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Objective: HIV genotype-resistance testing can help identify more effective antiretroviral treatment (ART) regimens for patients, substantially increasing the likelihood of viral suppression and immune recovery. We sought to evaluate the cost-effectiveness of genotype-resistance testing before first-line ART initiation in Brazil.

Design: We used a previously published microsimulation model of HIV disease (CEPAC-International) and data from Brazil to compare the clinical impact, costs, and cost-effectiveness of initial genotype testing (*Genotype*) with no initial genotype testing (*No genotype*).

Methods: Model parameters were derived from the HIV Clinical Cohort at the Evandro Chagas Clinical Research Institute and from published data, using Brazilian sources whenever possible. Baseline patient characteristics included 69% male, mean age of 36 years (SD, 10 years), mean CD4 count of 347 per microliter (SD, 300/μL) at ART initiation, annual ART costs from 2012 US $1400 to US $13,400, genotype test cost of US $230, and primary resistance prevalence of 4.4%. Life expectancy and costs were discounted 3% per year. *Genotype* was defined as "cost-effective" compared with *No Genotype* if its incremental cost-effectiveness ratio was less than 3 times the 2012 Brazilian per capita GDP of US $12,300.

Results: Compared with *No genotype*, *Genotype* increased life expectancy from 18.45 to 18.47 years and reduced lifetime cost from US $45,000 to $44,770; thus, in the base case, *Genotype* was cost saving. *Genotype* was cost-effective at primary resistance prevalence as low as 1.4% and remained cost-effective when subsequent-line ART costs decreased to 30% of baseline value. Cost-inefficient results were observed only when simultaneously holding multiple parameters to extremes of their plausible ranges.

Conclusions: Genotype-resistance testing in ART-naive individuals in Brazil will improve survival and decrease costs and should be incorporated into HIV treatment guidelines in Brazil.

Key Words: genotype, cost-effectiveness, Brazil, HIV, drug resistance

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INTRODUCTION

The Brazilian Ministry of Health's response to the HIV/AIDS epidemic is recognized worldwide as a bold program for a middle-income country.[1–3] One of the most striking characteristics of the program is the universal provision of antiretroviral treatment (ART) free of charge to patients, which was guaranteed in 1996 through the passage of a federal law.[4] At the same time, an expert panel was designated to define guidelines for the treatment of infected individuals in the country. Noteworthy aspects of the most recent guidelines, issued in 2013, include CD4 count threshold for treatment initiation at <500 per microliter, regular use of CD4 count and HIV RNA quantification assays for treatment

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monitoring, subsequent-line regimens including drugs for salvage therapy, and use of genotype-resistance testing after treatment failure.[5]

One notable omission concerns the use of genotype-resistance testing before ART initiation for ART-naive patients. The guidelines exclude the widespread use of genotype-resistance testing for ART-naive patients, which is only recommended for pregnant women or individuals known to have acquired infection from a partner receiving ART. This omission is noteworthy, given that the epidemiology and economics of HIV have been shown to favor the use of genotype-resistance testing not only after failing an ART regimen in resource-rich[6,7] and resource-limited settings,[8] but also for patients who are ART naive in resource-rich settings.[9] By identifying individuals with primary resistance, genotype resistance testing can assist health care providers in determining ART regimens for patients that will have the highest likelihood of success. Specifically, patients whose resistance to nonnucleoside reverse transcriptase inhibitors (NNRTIs) is detected before first-line ART initiation can be assigned a protease inhibitor (PI)–based regimen. Still, the Brazilian national guidelines emphasize the need for additional studies demonstrating the clear benefit of this initial genotype test strategy.[5]

We hypothesized that the use of genotype-resistance testing, at a cost of $230 per test,[10] before ART initiation in ART-naive individuals within the scope of the Brazil National Health System would be a cost-effective strategy for the country. To examine this question, we used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International model to estimate the clinical impact, economic costs, and cost-effectiveness of adding primary genotype-resistance testing to the Brazilian Guidelines for HIV treatment.

METHODS

Analytic Overview

We used the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)-International model, a previously published microsimulation model of HIV disease,[11–13] to project the clinical and economic outcomes of performing a genotype test to detect NNRTI resistance before first-line ART initiation in Brazil. Resistance to NNRTI-based regimens was chosen because it accounts for more than 3 quarters of HIV primary drug resistance in Brazil and because Brazilian national guidelines currently recommend an NNRTI-based regimen as the preferred first-line therapy.[5,14] We examined 2 strategies: (1) No genotype testing before first-line ART initiation (*No genotype*), an approximation of the current standard of care in Brazil and (2) genotype testing before first-line ART initiation (*Genotype*). Both strategies include genotype-resistance testing after first-line failure, as recommended in the Brazilian National Guidelines. Within each strategy, we simulated both patients who did and did not have NNRTI resistance and weighted the results based on the prevalence of primary NNRTI resistance in Brazil (Fig. 1). The outcomes of interest included per person life expectancy and costs (both discounted at 3% per year), as well as the incremental cost-effectiveness ratios and net health benefit to provide comparative value of the *Genotype* strategy.[15] All costs were reported in 2012 US dollars. Based on the recommendations of the Commission on Macroeconomics and Health,[16] we defined a strategy to be "very cost-effective" (or "cost-effective") if its incremental cost-effectiveness ratio was less than 1 time (or 3 times) the 2012 Brazilian per capita GDP of US $12,300. Net health benefit was calculated as the difference in discounted effectiveness between the *Genotype* strategy and the *No genotype* strategy, minus the quotient of the difference in costs between the 2 strategies and the willingness-to-pay threshold (measured in dollars per additional life-year saved) and assumed to be the annual per capita GDP of Brazil.[17]

