Technical Appendix   1
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

Supplemental Digital Content:

Technical Appendix

The cost-effectiveness of genotype testing for primary resistance in Brazil

Luz et al.

In areas where computer programming and methods are identical, the text from this
appendix is similar to the online technical appendix available from:

Walensky RP, Ross EL, Kumarasamy N, et al. Cost-effectiveness of HIV treatment as
prevention in serodiscordant couples. *N Engl J Med.* Oct 31 2013;369(18):1715-1725.

Technical Appendix 2
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

CEPAC International Model

Overview

The CEPAC International Model is a computer-based, state-transition, Monte Carlo simulation model of the progression and outcomes of HIV disease in a hypothetical cohort of patients. "State-transition" means that the model characterizes the natural history of illness in an individual patient as a sequence of monthly transitions from one "health state" to another. "Monte Carlo" refers to a random number generator and set of estimated probabilities that are used to determine the sequence of movements between health states for a particular patient. Each individual patient's clinical course is followed from the time of entry into the model until death. A running tally is maintained of all clinical events, the length of time spent in each health state, and the costs associated with each health state. Upon the patient's death, summary statistics are recorded and a new patient enters the model. This process is then repeated for a large number of simulated patients (statistical convergence can typically be achieved with cohort sizes of one million), at which point overall performance measures such as average life expectancy and cost are computed.

Health States

In the Disease Model, health states are chosen to be descriptive of the patient's current health, relevant history, and resource utilization patterns. They are designed to be predictive of clinical prognosis, including disease progression, immune system deterioration, development and relapse of different opportunistic infections (OIs), toxic reactions to medications, resistance to therapy, and mortality. The model defines general categories of health states: chronic infection, acute

Technical Appendix   3
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

complication, and death. Most of the time, patients are in one of the chronic states, where progression of disease and immune system deterioration (CD4 decline) take place. Patients who develop an acute complication (e.g., an OI or drug-related toxicity) temporarily move to an acute health state, where both resource consumption levels and mortality rates are higher. Deaths can occur from either a chronic or an acute state and can be attributed to a particular OI, chronic AIDS (e.g., wasting), or non-AIDS-related causes.

The chronic and acute health states are stratified by: actual current and nadir CD4 count (>500/µl; 301–500/µl; 201–300/µl; 101–200/µl; 51–100/µl; and 0-50/µl) and current and set-point HIV RNA level (>100,000 copies/mL, 30,001-100,000 copies/mL; 10,001–30,000 copies/ mL; 3,001–10,000 copies/ mL; 501–3,000 copies/ mL; 51-500 copies/ mL; 0-50 copies/mL). Drawing from distributions of patient characteristics (age, sex, CD4 count and HIV RNA level) derived from the IPEC Cohort (see below), a patient is randomly assigned to a health state upon model entry. By permitting the user to define initial population distributions for patient age, sex, CD4 count, HIV RNA, and other demographic and clinical attributes, the model has the flexibility to explore a broad range of different patient cohorts.

At the start of each one-month cycle, the model records the patient's CD4 count, HIV RNA level, history of acute illness, and current therapies and uses these characteristics to determine the probabilities that indicate movement to a new state in the subsequent month. Monthly probabilities of events are estimated directly from the IPEC cohort and published data. The model treats HIV RNA as the primary driver of immune system deterioration, and thus the assigned viral load level determines the rate at which the patient's CD4 count will decline in the absence of ART.[1]

Technical Appendix   4
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

We are careful to distinguish in the model "actual" CD4 count and HIV RNA – i.e. the

underlying immunologic and virologic state, regardless of whether it is measured by a laboratory

test– from "observed" CD4 count and HIV RNA – that which is measured by a test and upon

which clinical decisions can be made. Clinical events within the model are predicated on

patient's "actual" CD4 count and viral load status, while treatment decisions remain based on

"observed" CD4 count and viral load status.

Clinical Visits and Laboratory Monitoring

Upon entry to the model, all patients undergo a clinic visit to observe their initial OI histories.

