CEPAC Program User Guide

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A. Introduction

The CEPAC (Cost Effectiveness of Preventing AIDS Complications) team has developed an AIDS treatment model and several other models, some of which are used to derive inputs for the treatment model and some take as input the outputs of the treatment model. This document only focuses on the treatment model, especially the programmatic piece of it. Within this document, the CEPAC model/program will refer specifically to the treatment model.

The CEPAC model is a computer-based, state-transition, Monte Carlo simulation model of the progression and outcomes of HIV disease. Disease progression of each simulated patient is characterized by a sequence of monthly transitions from one logical "health state" to another. Important determinants of a patient's state at any given point in time include age, gender, current and past CD4 and HVL levels, history of OI(s), HIV infection status, and currently administered therapies (including both OI prophylaxes and ART).

In the Monte Carlo approach to simulation, solutions are approximated by repeated statistical sampling from component probability distribution functions. (In contrast, a more conventional approach to numerical solution may involve solving a system of closed form equations describing the problem.) Multiple experiments (or "trials," or "histories") are done and observations are averaged to arrive at an expected solution.

A1. Major Changes from Version 2 to Version 3

Since version 2.5*x* of the CEPAC program, there were two executable versions representing two different CEPAC models: one tailored for the U.S. (and other developed countries like France) and one focused to less developed

countries (referred to as the LDC model, or at times the Africa model or the GAP model). With version 3.0 of the CEPAC program, these two versions have been merged into a single model, based primarily on the LDC model.

The key changes in version 3.0 of the program from the prior U.S. version include:
1. Elimination of the post-acute OI state – After an acute OI, patients had transitioned to a post-acute state, which implicitly incorporated maintenance therapy of the OI(s) and increased resource utilization. In version 3.0, secondary prophylaxes are explicitly specified for those patients with a history of OI(s).
2. Explicit modeling of clinic visits – Version 3.0 of the program makes explicit the notion that patients must make clinic visits to receive care. At a clinic visit, disease progression is monitored and treatment is administered as specified.
3. Allow increased heterogeneity of patients in cohort – New patient variables have been introduced, including parameters to specify patterns of clinic visits and propensity to initiate prophylaxis, ART, or no treatment at all.
4. Revamped ART regimen efficacy mechanism – At the initiation of an ART regimen, patients are now assigned to one of three predestined states: fully suppressed, partially suppressed, and failure. After an initial regimen-specific time period, suppressed patients incur a monthly probability of transitioning to the failure state. Each of the three states induces different immunologic and virologic responses in patients.

Version 3.0 of the program does not differ radically from the prior LDC versions, so no further description of changes from the LDC version is given here.

A2. Major Changes from Version 3 to Version 4

Version 4 of the model was a complete rewrite of the CEPAC model. All major functionality was maintained and there were no changes to the inputs and outputs of the model. Compatibility was maintained with the 3.2x input sheets and data extraction scripts still work properly on the model generated outputs.

The key changes that occurred in this rewrite are –
1. Object oriented C++ design – The code base was rewritten in C++ with a modular, object oriented approach for the model inputs, patient state, run time statistics, and functional units. This makes it much easier to read and understand the code, diagnose and fix errors, and add new functionality.
2. New and improved GUI – A new graphical user interface was written using a simpler, platform independent package. This allows for new features to be quickly implemented and the possibility of using the graphical interface on non-Windows platforms.
3. Functionality reordering – The functional units of the model were reordered to provide a clean separation between patient disease/health updates and clinical/treatment changes. This improves the logical flow of the model and eliminates unintended side effects that were present in the old version.
4. HIV Testing module integration – The HIV testing module has now been integrated into the main CEPAC model. HIV negative patients go through the main simulation loop but skip all unnecessary modules. This eliminates a lot of redundant and error prone code, while allowing for the possibility of developing new functionality that effects both HIV positive and negative patients.

A3. Note on Terminology and Conventions

For purposes of clarification, it is important to note terminology and conventions used within this document. **CD4** generally refers to patient CD4 T-cell count; distinction will be made between the numerical count of CD4 cells and the various CD4 strata as necessary. **HVL** is abbreviated for the HIV RNA viral load count of HIV infected patients. The actual numerical count of patients' HVL is not modeled; only a patient's current HVL stratum is tracked. Each simulated patient has **actual** CD4 and HVL levels in any given month. These counts may not be reflected in the patient's **observed** CD4 and HVL readings until the time of the respective CD4 and HVL tests.

Opportunistic infections (**OI**s) are broken out by specific categories, with the sole exception being the *OTHER OI* category, which includes all infections not covered by the other explicitly defined types. Tuberculosis (**TB**) is

treated apart from the regular OIs, and is described in a separate section in this document. A distinction is made between the actual occurrence of OIs and the observation of those OIs in the patients' histories by the care providers.

ART, also known as HAART in the literature, refers to antiretroviral therapy.

In this document, the term **model** encompasses CEPAC's assumptions, conception, and operation. In practice, the model is often broken down by the **data** elements – as represented by the input tables of the MS Excel spreadsheet – and the executable **program,** which performs the **simulation** of the hypothetical cohort. Human users of the program will be frequently referred as operators or simply users in this document.

Operators of the model specify all desired values as **input** to the program, which in turn produces **output** files containing results of the simulation(s). Each input file corresponds to one simulation **run**. Each run can optionally be grouped into a **set**. At program invocation, all accessible input files are grouped as a **batch**, and processed sequentially. In general, output files contain only summary results of the simulated cohort. The program can also produce **traces** of each patient, detailing state and event information of each patient's clinical course. Each run involves a **cohort** – typically very large in size – of individual patients, simulated sequentially. At the completion of each batch, the program writes **summary** information to a separate file (currently named `popstats.out`).

B. Basic Model Structure and Usage

Each simulated patient's clinical course is tracked from the time of entry into the model until death. The fundamental unit of time in the simulation is a month. Upon the patient's death, summary statistics are recorded and a new patient enters the model. The simulation run completes when the last patient in the cohort has passed through the model. The program maintains tallies of clinical events, duration spent in each health state, monthly life and quality-adjusted life expectancies, and costs.

Model analyses are primarily done from the societal perspective. The actual cost of patients' time is generally not included, as it is considered negligible compared to drug and hospitalization costs.

The model defines three general categories of health states as depicted in the following diagram: chronic, acute, and death. Normally, patients reside in one of the chronic states, where progression of disease and immune system deterioration occur. Patients who develop an acute complication, such as an OI, temporarily move in that month to an acute health state, where quality of life is lower and 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.
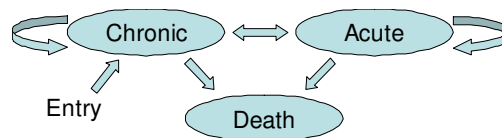
In general, all simulated individuals in the model may be considered as HIV infected patients that are detected as being HIV positive. The one exception to this rule occurs when the HIV testing component is enabled. In this case, the model is extended to define individuals in various states: HIV uninfected, acute HIV infected, asymptomatic chronic HIV infected, and symptomatic chronic HIV infected. In all HIV infected states, patients may be either detected or undetected. Once identified as HIV infected, those simulated individuals may then be linked to care and become eligible to begin treatment.

Immunologic function is assessed by infected patients' CD4 count; virologic function is assessed using HVL count. In the model, HVL drives immune function only to the extent that it determines the rate of CD4 cell count decline. HIV disease progression is interrupted through clinical care, such as prophylaxis against OIs and ART, which are described in their own sections below.

The 6 CD4 strata used in the model are generally defined as *VHI* (>500 cells/μL), *HI* (301-500 cells/μL), *MHI* (201-300 cells/μL), *MLO* (101-200 cells/μL), *LO* (51-100 cells/μL), and *VLO* (0-50 cells/μL). The user may redefine the strata boundaries in the run inputs.

The 7 HVL strata are defined as *VHI* (>100000 copies/mL), *HI* (30001-100000 copies/mL), *MHI* (10001-30000 copies/mL), *MED* (3001-10000 copies/mL), *MLO* (501-3000 copies/mL), *LO* (0-500 copies/mL), and *VLO* (0-50 copies/mL) – corresponding to roughly half a logarithm range for each stratum. The lowest stratum, *VLO*, is currently just a placeholder for future updated data to reflect more sensitive HVL tests. Currently, HVL less than 500 copies/mL is considered below detectable levels.

The program currently supports up to 15 categories of OIs. (Note that TB is modeled in more detail than other OIs but is still included in this 15.) Each type of OI may be classified as either mild or severe. The severity associated with each of these OIs affects the attribution effect assessed on the patients' probability of chronic AIDS death. Historically, the U.S. model defined 6 OI types: *PCP* (pneumocystis carinii pneumonia), *MAC* (mycobacterium avium complex), *TOXO* (toxoplasmosis), *CMV* (cytomegalovirus), *FUNG* (disseminated fungal infection), and *OTHER OI* (all other OIs). Early analyses focused on African countries have used the following OI categories: bacterial infections, fungal infections, tuberculosis, malaria, isospora, toxoplasmosis, mycobacterium avium complex, pneumocystis carinii pneumonia, and other OIs. These categorizations and the associated OI effects can be redefined by the user.

B1. Instructions for Running the Cepac Program

All the inputs to the Cepac program are contained in the `cepac_inputs4xx.xls` Microsoft Excel workbook. The workbook was developed in Office 2007 and is also compatible with Office 2003. `Cepac4 xx.exe` is the executable program that actually performs the model simulation. (See Note on Versions on the current naming scheme for both the program executable and input spreadsheet.)

The `cepac_inputs.xls` workbook is intended to allow the user to manipulate the actual inputs before a run input file is generated. When opening this workbook, you may be prompted by the following security dialog:
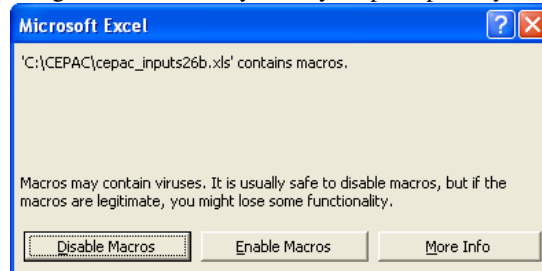
It is important to select "Enable Macros" in this case, as macros are defined for actually generating the run input files required by the program. (The scripts to produce the run input files are implemented in unsigned VBA and embedded within the `cepac_inputs4xx.xls` workbook itself.) Note in that some installations of Excel, the macro security level may be set to high to disable unsigned macros. To allow the necessary macro scripts to run, the security level must be lowered.

Under the "RunSpecs" worksheet in the `cepac_inputs4xx.xls` workbook, the "Save Run File" button is used to save specified inputs relating to a single **analysis**, or **run**:
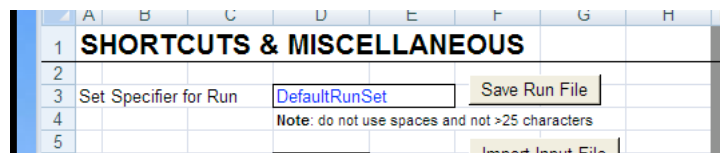
Typically you may want to save multiple analyses at one time before running the `cepac.exe` program. A set of analyses will be referred to as a batch of runs. The `cepac4`*xx*`.exe` program will locate all analyses in the batch at the start of execution, and then process each run individually.

For individual runs, define your analysis set and change the data inputs according to your needs. When the inputs for each run are completely specified, clicking on the "Save Run File" button results in a dialog like the following:
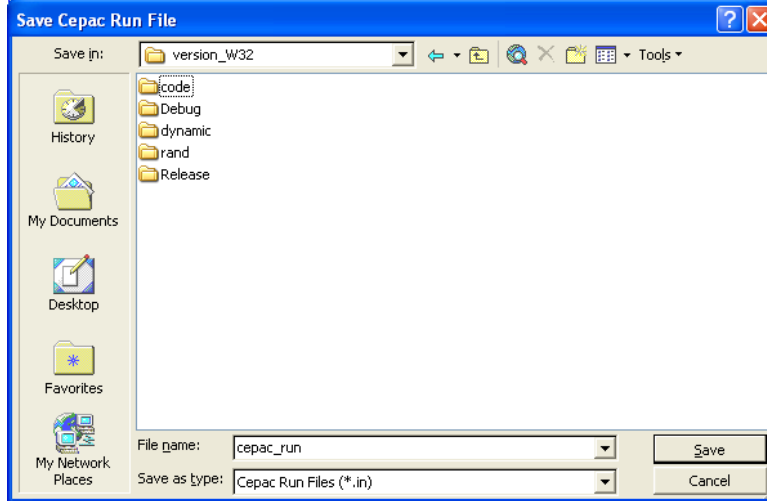
The "Save Cepac Run File" dialog should act like any other file-save dialog: choose a directory to save the run input file and then assign a name for the file. Typically, the run input files should be saved to the directory in which the `cepac4`*xx*`.exe` program executable resides. In the example dialog, the default run input filename of "cepac_run" is shown.

After clicking "Save" on the dialog, the Excel macro will attempt to generate a run file (with a file extension of "`in`") with the data inputs specified in the spreadsheet. If a run input file with the same name already exists, the following prompt will appear:
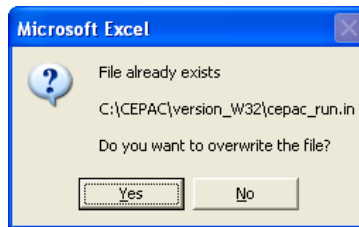
Clicking "Yes" on this dialog results in the previous file being overwritten with the data inputs currently specified in the `cepac_inputs4`*xx*`.xls` workbook. Clicking "No" on this dialog leads to the previous "Save Cepac Run File" dialog, which would allow a different filename to be specified.

Due to the large number of model inputs that needs to be specified, it is often useful to start an analysis with a default set of inputs. In older version of the model, there was a separate data workbook that would be linked into the `cepac_inputs4`*xx*`.xls` workbook to specify these default values for the country of interest. Starting in version cepac42b, this data workbook has been eliminated and there are Excel macros for importing inputs from prior analysis instead. A repository of baseline input files for various countries of interest and standards of care is being developed to serve as the starting point for future analysis. Below the "Save Run File" button in the "RunSpecs" tab, there are two other buttons for importing inputs – "Import Input File" and "Import Workbook".
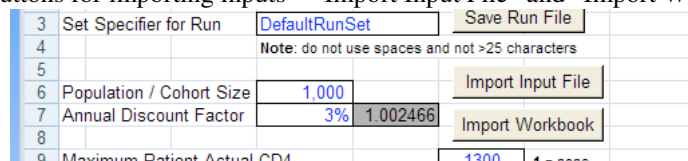
Running either of these macros will open the following file selection dialog window. The "Import Input File" macro will prompt the user to select a "CEPAC Input File (*.in)", while the "Import Workbook" will prompt them for an "Excel CEPAC input workbook (*.xls)".
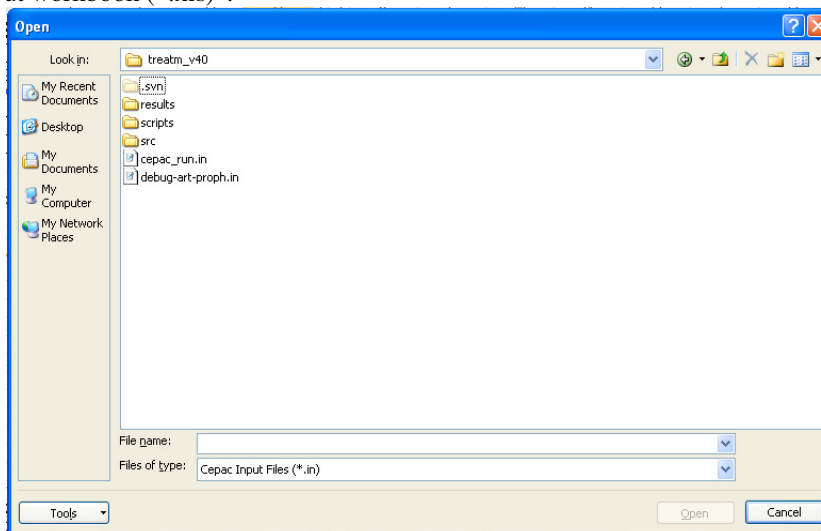
Once the file is selected, the macros will first verify that selected input file or workbook is of the same model version and display an error message if it is not. The current workbook will then have all of its input cells populated with the values specified in the selected file. The "Import Input File" macro should be used before starting any new analysis to import the appropriate default inputs. The "Import Workbook" should only be used to import into a new Excel workbook if the current one becomes corrupted or there is an issue with the macros. These macros and the "Save Run File" one can also be invoked by right clicking anywhere in the Excel workbook and selecting them from the dropdown menu.