The CEPAC-International Model

The CEPAC-International model is a microsimulation of HIV disease progression and treatment. The model simulates a distinct trajectory for each individual patient, using a random number generator and known transition probabilities to determine the occurrence of monthly transitions between "health states." The health states are defined to be both descriptive of the patient's current health (CD4 count, HIV RNA level, relevant history of opportunistic infections (OIs) and treatment-related toxicities, and resource use) and predictive of future disease progression (immune system deterioration, onset and relapse of OIs, ART status, toxic reactions to medications, resistance to therapy, and mortality). CD4 and HIV RNA levels dictate the rate of CD4 count decline, and CD4 count determines the probabilities of OIs and AIDS-related mortality. The model takes note of variability in patient adherence to medication and uses that information to estimate both initial and long-term virologic response to treatment and loss to follow-up. Results of multiple individual simulations are then aggregated to produce stable estimates of survival and costs. A more complete description of the model is provided in the Technical Appendix (see **Supplemental Digital Content**, http://links.lww.com/QAI/A595) and in the CEPAC Model User's Guide.[18]

At model entry, patients are assigned an adherence value (0%–100%) according to a distribution derived from a cohort of commercially insured HIV-infected patients in the United States,[19] indicating their likelihood to adhere to treatment. For each line of ART, patients are assigned an initial probability of achieving virologic suppression at 24 weeks, after which they face a monthly probability of virologic rebound and subsequent CD4 decline. Both the probability of suppression and the subsequent monthly probability of virologic rebound are dependent on a patient's adherence value. An initial genotype test is performed for all patients at ART initiation in the *Genotype* strategy. After failure on a regimen has been detected through standard viral load monitoring, patients in both strategies incur the cost and information of a genotype test before starting on the next line of ART. After failing the last of 5 available

