to one of three strategies defined below. Strategies, genotype availability, cohort resistance profiles, and ART regimens are detailed in the Technical Appendix (TA Table 1).

Sustained second-line: This strategy assumes that genotype testing and third-line ART are unavailable; therefore, all subjects remain on or restart second-line (virologically failed) ART. Guided by trial design estimates of projected frequencies of resistance and given their prior experience with this regimen, we assume that 80% of the cohort has resistance-

associated mutations to NRTIs, lopinavir/ritonavir, or efavirenz/nevirapine [35] and that only 20% of the cohort remains fully susceptible with wild-type virus (Table 1) [35]. For subjects with both sensitive and resistant virus, point estimates for 24-week suppression rates, 48-week CD4 responses and the monthly probability of late failure, as well as the wide ranges examined in sensitivity analyses for each of these values, are in Table 1 and TA Table 2. Those susceptible to second-line ART experience the same ART efficacy as those in the “*No resistance to second-line*” cohort of the A5288 strategy (see below). The sustained second-line strategy outcomes are a weighted average of the outcomes for those with and without resistance to second-line ART.

A5288 study strategy: Upon A5288 cohort entry, all subjects have a genotype assay performed, incurring a one-time cost of \$400 [20, 21, 46]. Per study protocol and the anticipated implementation process, subjects remain on their second-line regimen for 2 months pending genotype results. These results are used to assign subjects to one of 4 cohorts (A-D) with anticipated frequencies (weights) as indicated in parentheses: Cohort A demonstrates *No resistance to second-line* (20%), so these subjects remain on or restart second-line ART. Cohort B demonstrates NRTI, NNRTI or PI resistance, so this *Novel agent-susceptible* (55%) cohort begins RAL, DRV/RTV, and ETR. Cohort C is *ETR-resistant* (15%) and begins the best available NRTIs given the individual’s resistance pattern, RAL and DRV/RTV. Cohort D demonstrates multiple NRTI resistance mutations and/or DRV/RTV resistance, so this *NTRI/DRV-resistant* (10%) cohort begins the best available regimen, given the individual’s resistance pattern. Twenty-four-week suppression rates, 48-week CD4 responses, and the monthly probability of late failure for each of these cohorts are informed by the trial protocol and by treatment efficacy studies using these specific regimens in other settings (Table 1 and TA Table 2) [47, 48]. While other treatment regimens might also be viable, we modeled the specific regimens planned for the A5288 trial. The overall A5288 strategy is an average of the four groups described above, weighted by the anticipated percentage in each cohort.

Population-based third-line: In contrast to the sustained second-line strategy, the population-based third-line strategy assumes availability of potent third-line ART, regardless of individual resistance patterns. In lieu of a genotype assay, all subjects begin a third-line ART regimen of RAL+DRV/RTV+ETR at the time of second-line failure (Table 1 and TA Table 2). Seventy-five percent of subjects have virus susceptible to RAL+DRV/RTV+ETR and experience the same ART efficacy as those in the “*Novel agent-susceptible*” cohort of the A5288 strategy [35]. As with sustained second-line, the population-based third-line strategy outcomes are a weighted average of outcomes for those with and without resistance to the prescribed regimen.

Costs—We included direct medical costs for HIV-related care; utilization and cost estimates for inpatient and outpatient visits were derived from South African cohort data [32]. Direct non-medical costs and indirect costs were excluded. Costs were converted to 2009 US dollars using South African Gross Domestic Product (GDP) deflators and the 2009 mean exchange rate between the South African rand and the US dollar (8.40 rand = US\$1) [49]. Second-line ART costs \$42 per month, NRTIs + RAL + DRV/RTV costs \$205/month, and RAL+DRV/RTV+ETR costs \$307/month (Table 1) [19, 50]. We assume that the cost of the best available regimen for “*NTRI/DRV-resistant*” subjects is equivalent to the cost of RAL+DRV/RTV+ETR.

Sensitivity Analyses—We performed a broad range of sensitivity analyses on individual parameters to determine those most influential on outcomes. The most influential parameters were incorporated into multiway sensitivity analyses.