Input files from older version can be upgraded to the current version using the `upgrade_inputs4xx.exe` executable. When run, this program will scan the current directory for any older input files, perform the upgrade to the appropriate version, and place the upgraded input files in a subdirectory called "upgraded_inputs". This program can currently upgrade input files dating back to version cepac40a. The newly created input files can then be run directly with the appropriate CEPAC executable, or imported into a CEPAC inputs workbook for further modification using the "Import Input File" macro.
Note: Due to changes in the model input structure and functionality; the upgrade process cannot perfectly replicate the outcomes of the prior versions. In the absence of a perfect 1:1 correspondence between the inputs, the program attempts to convert the inputs in a logical manner to maintain the desired behavior. After upgrading, the new inputs should be verified and the outcomes validated.

When all the run inputs are specified, the last step is to launch the `cepac4xx.exe` program. The program allows the user to select a directory where the input files for the desired batch of runs are located by selecting File->Open. The program will search for all the files in the specified directory ending with the extension ".in" for run inputs. After selecting a directory, the program will display all of the input files that it located. In the above picture, the file is named "`cepac_run.in`" but it's recommended that more descriptive names be used, e.g. "`1M-no_ART-PCP proph.in`". One input file must be saved for each analysis. Below is an example view of the directory selection and the resulting GUI display –
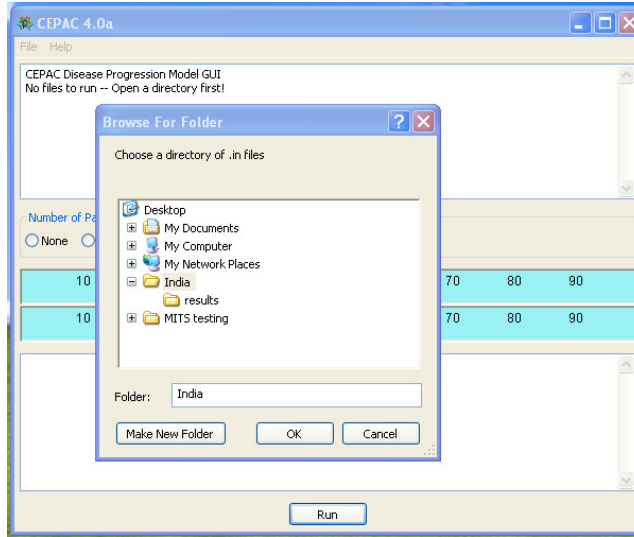
Once the input files have been located, simulation can be started by click on the Run button. If individual patient tracing is desired, the radio buttons can be used to select the number of patients to trace per run. These trace files are very useful for understanding how the model works and verifying that inputs are set up properly to produce the desired simulation. If a large number of patients is selected, these files may become quite large. It is recommended to always trace at least some patients in order to verify the program behavior.
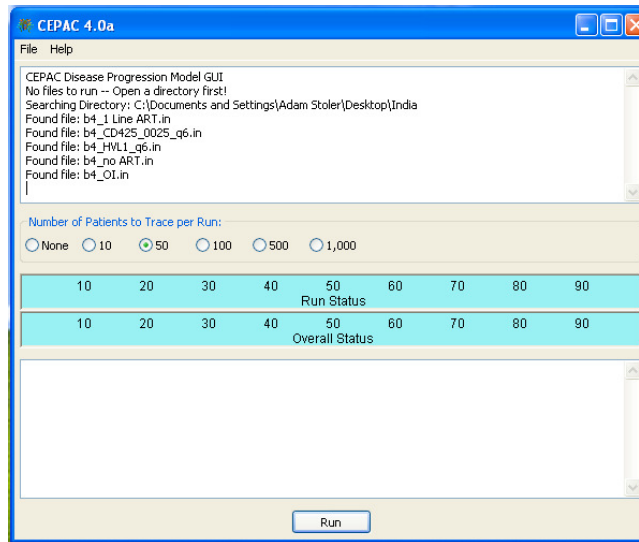
As the program is running, there will be several status updates of its progress. The top dialog box will display the name of the input file that is currently running. The two status bars will show the progress of the current run and overall progress of all runs in the batch. The bottom dialog box will display summary statistics for the completed runs. Below is a screenshot of a running CEPAC program.
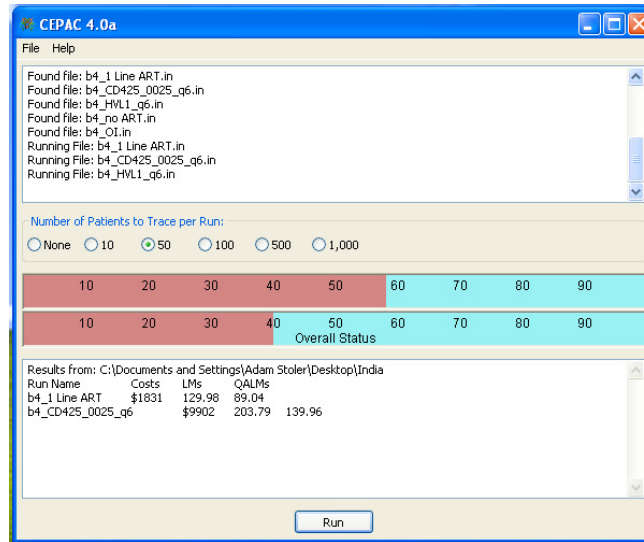
At the end of each simulation run, the program creates an ".out" file corresponding to the input filename in the "results" subdirectory of the input directory. This file contains statistics gathered during simulation of the entire cohort population. If tracing was specified, the tracing ".txt" files will also be created for each. The results of each analysis in the batch will be summarized in the popstats.out file.

In the popstats.out file, all summary results of the individual runs are sorted according to cost, from which incremental cost-effectiveness ratios are calculated. Often it is more useful to the user to calculate incremental cost-effectiveness ratios within smaller groups of analyses, called sets. For example, say you have 6 runs but wish to calculate incremental cost-effectiveness ratios in two separate groups of 3 runs each. The 6 runs are a batch and each group of 3 runs is a set. (Note that the number of analyses in a batch can be quite large, and the number of sets within each batch can be as numerous as you would like but not greater than the number of runs in your batch. Currently, the program is limited to a maximum of 1000 runs in a batch; but this can be easily extended if necessary.)

The name of each run set is specified by the "Set Specifier for Run" entry that is next to the "Save Run File" button in the "RunSpecs" worksheet. Note there is a current limitation for the set name: it cannot contain space characters. Typically, it is easier for the user if this name is more, rather than less, descriptive of your analysis. Remember, if you leave the field value to the default for all analyses, the cost-effectiveness ratios for the entire batch of runs will be calculated incremental to each other.

While the cepac4*xx*.exe program is actually running, do not access or modify the program's input ".in" files, output ".out" files, or the summary popstats.out file. However, once the program is done with an analysis, that run's ".out" file is available for inspection. Continuing our example, as soon as "cepac_run.out" appears, it is safe to open it. (Some Windows systems are set to hide file extensions. In those cases, it may be difficult to differentiate files by their extension types. The safest thing to do is to wait until the cepac4*xx*.exe completely finishes before inspecting any of the output files.)

B2. Note on Versions

Each version of the program is specified by major and minor version numbers and a build date. The current major version number is 4. The minor version numbers serve to differentiate incremental functionality of the program versions. The build date serves to denote modifications in processing that involve very little or no change in functionality. For example, a new build may be released to address logic or formatting errors that do not impact simulation results.

For example, the version "`40a (build 2009-11-03)`" contains the minor version number 0a, and was built on November 3rd, 2009. Such a version number should correspond to a program executable with the name `cepac40a.exe`.

The spreadsheets corresponding to this program version should have the names `cepac_data40a.xls` and `cepac_inputs40a.xls`. To ensure that input files are in sync with the program version, a data input version number is embedded in the spreadsheet. The same spreadsheet has the number "`201020430`" embedded within the inputs. Each executable program is hard-coded to look for such a matching version number. Because the nature of the inputs and the program logic itself change so frequently, the program will abort simulation of all runs with unmatched version inputs.

B3. Note on Discrete Events and Monthly Cycles

The basic unit of time in the model is a month. All acute events in the model occur for durations of time much smaller than a month. The result is that there are cases where the accounting of discrete events may not make much sense at initial inspection. (The halving of costs in a month of death is one simple manifestation of this issue.) The relative ordering of evaluating whether or not discrete events occur also has an impact on the results of the simulation. These events are generally arranged such that biological and disease progression events occur before any diagnostic or clinical ones. The result of this ordering is that disease progression will cause treatment changes within a given month, while the effects of the treatment changes will not manifest until the subsequent month.

B4. Note on Probabilities and Rates

The model relies heavily on the use of probabilities to determine the occurrence of discrete events and health state transitions. For the given probability of a certain event, a random number between 0 and 1 will be generated, and the event will be determined to occur if the number is below the specified probability. Many of these probabilities are fixed inputs, while others are calculated by combining multiple probabilities and/or modifying a probability by a risk factor. In order to perform these computations, the probabilities are converted to rates, and the additive and multiplicative properties of rates are used. The following formulas are used for the conversions –

Probability to Rate:
- $P = 1 - e^{\wedge}(-R)$

Rate to Probability:
- $R = -\ln(1 - P)$

When two probabilities need to be combined to determine likelihood that either or both will occur, the additive property of rates is used. The two probabilities are converted to rates, summed together, and converted back to a probability.

When a probability needs to get modified by a risk factor to increase or decrease the likelihood of the event occurring, the multiplicative property of rates is used. The base probability is converted to a rate, this rate is multiplied by the risk factor, and the resulting rate is converted back to a probability. All of model inputs that modify probabilities are specified as rate multipliers.

C. Detailed Model Structure

C1. Cohort Initialization

Upon model entry, individual patients are assigned chronic HIV disease characteristics drawn from initial probability distributions. Initial age (in months) and CD4 count are drawn from normal distributions. The user can

also set maximum and minimum age bounds for Initial age. Initial CD4 can also be configured to be drawn from a square root transform distribution (The model will first draw from a normal distribution and then square the result to get the actual initial CD4). Initial HVL level is broken down by percentage distribution among the possible HVL strata. A single percentage of male patients in the cohort is used to draw the gender of each individual patient. CD4 and HVL distributions are specified jointly, but all other initial attributes are drawn independently of each other.

When the HIV testing component of the program is enabled, the simulated individuals are first distributed among the four HIV infection states: uninfected, acute HIV infected, asymptomatic chronic HIV infected, and symptomatic chronic HIV infected. Information relevant only to the HIV infected (i.e. CD4 and HVL) is not assigned until an individual is actually determined to be infected. Individuals' age and gender are assigned at the beginning of simulation as usual.

In addition to those initial characteristics, the patient also draws for several parameters at model entry pertaining to possible treatment strategies. These include drawing from distributions of whether or not they will be eligible for ART treatments, ART response type, eligibility for OI prophylaxis, prophylaxis compliance, and criteria for clinic visits. These parameters will remain constant for the patient until death.

C1a. Prior OI History at Entry and Logging Mechanism

Before the simulation begins for each patient, the program independently assesses whether the patient has had a history of each OI type based on the patient's initial actual CD4 and HVL strata. Patients without a history of a particular OI are assessed a monthly probability for contracting a primary incidence of that OI. Patients with a history of an OI are assessed a different monthly probability for contracting a secondary incidence of that OI. The program treats histories of an OI acquired whether from an acute OI event in the monthly course of a patient simulation or from being assessed at patient initialization time on model entry as equivalent.

Complementary to this prior OI history at entry mechanism is the OI history logging functionality of the program. The purpose of this logging mechanism is to allow for the model simulation to generate the prior OI history probabilities, in the absence of empirical distributions. (Or, to put it another way, the simulation of a healthier cohort can be used to generate the incidences of OIs as input to another run of sicker patients, who have advanced further along in time in their disease progression.) In this sense, the user is expected to perform an "initialization run" to produce the probabilities of prior OI histories in the resulting `.out` file. These output tables can then be used as input values into the prior OI histories at entry table for the "actual run."

The specific parameters for the OI history logging mechanism are in the `User` worksheet of the input spreadsheet:

Log Prior OI Hist Probability***		0
		0 = disabled, **1** = enabled
Log OI Hists With # ART Failures		-1
	-1 = N/A (prog start), **0..N** = only spec # failures**	
Log OI Hists With CD4 Counts	Upper Bnd	10000
	Lower Bnd	-1
		-1 < x < 10000
Log OI Hists With HVL Strata	Upper Bnd	10
	Lower Bnd	-1
		-1 < x < 10
Log OI Hists in Pat Mths Without Specific OIs:		
PCP	0	FUNG	0
MAC	0	BACT	0
TOXO	0	OTHER OI	0
CMV	0		
0 = N/A (from prog start), **1** = only without this OI		

The `Log Prior OI Hist Probability` field, when set to `1`, turns the OI history logging mechanism on. When logging is enabled, the program outputs the simulated occurrences of OIs both as a proportion of all patients and in proportion to all patient months. In the former case, the program simply takes at a fixed time (i.e. the first

simulated month) the numbers of OIs each patient has had and the total number of patients alive, and simply divides those two numbers. The result is the proportion of patients at that specific point in time with histories of each OI type.

The computation of OI histories by patient months needs more explanation. In certain contexts, the proportion of patient months better approximates the probability of some patient presenting at some random time to the model with some history of an OI (or multiple OIs). Users of the program can use either of these types of outputs.

The OI history logging mechanism computes the probability of a patient having a prior history of a specific OI by the formula:

$$\frac{\textit{Number of patient months with a history of that specific OI}}{\textit{Total number of patient months}}$$

More precisely, the model simulation accumulates patient months by the patients' current true CD4 and HVL strata; the "total number of patient months" is then really the total number of patient months in a CD4 and HVL bucket. This is the reason the OI history probabilities tables are arranged jointly by CD4 and HVL. Also, the numerator can be more accurately described as those patient months when an acute incident of that OI occurs **or** for which the patient has had that OI in a previous month.