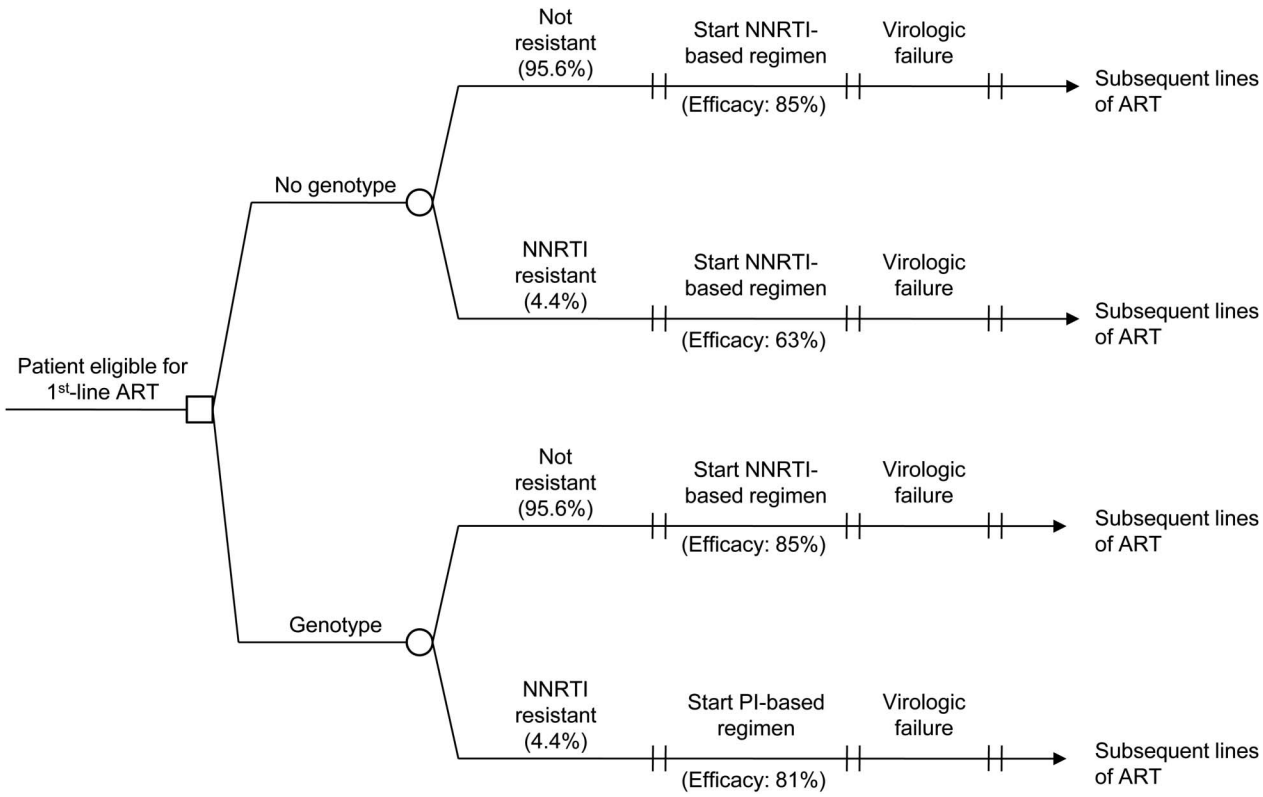

FIGURE 1. Decision tree diagram for a model of HIV genotype testing. Results of each of the 4 arms (*No Resistance, No Genotype*; *No Resistance, Genotype*; *Resistance, No Genotype*; *Resistance, Genotype*) are weighted based on the prevalence of NNRTI resistance in Brazil. Initial ART regimen and efficacy vary by arm. Subsequent-line ART regimens are identical for each arm.

regimens, patients remain on ART until death. Both the monthly probabilities of going loss to follow-up and of returning to care also are dependent on a patient's adherence value. We structure care in the model to conform to Brazilian national guidelines for HIV treatment. Specifically, patients begin antiretroviral therapy when their CD4 count drops below the current Brazil recommendation of <500 per microliter.[5] CD4 count tests are conducted every 3 months until patients are eligible for ART. Once on ART, patients' CD4 count and HIV RNA levels are monitored every 3 months. Patients received both prophylaxis and treatment for OIs in accordance with Brazilian guidelines.

Input Parameters for the Analysis

Data on cohort characteristics, natural history, and resource utilization were derived from the HIV Clinical Cohort at the Evandro Chagas Clinical Research Institute (IPEC) of the Oswaldo Cruz Foundation. IPEC is a public health care institution situated in Rio de Janeiro, Brazil. It is one of the Brazil's largest reference centers for HIV research and has provided care to over 5000 patients in the urban HIV-infected population of Rio de Janeiro Metropolitan area since 1986. A detailed description of the cohort and the methods of data collection and parameter estimation are in the Technical Appendix (see **Supplemental Digital Content,** http://links.lww.com/QAI/A595).

Cohort Characteristics

The simulated cohort consisted of treatment-naive HIV-infected adults, with age, sex, initial CD4 count, and HIV RNA levels estimated from the cohort of 1819 individuals who presented for HIV care at IPEC between 2000 and 2010 (Table 1). Sixty-nine percent were male, mean age was 36 years (SD, 10 years), and mean CD4 count at entry to care was 347 per microliter (SD, 300/μL). The prevalence of primary NNRTI resistance of 4.4% was derived from a surveillance study carried out in the 13 most populous Brazilian cities.[14]

Natural History

Natural history parameters were obtained from a study population that included adult patients (aged ≥18 years) who enrolled in the IPEC cohort and had a minimum follow-up of 60 days from 1986 through 2010. Natural history parameters included the incidence rate of OIs and mortality rates, stratified by both CD4 count and ART use as described in previous CEPAC Model publications.[33] Within each CD4 stratum, OI incidence and mortality rates were assumed to remain constant for the time period evaluated and were converted into monthly probabilities for model input.

ART Efficacy and Loss to Follow-up

ART efficacy and loss to follow-up inputs were stratified by ART adherence levels. A logit adherence distribution was fit

TABLE 1. Base-Case Inputs for a Model of HIV Genotype-Resistance Testing in Brazil