RESULTS

Base case analysis

Depending on resistance profile and regimen assigned, five-year survival rates (mean life expectancy) ranged from 44% (58.3 months) for subjects with resistant virus who receive sustained second-line to 82% (119.1 months) for subjects with no resistance or NRTI-resistance who receive population-based third-line (Table 2). Sustained second-line yields the lowest lifetime cost of care (\$12,180 for subjects with resistant virus), and A5288 novel agent susceptible is the highest (\$49,940 for susceptible subjects). After weighting each of the subject groups to determine the overall strategy outcomes, the sustained second-line strategy is associated with 47% five-year survival and a life expectancy of 61.1 months. A5288 increases five-year survival (life expectancy) to 72% (103.8 months); five-year survival with population-based third-line is 73% (104.2 months). The discounted lifetime cost of care is \$12,460 for sustained second-line, \$39,250 for A5288, and \$44,120 for population-based third-line. The ICER for the A5288 strategy compared to sustained second-line is \$7,500/YLS. Compared to the A5288 strategy, population-based third-line has an ICER of \$154,500/YLS (Table 2).

Sensitivity Analysis

Clinical outcomes—When varied individually, the most influential variables on five-year survival and life expectancy are mean CD4 at second-line failure, the availability of an additional ART regimen, and rates of ART suppression (Figure 1a, input assumptions for the additional ART regimen is provided in the TA). Clinical outcomes are less sensitive to the percent of the cohort susceptible to second-line ART if continued or RAL+DRV/RTV+ETR, and to the delay to third-line ART initiation. If the expected cohort size of the *No resistance to second-line* and *NRTI/DRV-resistant* cohorts in the A5288 strategy is doubled, five-year survival and life expectancy decrease (TA Tables 3, 4). Five-year survival and life expectancy associated with the A5288 strategy remain higher than sustained second-line over the range examined for each parameter.

Cost-effectiveness—The incremental cost-effectiveness of the A5288 strategy compared to sustained second-line is most sensitive to the cost of third-line ART, the CD4 count at second-line failure, and the addition of a subsequent ART regimen (Figure 1b). If the cost of third-line ART is reduced by half, the A5288 strategy becomes more attractive (ICER=\$4,000/YLS). Lower CD4 counts at second-line failure are less harmful for those expected to be on efficacious ART regimens (compared to sustained second-line), so the cost-effectiveness ratio of A5288 at lower CD4 counts decreases (ICER=\$6,900). If an additional ART regimen is provided (third-line [sustained second-line strategy] or fourth-line [for strategies 2 and 3]) for subjects failing ART in each strategy, it decreases the incremental cost-effectiveness ratio of A5288, as a greater number of subjects survive long enough to benefit from the extra line in A5288 than in sustained second-line (ICER=\$5,300/YLS). Most other parameters examined have a relatively small impact on the cost-effectiveness results.

There are several plausible scenarios in which the population-based third-line strategy becomes relatively more cost-effective compared with A5288. For example, when the mean CD4 of the cohort at second-line failure is 89/ μ l (SD = 25/ μ l), the ICER of population-based third-line compared to the A5288 strategy is \$27,700/YLS. In this case, the 2-month delay period in the A5288 strategy puts subjects who have already failed ART at greater risk of opportunistic infection and death (TA Table 5). Likewise, in sensitivity analyses examining alternative frequencies of resistance in the distribution of each of the A5288 cohorts, population-based third-line becomes more cost-effective if a greater proportion of

the cohort is susceptible to second-line ART (40% susceptible; incremental cost-effectiveness ratio of population-based third-line \$15,900/YLS) or if a greater proportion of the cohort has virus that demonstrates multiple NRTI resistance mutations and/or DRV/RTV resistance (\$24,600/YLS, TA Tables 3, 4).

In contrast, population-based third-line is dominated (i.e. more expensive and confers less survival benefit) than the A5288 strategy under several scenarios. For example, if fewer subjects have virus susceptible to second-line ART or if subjects with viral-resistance to RAL+DRV/RTV+ETR are administered this regimen and, as a result, experience a 20% reduction in the efficacy of a later fourth-line ART regimen, then the A5288 strategy becomes more effective and less costly than population-based third-line treatment.