Note that the patient months included in the numerator are always a subset of the patient months in the denominator. That is to say, for every patient month contributing to the denominator, the program does a simple Boolean test to see if the patient has a history of the OI for that month, and if s/he does, contributes a patient month to the numerator. Therefore, most of the discussion below is restricted to the denominator.

The other specific parameters for the OI history logging mechanism are used to further restrict the patient months the model simulation accumulates in the denominator. For example, to consider only patients with CD4 counts less than 25, with no history of CMV, and only up to the month (but not including that month) when they either get a case of CMV or exit the simulation because of death; we set the `Upper Bnd` field for `Log OI Hists With CD4 Counts` to 25, and the `CMV` field in `Log OI Hists in Pat Mths Without Specific OIs` to 1.

The `Log OI Hists With # ART Failures` field deserves special attention, as the rule it effects is somewhat vague. By default, its value is set to -1, which indicates to the model simulation to disregard the number of ARTs in determining which patient months to accumulate. For any nonnegative values in this field, the following patient state diagram is illustrative:
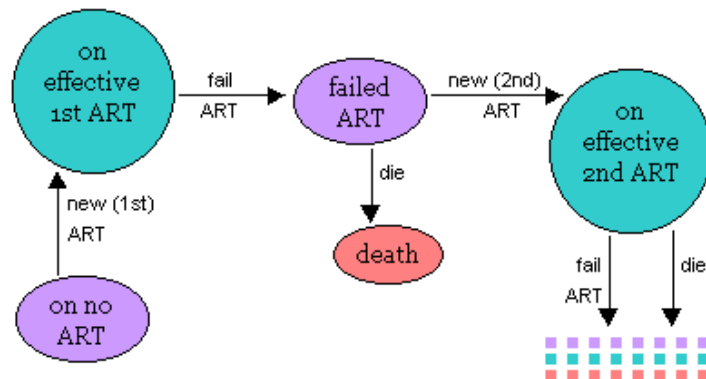
With nonnegative values, the only accumulated patient months are in the purple *on no ART* or *failed ART* states (in the latter case, the patient has been taken off the failed ART, and therefore is also "on no ART"). For example, with the value 2, the simulation model will only accrue those patient months after the patient has failed 2 ART regimens

and until the patient begins a new ART (or exits the simulation with a death event). Currently the model allows the user to specify this "window" of patient months between ART regimens in two limited ways:

1. By a fixed number of months – this is accomplished by utilizing the existing, single `Mths Wait from ART Fail to Next` input value, also in the `User` worksheet. Say we want patients to wait 12 months from the time they're taken off a failed ART, up to the time they're begun on a new ART regimen (if any remaining): we simply set this `Mths Wait from ART Fail to Next` field to 12.
2. Indefinitely – by specifying no additional ART regimens after the failure point we're interested in.

Say we have one hypothetical patient following the timeline below:
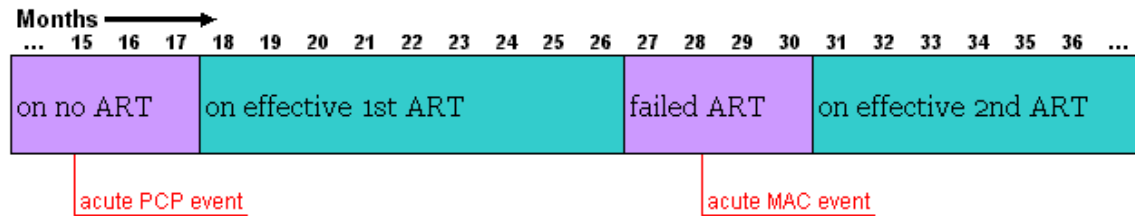
And we set `Log OI Hists with # ART Failures` to 1. The simulation model will then accumulate 4 months (i.e. months #27, #28, #29, and #30) in the denominator. For the OI PCP, all 4 months also contribute to the numerator, as the patient has had a history of PCP since month #15. For the MAC case, only 3 patient months would contribute to the numerator. For all the other OI's, none of the 4 relevant patient months are added to the numerator.

C2. Natural History

The natural history component of the model specifies the fundamental biological assumptions of disease progression. It includes the monthly risk of getting an acute OI event, of dying because of that OI event, and of dying from chronic AIDS causes. In addition, there is the possibility of death from non-AIDS-related causes, stratified by gender and age, including all competing mortality risks not directly attributable to AIDS. Natural history also includes the monthly decline of CD4 count in the absence of effective ART.

CD4 count is the primary driver of disease progression in the model. The patient's actual CD4 stratum determines susceptibility to OIs in the current monthly cycle, as well as the risk of dying that month due to the OI. Actual CD4 also determines the patient's specific risk to chronic AIDS death for the current month. HVL is modeled as a secondary marker of disease progression: a patient's actual HVL influences the rate of CD4 decline, which in turn drives the patient's transitions among the chronic, acute, and death states.

In addition to CD4, risk of OI events and chronic AIDS death varies along a secondary dimension: whether the patient has had a history of any OI event. Stratification by OI history reflects the "attribution" effect found in data analyses performed by the CEPAC team of the Multicenter AIDS Cohort Study (MACS) and elsewhere. The change in chronic AIDS death probabilities attributable to OI History is limited to only occur within a set number of months after the OI event. If the specified number of months has passed since the last severe OI event, the probability will revert back to the standard mortality rate.

During program execution, the program assesses whether the patient contracts any of the specific OIs. If the patient contracts a specific OI, the program performs a second draw in that month to determine whether the patient dies from the acute OI event. If death does not occur, a random draw is performed to determine whether the patient dies from chronic AIDS or non-AIDS causes. None or at most one of these events would occur in any given month. Chronic AIDS death, non-AIDS death, and death from an OI – and in more recent versions of the program, death from drug toxicity – are the only means by which patients exit the model.

In the absence of effective ART, the patient's actual CD4 count is reduced each month by an amount drawn randomly from a normal distribution with some mean and standard deviation. The program allows for stratification of this baseline CD4 decline by both current actual CD4 and HVL. In addition, each person has their own baseline CD4 decline standard deviation multiplier which is drawn once for each person at birth. This number changes the standard deviation of the monthly CD4 decline by a factor.

Less explicit in the program is the assumption of HVL progression. In the natural history case, a patient's HVL remains stable at a HVL "setpoint." A patient's current actual HVL is decreased by effective ART; failure of ART leads to actual HVL returning up to, and no higher than the HVL setpoint. In the absence of applicable therapy, HVL remains at the setpoint value until the patient's death. The only exception to this is while the patient is in the acute HIV stage, which is further described in the HIV testing section. There is no movement in HVL levels at the end stage of AIDS progression.

C2a. Monthly Incidence of OI

Monthly incidence of each OI is specified as an independent probability. The program allows for at most one acute OI in any given month. To draw which one OI occurs in the month, the program follows the procedure:
1. take the probability $P_0(i)$ for each OI i
2. convert OI probability to a rate, modify the OI rate by factors from OI prophylaxis (discussed later), and convert the OI rate back to a monthly probability
3. calculate the probability of no OI during the month as: $P(\text{no OI}) = \prod (1 - P(i))$
4. calculate the probability of having an OI during the month: $P(\text{OI}) = 1 - P(\text{no OI})$
5. if an OI is determined to occur in the month, determine which OI:
    a. calculate monthly rate of having each individual OI and none of the other ones:
        $$P(\text{indiv OI}) = P(i) * \prod (1 - P(j))$$
    b. normalize the individual OI probabilities by dividing by their sum
    c. determine which OI occurs by randomly drawing from this distribution

C2b. Fraction of Benefit

Historically, the fraction of benefit mechanism was incorporated into the U.S. program as a possible means to reflect varying efficacy of reconstituted CD4 cells from ART. To date, this mechanism has generally not been used in analyses and left in the program for legacy reasons.

The function of fraction of benefit (FOB) is given by the formula:

$$\text{Prob}_{mth} = \text{FOB} * \text{Prob}_{curr\text{-}CD4} + (1 - \text{FOB}) * \text{Prob}_{min\text{-}CD4}$$

which means that the probability of a given event in the current month is the weighted average of probabilities defined by the patient's current and minimum actual CD4 strata. The types of events for which the FOB may be modified are the monthly incidence probabilities of each OI type, of death from each acute OI event, and of chronic AIDS death.

C3. Mortality

There are many possible causes of death for the patient that must be evaluated for each simulated month. These include death from acute OIs, chronic AIDS causes, non-AIDS causes, and drug toxicity. In order to properly determine if death occurs in a given month and to fairly attribute the cause, these independent probabilities must be evaluated together. During mode execution, the probability of each type of mortality occurring for that month is determined, and if it is greater than zero, is added to a list of mortality risks. Once all mortality risks for that month have been determined, mortality is evaluated with the following algorithm (similar to the one used for acute OIs) –

1. take the probability P(*i*) for each Mortality Risk *i*
2. calculate the probability of No Death during the month as: $P(\text{No Death}) = \prod (1 - P(i))$
3. calculate the probability of mortality during the month: $P(\text{Death}) = 1 - P(\text{No Death})$
4. roll for death occurring, and if so, determine the cause of death -
   a. calculate monthly rate of each individual cause occurring:
      $$R(i) = -\ln(1 - P(i))$$
   b. normalize the individual Mortality rates by dividing each by their sum
      $R\_normalized(i) = R(i)/(\Sigma\ R(i))$
   c. determine the attributable cause of death by randomly drawing from the normalized distribution of rates

C4. Clinic Visits and CD4 and HVL Tests

HIV disease progression and treatment efficacy are monitored through regular assessments of patients' OI histories and observed CD4 and HVL. The OI histories are determined at every clinic visits, based on an inputted probability of observance. The CD4 and HVL tests, when available, are normally given during the clinic visit as well. They also may be given at special times due to the patient's ART treatment programs. The patient's observed health state is then uses to create or modify their treatment program according to the specified criteria.

Each clinic visit incurs a cost in the month in which it occurs. Additionally, the occurrence of either a CD4 or HVL test incurs an additional cost.

C4a. Scheduling of Clinic Visits

If detected as HIV positive upon entry to the model, all patients are generally assumed to undergo a clinic visit to observe their initial OI histories. The user may specify that CD4 and HVL tests should be given at this time as well, or if they should be given later on or not at all (described in the next section). At this initial visit, the program may initiate patients on prophylaxis and antiretroviral therapies as specified by the criteria for treatment. Subsequent clinic visits will then be scheduled at regular monthly intervals.

Other than the initial clinic visit on model entry, patients present to clinic visits based on their assigned clinic visit types. There are three clinic visit types that a patient can be assigned to:
1. those who make the regularly scheduled visits only if they are currently on AIDS treatments (i.e. prophylaxis or ART)
2. those who make the regularly scheduled visits if they are currently on AIDS treatments, or the special clinic visit in the event of an acute OI
3. those who make the regularly scheduled visits regardless of current AIDS treatment status, or the special clinic visit in the event of an acute OI

In addition to the regularly scheduled clinic visits, certain events may trigger an emergency clinic visit to occur in that month. An emergency clinic visit works exactly like a regular one, and at most one clinic visit can occur in a given month. A user specified parameter determines whether an emergency visit should cause the next regular visit to be rescheduled based on the interval or if the existing schedule should be maintained.

The occurrence of an acute OI is one of the events that may trigger an emergency OI. The user can specify that certain patients do not have emergency clinic visits for OIs; and the associated OI costs, OI-related death costs, and OI-related mortality can be varied based on whether this special clinic visit occurs. The specific acute OI that leads to the clinic visit is always added to the patient's observed OI history. If an OI does not trigger a clinic visit, a probability can be specified for whether or not it will be observed at their subsequent clinic visit.

In version cepac40a and before, acute OIs were the only events that could trigger an emergency clinic visit. In this latest version, emergency clinic visits can also be triggered when a severe ART toxicity or prophylaxis toxicity occurs, when ART failure criteria is met, when TB treatment is scheduled to begin, and at the conclusion of TB

treatment. This was done in order to make all of the diagnostic testing and treatment changes occur at the clinic visit. Regularly scheduled CD4 and HVL tests can also trigger a clinic visit if they are scheduled to occur before the next clinic visit. The only diagnostics that can occur outside of the clinic visit are the special CD4/HVL tests described below.

C4b. CD4 and HVL Tests

Regular CD4 and HVL tests are scheduled at monthly intervals, but because they are administered only in the event of a clinic visit, they will trigger emergency clinic visits if they are scheduled to occur before the next regular visit. Both HVL and CD4 tests are typically specified to be done at three-month intervals. Testing frequency can be varied (or even set to not be administered at all) based on the stage of ART that the patient is in:
1. before starting any ART regimen, and with an observed CD4 above the specified threshold
2. before starting any ART regimen, and with an observed CD4 below the specified threshold
3. taken an ART regimen that is not the last one, and less than the specified number of months since init
4. taken an ART regimen that is not the last one, and greater than the specified number of months since init
5. taken the last ART regimen, and less than the specified number of months since init
6. taken the last ART regimen, and greater than the specified number of months since init
7. after the patient has been observed to fail the last available line of ART

Scheduling of either the next CD4 or HVL test is done by computing from the current month of testing when the subsequent test should occur. The basic intuition behind this structure is that it reflects a doctor's discretion of decreasing or increasing the number of intervening months to the next scheduled month of patient testing. For example, a low observed CD4 level for a sicker patient may warrant more frequent testing; a high observed CD4 for a healthier patient may allow the next CD4 test to be scheduled further out in time. The tests will be given at the next clinic visit after the desired interval between tests has been reached.

The regular schedule of CD4 and HVL testing may be interrupted in a few particular cases. When a patient first starts an ART regimen, the user may specify that CD4 and HVL tests are to be given that month and for a specified number of months after that. The user may also specify that after a test indicating ART failure occurs, additional tests will be given in the subsequent months to confirm the failure. Observation of ART regimen failure can be made by drops in observed CD4 or increases in observed HVL (or, thirdly, by observed OIs). Complete observed failure of the ART regimen is typically defined as two successive failure diagnoses, at which point an emergency clinic visit is triggered. It is also possible to specify that CD4 tests should be given to confirm clinical failure, or that HVL tests should be given to confirm immunologic or clinical failure. These special tests are given outside of the clinic visit, and always occur at the desired month.

The program allows for variability in CD4 and HVL test results. For HVL tests, the operator may specify the probability of each HVL test returning an observed HVL result one stratum higher or lower than the patient's current actual HVL. For CD4 tests, the specified percentage of the actual CD4 value is used as a standard deviation to add observed CD4 count fluctuations from a normal distribution. In addition CD4 tests can be specified with a bias to the observed value.

The user can also set certain conditions to turn off CD4 monitoring for those on suppressive ART that satisfy certain conditions (CD4 threshold and months past ART init). They will resume CD4 monitoring when there is an observed failure of the ART regimen.