CD4/HIV RNA monitoring also occur at model entry. At this initial visit, if specific criteria are

met, patients will initiate prophylaxis and antiretroviral therapies. Subsequent clinic visits will

then be scheduled at regularly specified intervals to determine ART eligibility criteria and to

monitor treatment success or failure. In addition to the regularly scheduled clinic visits, certain

events (OIs) may trigger an emergency clinic visit to occur in that month. An emergency clinic

visit is associated with the same costs and clinical decision-making opportunities as a routine

visit, and at most one clinic visit can occur in a given month.

Because CD4 and/or HIV RNA monitoring is available, these tests are generally administered at

the time of a clinic visit. Standard testing frequency may be user-defined; other conditions may

also trigger additional tests, including observed ART failures that require confirmation by CD4

or viral load, depending on the confirmation method specified by the user.

Technical Appendix   5
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

ART and ART Efficacy

The model has capacity to simulate up to ten lines of ART, to be administered sequentially. The

current analysis focused in Brazil utilizes five sequential regimens. A patient is evaluated for

starting, stopping, or switching the ART regimen at every clinic visit. The criteria for regimen

change can be specified differently for each individual regimen. Upon meeting criteria for ART

initiation (or switching), the patient is started on the first (or next) specified regimen.

A patient may be evaluated to start an ART regimen based on the following criteria: current CD4

count (if observable data available), current HIV RNA (if observable data available), a

combination of CD4 count and HIV RNA, observed OIs since the previous regimen, or CD4

count and observed OIs. Since this structure enumerates the logical combinations of the

individual criteria, they can be independently specified and evaluated. If the specified criteria are

met, the patient will be started on that ART regimen. The first regimen criteria are evaluated at

each clinic visit until treatment is initiated. Patients with no NNRTI resistance, or those with

NNRTI resistance not receiving a genotype test, first receive an NNRTI-based regiment. Patients

with NNRTI resistance who do receive a genotype test initiate a PI-based regiment. Lines 2-5 are

identical for all patients and are structured with increasing complexity and costs as follows: 2)

protease inhibitor (PI) based regimen; 3) integrase inhibitor (INSTI) containing regimen; 4) 2nd

generation NNRTI containing regimen; and 5) C-C chemokine receptor type 5 (CCR5)

containing regimen.

The model's handling of efficacy and durability of antiretroviral therapy is as follows: we

estimate efficacy from data on viral suppression and CD4 count change over time, as reported in

cohort studies and randomized trials. From these data, we derive a probability of "early" (within

Technical Appendix   6
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

12 months) and "late" (beyond 12 months) failure for each antiretroviral regimen to be considered. This structure allows patients to transition from virologic suppression to "failure" with the appropriate change in HIV RNA and CD4 count. Virologic suppression results in CD4 increases, also in these two time phases, that occur in concordance with data reported in clinical trials. An initial large CD4 benefit occurs in the "early" period, followed by a modest benefit that occurs over a longer time horizon, as long as the patient remains virologically suppressed. We assume an identical CD4 increase for the first two ART regimens.

The model makes a distinction between patients actually failing an ART regimen and those who are observed to fail a regimen. The former can be regarded as patients in whom therapy stops providing any substantive biological benefit to the patient. The latter simulates the clinical observation of a new OI, or laboratory detection of CD4 decline or viral load increase, indicating a regimen's lack of continued benefit, at which point the patients may be taken off that regimen. Upon laboratory-observed and confirmed failure – defined by HIV RNA>500 copies/ml, CD4 count decrease >25%, or CD4 below the pre-ART nadir – patients are initiated on a subsequent-line regimen, until no others are available. At that point, patients remain on their final regimen until death. Patients may be lost to follow-up prior to starting or while on ART. Patients may also experience toxicity events due to ART, with regimen-specific probabilities, case mortality rates, and associated costs.