Two-way Sensitivity Analysis: Delay to Third-line ART Initiation and CD4 Count at Second-Line Failure—In this sensitivity analysis, we assume that the delay on failing treatment results in acquisition of further resistance mutations and reduces the probability of suppression on the next ART regimen by 1% per month (i.e. a 4-month delay would reduce ART suppression by 4%). A cohort with mean CD4 50/ μ l that waits >4 months to initiate ART has a five-year survival <50% (Figure 2). Fifty to 64% five-year survival is achieved in cohorts with CD4 <50/ μ l and a delay 4 months. We examined delays up to and including 12 months, and within this range, five-year survival rates remain higher than sustained second-line, regardless of CD4 count at second-line failure.

As the delay to initiate ART increases and the mean CD4 at second-line failure decreases, population-based third-line becomes more clinically advantageous and more cost-effective relative to A5288. If the delay is 6 months and mean CD4 is 50/ μ l, population-based third-line has a life expectancy of 82.3 months (A5288=69.5) and an ICER of \$8,300/YLS. When the delay is 12 months and CD4 is CD4 100/ μ l, population-based third-line weakly dominates A5288 (TA Figure 1).

DISCUSSION

The A5288 trial will assess the efficacy of a genotype assay and third-line therapy in resource-limited settings. This intervention holds promise for improved individual outcomes, but will require additional laboratory and ART resources. In a simulation of the projected A5288 protocol, we find that these investments in genotype assay and third-line ART are likely to demonstrate good value for money in South Africa. As such, conducting the trial remains critically important for providing evidence of efficacy.

If sustained second-line ART is the current standard in most trial sites, we anticipate that the A5288 strategy will substantially improve clinical outcomes. When compared with sustained second-line, the addition of third-line ART and a genotype assay (A5288 strategy) increases projected five-year survival (life expectancy) from 47% (61.1 months) to 72% (103.8 months). In sensitivity analyses, the clinical benefits of A5288 remain greater than those of sustained second-line across reasonable ranges.

In the absence of genotype test availability, one might consider an empiric “public health approach” to third-line treatment. This approach – what we call population-based third-line – offers modest increases in five-year survival and life expectancy over the A5288 strategy. Among the most important parameters in the decision to use the genotype test is the mean CD4 count at the time of observed second-line failure. If the mean CD4 count at treatment failure is low, especially <50/ μ l, and is coupled with lengthy delays to obtain genotype results, the clinical outcome might be worse. This is due to the increased mortality associated with low CD4 counts before a switch in regimens is made. In such situations, we

find that a population-based third-line strategy offers five-year survival rates more than 10% higher compared to A5288. In the few resource-limited settings where third-line ART is already available and lengthy genotype delays are unavoidable, patients with lower CD4 counts would be best served by switching to an empiric third-line regimen, which could be adjusted upon receipt of genotype results.

With an incremental cost-effectiveness ratio of \$7,500/YLS, the use of a genotype assay for selection of third-line ART will be an economically attractive use of resources. In South Africa, this incremental cost-effectiveness ratio is within the range of other interventions recommended in HIV care, including first-line ART treatment with tenofovir/lamivudine/efavirenz (\$7,000/QALY) [51], first-line lopinavir/ritonavir for women previously exposed to single-dose nevirapine to prevent mother-to-child HIV transmission (\$1,600/YLS) [52], and second-line ART including a second-generation boosted PI coupled with viral load monitoring (\$6,500/YLS, all ratios adjusted to 2009 USD) [53].

Although test costs are often cited as the greatest barriers to implementation, the cost of the genotype test has little impact on cost-effectiveness (Figure 1b). The cost-effectiveness of the A5288 strategy is most sensitive to the cost of third-line ART (Figure 1b). Third-party price negotiations have substantially lowered the cost of second-line ART in the last two years [54], suggesting that the cost of third-line ART is not only the most influential parameter in determining cost-effectiveness, but also the most malleable one. Genotype testing can help providers use third-line ART most effectively and cost-effectively in subjects with drug resistance, saving money by avoiding unnecessary switches to third-line ART for those still susceptible to second-line. This is particularly important given the substantial portion of subjects likely to have susceptible virus, as well as the additional expertise and expense required for third-line ART regimens.