C5. Costs and Life Expectancy

C5a. Discounting

Projected costs and life expectancy are discounted on a monthly basis. The program expects the discount factor to be of the form `1 + r`, where `r` is the desired discount rate. For example, a monthly discount rate of 1% would be entered as `1.01` (i.e. `1 + 0.01`) to the program. The program uses this discount factor as the divisor for all

projected costs and life months accrued by each patient. The first monthly cycle for each simulated patient is always undiscounted; subsequent months are discounted by the discount factor, compounded on a monthly basis. The model has a base discount rate input which is used to determine most discounted values. In addition if the multiple discount rate feature is turned on, up to 3 additional discount rates can be displayed for overall costs and life months.

The default monthly discount rate used results in an annualized discount rate of 3%; the discount factor used for the program is 1.00247, calculated by $(1 + 0.03)^{1/12}$, accounting for the conversion from an annualized to a monthly basis. For debugging purposes, the discount rate is often changed to 0% – in this case, the discount factor used in the program is 1.

C5b. Quality of Life

In addition to tracking overall survival, the model also records the patient's Quality Adjusted Life Months (QALMs). Quality of life (QOL) multipliers are specified in the model to indicate the 0-1 valued standard gamble (SG) utilities of the patient's current health state. A baseline QOL value that varies by the patient's age and gender is set for each month, and subsequent QOL values are then multiplicatively applied to it.

In a regular monthly cycle, the patient also accrues a routine care QOL modifier based on their disease progression state. This value is based on their HIV true infection state, if they are detected as HIV positive, the patient's OI history, and their current actual CD4. User specified values will be used if the patient is HIV-negative or undetected HIV-positive. For detected HIV-positive patients with no OI history, the QOL multiplier will be determined by their true CD4 strata. If they have a history of OIs, the lowest of the QOL values for each OI they have a history of will be used. The model also reduces the QALM by 20% in all months where the patient has a history of more than one OI event. In the month of the patient's death, this routine care QALM value is based on the cause of death.

Additional quality of life multipliers will be applied elsewhere in the model, primarily due to toxicity events resulting from treatment options. In the event of minor, chronic, or major toxicity events from OI prophylaxes or from ART regimens, the specified QOL multiplier value is multiplied with that month's base QALM value. Also, QOL multipliers from chronic CHRMs events will be applied monthly to the patients overall QALM value.

C5c. Routine Costs

In each month, patients accrue a monthly routine cost based on their CD4 and OI history state. If a patient has no history of OIs, the cost is based on just the patient's CD4. If a patient has a history of an OI, the cost is based on that OI type and the patient's CD4. In the case of multiple OIs in the patient's history, the highest cost among the applicable OI types is selected for the patient's CD4 stratum. If a patient is HIV-negative, a monthly cost based on their age and gender will be assessed.

In addition to these base routine monthly costs, patients accrue costs for each type of acute event (e.g. acute OI, toxicity, visits, tests, death) as well as monthly drug (i.e. ART, OI prophylaxes) costs.

In addition, each month patients will accrue a general medicine cost, based on their age group. This number can be varied by the care state of the patient. Patients can be in one of four care states (undetected, detected but unlinked, in care, and lost to follow up).

C5d. Month of Death

All patient death events are treated in the program as if they occurred in the middle of the monthly cycle. The primary result of this generalization in terms of accounting is that patient costs and life months (both nominal and quality-adjusted) are halved in the month of death. The quality-adjusted life month is accrued according to the type of event: chronic AIDs, non-AIDS-related, OI-related, or major ART toxicity-related death.

The specific costs halved in the month of death are:
- monthly prophylaxis cost
- monthly state routine cost (e.g. by CD4, OI history, etc.)
- monthly ART treatment cost

Clinical diagnostic and treatment costs are ignored in the month of death since these are considered to be included in the cost of death. All other costs are incurred in full.

C6. OI Prophylaxis

Initiation of prophylaxis for each type of OI is usually specified by the patient's current observed CD4 stratum. Other policy criteria include the patient's minimum observed CD4 as well as whether the patient has or has not had a history of each OI. For the OI criteria to be met, that patient must have a history of at least one of the "has history" OIs and none of the "has no history" OIs. These criteria choices can be combined through either OR or AND evaluation. If OR is selected, meeting any one of the specified criteria will trigger prophylaxis initiation. If AND is select, all of the specified criteria must be met. Additionally, a minimum month number can be set to indicate that nobody can start prophylaxis until that month of simulation.

The stopping criteria for each type of prophylaxis, likewise, can be specified by the patient's current observed CD4 stratum, minimum observed CD4 stratum, and history of OIs. Instead of specifying a minimum month number to stop, the user can set a maximum month number or months since prophylaxis initiating to force a stop of treatment. If either of these parameters is set, they will override the other stopping criteria and cause an emergency clinic visit to occur at the specified month. The program currently reevaluates changes to a patient's prophylaxis regimen during every clinic visit.

The program allows for up to three different lines of prophylaxis drugs for each OI type. A patient will start with the first specified line and will always use that one for subsequent restarts. They will only be switched to the next line in the event of toxicity or if the prophylaxis is specified to cause an automatic switch after a given number of months. If a switch needs to occur, an emergency clinic visit will be triggered that month to enable the treatment change. If no more lines are available, the patient will stop taking prophylaxis for that particular OI.

Patients on an OI prophylaxis gain a protective benefit from that particular OI (and potentially other OIs). The prophylaxis' efficacy is specified as a rate multiplier by which the patient's monthly risk for that OI (and possibly other OIs) is reduced.

Each line of prophylaxis drug has its own independent risk of minor and major toxicity. The types of toxicity are specified by some probability of occurrence and a fixed time after prophylaxis initiation when it should occur. The toxicities are additively combined to first determine if no toxicity occurs. If toxicity is found to occur, then a distribution of the individual probabilities is used to determine whether the toxicity was major or minor. Minor and major toxicity events incur increased costs and decreased QOL in the month of the event. Major toxicity also has a specified probability of mortality that will be evaluated after the toxicity is determined to occur. Both major and minor toxicities may trigger a switch to the next line of prophylaxis; the user can individually specify whether or not each type should cause the switch.

Prophylaxis resistance, likewise, is assessed by a resistance probability at the time of initiation. If resistance does occur, the effect begins at the specified number of months after initiation. Prophylaxis resistance causes the monthly risk of that particular OI to be increased by some specified percentage. Resistance also entails a multiplicative factor by which the cost of OI treatment is increased, as well as a multiplicative factor by which the rate of death from an acute event of that OI type is increased.

C7. Antiretroviral Therapy

Antiretroviral therapy, or ART, in its simplest form can be thought as just some intervention that interrupts a patient's natural history CD4 decline and provides some virologic benefit in the form of decreased HVL levels.

Because of a paucity of data for individual ART drugs, the ART mechanism deals with aggregate regimens – component drugs of each therapy are not tracked. Moreover, there are currently no explicit means in the program to explore drug-level interactions (e.g. specific drug toxicities and drug-drug cross interactions either within the same class of drugs or drugs of different classes). Costs, toxicities, QOL impacts, and virologic suppression are expressed at the regimen level.

The program currently allows for up to ten lines of ART therapy, or ART regimens, to be administered sequentially. A patient will be 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, the patient will be started on the first specified regimen. For most subsequent treatment changes, the patient will be switched to the next specified regimen. The only exceptions to this are for Structured Treatment Interruptions (STI) or restarting after being Lost to Follow Up (LTFU); both discussed below.

A patient will be evaluated to start an ART regimen based on the following criteria – current CD4 count, current HVL strata, a combination of CD4 count and HVL strata, observed OIs since the previous regimen, or CD4 count and observed OIs. There is also a criteria that can be set which skips that line of ART if the maximum months(calendar time) to start that line has passed. Since this structure enumerates the logical combinations of the individual criteria, they can be specified and evaluated independently of each other. If any of the specified criteria are met, the patient will be started on that ART regimen. The first regimen criteria will be evaluated at each clinic visit until they are determined to begin. For subsequent regimens, the starting criteria will be evaluated right after the patient is taken off of the previous regimen and at all future clinic visits.

The model makes a distinction between patients actually failing an ART regimen and being diagnosed as failing that regimen. The former can be regarded as the point when the therapy stops providing any substantive biological benefit to the patient. The latter simulates the clinical observation of the regimen's lack of continued benefit, at which point the patient is likely to be taken off that regimen.

Diagnosis of ART failure may be observed by immunologic, virologic, or clinical markers in patients on ART. Diagnosis of immunologic failure may be specified as some percentage drop in observed CD4 from on-treatment peak CD4, when patient's observed CD4 reaches a specified level, or when CD4 reaches the pre-ART nadir level. It is also possible to specify the additional criteria of CD4 level and months since ART initiation that must also be met. Diagnosis of virologic failure may be defined as an observed number of HVL strata increase from the minimum, the HVL reaching a specified level, or the HVL returning to the setpoint value. Additionally, a minimum number of months on ART before virologic failure can be specified. A diagnosis of failure via clinical markers can be made on observation of specified OI types in patients' histories. A total number of observed OIs can be specified along with the number of months on ART before counting as clinical failure. All of the three types of observed failure that are specified will be evaluated independently at each clinic visit, and whichever is met first will cause the diagnoses. The user can set the number of failed tests, indicating that the patient must meet the criteria for failure for that many consecutive CD4 or HVL tests before it truly counts as a diagnosed failure. This count will be reset to zero if a test is given that does not meet the failure criteria. They can also specify that CD4 tests will be used after clinical failure, or that HVL tests will be used after clinical or immunological failure, and the specified number of consecutive confirmatory tests that must be failed before the diagnoses is made. If one of these tests does not meet the failure criteria, the original count of clinical or immunologic failure tests will also be reset to zero.

After failure has been observed, the patient may be taken off the current regimen if its stopping criteria are met. The stopping criteria after observed failure include stopping immediately upon failure, when the CD4 count is below a certain level, after the observance of a severe OI, or after a certain number of months since the observe failure. A minimum month number and months on ART before stopping can additionally be specified. The user may also set a maximum number of months after which the patient will automatically stop the regimen or if they should be stopped after a major toxicity, regardless of whether or not they have been diagnosed as failing it. If specified, these will trigger an emergency clinic visit at the given month or after the toxicity, and cause the regimen to be stopped. As soon as the patient's regimen is stopped, the starting criteria for the next regimen will be evaluated and they may begin the new regimen that same month.

When a patient is initiated on an ART regimen, the patient's propensity to respond on that regimen will be determined. This propensity level will be calculated based on their baseline likelihood, disease state adjustment

factors, and regimen specific adjustment factors. The user may specify a duration for the regimen specific adjustment factor after which the patient will return to their pre-ART propensity. The user may also specify the effects from generic risk factors, and the prevalence and incidence of these risk factors in the population. The resulting propensity indicates their level of adherence to the treatment program and categorizing them in one of three response types – full responder, partial responder, or non-responder. This categorization is determined by user specified propensity threshold levels. Full responders will receive the full clinical effects of the ART treatment while non-responders will receive none of the effects. Partial responders will receive effects that are a weighted average of the levels for full and non-responders, calculated as follows -

- resp_factor = (patient_resp – non_resp_thresh) / (full_resp_thresh – non_resp_thresh)

At ART initiation, the patient will also be assigned into one of three treatment states: fully suppressed, partially suppressed, or failure. Full responders will have the regimen's full probability of suppression, partial responders will have this probability reduced by their response factor, and non-responders will have no chance of suppression. Virologically, a fully suppressed patient's HVL would fall to undetectable levels. A partially suppressed patient's HVL would fall by 1 to 3 HVL strata, but would not fall enough to have undetectable levels of HVL. A patient failing the ART regimen would have HVL either staying at or rising back up to the pre-treatment HVL setpoint level. Currently the program considers the HVL *LO* stratum as virologically undetectable, i.e. suppressed for all intents and purposes.

Each ART regimen has a fixed time period (i.e. a configurable setting called the regimen's *time horizon*) in which the patient would remain in this initially assigned treatment state. After the time horizon, suppressed patients have a monthly risk of transitioning to either the partially suppressed state (via a *late partial suppression* probability) or the failure state (via a *late failure* probability); partially suppressed patients have a monthly risk of transitioning to the failure state (via a separate *late failure* probability). The likelihood of remaining in a suppressed state each month will be reduced by the response factor for partial responders; resulting in an increased rate of late failure. The rate multiplier that is used to determine this probability of late failure is the inverse of the response factor –

- rate_mult = 1 / resp_factor

CD4 response affected by each ART regimen varies according to which of the three treatment states the patient is assigned, their predisposed CD4 response type, and the number of months spent in that efficacy state. The time component is broken up into three user-specified time segments, and the time is reset to zero upon a late stage transition (i.e. late failure). For suppressive states, the CD4 response is specified by a normal distribution that will be drawn from once and used for the duration of that time segment. Full responders will receive the full value of this CD4 change while partial responders will have it reduced by their response factor. For the failure state, a multiplier will be specified to either reduce or increase the natural history decline during that time segment. The first time period for this multiplier is often used to create a time lag before the patient's CD4 declines, and is only applied when late failure occurs. If the patient initially draws failure, they will automatically skip to use the multiplier for the second time period. An additional CD4 standard deviation can be specified that will be applied to CD4 change every month on ART for all efficacy states. The CD4 response will always be bounded by the patient's nadir CD4 level and the rate of decline below it can never exceed the natural history decline.

The ART regimen will also affect CD4 after the patient is taken off of the regimen and up until they start the next one (if ever). When a patient is no longer on ART, a natural history decline multiplier will be used based on the efficacy state of the previous regimen at the time they stopped, and whether or not they have returned to their HVL setpoint. This CD4 response will also be bounded by the patient's nadir CD4 level and the rate of decline below it can never exceed the natural history decline.

The health benefits of patients on ART are primarily provided by the increases in CD4. Efficacy of regenerated CD4 cells can be modified by the fraction of benefit mechanism (FOB), discussed previously. Additionally, a general benefit, referred to as the ART effect, may be specified for patients on ART to reduce the incidence of acute OIs and chronic AIDS mortality. Non-responders will receive no ART effect, and partial responders will receive an ART effect proportional to their response factor that is between no ART effect and the full ART effect.

C7a. ART Toxicity

Patients on ART are subject to drug toxicities that fall under one of three categories: acute minor, acute major, and chronic. All types of toxicities can result in a decrease in quality of life and additional patient care costs. Major and chronic toxicities have additional mortality related effects.

The ART toxicity module also introduces the concept of subregimens which represent interchangeable combinations of drugs within a HAART regimen. Subregimens model the practice of substituting individual drugs of the same class for prevention of or in response to the occurrence of a specific toxicity. Each subregimen of a specific HAART regimen has identical costs and viral suppression efficacy but differ in the possible set of toxicity effects.[1] For each of the toxicities that occur during a particular subregimen, the user can specify which subregimen the patient will switch to in response. They can also specify that the subregimen will automatically be switched after a certain number of months. If either the occurrence of such toxicity or reaching the month limit occurs, an emergency clinic visit will be triggered for that month and the switch will occur.