Variable	Base-Case Value						Reference
Cohort characteristics							
Age, mean (SD), yrs	36 (10)						
Male sex, (%)	69						
Initial CD4 count, mean cells/μL (SD)	347 (300)						
HIV RNA distribution, (%)							
>100,000 copies/mL	35						
30,001–100,000 copies/mL	22						
10,001–30,000 copies/mL	18						
3001–10,000 copies/mL	12						
501–3000	7						
<500 copies/mL	6						
Prevalence of NNRTI resistance (%)	4.4						14
Natural history	CD4 count (cells/μL)						
	>500	350–500	200–350	100–200	50–100	0–50	
Mean baseline CD4 decline by HIV RNA, monthly (SD)							Calculated from Refs. 20–22
>30,000 copies/mL	9.5 (0.3)	7.9 (0.3)	6.3 (0.3)	4.7 (0.3)	3.3 (0.3)	1.4 (0.3)	
10,001–30,000 copies/mL	6.8 (0.2)	5.7 (0.2)	4.6 (0.2)	3.3 (0.2)	2.4 (0.2)	1.0 (0.2)	
3001–10,000 copies/mL	5.9 (0.2)	4.9 (0.2)	3.9 (0.2)	2.9 (0.2)	2.0 (0.2)	0.8 (0.2)	
501–3000	4.8 (0.2)	4.0 (0.2)	3.2 (0.2)	2.3 (0.2)	1.6 (0.2)	0.7 (0.2)	
<500 copies/mL	2.4 (0.3)	2.0 (0.3)	1.6 (0.3)	1.2 (0.3)	0.8 (0.3)	0.4 (0.3)	
Chronic AIDS death probability, monthly							
No OI History	0.00018	0.00126	0.00126	0.00279	0.00797	0.00817	
OI History	0.00018	0.00126	0.03692	0.03692	0.05665	0.05665	
OI probability, monthly							
Combination OI (PCP, MAC, CMV)	0.00010	0.00014	0.00063	0.00338	0.00400	0.01724	
Toxoplasmosis	0.00003	0.00026	0.00026	0.00135	0.00334	0.00496	
Tuberculosis	0.00037	0.00092	0.00272	0.00941	0.00941	0.01317	
Other OI	0.00124	0.00225	0.00301	0.00765	0.01197	0.02212	
	All CD4 strata						
Death from OI probability, monthly							
Combination OI (PCP, MAC, CMV)	0.13433						
Toxoplasmosis	0.12500						
Tuberculosis	0.05145						
Other OI	0.06631						
ART efficacy and loss to follow-up							
Adherence distribution							19
% with adherence >95%	45						
% with adherence between 50 and 95%	54.5						
% with adherence <50%	0.5						
HIV RNA suppression (%) and mean CD4 gain (cells/μL)	HIV RNA suppression*			Mean CD4 gain†			
First-line NNRTI regimen without NNRTI resistance	85			197			23
First-line NNRTI regimen with NNRTI resistance	63			197			23,34
First-line PI regimen with NNRTI resistance	81			197			24
Second-line PI regimen	80			197			25
Third-line INSTI-containing regimen	75			148			26
Fourth-line second generation NNRTI-containing regimen	70			107			27,28
Fifth-line CCR5-containing regimen	60			141			29,30
Virologic failure rate after 6 months (/100 PY)							Assumption

(*continued on next page*)

TABLE 1. (*Continued*) Base-Case Inputs for a Model of HIV Genotype-Resistance Testing in Brazil

Variable	Base-Case Value	Reference
All regimens, except NNRTI with NNRTI resistance		
Adherence >95%	0.3	
Adherence <50%	16.2	
Overall average for first-line regimen§	1.5	
NNRTI with NNRTI resistance		
All adherence levels	16.2	
Loss to follow-up (/100 PY)		
Rate of loss to follow-up, overall average	4.1	
Rate of return to care, overall average	81.8	
Costs (2012 US $)		
Routine care costs, annual	60–660‖	31,32
Test costs, per test		10
CD4	20	
HIV RNA	23	
Genotype	230	
Antiretroviral therapy, annual		10
NNRTI regimen	1400	
PI regimen as first-line ART	2200	
PI regimen as second-line ART	1800	
INSTI regimen	12,800	
Second generation NNRTI regimen	13,400	
CCR5 regimen	6700	
Acute OI event	300–700	31,32
Mortality cost	1,100	

*Assuming that patients who take <5% of their medication cannot achieve virologic suppression (ie, 0% suppression), we calibrated the probability of virologic suppression for patients who take >95% of their medication (a model input), so that the overall average suppression for all patients at 6 months matched data from published literature.

†Mean CD4 gain is reported at 12 months for suppressed patients and was calculated from 48- or 96-week immunologic data from published literature. CD4 gain for suppressed patients was assumed to be equal for first- and second-line regimens (Personal communication with Beatriz Grinsztejn and Paul Sax).

‡Virologic failure rates were calibrated to reflect a reasonable distribution of time spent on each line of ART according to expert clinician consultation.

§Although the model inputs for the virologic failure rate after 6 months for patients who take <50% of their medication and >95% of their medication remain the same for each line of ART, the overall average virologic failure rate will differ by regimen, as it is dependent on the distribution and characteristics of the patients starting on each line of ART (eg, adherence levels, proportion of patients starting on each line of ART, etc.).

‖Routine annual care costs were stratified by CD4 stratum, where patients with higher CD4 counts accrued fewer costs than those with lower CD4 counts.

CCR5, C–C chemokine receptor type 5; CMV, cytomegalovirus; INSTI, integrase inhibitor; MAC, mycobacterium avium complex; PCP, *Pneumocystis jirovecii* pneumonia; PY, person-years.

to a retrospective database study in the United States.[19] We assumed that 0.5% of the cohort had poor adherence to ART (ie, <50% adherence), that 45% of the cohort had excellent adherence to ART (ie, >95% adherence), and that the remaining 54.5% fell between these 2 extremes. To determine ART efficacy, we assumed that patients who almost never take their medication (ie, those whose adherence is below 5%) do not achieve virologic suppression. We then calibrated the probability of virologic suppression for excellent adherers (>95%), interpolating linearly for all other adherence values, so that the overall average suppression for the entire cohort matched data from published literature for each regimen (Table 1). Patients who were suppressed on a given regimen faced an adherence-dependent monthly probability of virologic rebound. This risk was calibrated so that fewer than 2% of patients reach the last line of ART. Rates of loss to follow-up and return to care were derived from data from the IPEC cohort and were calculated to be 4.1 and 81.8 per 100 person-years, respectively (see **Technical Appendix, Supplemental Digital Content**, http://links.lww.com/QAI/A595).