This analysis has several limitations. First, we used input data from South Africa, which may not be representative of the multiple countries where the trial will be enrolling, but which do support conducting this trial. Second, although there is a robust literature from which to estimate ART regimen efficacies, the actual values that will come from the trial remain unknown. Third, making genotype assays available may require additional investment in physical and human resources, which, as is convention in cost-effectiveness analysis [25], we excluded. Although 13 ACTG sites in 10 resource-limited countries have reported genotype testing availability, others may require a sizable outlay to make these assays available, especially if they limit the genotype turnaround time to 2 months [35]. However, even if infrastructure costs are amortized into the genotype test costs, results show that the genotype test costs are far less important than third-line ART costs.

Finally, we did not account for any transmission reduction in wild-type or resistant virus resulting from an additional suppressive ART regimen. More active therapy may help to reduce viral transmission. However, it may also serve to foster the evolution of drug resistance which could, over time, diminish the efficacy of first-line therapy for drug-naïve patients. Although any reduction in transmission would make the A5288 strategy and population-based third-line therapy even more advantageous in this analysis, the impact of transmitted resistance merits further research.

Using a model-based assessment of an anticipated ACTG trial, we project that an empiric public health approach to third-line ART, at current drug prices, is neither affordable nor cost-effective, compared to a genotype strategy. We also find that the use of a genotype assay to determine third-line ART susceptibility (and algorithmically chosen therapy) – if effective at correctly identifying resistance patterns in resource-limited settings -- will improve clinical outcomes and be cost-effective in South Africa. These results support the

value of the A5288 trial to determine the efficacy of this intervention. Special attention should be paid to subjects who present to care with low CD4 counts ($< 200/\mu\text{l}$), since these subjects are at risk for increased mortality if lengthy delays occur before initiating a new ART regimen.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1a