Costs

In each month, patients accrue a monthly routine care cost, based on their current CD4 and OI history state. If a patient has a history of an OI, the cost is based on that OI type and the patient's CD4 count. In addition to these base routine monthly costs, patients accrue costs for each type of

Technical Appendix   7
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

acute event (e.g. acute OI, toxicity, visits, tests, death) as well as monthly drug (i.e. ART, OI

prophylaxis) costs.

Monthly Cycle of the Model

Because all events in the program occur discretely, it is important to keep in mind the order of

evaluation in each month of a simulated patient. Taking all the mechanisms described above

together for HIV-infected patients, each regular monthly cycle in the program involve the

following steps in order:

1. increase the patient's age, in months

2. compute whether a CD4 and/or HVL test(s) should be performed this month, based on

    last tests

3. if a CD4 test is to be performed, do so

    a. start and stop OI prophylaxes as necessary based on the patient's new observed

        CD4

4. if a viral load test is to be performed, do so

    a. if the patient is on an ART, see if the new observed viral load (and CD4) results in

        a failed ART diagnosis

        i.   if the number of repeat failure diagnoses is enough for a confirmed failure,

             take the patient off the ART regimen

        ii. if the patient has not actually failed the ART regimen (i.e. the failure

             diagnoses are incorrect), treat the patient's CD4 and HIV RNA levels as in

             ART failure to reflect the discontinuation of the effective therapy

Technical Appendix   8
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

5. if the patient is not on any ART regimen and qualifies for a new line of ART (per
    observed CD4 and HIV RNA, number of lag months between ARTs, etc.), start the
    patient on the next regimen

6. for all prophylaxes the patient is currently on, see if an associated toxic event occurs

7. if the patient is on an ART regimen, see if an associated toxic event occurs

    a. if an ART major toxicity event occurred, see if it also caused death – if death did
        occur, stop the patient simulation

8. determine if the patient dies from chronic AIDS or non-AIDS causes

    a. if death occurs, stop the patient simulation

9. for each prophylaxis the patient is on, determine if resistance is to start in the current
    month

10. determine if an acute OI event will occur this month

    a. if an OI event occurs, see if it also causes death from the OI and thus stop the
        patient simulation

    b. if the patient is not detected as HIV+, make the patient detected

11. update the patient's CD4 and HIV RNA for the month

12. update the patient's accumulated costs, life months, and quality adjusted life months

Description of the IPEC HIV Clinical Cohort

The Laboratory for HIV/AIDS Clinical Research (LaPClin) is situated within the Evandro

Chagas Clinical Research Institute (IPEC) of the Oswaldo Cruz Foundation (FIOCRUZ) in Rio

Technical Appendix 9
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

de Janeiro, Brazil. IPEC is a national reference center for infectious diseases and LaPClin has

been a reference center for care, research, and training related to HIV/AIDS since 1986. LaPClin

is one of the largest providers of primary, specialty, and tertiary care for HIV-infected

individuals in the state of Rio de Janeiro.

The IPEC HIV Clinical Cohort is a seroprevalent cohort with follow-up since the start of the

AIDS epidemic in Brazil in 1986. Since then, over 5,000 HIV infected individuals have received

care at IPEC. An observational, longitudinal, clinical database was established in 1998 (when all

patients seen from 1986 to 1998 were retrospectively included) and is updated for all patients

receiving HIV and specialty care (including cardiology, endocrinology, ophthalmology,

dermatology, gastroenterology, gynecology and proctology) at IPEC.

The database is comprehensive in that it includes demographic, behavioral, clinical, laboratory,

and therapeutic information (including the prescription of antiretroviral drugs) abstracted from

the medical records of patients. Patients are seen by the medical provider as recommended by the

Brazilian HIV treatment guidelines. The medical record was paper-based until 2004 and is

currently in an electronic format. Trained abstractors record all information onto standardized

forms. Longitudinal databases include laboratory results (including hemoglobin, CD4/CD8, and

HIV viral load counts, among others), types and dates of prophylaxis use, serology for hepatitis

B and C among others, vaccinations, AIDS-related and non-AIDS related diagnosis (both

outpatient and inpatient), and use of licit and illicit drugs. Longitudinal information regarding

antiretroviral therapy prescribed includes start and stop dates for each drug of each regimen. It is

important to note that when a new patient is included in the cohort, efforts are made to ensure the

Technical Appendix   10
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

collection of information for the time prior to enrollment, including HIV-related diagnoses, laboratory results, and antiretroviral treatment.