No NNRTI Resistance, With and Without Genotype

In the model, patients who did not have NNRTI resistance were eligible to receive up to 5 sequential lines of ART. First-line therapy was an NNRTI-based regimen, and second-line therapy was a PI-based regimen. Patients who failed first- and second-line therapy received subsequent lines of ART that increased in regimen complexity and cost and decreased in rates of suppression (Table 1).

NNRTI Resistance Without Genotype

Patients who had NNRTI resistance but did not receive a genotype test received the same sequence of ART regimens as patients who did not have NNRTI resistance; however, their ability to successfully respond to the first NNRTI-based regimen was decreased. We lowered the virologic suppression rate at 24 weeks for the NNRTI regimen by applying a calculated relative risk of failure of 2.6,[34] decreasing the overall average suppression from 85% to 63%. We assumed that all patients with NNRTI resistance who become suppressed at 24 weeks, regardless of their adherence level, face

a rate of "late failure" on the NNRTI regimen of 16.2/100 person-years—equivalent to the rate of late failure after 24 weeks for poorly adherent patients without NNRTI resistance.

NNRTI Resistance With Genotype

Patients who had NNRTI resistance and received a genotype test received a PI-based regimen as their first-line ART, instead of an NNRTI-based regimen. After first-line failure, these patients began the same PI-based regimen that all patients received as second-line ART. Thereafter, these patients received the same third- through fifth-line ART as those without NNRTI resistance, with the same probability of suppression as nonresistant patients.

Costs

We conducted the economic analysis from the perspective of the public National Health System and, therefore, restricted our attention to direct HIV-related medical costs. All unit costs were obtained either from the Brazilian Ministry of Health or from the administrative department of IPEC and converted from Brazilian reais to 2012 US dollars using a GDP deflator and the average exchange rate for 2012.[35] Costs for routine care and acute OI events were calculated by multiplying the unit costs for inpatient and outpatient visits by the number of inpatient and outpatient days associated with routine chronic care (stratified by CD4 count), acute events, and death, reported between 2005 and 2010 for the HIV Clinical Cohort at IPEC (see **Technical Appendix, Supplemental Digital Content**, http://links.lww.com/QAI/A595). The annual cost of the individual lines of ART ranged from $1400 to $13,400 (Table 1), and the cost of the genotype test was $230.[10]

Sensitivity Analyses

To understand the impact of data uncertainty on our findings, we conducted univariate and multivariate sensitivity analyses. Ranges explored for each parameter were derived from the literature (eg, NNRTI resistance prevalence) or defined based on plausible ranges (eg, NNRTI regimen efficacy in patients who had NNRTI resistance but did not receive a genotype test, genotype test cost, and subsequent-line ART costs). Multivariate sensitivity analyses were conducted on 3 of the most influential parameters to demonstrate their interactions.

RESULTS

Base Case

Among patients without NNRTI resistance, genotyping had no impact on discounted life expectancy (221.6 months) but slightly increased projected per-person lifetime costs from $43,980 to $44,290 (Table 2). For patients with NNRTI resistance, however, genotyping produced a substantial improvement in life expectancy (from 217.7 to 221.2 months) and a reduction in costs (from $67,200 to $55,130). These reduced costs are a result of fewer complications associated with viral load rebound and with a smaller proportion of time spent on more expensive third through fifth lines of ART. When weighting these results based on the prevalence of NNRTI resistance in Brazil (4.4%), the current standard of care in Brazil yielded a discounted life expectancy of 221.4 months (18.45 years) and a discounted lifetime cost of US $45,000. The use of genotype-resistance testing before ART initiation yielded a higher discounted life expectancy of 221.6 months (18.47 years) and a lower discounted lifetime cost of US $44,770. Therefore, the *Genotype* strategy was cost saving compared with *No Genotype*, because it costs less and yielded greater life expectancy. *Genotype* had a positive net health benefit of 0.035 discounted years of life saved (YLS); that is, it rendered a gain in net health benefit when compared with the *No Genotype* strategy.