The following outlines the characteristics of all ART toxicities:

- Probability of toxicity: A one-time probability which determines whether the patient experiences toxicity. The value must be between 0 and 1. Full and partial responders will use this probability of toxicity, while non-responders will have no risk of toxicity.
- Time to toxicity: A distribution which determines which month (since the start of the current ART sub-regimen) that the *probability of toxicity* will be applied
- QOL mult: This multiplier will be applied patient's current QOL for each month that the patient experiences QOL mult effects. Set to 1.0 for no effect. A longer duration of QOL effects explores various types of quality of life impairments due to fat redistribution symptoms and the like. Such quality of life issues include impairments in self-esteem and social relations, anxiety around forced HIV identification, and depression. The program currently does not allow for the percentage reduction in utility weight to diminish over time; this appears to be a reasonable assumption given that no effective treatments for fat redistribution symptoms have been reported and because the symptoms appear to persist even after patients switch ART regimens.
- QOL duration :
  - These determine the length of time that the patient will experience QOL multiplier effects. The model provides 4 options:
    - 1 Month – Effect will stop 1 month after the occurrence of toxicity
    - Switch from Subregimen – Effect will stop when patient switches from the ART subregimen that caused the ART toxicity
    - Switch from ART regimen – Effect will last until patient switches from the ART regimen that the user was on when they experienced toxicity. Switching subregimens within the toxicity causing regimen will not stop the effect.
    - Until Death – The patient will suffer from the effect until death.
- Tox cost: This value is added to total patient cost for each month that the patient experiences cost effects.
- Tox cost duration: The options for toxicity cost duration are the same as QOL duration. Toxicity cost duration functions independently from *QOL duration*.

Additional Features of Major Toxicity:
- Acute Death Probability – this gets applied once immediately upon occurrence of a major toxicity. If the patient dies, then an *Acute Death Cost* is incurred

Additional Feature for Chronic Toxicity
- Time to Chr dth impact (mth): Allows user to specify a time after the occurrence of a chronic toxicity when *Chr dth incr* will apply.

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[1] Users can specify that patients be taken off ART in the event of regimen toxicity, in which case those patients would be eligible for the subsequent line of ART. The implicit ART drug switching described here allows the program to treat patients as continuing on the same line of ART.

- Chr dth incr: Models the increase in mortality due to chronic toxicity. Chr dth incr is a rate multiplier gets included with the persistent chronic death probability for the specified duration. Every month, the cumulative probability is combined with the current non-AIDS death mortality rate.
- Chr dth duration: The options for chronic death rate multiplier duration are the same as QOL duration and functions independently of the other effect durations.

C7b. Resistance Penalty

Patient months spent in the failed or partially suppressed states on an ART regimen contribute to a resistance penalty for subsequent lines of ART. This full penalty is accumulated for full and partial responders, while no penalty is accumulated for non-responders. The resistance penalty is manifested as a rate reduction in the baseline probabilities of suppression and partial suppression of the currently initiated ART regimen.

The program tracks the total cumulative number of months that a patient has spent while not fully suppressed in each of the viral load strata and on each previous line of ART. Users specify the probability reductions for months spent on each prior regimen and in each HVL strata. The prior regimen factors can be specified differently for each subsequent regimen, while the HVL ones are the same for all regimens. For a newly initiated ART regimen, the program modifies the probability for the patient to be fully suppressed in the ART's initial time horizon with the following algorithm –

- o Set the initial probability of suppression for the regimen
- o For each month spent on each previous regimen, use the appropriate resistance factor for the newly initiated regimen and multiply the probability by (1 – resistance_factor)
- o For each HVL strata and each month spent on any non-suppressed ART regimen at that HVL strata, use the appropriate resistance factor and multiply the probability by (1 – resistance_factor)

The same process is then repeated to determine the probability of partial suppression, and the remaining probability is attributed to failure. The model will then use these calculated probabilities as a distribution and draw for the patient's initial ART efficacy.

C7c. CD4 Envelope

Patients generally receive the largest amount of CD4 increase in the first few months on ART. If patients stop and switch ART regimen in quick succession, they may have a better response than if the original regimen had continued to suppress. In clinical trials, the nth-line ART regimen typically starts with patients at lower CD4 counts than would have been the case had they been enrolled promptly after failing the previous line, when their CD4 count was still relatively high. Thus, a CD4 envelope mechanism was added to the model to disallow a patient's CD4 count to increase to a higher level than it would have reached if the 1st line of ART had remained successful indefinitely.

A patient's first successful ART regimen determines the CD4 trajectory that serves as their upper bound over time. This upper bound CD4 envelope would depend on (1) the CD4 count at the time of initiation of the first successful ART and (2) the time since initiation of that first successful ART regimen. Due to the possibility of discordant responses, the CD4 trajectory on the patient's 1st suppressed line may actually have a negative slope. If this is the case, the patient's CD4 envelope is set to have a flat slope and will remain at the initial CD4 value indefinitely. If a patient's CD4 count at any point in time is calculated to exceed the value of the envelope, the CD4 is instead set at the envelope level.

In addition to this overall CD4 envelope, there is also a regimen specific CD4 envelope. This was introduced to handle the case where a patient could repeatedly restart a single regimen and have a better response than if they had remained suppressed on it the entire time. This envelope is reset and established the first time a patient suppresses on each regimen. The patient's actual CD4 will be bounded by the minimum of both the overall and regimen specific CD4 envelopes.

C7d. Structured Treatment Interruption

Structured treatment interruption (STI) allows an ART regimen to be stopped and restarted according to certain criteria and can be specified for any line of ART. The associated ART regimen is initiated per the regular ART starting criteria. Once on ART, the patient is assessed by observed immunologic, virologic, and clinical markers for determining if and when a treatment interruption should occur. When the criteria for the first interruption are met, the patient is taken off the ART regimen. The patient's CD4 and HVL are observed at subsequent clinic visits to alternate re-starting and re-interrupting the administration of the ART regimen. These cycles of treatment interruption are alternated until the patient meets the endpoint criteria for the STI.

When ART is interrupted, the patient's HVL and CD4 behave the same as if they had been taken off of the ART line for regular clinical reasons. HVL trends up towards the setpoint, moving the specified number of stratum based on a monthly probability. The CD4 decreases using the natural history multiplier that is specified by the ART regimen's suppression state at the time of interruption and whether or not the HVL setpoint has been reached.

When ART is restarted in the interruption regime, the regimen's suppression state is redrawn as if it was a new regimen. These probabilities will be affected by any accrued resistance from before the interruption. The subsequent CD4 and HVL responses will be adjusted according to normal ART regimen behavior. Once the STI endpoint criteria are met, the STI cycles will conclude and the patient will be considered to have been diagnosed with observed failure. The patient may then continue on the regimen until the normal stopping after observed failure criteria are met.

C7e. Heterogeneity

Heterogeneity refers to how well patients adhere to their regimens and what their outcomes are based on how well they take their medication. The model assumes that every patient in the model has a propensity to respond to each regimen which is a measure of how well that patient adheres to their prescribed regimens. This propensity is a number from 0 to 1 with 1 meaning that they take all their medication and 0 meaning that they take none of it. This value is used to determine the following list of outcomes upon taking the ART regimen.

Suppression	Probability of suppression
late failure	Probability of late failure
ART Effect OI	Determines the multiplier for probability of getting OI's while on ART
ART Effect CHRMs	Determines the multiplier for probability of getting CHRMs while on ART
ART Effect Mortality	Determines the multiplier for probability of dying while on ART
resistance	Resistance penalty for failing ART (Only full responders get the penalty)
toxicity	Rate Multiplier for probability of Toxicity on ART regimen
cost	ART regimen costs(Full Responders get all the costs while Non Responders get no costs)
restart regimen	Probability restart regimen after failure (Each zone of response gets a flat probability)

For each outcome we define two points (L1 and L2) on the propensity scale which determine three zones of responders. In addition we define two points (O1 and O2) on the outcome scale which are the values of the outcome (e.g. prob of suppression) for people at the L1 and L2 points respectively.

Non Responders
 If the person's propensity for that outcome falls below L1 they are called Non-Responders and always take the O1 value for that outcome. These people take doses which are therapeutically equivalent to lost-to-follow-up.

Full Responders
If they have a propensity above L2 they are called Full-Responders and they would always take the O2 value. They take all their dose (may occasionally miss some doses but not enough to make any difference).

Partial Responders

If their propensity falls between L1 and L2 they are called Partial-Responders and they would take a value which is an interpolation of the O1 and O2 values. These people take incomplete and sporadic doses.
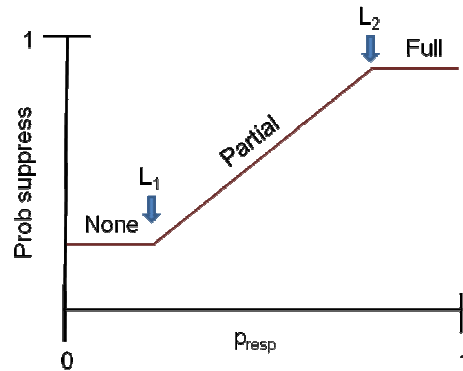
Graph of sample propensity to respond with an outcome (suppress). In this case we are using linear interpolation between L1 and L2

In order to specify the propensity to respond for each type of person we specify several values on the logit scale for different types of people. Each person starts with a baseline general propensity to respond which is drawn from a normal distribution at birth. When the person starts an ART regimen this value is then combined with a set of adjustment factor logits to account for demographics(age, gender), clinical history(CD4, OI History, Prior ART Toxicity), and a factor drawn from normal distribution that is specific for each regimen (so that an individual with a poor general propensity to respond can still have a chance of adhering at least partially to the next regimen, and vice versa).

C7f. Adherence Interventions

The model allows users to define time-dependant adherence interventions which can modify the propensity to respond of the patient for a set duration. The intervention is assumed to start at model start with a duration drawn from a normal distribution. During that duration the person's propensity is increased by another number drawn from a distribution. They will incur both a startup cost for the intervention as well as monthly costs. If the patient goes LTFU while on an intervention and RTC before the duration is complete, they will roll to see if they resume the intervention with an additional RTC booster cost.

C8. Loss to Follow Up

While by default a patient who has been linked to care continues to attend clinic visits and go on ART regimens, some patients can be lost to follow up using the inputs in the LTFU tab. After being lost, the patient no longer attends clinic visits or receives ART. Among those who are lost, they may later return to care (RTC) dependent on their CD4 level or the occurrence of an acute OI. There are three stages to the LTFU algorithm in the model: determining the probability of being lost, determining what happens to the patient while lost, and determining when the patient might return to care and what that care will be. The user may turn off all LTFU and RTC functionality with a single Boolean input on the LTFU tab.

C8a. Determine Probability of LTFU

Patients linked to care are subject to a monthly probability of being lost to follow up. The probability is calculated using logistic regression and differs depending on whether or not the patient has started ART.

The probability of becoming LTFU is specified in the same way as the heterogeneity table for ART. The user can define two periods with different LTFU probabilities depending on if they are on an adherence intervention or not.

C8b. While a Patient is Lost

While a patient is lost to follow up, they are taken off their current ART regiment. However, they may stay on any current OI prophylaxis depending on a user-inputted probability $pProph_{LTFU}$. The probabilities of OI incidence stay at the natural history levels based on current CD4 (although they may be affected by any remaining prophylaxis regimens). If the patient develops an acute OI while lost and does not subsequently return to care, OI treatment will be applied based on a second user input, $pOITreat_{LTFU}$.

The patient's CD4 and viral load trajectory follow the same pattern as when they are taken off ART for other reasons.

C8c. Return to Care (RTC)

A patient will remain lost for at least the user specified *minTimeLost* number of months, after which point they will be eligible for RTC. The one exception is that if they contract an acute OI, they are always eligible for RTC, regardless of whether or not *minTimeLost* has passed. Those who are eligible, either because they have an acute OI or because enough time has passed, will be subject to RTC defined by:

$$pRTC = (1 + \exp(-z))^{-1}$$

where z is again the logit defined by user inputs for background (*L*), CD4 threshold (*M*), and presence of an acute OI (*N*).

$$z = L + M \cdot (CD4 < CD4_{threshold}) + N \cdot (\text{has acute OI?})$$

The $CD4_{threshold}$ is user defined. The coefficient for an acute OI will take one of two different values depending on whether the user has classified that OI as severe or mild for the purposes of RTC.

For those who were LTFU prior to ART initiation and were chosen to RTC, ART initiation will depend on the standard ART initiation criteria, defined by the user. Those who had been LTFU while on ART will be subject to the following algorithm with respect to which ART regimen to continue with:

a) If the patient was on suppressive ART when lost, the patient will restart with the same ART regimen.
b) If the patient was on ART with observed failure and time on failed ART was greater than the user specified number of months, the patient will begin the next available ART regimen.
c) If the patient was on ART with an unobserved failure, the patient will either begin the previous (failed) regimen or the next available regimen based on a user inputted probability.

If the patient is determined to restart their previous regimen upon return to care, there are different parameters for the probability of being suppressed upon restart. These inputs override the ART regimen probability of suppression inputs. They are stratified by both the ART regimen number and the efficacy state of the patient at the time they were lost. This allows for the possibility of either an increased or decreased probability of suppression due to the time spent while lost. If the patient is suppressed after restarting the regimen, they will also skip the efficacy time horizon and could possibly undergo late failure the following month.

C9. HIV Testing

The HIV testing module is aimed primarily to inform priority setting in HIV counseling, testing, and referral (CTR) in a generalized population, and has been integrated into the main CEPAC simulation. This is a new feature in version 4; prior versions treated the HIV testing module as a separate front end to the main treatment model. HIV-negative patients will now go through the same simulation loop as HIV-positive ones, but will skip many of the modules dealing with disease progression. The HIV negative patients will only roll for monthly HIV infection, have HIV tests performed, roll for monthly non-AIDS death, and update survival statistics.

The HIV testing module also introduces the concept of HIV detection in the model. With the HIV testing module disabled, all patients are assumed to be HIV-positive, detected as such, and linked to care. When the module is enabled, HIV-positive individuals are only eligible for care when they become detected as seropositive. Detection

of HIV infection can occur via one of three discrete mechanisms. First, an infected individual can receive a HIV-positive test result within the context of a specific CTR program. Secondly, an infected individual can receive a HIV-positive test result within the context of any other background testing mechanism. Finally, detection of HIV infection can occur because the infected individual seeks medical care for some AIDS-defining complication, i.e. an opportunistic infection.

C9a. HIV States

With the HIV testing module enabled, there are four distinct HIV states for patients: HIV-negative, HIV-positive acute, HIV-positive chronic asymptomatic and HIV-positive chronic symptomatic. The HIV-negative state itself is divided, in some cases, into the high risk HIV-negative and low risk HIV-negative states – primarily to allow for up to two risk profiles for incident HIV infection.

At initialization, the patient is drawn to be either HIV-negative low risk, HIV-negative high risk, HIV-positive acute, or HIV-positive chronic. If the patient is determine to be HIV-positive chronic, they will draw for their initial CD4 and HVL levels from the same inputs as when the HIV testing module is disabled. They will also draw for a history of each OI from the same inputs, and will be set as asymptomatic or symptomatic based on their drawn OI histories. Those determine to be HIV-positive acute will draw from a different set of parameters for their initial CD4 and HVL levels, and will be set to have no OI histories. Additionally, all prevalent HIV-positive patients will draw for entering the model already being detected HIV-positive using a probability based on their HIV state.