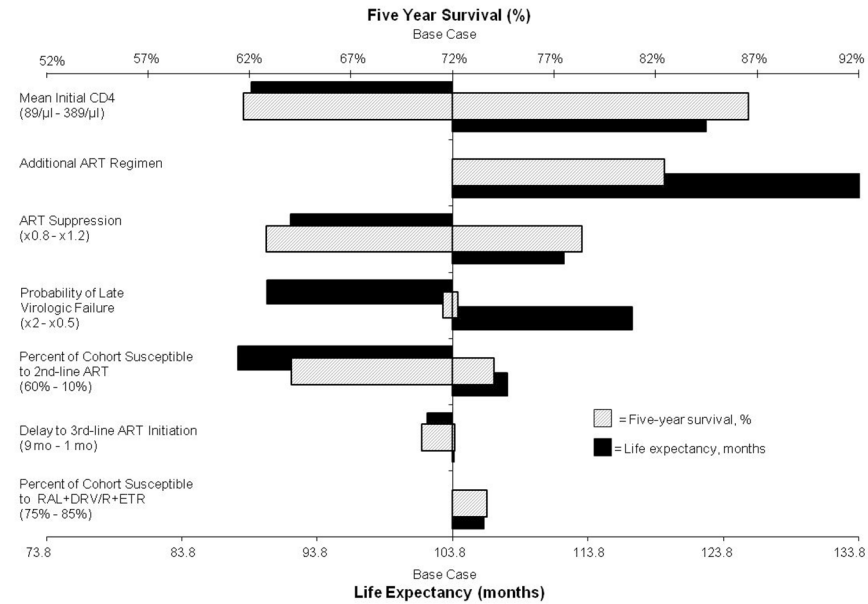


Figure 1b

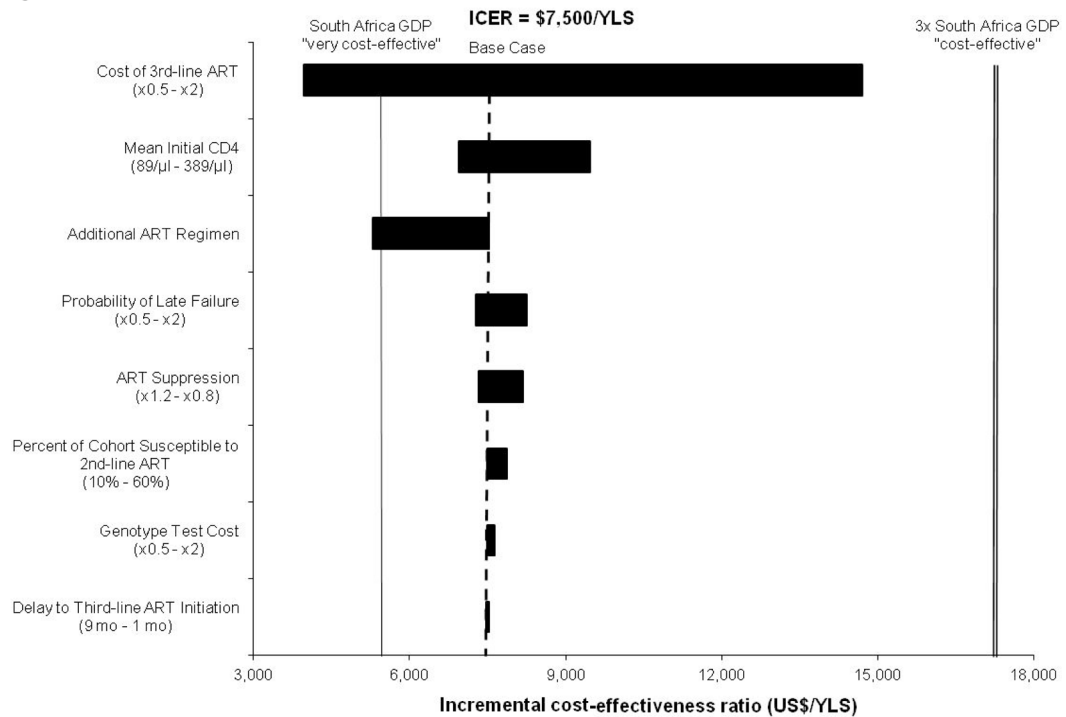


Figure 1. Figure 1a. One-way Sensitivity Analyses: Five-year Survival and Life Expectancy in A5288. Tornado diagram summarizing the results of one-way sensitivity analyses on the clinical outcomes of A5288. The lower horizontal axis shows change in life expectancy (months) and the upper horizontal axis shows change in five-year survival (%) with changes in selected model variables. Changes in life expectancy are shown by solid black bars; changes in five-year survival by hatched gray bars. The range examined for each parameter is in

parentheses. The vertical line represents the base case life expectancy and five-year survival, 103.8 months and 72%, respectively. The percentages at the end of each bar denote the absolute five-year survival at the upper and lower bound of the range examined. ACTG: AIDS Clinical Trials Group; ART: Antiretroviral Therapy; RAL: Raltegravir; DRV/RTV: Darunavir/ritonavir; ETR: Etravirine.

Figure 1b. One-way Sensitivity Analyses: Incremental Cost-Effectiveness Ratio (ICER) of A5288 Compared to the Sustained Second-Line Strategy. The horizontal axis shows variations in the ICER (\$/YLS) due to changes in selected model variables (range for each parameter is in parentheses). The dashed vertical line represents the base case ICER (\$7,500/YLS) while the solid single and double vertical lines represent 1x and 3x the South Africa annual *per capita* GDP (\$5,800 and \$17,400). Guided by the WHO, we consider ICERs less than 3x the South Africa *per capita* GDP to be “cost-effective” and less than 1x the *per capita* GDP to be “very cost-effective” [27]. ACTG: AIDS Clinical Trials Group; ICER: incremental cost-effectiveness ratio; YLS: year of life saved; GDP: Gross Domestic Product; WHO: World Health Organization.