Univariate Sensitivity Analysis

In univariate sensitivity analyses, we varied major input parameters independently within their plausible ranges. One-

TABLE 2. Base-Case Results for an Analysis of HIV Genotype Testing in Brazil

	Discounted Cost (2012 US $)	Undiscounted LE (months)	Discounted LE (months)	NHB* (YLS)	ICER† ($/YLS)
Cohort-based outcomes					
No NNRTI resistance *No genotype*	43,980	389.4	221.6	—	—
No NNRTI resistance *Genotype*	44,290	389.4	221.6	—	—
NNRTI resistance *No genotype*	67,200	381.1	217.7	—	—
NNRTI resistance *Genotype*	55,130	388.5	221.2	—	—
Population-wide outcomes, weighted by the prevalence of resistance (4.4%)					
No genotype	45,000	389.0	221.4	—	—
Genotype	44,770	389.4	221.6	0.035	Cost saving

*Gain in net health benefit (NHB) rendered with a given strategy as compared with that rendered with the reference strategy was calculated as the difference in discounted effectiveness between the *Genotype* strategy and the *No Genotype* strategy, minus the quotient of the difference in discounted cost between the *Genotype* strategy and the *No Genotype* strategy and the willingness-to-pay threshold, here assumed to be 1 time the per capita Gross Domestic Product of the Brazil (2012 per capita GDP = $12,300).

†ICER, reported in 2012 US $ per life-year saved, was calculated as the incremental difference in cost divided by the incremental difference in life-years. By convention, a strategy that costs less and yields greater life savings compared with the reference strategy is labeled cost saving and no ICER is reported.

ICER, incremental cost-effectiveness ratio; LE, life expectancy; NHB, net health benefit.

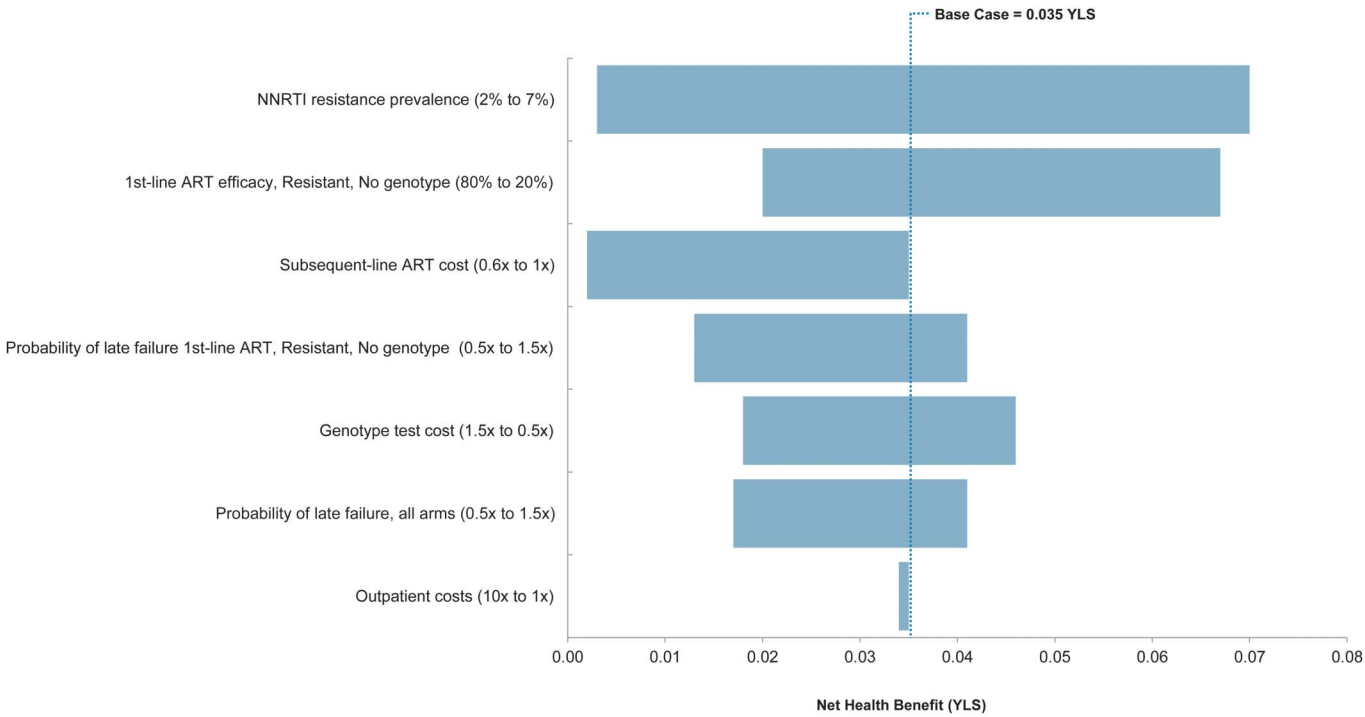

FIGURE 2. Univariate sensitivity analysis tornado plot of selected parameters. The diagram summarizes the results of a series of 1-way sensitivity analyses on the net health benefit of genotyping. Each horizontal bar represents the range of net health benefit produced by varying a given model parameter across the parameter ranges in parentheses. Net health benefit is defined as the YLS minus the quotient of the difference in cost between the 2 strategies and the annual willingness-to-pay threshold (here, the 2012 annual per capita GDP of Brazil US $12,300). The vertical line represents the base-case net health benefit for the *Genotype* strategy. NHB, net health benefit; LE, life expectancy.