Patients that enter the model as HIV-negative will not have any CD4 or HVL values set. They will roll monthly for becoming HIV infected from a probability based on their risk group and age. Those that become infected with HIV are assigned to the HIV-acute state, and draw for initial CD4 and HVL levels from the same parameters as the prevalent HIV-positive acute patients. After their primary acute HIV infection, both incident and prevalent, patients are transitioned to either of the two chronic HIV states, HIV-asymptomatic if the patient has had no AIDS-defining complication (i.e. OI) or HIV-symptomatic otherwise. The time for that transition from acute to chronic state is a user-specified option. In the month of the transition, the patients' current actual CD4, HVL, and HVL setpoint can also be adjusted, again by user input.

C9b. HIV Screening Program

Various types of CTR interventions are modeled by the catch-all screening program functionality of the HIV testing module. This testing program is used to systematically test and refer HIV-positive patients into care in the main simulation. In most cases, the focus is really the evaluation of the various types of screening programs; the background testing and presentation by AIDS complications are used primarily to reflect the competing means of detection of those HIV-positive individuals.

If a screening program is available, it is offered to all HIV-negative and undetected HIV-positive individuals. Every patient will draw from a distribution of testing intervals that will specify how often, if ever, they will be offered an HIV test. Program enrollees leave the screening program when they are detected as HIV-positive or die.
When offered a test, each patient has some probability of refusing that test. After the test has been given, there is another probability of whether or not they return to receive their results.

Individuals in the screening program are given HIV tests with sensitivities, specificities, costs, and QOL adjustments according to user inputs. Note that to make the code simpler, sensitivities and specificities are entered as the probabilities of the HIV test returning a positive result for the HIV-negative and HIV-positive states. Moreover, costs and QOL adjustments can be specified for either positive or negative test results for each of the HIV states. A false negative tests results in a truly infected patient not being detected, while a false positive results only in additional costs and QOL adjustments. It is assumed that the false positive cases will be properly identified before undergoing further treatment, and that the costs and QOL parameters will account for all of the unnecessary diagnostics that may have been performed.

Upon being detected as HIV-positive, there is an addition cost and QOL adjustment in the month of detection. All patients will be scheduled to attend clinic that month, and possibly be scheduled for CD4 and HVL tests as well.

The user can set an age to stop regular testing.

Background testing can be specified similarily to regular testing. They will be offered each month. The user can specify the probability of accepting the test, returning for the results and sensitivity, specificity of the test, costs associated with the test and a start age to be offered the test. They will also have a separate probability of linkage from the background test.

C9c. Accounting of Costs and Life Expectancies

With the addition of new patient HIV states, new monthly cost and quality of life inputs were added for the HIV-negative and undetected HIV-positive states. All detected HIV-positive individuals incur the same costs and life expectancies as they would without the HIV testing module enabled. The HIV testing module specifies the monthly cost and QOL for HIV-negative patients and undetected HIV-positive patients. All costs and life expectancies are discounted by the single discount factor of the simulation run.

The HIV testing module also associates user-specified costs with the following events: startup of the screening program, not returning for individual program tests, detection of HIV-positive status, the administration of a positive background HIV test, administration of each screening program HIV test, and either positive or negative results from a screening program HIV test.

C9d. Stopping Rule for Cohort Simulation

Without the HIV testing module enabled, each simulation ends after running through the specified number of patients in the cohort. With the testing module enabled, this number will include all of the HIV-negative patients as well. Simulations involving very low HIV prevalence rates, incidence rates, or both may result in very small numbers of HIV-positive individuals – which usually leads to unstable cost and life expectancy estimates. To address this, a program option was added to have the simulation stop only after the specified number of patients in the cohort become HIV-positive and a total cohort size is reached, or an absolute max cohort size is reached.

C9e. Lab Staging Module

If the Lab Staging module is turned on, the patient has an extra set of steps to run through after getting their HIV test before they can get a clinic visit and be linked into care. After getting a true positive result on their HIV test, patients are then offered a CD4 Test (Lab Staging). In the same way that the testing module works, the patient can accept or refuse the test, and choose whether to come back for their results. If they return for their results they roll for a chance to link into care based on their observed CD4.

C9f. Pre-Exposure Prophylaxis (PrEP)

Built into the CEPAC Model's HIV Testing framework are a number of structural features that permit us explore outcomes associated with different HIV counseling, testing, and referral program designs and events. These include features to simulate prevention counseling, behavioral response (among both HIV-infected and HIV-negative persons, as well as between both tested and untested persons), and the aftermath of false-positive reports in uninfected persons. These features can also be employed to simulate a PrEP intervention. Specifically,

- The HIV Testing module permits us to assign unique costs, quality of life effects, and behavioral responses (e.g., acceptance and return rates), to the first-time HIV test. In simulating a PrEP intervention, these are used to assign a fixed cost to treatment initiation.

- The HIV Testing module permits us to modify test periodicity and return rates. In simulating PrEP, these are used to simulate the likelihood that individuals remain adherent to prophylaxis over time.

- The HIV Testing module's counseling component is adapted to accommodate PrEP uptake

- The HIV testing module includes a feature that assigns a quality of life decrement to capture the impact of false positive results. In simulating PrEP, we use this feature to assign both a quality of life decrement and cost to possible PrEP toxicity.

Users can specify variables governing the provision, suspension, performance, and cost of counseling services and PrEP. This framework has the flexibility to capture a range of program intensities, from no intervention to basic risk counseling and more elaborate behavioral and chemoprophylactic prevention. For patients receiving PrEP, the model tracks changes in risk-taking behavior, toxicity, occurrence of drug resistance in individuals who develop HIV infection and are subsequently treated with ART, quality of life, and cost of HIV-related care. The model can also capture the clinical and economic outcomes associated with HIV transmission, detection, and referral activities. The model estimates lifetime infection risk under alternative PrEP scenarios. The model also conveys information to the Disease Model on HIV infection status; whether and when HIV detection, follow-up, and linkage to care occur; and whether an infected person had previously received PrEP. The Disease Model then combines this information with its own output on the timing of complications to establish whether, when, and how an individual case of HIV infection will be treated.

C10. Tuberculosis (TB)

Tuberculosis is treated separately from the other OIs to reflect the different short-term and long-term impacts on outcomes for patients with HIV infection.
See Appendix 1 for a detailed description of the TB Module.

C11. Chronic Events (CHRMs)

In addition to the AIDS complications discussed previously, the HIV virus also causes an increase risk of cardiovascular disease and other serious chronic medical conditions. As better and more readily available antiretroviral treatments have lessened the mortality from OIs and acute AIDS complications, these chronic conditions have become a much more serious problem for HIV infected patients. Starting in version cepac43a of the model, the CHRMs module was developed to simulate the risks from such conditions. The CHRMs module is named for the four main categories of these – cardiovascular, hepatic, renal, and malignancy. While the module can be used to model any other chronic condition, these four categories are considered to be the most important and will be the default ones used in the model.

The prevalence and incidence of CHRMs are also modeled for HIV-negative patients in the programs. HIV-negative and HIV-positive patients will have different probabilities of developing CHRMs and mortality, but will incur the same costs and utilities if they do occur. Once a patient develops one of the CHRMs conditions in the model, they will have it until death. The effects of each CHRM may be specified to vary over time to simulate different periods of the condition's progression.

At model entry, the program will determine for each patient whether or not they will begin simulation with each type of CHRM. These prevalence probabilities will be based on the type of CHRM, gender, age, and true CD4 strata; and may be further modified by logit adjustments for generic risk factors. The stage of the condition (the number months since it began) will also be determined for prevalent cases. The algorithm for determining the probability of CHRMs prevalence is –

1. Set the base probability of prevalent CHRM by HIV-state, CD4, gender, and age
   - probCHRM
2. Convert the probability of CHRM (prevalence to a logit

- logitCHRM = ln(probCHRM / (1 - probCHRM)
3. For all generic risk factors that the patients has, add the corresponding logit adjustments
    - adjlogitCHRM = logitCHRM + RF1 + RF2 …..
4. Convert the adjusted logit back to a probability
    - adjprobCHRM = 1 / (1 + e^(-1 * adjlogitCHRM))

In each month of simulation, the program will evaluate whether or not the patient develops any of the CHRMs that they do not already have. These incidence probabilities will also be based on the type of CHRM, gender, age, and true CD4 strata. The probabilities will further be modified by a rate multiplier for the heterogeneity based ART effect if they are on ART treatment, and logit adjustments for the patient's generic risk factors and history of other CHRMs. The algorithm for determining the probability of CHRMs incidence is –

1. Set the base probability of incident CHRM by HIV-state, CD4, gender, and age
    - probCHRM
2. If on ART treatment, apply the CHRM specific ART effect rate multiplier
    - adjprobCHRM = 1 – (1 – probCHRM) ^ rateMult
3. Convert the adjusted probability of CHRM prevalence to a logit
    - logitCHRM = ln(adjprobCHRM / (1 - adjprobCHRM)
4. For all generic risk factors that the patients has, add the corresponding logit adjustments
    - adjlogitCHRM = logitCHRM + RF1 + RF2 …..
5. For all other CHRMs that the patients has, add the corresponding logit adjustments
    - adjlogitCHRM = adjlogitCHRM + OC1 + OC2 …..
6. Convert the adjusted logit back to a probability
    - adjprobCHRM = 1 / (1 + e^(-1 * adjlogitCHRM))

Once a patient develops a CHRM, they will incur a risk of mortality, associated cost, and QOL modifier each month. As mentioned before, these effects will all depend on how long the patient has had the condition. The user can specify these time periods independently for each individual CHRM and each of its effects (mortality, cost and QOL). The probability of death will be stratified by the type of CHRM, time period, gender, age, and true CD4 strata. The risks of mortality from multiple CHRMs will be additively combined and the cause of death attributed using the same algorithm described in the Mortality section (C3).

Costs and QOL multipliers are both stratified by the type of CHRM, time period, gender, and age. Costs from multiple CHRMs will be treated independently and additively combined. QOL multipliers will also be applied independently for each CHRM, resulting in a multiplicative combination of their effects. In the month of death, there will also be an additional cost and QOL multiplier if the cause of death was attributed to one of the CHRMs. These values are only stratified by the type of CHRM.

If the Orphans model is turned on we can use CHRMS as a proxy to represent orphaned children of patients in the model. In the orphans model, CHRMS1 represents the firstborn child, CHRMS2 the secondborn and so on. There is a restriction that the patient can only have the second child if they already have a first child and so on. In adition it is possible to specify preexisting ages of children for patients entering the model as prevalent chrms with some time since infection. The model will also generate an additional Orphans file with detailed information about the orphans in the run.

C12. Pediatrics

The model can support a cohort population of any age range, but the patient's age is not a major driver of outcomes. The only age dependent calculations in the model are the probability of non-AIDS death, incidence of CHRMs, routine care costs, and baseline utility (QOL). While this is sufficient for a population that is almost entirely adults, it does not accurately represent disease progression and treatment effects in children. Beginning in version 43a of the model, the Pediatrics module was added to more accurately simulate children. When enabled, this module uses

different inputs and calculations during childhood. If disabled, the model will revert to the old behavior and all cohorts (including children) will use the adult inputs.

C12a. Initialization and Pediatric Stages

Activating the Pediatrics module will cause every patient in the cohort to begin the simulation at a young age, specified by drawing from a distribution. At initialization, they will draw for being HIV-positive or HIV-negative, and whether they were infected intrauterine (IU) or intrapartum (IP) if HIV-positive. They will also draw for several maternal characteristics that are tracked during simulation. These are discussed more in the Maternal Status section. Instead of starting with an initial absolute CD4 count, Pediatric patients will draw for an initial CD4 percentage. Patients will also draw for an initial HVL strata value that will be their setpoint during childhood.

Patient simulation is broken up into three chronological stages – early childhood (0-4 years old), late childhood (5-12 years old), and adulthood (13 years old and beyond). During early childhood, the patient's CD4 percentage and age are the primary drivers for disease progression and treatment policy. Their HVL level has no health impact during this time period, and is often ignored for clinical care decisions. During late childhood, the patient's absolute CD4 count and HVL strata are the primary drivers for simulated events. This is similar to how the model functions for adults, but different input values can be specified for use during the late childhood period. Once the patient reaches age 13, they will subsequently use all of the adult input values and the model will function exactly as it would without the Pediatrics module enabled.

The transition from early childhood to late childhood at age 5 requires some special behavior in the model. The patient's CD4 percentage will be converted into an absolute CD4 count. This is done by drawing from a normal distribution, with the mean and standard deviation depending on the patient's CD4 percentage. If the patient is on suppressive ART, a CD4 slope for the current time period will also need to be drawn. Additionally, the patient will draw for a new adult HVL setpoint using a transition matrix that specifies the likelihood of each new HVL value occurring given the previous one. The prior monitoring state and CD4 envelopes are also reset to avoid any continuity problems in the model. No special behavior is required for the transition to adulthood at age 13.

C12b. Disease Progression

During early childhood, the patient will have a natural history CD4 percentage decline each month that is stratified by their type of infection (prevalent or incident), age, and current CD4 percentage. The monthly probability of chronic AIDS death will be calculated based on the patient's OI history, age, and CD4 percentage. The probability of non-AIDS death is stratified by age and gender like the adult inputs, but at a finer granularity of time segments. Monthly probabilities of acute OIs are stratified by OI type, prior history of that OI, age, and CD4 percentage. Mortality from OIs is stratified by OI type, OI history, whether or not they are treated, and age.

All other disease progression transition probabilities in the model are specified using the regular adult input values. Since many of these occurrences are determined by CD4 strata and not CD4 percentage, the model must map the patient's early childhood state to a CD4 strata value. This mapping is user-specified and is dependent on both the patient's age and CD4 percentage. Such a calculation enables all of these other probabilities to be driven by both CD4 percentage and age without requiring new input structures or data values.

During late childhood, the patient will use the same CD4/HVL based natural history CD4 count decline inputs that adults use. The inputs for chronic AIDS mortality, non-AIDS mortality, acute OI incidence, and acute OI mortality will have the same structure as their adult counterparts, but may be redefined with different input values. All of the adult input values will be used after the transition to adulthood.

C12c. ART Treatment

The policy decisions to start a regimen, observe failure, or stop ART all function differently in the Pediatrics module. Most notably, during early childhood the patient's observed CD4 percentage count is used for immunologic criteria instead of the absolute CD4 count. These criteria are used in addition to the virologic and clinical criteria that are specified for adults. The user can also specify different testing intervals for when CD4 percentage and HVL strata are observed during early and late childhood.

An ART regimen can be specified to start if the patient's CD4 percentage falls within a given range, if the CD4 percentage and HVL are within given ranges, or if the patient has reached a given age. Failure can be observed if there is a decrease of a given number of CD4 percentage points from the maximum, if the CD4 percentage drops below the pre-ART nadir, or if the CD4 percentage falls within a given range. Stopping an ART regimen can be specified to occur at a given patient age or if the CD4 percentage count drops below a given level after failure has been observed.

The impact of ART treatment on disease progression is also different in the Pediatrics module. During early childhood, the ART effects for the probability of chronic AIDS death and acute OI incidence are stratified by CD4 percentage and time on the ART regimen. In late childhood, the ART effect input structure is the same as what is used for adults, but the parameter values can be specified differently. For all other transition probabilities, the adult inputs for ART effects will be used. The development of ART toxicity and the accumulation of resistance penalty is the same as for adults. This was done to simplify the Pediatrics module and may be changed in the future.