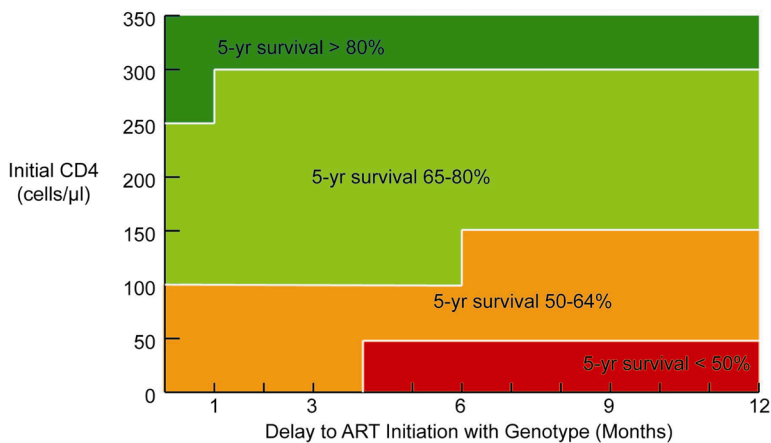


Figure 2. Two-way Sensitivity Analysis: Effect of CD4 Count at Second-Line Failure and Delay to Third-line ART Initiation on Five-Year Survival in A5288

The figure reports ranges of five-year survival as a function of the time delay to third-line ART initiation with a genotype assay (horizontal axis) and mean CD4 count (vertical axis). Five-year survival ranged from less than 50% (denoted by the red shading), to greater than 80% (denoted by the dark green shading). ART: Antiretroviral Therapy; ACTG: AIDS Clinical Trials Group.

Table 1

Model input parameters for analysis of genotype assay and third-line ART in resource-limited settings.

Variable	Estimate	Range examined	Reference
A5288 cohort characteristics			
Age, mean years \pm SD	45.4 \pm 25		ART-naïve cohort simulation results
Male, %	54.6		[30]
Distribution of CD4 at second-line failure, mean cells/ μ l \pm SD	189 \pm 25	(50 – 389)	ART-naïve cohort simulation results
History of severe opportunistic infection, %	26		ART-naïve cohort simulation results
History of tuberculosis, %	33		ART-naïve cohort simulation results
HIV RNA distribution, %			ART-naïve cohort simulation results
>100,000 copies/ml	43.4		
30,001 – 100,000 copies/ml	28.3		
10,001 – 30,000 copies/ml	18.2		
3,001 – 10,000 copies/ml	8.1		
501 – 3,000 copies/ml	2.0		
<500 copies/ml	0.0		
Natural History of disease			[29]
Mean monthly CD4 decline, cells/ μ l, by HIV RNA stratum			
>30,000 copies/ml	6.4		
10,001 – 30,000 copies/ml	5.4		
3,001 – 10,000 copies/ml	4.6		
501 – 3,000 copies/ml	3.7		
Monthly risk of severe opportunistic infections, % ^a			[30]
Active tuberculosis	0.16 – 1.96		
Other severe bacterial infection	0.04 – 0.71		
Other WHO stage III-IV, visceral	0.04 – 1.52		
Other WHO stage III-IV, mucocutaneous	0.02 – 2.26		
Other WHO stage III-IV, non-specific	0.02 – 0.71		
Non WHO stage III-IV event	0.20 – 1.67		
Monthly risk of mild opportunistic diseases, % ^a			[30]
Fungal infections	1.76 – 3.14		
Other WHO stage II	2.33 – 2.67		
Efficacy of co-trimoxazole, % reduction in probability of infection			[33, 34]
Other severe bacterial infection	49.8		
Other WHO stage III-IV, visceral	17.9		
Non WHO stage III-IV event	17.9		
Mild fungal infections ^b	-46.4		
ART efficacy^c			
Sustained second-line: NRTI resistant			