$$\mathrm{NHB} = \left(\mathrm{LE}_{Genotype} - \mathrm{LE}_{NoGenotype}\right) - \left(\frac{\mathrm{Cost}_{Genotype} - \mathrm{Cost}_{NoGenotype}}{\text{Willingness to pay threshold}}\right).$$

way sensitivity analyses yielded positive net health benefit across all plausible parameter ranges (Fig. 2). They also identified influential parameters that could produce noteworthy changes in net health benefit findings. The most influential parameter was NNRTI resistance prevalence which, when varied from 2% to 7%, yielded net health benefit values ranging from 0.003 to 0.070 YLS. As the efficacy of first-line NNRTI-based ART in resistant patients not receiving genotype testing increased, thus reducing the detrimental effect of NNRTI resistance, overall net health benefit of *Genotype* decreased. Reducing subsequent-line ART costs by 60% decreased the net health benefit of the *Genotype* strategy from the base-case value of 0.035 to 0.002 YLS. Other parameter variations that caused an appreciable decrease in net health benefit were increasing the genotype test cost and decreasing the probability of virologic failure after suppression for resistant patients not receiving a genotype test.

Multivariate Sensitivity Analysis

Figure 3 depicts the behavior of the cost-effectiveness findings as we varied 3 of the more influential parameters identified in the 1-way sensitivity analyses: the cost of the genotype test (increased and decreased 50% from baseline value); the cost of subsequent ART regimens (from 100% to 10% baseline value); and the prevalence of NNRTI primary resistance (from 0.1% to 5.0%). In the base-case scenario (depicted by the black dot in the central panel), we observed cost savings. *Genotype* was cost saving, for example, even when both subsequent-line ART costs decreased to 80% of baseline values and resistance prevalence decreased to 3.7%. If the cost of the genotype test was reduced by 50% (right panel), cost savings were achieved in a wider range of scenarios, including at resistance prevalence as low as 1.3%. Even when the genotype test cost was increased to 150% of baseline value (left panel), initial genotype remained a cost-effective strategy over a broad range of plausible parameter changes, such as reducing the cost of subsequent ART to 60% of baseline value while resistance prevalence decreased to 3.4%.

DISCUSSION

Since 1996, the Brazilian government has guaranteed universal provision of ART, free of charge, to HIV–infected individuals.[4] ART guidelines for the country are set forth by the Department of Sexually Transmitted Diseases, AIDS, and Viral Hepatitis within the Ministry of Health. Although the

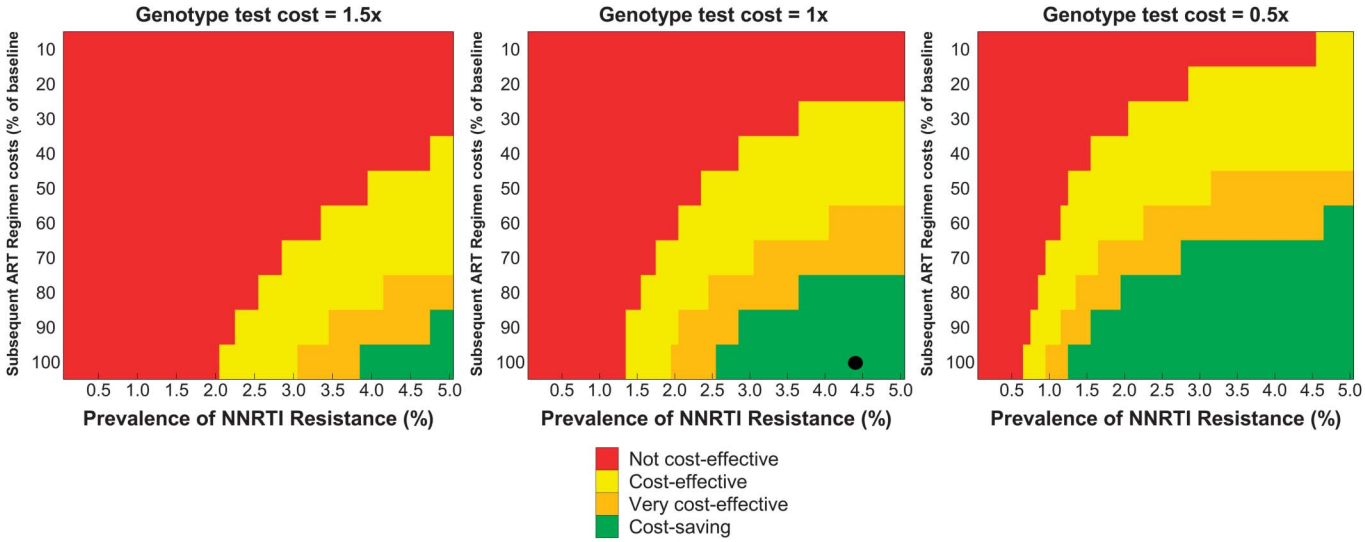

FIGURE 3. Multivariate sensitivity analysis color plot. Parameters varied simultaneously were genotype test cost, subsequent-line ART costs, and primary NNRTI resistance prevalence. Colors are arranged from green (cost saving) to red (not cost-effective). The black dot in the middle panel indicates the base-case result. ICER: Incremental cost-effectiveness ratio; not cost-effective: ICER >3 times the 2012 annual per capita GDP of Brazil of 2012 (ICER >$36,900); cost-effective: 1 time < ICER <3times the 2012 annual per capita GDP of Brazil ($12,300 < ICER < $36,900); very cost-effective: ICER $0 < ICER < 1 time the 2012 annual per capita GDP of Brazil ($0 < ICER < $12,300); cost saving: ICER <$0.