For each ART regimen, the probably of initial suppression, late failure, and costs can be specified separately for early and late childhood. During early childhood, the CD4 percentage increase while suppressed is stratified by time on ART, age they started art, and CD4 response type. During late childhood, the CD4 count increase uses the same structure as the adult inputs but can have different parameter values. The decline multiplier for failing ART, the decline multiplier off ART, and the HVL change rate use the same input structures as adults but with different values for early and late childhood. The overall and regimen specific CD4 envelopes are used during early childhood, but will be based on CD4 percentage instead of absolute CD4 count. These are reset at the transition to late childhood and the next suppressive ART regimen establishes the absolute CD4 count envelope.

C12d. Maternal Status, Transmission, Simplified Behavior, and Costs

As mentioned previously, some state for the mother's status will be stored and updated along with the child's health state. Initially, the mother's HIV state and her treatment status will be drawn from a distribution. If the mother is on ART she can be in either the suppressed or non-suppressed state. The type and duration of breastfeeding will also be determined. Mothers that are HIV-negative will have a monthly probability of becoming HIV infected. All mothers will have of monthly probability of death based on their HIV-state and treatment status. Each month the mother can also transition between being off ART, on suppressed ART or on failed ART. No other changes to the maternal state can occur, and their health is assumed to be relatively constant during the life of the child.

This maternal state in turn affects the health state and risk factors of the child. If the mother is HIV-positive and the child HIV-negative, there is a monthly probability of postpartum (PP) infection for the child based on breastfeeding status, the maternal HIV state, and maternal treatments. Rate multipliers for the child's risk of mortality will also be applied if the mother is no longer alive or if the child is only being replacement fed.

To facilitate experiments where there is limited data on the natural history of children, a simplified Pediatrics behavior can be enabled. This will cause all of the regular mortality risks to be ignored and only the simplified Pediatric life tables will be used. These are stratified by the child's age, gender, maternal HIV-state, and the child's HIV-state. When the simplified behavior is disabled, these inputs will be ignored.

In order to conduct a basic cost-effectiveness analysis within the pediatric model, basic monthly cost inputs were added starting in version 44c. One of six user-specified monthly costs is accrued each month during the simplified pediatric model based on which of the following six states the patient is in:
- HIV negative, unexposed,
- HIV negative, exposed to HIV,

- HIV positive (IU/IP), off ART,
- HIV positive (IU/IP), on ART,
- HIV positive (PP), off ART,
- HIV positive (PP), on ART.

C12e. Early Infant Diagnosis (EID)

The model can also be used to model detailed testing of infants in the Pediatrics Model. See Appendix 2 for a detailed explanation.

C13. SubCohorts

When doing CEPAC analysis the run time can be very high due to the number of patients run through the model. The subcohorts module can be a useful diagnostic tool to determine the minimum number of patients needed for a particular run. The model has the capability to run multiple subcohorts of differing amounts of patients in a single run. The life months and costs of each subcohort will then be output in the .out file. The noise of each subcohort can then be analyzed to determine at which cohort size the run will converge. If fixed seed is turned on the subcohorts will be correlated i.e. patient one will be the same in all subcohorts etc.

C14. Community Viral Load(CVL)

We define Community viral load as an instantaneous measure of the amount of HIV virus in the population of interest at a given moment in time. The community viral load at time t , *CVL(t)*, is given by:

$$CVL(t) = N(t) * \sum_{\forall s \in S} p_s(t) * VL_s$$

$N(t)\equiv$ size of the HIV-infected population at time t.
$S\equiv$the set of HIV RNA strata; (s is a specific HIV RNA stratum, $s \in S$)
$p_s(t)\equiv$the proportion of the population in HIV RNA stratum s at a given time t
$VL_s\equiv$ the average per person viral load in HIV RNA stratum s.

If the CVL feature is enabled, we can use the model to estimate the number of primary transmissions attributable to the modeled cohort.

We can compute *X(m)*, the total number of primary HIV transmissions that occurred in any month as

$$X(m) = \frac{1}{1200} * \sum_{\forall s \in S} C_s(m) * X_s$$

where X_s is the number of primary HIV transmissions per 100 person-years spent in viral load stratum s. The Transmission rate can be modified by certain multipliers such as risk category, age and calendar month.

C15. Detailed Costs Output

If enabled the model will print out a detailed costs summary file (.cout) containing detailed costing information of all the costs in the model stratified by HIV status, Obsv CD4 strata, HIV Care state, and ART state.

D. Monthly Cycle of the Model

Because all events in the program occur discretely, it is important on occasion to keep in mind the order of evaluation in each month of a simulated patient. Taking all of the mechanisms described above together, each regular monthly cycle in the program involves the following steps, in this order:

1. if the patient is HIV-negative
    - determine if infection occurs this month, if so set the infected state to acute, roll for initial CD4 and HVL, and schedule the initial clinic visit
2. if the patient is in the acute HIV state:
    - if the patient has reached the number of months to transition to the chronic HIV state, set to the new state and apply the HVL and CD4 changes for the transition
3. determine if any new CHRMs occur and update state with the effects of all existing CHRMs
4. if the patient is on an ART regimen, see if an associated toxic event occurs
5. if an ART major toxicity event occurs, add the associated risk of mortality for all prophylaxis the patient is currently on, see if an associated toxic event occurs
6. If a prophylaxis major toxicity occurs, add the associated risk of mortality determine if there is any change to the patients TB state
    - roll for possible initial infection, reinfection, relapse, or spontaneous resolution depending on the prior state
    - count any new active infection as an acute OI for the month, add the risk of acute/extended TB mortality, and determine if acute TB leads to HIV detection and schedule the initial clinic visit
7. if acute TB did not occur this month, determine if an acute OI event will occur
    - if an OI event occurs, add the associated risk of mortality
    - if the patient is not detected as HIV+, determine if the OI causes patient detection and schedule the initial clinic visit
8. determine if death occurs this month
    - Account for risk of non-AIDS and chronic AIDS death
    - if death occurs, determine the cause and stop the patient simulation
9. update the patient's CD4 and HVL for the month
10. if the patient has not been detected HIV-positive, determine if the patient gets detected by screening
    - if the detected by regular or background screening, schedule the initial clinic visit
11. determine if the patient becomes lost to follow up or returns to care
    - cancel scheduled clinic visits and stop treatments if they become lost
    - reschedule a clinic visit for the current month if they return
12. for any ART, prophylaxis, or TB treatment the patient is on
    - determine if any efficacy changes (suppression, resistance, failure) occurs in the drugs
13. determine whether a regularly scheduled or emergency clinic visit should be performed this month
14. determine if a CD4 test should occur this month and perform if so
    - exceeded month interval since prior visit and clinic visit is occurring this month
    - triggered by ART initiation or needed for ART failure confirmation
15. determine if an HVL test should occur this month and perform if so
    - exceeded month interval since prior visit and clinic visit is occurring this month
    - triggered by ART initiation or needed for ART failure confirmation
16. if clinic visit will occur this month, perform the standard clinic visit tasks
    - observe acute OIs and determine if prior OIs are observed
    - determine if the current ART regimen is observed to have failed, should be stopped, or if the next line should be started
    - determine if OI prophylaxis should be stopped or started
    - determine if TB prophylaxis or treatment should be stopped or started
17. update the patient's accumulated costs, life months, and quality adjusted life months
18. increase the patient's age, in months

E. Program Inputs for the Model

Below is a description of all input fields in the `cepac_inputs.xls` spreadsheet. (Because fields in the `cepac_data.xls` workbook should map directly to those in the `cepac_inputs.xls` workbook, no separate description of those inputs are given.)

Section	Table/Field	Description	Program Variables
RunSpecs worksheet			
Shortcuts & Miscellaneous	Set Specifier for Run	Specifies which set of runs this particular run belongs to in the simulation program's batch of runs, used for calculated ICERs within groups in a batch of runs.	runSetName
Shortcuts & Miscellaneous	Population/Cohort Size	Specifies the number of patients in a single simulation run.	numCohorts
Shortcuts & Miscellaneous	Annual Discount Factor	Specifies the exponential rate at which monthly costs and QOL values for the patient are discounted. This factor is converted into a monthly basis, which is then used in the program. To get undiscounted results, use the value 1.	discountFactor
Shortcuts & Miscellaneous	Data Set Shortcut	Specifies which set of default input values from the `cepac_data.xls` spreadsheet should be used for many of the tables in the inputs workbook.	
Shortcuts & Miscellaneous	Maximum Patient Actual CD4	Specifies the maximum actual CD4 patients can attain in the simulation. Use the value –1 for no cap on maximum CD4.	maxPatientCD4
Shortcuts & Miscellaneous	Enable CD4 Envelope for Subsequent ARTs	Specifies whether a CD4 envelope will be applied to all subsequent ART regimens following the first successful regimen.	enableARTCD4Envelope
Shortcuts & Miscellaneous	Longitudinal Log of Cohort	Can be either the values 0, 1, 2, or 3. A non-zero value specifies that summary information about the patient cohort longitudinally over time should be included in the run's .out output file. A value of 1 produces detailed summary information on a monthly basis. A value of 2 produces abridged summary information on a monthly basis. A value of 3 produces detailed summary information on a yearly basis.	longitLoggingLevel
Shortcuts & Miscellaneous	Log as "First" OI in Simulation	Specifies a set of OIs out of which each patient may be reported as having the "first" OI in the outputs. Note that this distinction between those who have and have not encountered their "first" OI is used primarily in the longitudinal log outputs. This "first" OI setting currently does not affect a patient's disease progression.	firstOIsLongitLogging firstOIsChronicLongitLogging
Shortcuts & Miscellaneous	Time Point 1/2/3 (Month) to Record ART Efficacy	Specifies at what number of months after ART initiation to record selected ART regimen efficacy information.	monthRecordARTEfficacy
Shortcuts & Miscellaneous	Random Initial Seed by Curr Time	Can be either the value 0 or 1. A value of zero specifies the use of the same starting seed for the random number generator in the program, and that it should be reseeded for each new number based on the program location, the patient number, and the month number. A value of one specifies the use of the current system time as the starting seed.	randonSeedByTime
Shortcuts & Miscellaneous	Fractions of Benefit, OI	Used to linearly combine monthly OI probabilities for each patient month based on the current actual CD4 stratum and the minimum actual CD4 stratum.	OIsFractionOfBenefit
Shortcuts & Miscellaneous	Fractions of Benefit, Death	Used to linearly combine monthly OI death and chronic AIDS death probabilities for each patient month based on the current actual CD4 stratum and the minimum actual CD4 stratum.	deathFractionOfBenefit
Shortcuts & Miscellaneous	Classification of Severe OIs	Indicates which of the specified OIs are considered severe with a value of 1. OIs considered mild, or not severe, are indicated with 0. The number of mild and severe OIs in each patient's history primarily affects the chronic AIDS death probability.	severeOIs
Shortcuts & Miscellaneous	CD4 Strata Bounds	Allows the user to override the default boundary values for the various CD4 strata used throughout the model inputs.	CD4StrataUpperBounds
Cohort Logging	Log Prior OI History Probability	Used to turn on/off the program recording of the proportion of patients with a given history of OIs up to some prespecified duration of time. This proportion of patients with OI histories in the output files can be used as priori OI history inputs in subsequent runs of the program.	enableOIHistoryLogging
Cohort Logging	Log OI Histories with # ART Failures	Specifies the number of ART failures before OI history logging will begin. Use value -1 to disregard, for positive values it will record OIs after that ART line has failed and before the next line is begun.	numARTFailuresForOIHistoryLogging
Cohort Logging	Log OI Histories with CD4 Counts	CD4 bounds for when OI history logging will begin, patients true CD4 value must be within these bounds, inclusively	CD4BoundsForOIHistoryLogging
Cohort Logging	Log OI Histories with HVL Strata	HVL bounds for when OI history logging will begin, patients true HVL strata must be within these bounds, inclusively	HVLBoundsForOIHistoryLogging
Cohort Logging	Log OI Histories in Patient Months without Specific OIs	Only log OIs for patients that do not have a history of any of the OIs specified with a value of 1	OIsToExcludeOIHistoryLogging
Outputs	Enable Cost Outputs for Multiple Discount Rates	Turn on multiple discount rates	enableMultipleDiscountRates
Outputs	Annual Discount Rate	Discount rates for mult disc	multDiscountRatesCost
Output worksheet			
Output	Sub-Cohort Table	Specifies weather to enable subcohorts and how many people to include in each subcohort.	enableSubCohort, subCohorts

Cohort worksheet

Cohort Characteristics	Distribution of Initial CD4	Mean and standard deviation distribution of patients' actual CD4 counts on entry to the simulation program. Drawing a CD4 value below or above max CD4 is redrawn. This can also be set to use a square root transform in which the value is drawn from the distribution and then squared to get the actual CD4 value the model uses.	initialCD4Mean initialCD4StdDev initialCD4MeanSqrt initialCD4StdDevSqrt
Cohort Characteristics	Distribution of Initial HVL	Probability distribution of patients into the possible HVL strata on entry to the simulation program. The starting HVL stratum chosen for each patient is also the HVL setpoint for the patient. The HVL distribution is chosen dependent on the actual CD4 stratum the individual is assigned to. The probabilities across all HVL strata should sum to 1.	initialHVLDistribution
Cohort Characteristics	Distribution of Initial Age (in Months)	Mean and standard deviation distribution of patients' age, in months, on entry to the simulation program. Ages below zero will be set zero, age over 100 years will be set to 100 years.	initialAgeMean initialAgeStdDev
Cohort Characteristics	Gender Distribution	Percentage distribution of cohort that is male, the remainder will be female.	maleGenderDistribution
Cohort Characteristics	OI Prophylaxis NonCompliance Risk	Probability that a patient will be a non-complier of OI prophylaxis, assessed at the beginning of the simulation.	OIProphNonComplianceRisk
Cohort Characteristics	OI Prophylaxis NonCompliance Degree	Percentage reduction in any OI prophylaxis the patient may take if patient assessed as non-complier.	OIProphNonComplianceDegree
Cohort Characteristics	Distribution of Clinic Visitor Types	Distribution of cohort into the three clinic visit types: those who make visits at the very beginning of the simulation and when on ART/prophylaxis; visits at the very beginning, on ART/prophylaxis, or at the event of an OI; and visis at the very beginning, on ART/prophylaxis, at the event of an OI, and on a regular schedule.	clinicVisitTypeDistribution
Cohort Characteristics	Distribution of Implementing ART/Prophylaxis	Distribution of cohort into those who will never start ART or prophylaxis; those who may start OI prophylaxis, and those who may start OI prophylaxis and ART.	therapyImplementationDistribution
Cohort Characteristics	CD4 Response Type on ART	Distribution of cohort into their predisposed type of response to ART treatment, the specified groups will be used for characterizing their CD4 trajaectory	CD4ResponseTypeOnARTDistribution
Cohort Characteristics	Probability of Prior OI History at Entry	Probability assessed for each patient on simulation entry of having a prior history of each OI.	probOIHistoryAtEntry
Probability of Generic Risk Factors	Prevalence at init	Specifies the initial prevalence of patients having each generic risk factor	probRiskFactorPrev
Probability of Generic Risk Factors	Monthly Incidence	Specifies the monthly probability of incidence of the patient acquiring each risk factor	probRiskFactorIncid