Variable	Estimate	Range examined	Reference
Strategy proportion, %	80		
HIV RNA suppressed at 24 weeks, %	30	(21 – 39)	assumption
Mean CD4 increase at 48 weeks, cells/ μ L	87		assumption
Sustained second-line: No resistance			
Strategy proportion, %	20		
HIV RNA suppressed at 24 weeks, %	50	(35 – 65)	[35]
Mean CD4 increase at 48 weeks, cells/ μ L	87		assumption
A5288: No resistance to second-line			
Strategy proportion, %	20		
HIV RNA suppressed at 24 weeks, %	50	(35 – 65)	[35]
Mean CD4 increase at 48 weeks, cells/ μ L	87		assumption
A5288: Novel agent-susceptible			
Strategy proportion, %	55		
HIV RNA suppressed at 24 weeks, %	90	(63 – 100)	[35, 47]
Mean CD4 increase at 48 weeks, cells/ μ L	109		[55]
A5288: ETR-resistant			
Strategy proportion, %	15		[35]
HIV RNA suppressed at 48 weeks, % ^d	70	(49 – 91)	[35, 48]
Mean CD4 increase at 48 weeks, cells/ μ L	109		[55]
A5288: NRTI/DRV-resistant			
Strategy proportion, %	10		[35]
HIV RNA suppressed at 24 weeks, %	50	(35 – 65)	[35]
Mean CD4 increase at 48 weeks, cells/ μ L	109		[55]
Population-based third-line:			
DRV and/or ETR resistant			
Strategy proportion, %	25		[35]
HIV RNA suppressed at 24 weeks, %	30	(21 – 39)	Assumption
Mean CD4 increase at 48 weeks, cells/ μ L	109		[55]
Population-based third-line:			
No resistance or NRTI resistant			
Strategy proportion, %	75		[35]
HIV RNA suppressed at 24 weeks, %	90	(63 – 100)	[35, 47]
Mean CD4 increase at 48 weeks, cells/ μ L	109		[55]
Delay to third-line ART initiation after observed failure of second-line ART, months	2	(1 – 12)	[35]
Costs			
Co-trimoxazole prophylaxis,	1.03		[33]
Second-line ART, monthly	42.00		[50]
Third-line ART, monthly			[19]
With Etravirine	307.00	(153.00 – 614.00)	
Without Etravirine	205.00	(103.00 – 410.00)	
Routine care ^a , monthly	46.06 – 659.93		[30]

Variable	Estimate	Range examined	Reference
Inpatient hospital care, per day	234.93		[32]
Outpatient hospital care, per	11.40		[32]
Genotype assay visit	400.00	(200.00 – 800.00)	[20, 21, 46]
HIV RNA test	52.84		[56]
CD4 count test	10.57		[56]
Annual discount rate, %	3		[25]

SD: Standard deviation; WHO: World Health Organization; ART: Antiretroviral therapy, ETR: etravirine; NNRTI: non-nucleoside reverse transcriptase inhibitor; DRV: darunavir; NRTI: nucleoside/tide reverse transcriptase inhibitor.

^aRange indicated by CD4 count.

^bThe percent monthly risk of mild fungal infections is increased by 46.4% in the presence of co-trimoxazole.

^cHIV RNA suppression is defined as HIV RNA < 200 copies/mL [35].

^dThis regimen demonstrated increasing rates of suppression until 48 weeks after ART initiation, so we modeled initial efficacy until the 48-week time point [48, 55].

Table 2
Clinical outcomes, cost, and cost-effectiveness of A5288 and comparator strategies

	Five-year survival (%)	Per person lifetime costs (2009 USD)	Per person life expectancy (months)	Incremental cost- effectiveness ratio (\$/YLS)
Base case results: Individual cohorts depending on resistance				
Sustained second-line: NRTI-resistant	44	12,180	58.3	---
Sustained second-line: No resistance	57	13,590	72.4	---
<hr/>				
A5288: No resistance to second-line	56	14,590	72.0	---
A5288: Novel agent-susceptible	82	49,940	118.8	---
A5288: ETR-resistant	70	34,040	103.4	---
A5288: NRTI/DRV-resistant	57	37,600	85.0	---
<hr/>				
Population-based third-line: DRV- and/or ETR-resistant	45	27,990	59.2	---
Population-based third-line: No resistance or NRTI-resistant	82	49,500	119.1	---
<hr/>				
Base case results: Weighted average of relevant cohorts				
Sustained second-line	47	12,460	61.1	
A5288	72	39,250	103.8	7,500
Population-based third-line	73	44,120	104.2	154,500

ACTG: AIDS Clinical Trials Group; USD: United States Dollar; YLS: Year of Life Saved; NRTI: Nucleoside analogue Reverse-Transcriptase Inhibitors; ART: Antiretroviral Therapy; DRV: Darunavir; ETR: Etravirine.