Information regarding vital status is checked using the patients' medical charts, through active contact with individuals and family members, and by linkage with the Rio de Janeiro mortality database using a previously validated algorithm.[2] Descriptions of the cohort procedures and results have been published elsewhere.[3-6]

Collection of IPEC Cohort Data for the CEPAC Model

Cohort characteristics

To estimate the characteristics of the individuals who currently seek and enroll into HIV care in Brazil, the study population included ART-naïve adult patients (age ≥ 18 years) who enrolled in the cohort and had a minimum follow-up of 60 days, from January 01, 2000 through December 31, 2010 (1,819 patients). CD4 counts and HIV viral load were defined within a window of 90 days of enrollment, and if more than one measurement was available, the value closest to the date of enrollment was chosen.

Natural History

For the natural history parameters, the study population included adult patients (age ≥ 18 years) who enrolled in the IPEC cohort and had a minimum follow-up of 60 days from September 12, 1986 (the date of the first enrollee) through December 31, 2010. In order to adequately estimate parameters that could populate the CEPAC-International Model, a patient's follow-up time was stratified into the following broad categories of states: Acute Disease, Chronic HIV, and Death.

Technical Appendix   11
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

The Chronic HIV Health State consists of the time contributed by each patient stratified by CD4 count strata. The following CD4 count strata were considered: >500/µl, 301–500/µl, 201–300/µl, 101–200/µl, 51–100/µl, or <50/µl. Each patient could contribute time to either one or multiple time periods within each CD4 stratum. Linear interpolation between two known CD4 measures was implemented to estimate the time points when a patient crossed the boundary between CD4 strata. Time contributed to the Chronic HIV category was censored in two different situations. First, for patients who were diagnosed with a specific AIDS-defining event, follow-up was censored for both the month preceding and the two months following an opportunistic illness diagnosis. Second, for patients who died, follow-up was censored at one month prior to the date of death. Whenever possible, follow-up time was further stratified by use of antiretroviral therapy yielding periods on ART and off ART. That is, patients could contribute a certain portion of their follow-up time to an off-ART period and a certain portion of their follow-up time to an on-ART period. Also, whenever possible, separate analyses were performed for patients with and without a documented history of any AIDS-defining illness, defined by the 1993 CDC definitions,[7] at cohort entry. The following AIDS-defining illnesses were specifically evaluated: Pneumocystis jirovecii pneumonia, Mycobacterium avium complex, toxoplasmic encephalitis, cytomegalovirus, tuberculosis, and other AIDS-defining events.

The Acute Disease Health State was defined by the time period from one month prior to two months after the diagnosis of a specific AIDS-defining illness. Thus, it was defined only for patients who had an AIDS-defining event(s) during the follow-up time. Time contributed to the this health state was censored before the end of the two months after illness diagnosis if the patient died, in which case the time contributed was counted for the Death Health State.

Technical Appendix   12
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

The Death Health State was the period of time defined by the one month preceding the date of

death.

Incidence rate of opportunistic infections

The occurrence of an opportunistic infection was defined for the first occurrence of a CDC 1993

disease. For patients who never experienced an opportunistic infection, end of follow-up was

defined as the earlier of death or December 31 2010 when administrative censoring was applied.

Opportunistic infections were stratified into four groups according to their frequency:

tuberculosis, toxoplasmosis, PCP+MAC+CMV, and others. The incidence rates were calculated

by dividing the number of opportunistic infections by the sum of the follow-up time for all

individuals in each of the Chronic HIV Health States. Additional estimates included the

incidence rate of opportunistic infections stratified by the use of antiretroviral therapy when

events and follow-up time were divided into periods when a specific patient had not yet started

ART and after the start of ART. Incidence rates were assumed to remain constant over the time

period evaluated and converted into monthly probabilities for model input (Table 1).