current 2013 Brazilian national guidelines recommend genotype testing after failure of first-line ART, they do not recommend routine use of genotype testing before initiating first-line ART, citing a lack of evidence for the clear benefits of this strategy.

Genotype-resistance testing can help identify more effective antiretroviral regimens for patients, thus substantially increasing the likelihood of viral suppression and immune recovery.[36] We used the most recent surveillance study of primary resistance conducted in 20 centers from 13 highly populous cities in Brazil[14] and data from a large Brazilian clinical cohort to derive inputs for a simulation model for the present analysis. We found that genotype-resistance testing was cost saving at resistance prevalence as low as 2.6%, much lower than the reported value of 4.4%.

Although primary resistance prevalence was the most influential factor on the cost-effectiveness of initial genotype-resistance testing, subsequent-line ART costs were also an important factor. This is because, without a genotype test, resistant patients are likely to fail their initial regimen, experience poorer clinical outcomes, and spend an increased proportion of their lives on more expensive and less tolerable subsequent-line regimens. Over time, it is likely that these expensive regimen costs will decrease, making initial genotype-resistance testing less attractive. However, our results suggest that *Genotype* will remain cost-effective unless subsequent-line ART costs fall below 30% of their current value. Given that the *Genotype* strategy is projected to decrease per-patient lifetime costs by US $230 (Table 2), for an estimated 45,000 patients initiating ART in Brazil each year,[10] and with stable costs over time, the *Genotype* strategy could yield a projected annual cost savings of US $10.4 million.

The results of this analysis should be interpreted in light of certain limitations in model parameters and assumptions. First, in the base case, we assumed that the prevalence of primary NNRTI resistance, a key parameter of this analysis, was similar across the country. Though this is certainly not the case, the HIV epidemic is mostly concentrated in large urban centers, and these were appropriately chosen for the nationwide primary resistance prevalence study that was used to derive model inputs. Nonetheless, we conducted univariate and multivariate sensitivity analyses to evaluate the impact of plausible variation in NNRTI resistance prevalence. These analyses showed that, for most of the explored prevalence, the *Genotype* strategy either remained cost saving or reached cost-effective results. Second, although our standard-of-care strategy assumed that no one starting treatment would be offered a genotype test, the most recent guidelines published in 2013 state that pregnant women and individuals infected by an HIV-infected partner on ART could make use of the test. It is possible that, if we included these exceptions to the current *Genotype* strategy, the strategy would become less appealing. However, such changes would not alter our conclusions substantially because these populations represent only a small fraction of those starting ART in Brazil.[37–39] Third, to obtain input data estimates for the model, we used data from the HIV-infected Cohort at IPEC and other published official Brazilian government sources. We used sensitivity analysis to evaluate which of these parameters influenced our findings most strongly and how our conclusions would be affected by the variation in the parameter values; we found that our conclusions were robust. Fourth, when modeling the *Genotype* strategy, we assumed it was completely implemented; inadequate implementation would yield both life expectancy and cost for the genotype strategy that are lower, though the cost-effectiveness

ratio would be similar. Finally, the present analysis focuses on the health benefits that accrue to the individual and the economic implications for the health system but does not address potential population-level effects of primary resistance testing. Such population benefits might include decreased transmission of resistant virus to HIV-uninfected individuals, which would make the *Genotype* strategy even more appealing.

Previous economic analyses have shown the cost-effectiveness of initial genotype-resistance testing before initiating first-line ART therapy in the United States.[9] Here, we present the first analysis to show the potential cost savings of this initial genotype strategy in a middle-income country. In Brazil, similar to antiretroviral drugs and other laboratory tests, genotype-resistance testing is provided by the federal government, free of charge, to patients in 24 reference centers throughout the country. Although obstacles were experienced during its implementation in 2001, the procedures required for performing the test are currently well established. Furthermore, the interpretation of the test result is carried out by a designated group of experts and follows a standardized procedure that includes evaluating the results in light of each patient's ART history and recommending a new ART regimen. By identifying individuals with primary resistance, genotype-resistance testing, with its 1-time cost, provides an opportunity for the health care provider to allocate patients to a regimen with a high likelihood of success and for the government to reduce overall costs of HIV care. We find that initial genotype-resistance testing will improve survival and decrease costs and should be incorporated into both HIV treatment guidelines and the standards of care in Brazil.

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