Mortality rates

Start of follow-up was defined as the date of cohort enrollment and end of follow-up was defined

as the earlier of either death or December 31, 2010 when administrative censoring was applied.

Mortality rates were then calculated by dividing the number of deaths by the sum of the follow-

up time of each individual in the Chronic HIV Health State. Additional estimates included the

mortality rate stratified by the use of antiretroviral therapy and by the history of prior

opportunistic infection, defined as an opportunistic infection occurring prior to cohort

Technical Appendix   13
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

enrollment. Mortality rates were assumed constant for the time period evaluated and converted

into monthly probabilities for model input.

Resource utilization

Resource utilization was estimated for the period when a longitudinal database of outpatient

visits per patient, compiled from the administrative records of IPEC, was available by specialty.

This period ranged from January 2005 to December 2010. A longitudinal database of inpatient

days is also available for this period giving the date of hospital admission and discharge per

patient. Using this data, the number of outpatient visits to the infectious disease physician per

month and the fraction of a month spent as an inpatient were calculated for each of the health

states described above.

Loss to Follow-up (LTFU) and Return to Care (RTC)

LTFU rates were ascertained from lab monitoring visits for each patient. Patients enrolling in the

cohort, defined by a minimum follow-up of 60 days after January 1, 2000, were included. Start

of follow-up was defined as the date of cohort enrollment and end of follow-up was defined as

the earlier of either death or December 31, 2012 when administrative censoring was applied.

Patients exhibiting a lab monitoring gap of greater than 12 months were considered lost to follow

up. An average monthly probability of being lost to follow up was calculated over months 24 to

95 and was used to estimate the proportion of patients in care, excluding return to care and death,

at 6-, 36-, and 72-month time points. Model inputs were calibrated to reflect these values of

proportion in care. Those with adherence <50% were subject to a rate of LTFU of 16.2/100PY,

and those with adherence >95% were subject to a rate of LTFU of 0.3/100PY. LTFU rates were

Technical Appendix   14
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

linearly interpolated by adherence level for the remainder of patients to calibrate to the

proportion in care at the 6-, 36-, and 72-month time points.

For the subset of patients who were lost to follow-up, a rate of RTC was calculated as the

number of patients who returned to care divided by the total person-months lost to follow-up.

This rate of 81.8/100 person-years was assumed for all patients lost to follow up, regardless of

adherence level.

Costs

We conducted this analysis from the perspective of the Brazilian National Health System

(Sistema Unico de Saude, SUS), overseen by the Brazilian Government, which provides

HIV/AIDS clinical care and health related services in a network of outpatient clinics, hospitals,

and laboratories free-of-charge to patients. Our analysis was thus confined to direct medical

costs. Patients have access to HIV specialized clinical care, HIV monitoring laboratory tests

(CD4 count, HIV viral load measurements, genotype resistance testing, and others), drugs for

prophylaxis and treatment of opportunistic infections, and antiretroviral drugs. In fact, diagnostic

and treatment for non-AIDS diseases are also provided under the umbrella of SUS.

Outpatient visits and Inpatient days

The costs of outpatient visits and inpatient days were obtained from the official website of the

Informatics Department of Brazilian Government (DATASUS,

http://www2.datasus.gov.br/DATASUS/index.php). Through DATASUS, a diverse set of health

information can be obtained including the mean cost and length of stay of an HIV/AIDS-related

hospitalization. The cost of the outpatient visit was obtained through DATASUS in the

Technical Appendix   15
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

Managerial Table of Procedures and Health Care Related Resources

(http://sigtap.datasus.gov.br/tabela-unificada/app/sec/inicio.jsp).

Laboratory tests

Costs paid by the government for laboratory tests (CD4 count, HIV viral load and genotyping)
were provided by the Department of STD, HIV/AIDS and Viral Hepatitis of the Ministry of
Health (http://www.aids.gov.br/) following the official procedures for data request that consist of
a form sent to the department with the inquiry.

Drugs

Drug costs were obtained through direct contact with personnel in the Ministry of Health and the
administrative department of IPEC. Costs paid by the government for antiretroviral drugs (except
for maraviroc) were provided by the Department of STD, HIV/AIDS and Viral Hepatitis of the
Ministry of Health following the official procedures for data request that consist of a form sent to
the department with the inquiry. Given that maraviroc is not yet routinely purchased by the
government, its cost was provided in a separate official document sent by the Department of
STD, HIV/AIDS and Viral Hepatitis of the Ministry of Health providing the cost for the
purchase of the drug. The cost of tuberculosis treatment and prevention were provided by the
tuberculosis division of the Ministry of Health through personal communication. The costs of
drugs used for prophylaxis and treatment of opportunistic infections were provided by the
administrative department of IPEC.

Technical Appendix   16
The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

Cost-effectiveness analysis

Cost-effectiveness analysis evaluates the costs and effectiveness of one health intervention compared to another. The appropriate metric for resource allocation is the incremental cost-effectiveness ratio. For an evaluation of two interventions, A and B, assuming B costs more and generates greater effectiveness, the incremental cost-effectiveness ratio (ICER) of B relative to A is given by:

ICER = (Costs of B – Costs of A) / (Effectiveness of B – Effectiveness of A)

The ICER provides us with a measure of value for money. This can facilitate comparisons with alternative health care investments. An intervention might be considered economically attractive if its ICER compares favorable to estimates of the societal willingness-to-pay for additional health gains. The World Health Organization (WHO) Commission on Macroeconomics in Health suggests that cost-effectiveness thresholds should reflect a nation's ability to pay. Specifically, the WHO defines an intervention to be "very cost-effective" if its cost-effectiveness ratio is less than the country's *per capita* Gross Domestic Product (GDP), and "cost-effective" if its cost-effectiveness ratio is less than three times the *per capita* GDP. According to the International Monetary Fund, Brazil's 2012 GDP *per capita* is US$12,300. Therefore, the "very cost-effective" threshold is US$12,300 per QALY saved and the "cost-effective" threshold is US$36,900 per QALY saved. Any new strategy with an ICER below the willingness-to-pay threshold might be considered attractive from the societal point of view in this context.

The cost-effectiveness of genotype testing for primary resistance in Brazil
Luz et al.

REFERENCES

1.   Mellors JW, Muñoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med.* 1997;126(12):946-954.

2.   Pacheco AG, Saraceni V, Tuboi SH, et al. Validation of a hierarchical deterministic record-linkage algorithm using data from 2 different cohorts of human immunodeficiency virus-infected persons and mortality databases in Brazil. *Am J Epidemiol.* Dec 1 2008;168(11):1326-1332.

3.   Campos DP, Ribeiro SR, Grinsztejn B, et al. Survival of AIDS patients using two case definitions, Rio de Janeiro, Brazil, 1986-2003. *AIDS.* Oct 2005;19 Suppl 4:S22-26.

4.   Grinsztejn B, Veloso VG, Friedman RK, et al. Early mortality and cause of deaths in patients using HAART in Brazil and the United States. *AIDS.* Oct 23 2009;23(16):2107-2114.

5.   Grinsztejn B, Luz PM, Pacheco AG, et al. Changing mortality profile among HIV-infected patients in Rio de Janeiro, Brazil: shifting from AIDS to non-AIDS related conditions in the HAART era. *PLoS One.* 2013;8(4):e59768.

6.   Moreira RI, Luz PM, Struchiner CJ, et al. Immune status at presentation for HIV clinical care in Rio de Janeiro and Baltimore. *J Acquir Immune Defic Syndr.* Aug 2011;57 Suppl 3:S171-178.

7.   US Center for Disease Control. 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults. 1992. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00018871.htm. Accessed March 20, 2014.