Treatment worksheet

ART Regimen Starting Policy	CD4 Count	Specifies the observed CD4 range (inclusive) when eligible patients should start each line of ART regimen.	startART.CD4BoundsOnly
ART Regimen Starting Policy	HVL Strata	Specifies the observed HVL range (inclusive) when eligible patients should start each line of ART regimen.	startART.HVLBoundsOnly
ART Regimen Starting Policy	CD4 Count and HVL Strata	Specifies the joint observed CD4 and HVL ranges (inclusive) when eligible patients should start each line of ART regimen.	startART.CD4BoundsWithHVL startART.HVLBoundsWithCD4
ART Regimen Starting Policy	Observed Acute OI	Specifies the OIs observed in the patient's history since the previous ART regimen was observed to have failed or was stopped to start the subsequent ART regimen. The number of observed OIs needed to start ART is subject to the # OIs to Start ART input.	startART.OIHistory
ART Regimen Starting Policy	# OIs to Start ART	Specifies the number of observed OIs in Observed Acute OI necessary to start the subsequent line of ART.	startART.numOIs
ART Regimen Starting Policy	CD4 Count and Observed Acute OI	Specifies the joint observed CD4 range (inclusive) and observed OIs in patient's lifetime history to start the subsequent ART regimen.	startART.OIHistoryWithCD4
ART Regimen Starting Policy	Minimum Month # for starting ART	Specifies the minimum month number in the simulation before which each line of ART would not be started. This month condition is purely a precondition before the other CD4/HVL/OI starting conditions are considered for starting a patient on the subsequent line of ART.	startART.minMonthsNum
ART Regimen Starting Policy	Maximum Month # for starting ART	Specifies the maximum month number in the simulation after which each line of ART would not be started. This month condition is purely a precondition before the other CD4/HVL/OI starting conditions are considered for starting a patient on the subsequent line of ART.	startART.maxMonthsNum
ART Regimen Starting Policty	Time elapsed since prev regimen stop	Specifies the number of months since the previous ART regimen was stopped before the patient may begin the next line, used purely as a precondition before the other starting criteria are evaluated.	startART.monthsSincePrevRegimen
Order of Administering ART Regimens	ART #	Specifies the number of ART regimen within the spreadsheet to be used for each line of ART treatment. This is a setting internal to the spreadsheet to select the order of available ART regimens; ART regimen information is ultimately input into the simulation program in the order specified here.	
Order of Administering ART Regimens	Additional Regimen Costs At Regimen Startup	Costs added to the selected regimen's startup costs. This cost is not separately input into the program; it is combined with the corresponding ART regimen's initialization cost.	
Order of Administering ART Regimens	Additional Regimen Costs, Monthly on Regimen	Costs added to the selected regimen's monthly costs. This cost is not separately input into the program; it is combined with the corresponding ART regimen's monthly cost.	
Order of Administering ART Regimens	Enable STI	Indicates whether the corresponding line of ART would be eligible for structured treatment interruption. The actual criteria used for initiating interruption are specified in the STI worksheet.	enableSTIForART
ART Regimen Observed Failure Policy	Number HVL Strata Increase	Specifies the number of observed HVL strata above their minimum HVL while on the current ART regimen to indicate an observed failure diagnosis.	failART.HVLNumIncrease

ART Regimen Observed Failure Policy	HVL Count	Range of observed HVL (exclusive) strata outside of which is considered to be a failure diagnosis of current ART regimen.	failART.HVLBounds
ART Regimen Observed Failure Policy	HVL at Setpoint (not suppressed)	Indicates whether patients observed at HVL setpoint would be considered as a diagnosis of failing the current ART regimen.	failART.HVLFailAtSetpoint
ART Regimen Observed Failure Policy	# Mths post-ART Init	Specifies the number of months since ART initiation after which virologic criteria will be able to count towards diagnosed failure.	failART.HVLMonthsFromInit
ART Regimen Observed Failure Policy	CD4 Count Percent Drop	Specifies the percentage drop from maximum observed CD4 on the current ART regimen to be considered regimen failure diagnosis.	failART.CD4PercentageDrop
ART Regimen Observed Failure Policy	CD4 Count Below pre-ART Nadir	Specifies whether or not the CD4 count reaching the pre-ART nadir level should qualify as a diagnoses of observed failure.	failART.CD4BelowPreARTNadir
ART Regimen Observed Failure Policy	(or) CD4 Count	Range of observed CD4 (exclusive) outside of which is considered to be a failure diagnosis of current ART regimen. Will be evaluated independently of the other failure criteria and at least one must be met to diagnose failure.	failART.CD4BoundsOR
ART Regimen Observed Failure Policy	(and) CD4 Count	Range of observed CD4 (exclusive) outside of which is considered to be a failure diagnosis of current ART regimen. Will be evaluated along with other failure criteria and must also be met to count as a diagnosis.	failART.CD4BoundsAND
ART Regimen Observed Failure Policy	# Mths post-ART Init	Specifies the number of months since ART initiation after which immunologic criteria will be able to count towards diagnosed failure.	failART.CD4MonthsFromInit
ART Regimen Observed Failure Policy	OI Event	Specifies the observed OIs that would lead to failing the current line of ART. The user must have the number of OIs specified by the next input to be considered as an observed failure.	failART.OIsEvent
ART Regimen Observed Failure Policy	# OIs to Fail ART	Number of the appropriate OIs needed to be observed to fail the current ART.	failART.OIsMinNum
ART Regimen Observed Failure Policy	# Mths Post-ART Init	Number of months after ART initialization to begin counting observed OIs for failing the current ART regimen.	failART.OIsMonthsFromInit
ART Regimen Observed Failure Policy	# Successive CD4/HVL Tests for Fail Diagnosis	Specifies the number of successive CD4 or HVL tests with observed levels to indicate observed ART regimen failure, the count resets back to zero if a test does not meet failure criteria.	failART.diagnoseNumTestsFail
ART Regimen Observed Failure Policy	Confirm immunologic or clinical failure with HVL tests	Specifies if HVL tests should also be given to confirm failure after the criteria for immunologic or clinical failure have been reached.	failART.diagnoseUseHVLTestsConfirm
ART Regimen Observed Failure Policy	Confirm clinical failure with CD4 tests	Specifies if CD4 tests should also be given to confirm failure after the criteria for clinical failure have been reached.	failART.diagnoseUseCD4TestsConfirm
ART Regimen Observed Failure Policy	# Successive CD4/HVL Tests for Confirmation of Fail Diagnosis	Specifies the number of successive failed CD4/HVL tests that will be used to confirm failure if the above parameter is set, the count resets back to zero if a test does not meet failure criteria.	failART.diagnoseNumTestsConfirm
ART Regimen Stopping Policy	Max Months on ART	Specifies the maximum number of months patients are allowed to be on the current ART regimen before the regimen is forced to be stopped, even if failure was never observed.	stopART.maxMonthsOnART
ART Regimen Stopping Policy	On Major Toxicity	Specifies whether or not the regimen should be stopped after a major toxicity occurs, even if failure was never observed.	stopART.withMajorToxicity
ART Regimen Stopping Policy	Stop Immediately	Specifies that the current ART regimen should be stopped immediately upon observed failure, evaluated only after observed failure	stopART.afterFailImmediate
ART Regimen Stopping Policy	CurrCD4 <=	Specifies a CD4 lower bound (inclusive) below which the ART regimen should be stopped, evaluated only after observed failure	stopART.afterFailCD4LowerBound
ART Regimen Stopping Policy	Observed Severe OI	Specifies if the ART regimen should be stopped after the occurrence of a severe OI, evaluated only after observed failure	stopART.afterFailWithSevereOI
ART Regimen Stopping Policy	# Mths after observed failure	Specifies the number months after observed failure after which the regimen will be stopped, evaluated only after observed failure	stopART.afterFailMonthsFromObserved
ART Regimen Stopping Policy	Minimum Month #	Specifies the month number after which the criteria for stopping ART will be begin to be evaluated.	stopART.afterFailMinMonthNum
ART Regimen Stopping Policy	# Mths post-ART init	Specifies the number of months since regimen initiation after which the criteria for stopping ART will be begin to be evaluated.	stopART.afterFailMonthsFromInit
ART Regimen Resistance Penalties	Prob Reduction in Intial Success	Fractional reduction in the initial probability of success for each newly initiated ART regimen, specified fraction is accumulated for each month spent on each previous regimen.	ARTResistancePriorRegimen
ART Regimen Resistance Penalties	Prob Reduction by HVL Strata	Fractional reduction in the initial probability of success for any newly initiated ART regimen, specified fraction is accumulated for each month spent in each HVL strata on all previous regimens.	ARTResistanceHVL
Primary OI Prophylaxis Starting Policy	AND/OR Condition	Specifies how the various starting critieria are combined: whether one criterion is sufficient to start, or all criteria need to be met.	startProph.useOrEvaluation
Primary OI Prophylaxis Starting Policy	Current CD4 Range	Specifies the observed current CD4 ranges (inclusive) to have a patient begin primary prophylaxis for a given OI.	startProph.currCD4Bounds
Primary OI Prophylaxis Starting Policy	Minimum CD4 Range	Specifies the observed minimum CD4 ranges (inclusive) to have a patient begin primary prophylaxis for a given OI.	startProph.minCD4Bounds
Primary OI Prophylaxis Starting Policy	OI History	Specifies the observed OI history criteria to have a patient begin primary prophylaxis for a given OI. Patient must have a history of at least one of the OIs specified with a 1, and none of the OIs specified with a 0. Criteria will be skipped if all OIs are set to -1.	startProph.OIHistory
Primary OI Prophylaxis Starting Policy	Current Mth # is at least	Specifies the minimum month number in the simulation before primary prophylaxis may be started, will be evaluated as a precondition before other criteria may be evaluated.	startProph.minMonthNum
Primary OI Prophylaxis Stopping Policy	AND/OR Condition	Specifies how the various stopping critieria are combined: whether one criterion is sufficient to stop, or all criteria need to be met.	stopProph.useOrEvaluation
Primary OI Prophylaxis Stopping Policy	Current CD4 Range	Specifies the observed current CD4 ranges (exclusive) outside which the patient will stop primary prophylaxis for a given OI.	stopProph.currCD4Bounds

Primary OI Prophylaxis Stopping Policy	Minimum CD4 Range	Specifies the observed minimum CD4 ranges (exclusive) outside which the patient will stop primary prophylaxis for a given OI.	stopProph.minCD4Bounds
Primary OI Prophylaxis Stopping Policy	OI History	Specifies the observed OI history criteria to have a patient stop primary prophylaxis for a given OI. Patient must have a history of at least one of the OIs specified with a 1, and none of the OIs specified with a 0. Criteria will be skipped if all OIs are set to -1.	stopProph.OIHistory
Primary OI Prophylaxis Stopping Policy	Current Mth # is at least	Specifies the month number in the simulation after which primary prophylaxis will automatically be stopped, will override other criteria for stopping.	stopProph.minMonthNum
Primary OI Prophylaxis Stopping Policy	# Mths since proph init	Specifies the number of months since prophylaxis initiation after which primary prophylaxis will automatically be stopped, will override other criteria for stopping.	stopProph.monthsOnProph
Secondary OI Prophylaxis Starting Policy	AND/OR Condition	Specifies how the various starting critieria are combined: whether one criterion is sufficient to start, or all criteria need to be met.	startProph.useOrEvaluation
Secondary OI Prophylaxis Starting Policy	Current CD4 Range	Specifies the observed current CD4 ranges (inclusive) to have a patient begin secondary prophylaxis for a given OI.	startProph.currCD4Bounds
Secondary OI Prophylaxis Starting Policy	Minimum CD4 Range	Specifies the observed minimum CD4 ranges (inclusive) to have a patient begin secondary prophylaxis for a given OI.	startProph.minCD4Bounds
Secondary OI Prophylaxis Starting Policy	OI History	Specifies the observed OI history criteria to have a patient begin secondary prophylaxis for a given OI. Patient must have a history of at least one of the OIs specified with a 1, and none of the OIs specified with a 0. Criteria will be skipped if all OIs are set to -1.	startProph.OIHistory
Secondary OI Prophylaxis Starting Policy	Current Mth # is at least	Specifies the minimum month number in the simulation before secondary prophylaxis may be started, will be evaluated as a precondition before other criteria may be evaluated.	startProph.minMonthNum
Secondary OI Prophylaxis Stopping Policy	AND/OR Condition	Specifies how the various stopping critieria are combined: whether one criterion is sufficient to stop, or all criteria need to be met.	stopProph.useOrEvaluation
Secondary OI Prophylaxis Stopping Policy	Current CD4 Range	Specifies the observed current CD4 ranges (exclusive) outside which the patient will stop secondary prophylaxis for a given OI.	stopProph.currCD4Bounds
Secondary OI Prophylaxis Stopping Policy	Minimum CD4 Range	Specifies the observed minimum CD4 ranges (exclusive) outside which the patient will stop secondary prophylaxis for a given OI.	stopProph.minCD4Bounds
Secondary OI Prophylaxis Stopping Policy	OI History	Specifies the observed OI history criteria to have a patient stop secondary prophylaxis for a given OI. Patient must have a history of at least one of the OIs specified with a 1, and none of the OIs specified with a 0. Criteria will be skipped if all OIs are set to -1.	stopProph.OIHistory
Secondary OI Prophylaxis Stopping Policy	Current Mth # is at least	Specifies the month number in the simulation after which secondary prophylaxis will automatically be stopped, will override other criteria for stopping.	stopProph.minMonthNum
Secondary OI Prophylaxis Stopping Policy	# Mths since proph init	Specifies the number of months since prophylaxis initiation after which secondary prophylaxis will automatically be stopped, will override other criteria for stopping.	stopProph.monthsOnProph
OI Prophylaxis Policies	Order of Administering Primary OI Prophylaxes	This is a setting internal to the spreadsheet to select the order of primary prophylaxes for each specific OI type. Prophylaxis information is ultimately input into the simulation program in the order specified here, without this table per se.	
OI Prophylaxis Policies	Order of Administering Secondary OI Prophylaxes	This is a setting internal to the spreadsheet to select the order of secondary prophylaxes for each specific OI type. Prophylaxis information is ultimately input into the simulation program in the order specified here, without this table per se.	
Frequency of CD4, HVL Testing	CD4 Threshold	Specifies a threshold of observed CD4 separating the two different periods of CD4/HVL test scheduling. These two periods allow different CD4/HVL test intervals before patients have started first line ART.	testingIntervalCD4Threshold
Frequency of CD4, HVL Testing	N1, N2	Specifies the months since ART initiation thresholds that separate the different time periods for CD4/HVL testing frequency, can be set differently for all lines before the last line and the last line.	
Frequency of CD4, HVL Testing	Mths Between CD4 Test	Specifies the number of elapsed patient months from a month with a CD4 test before another regularly scheduled CD4 test is to be given. The CD4 test will be give with the next clinic visit after this time period has elapsed. Note that the regular schedule of CD4 tests may be interrupted by ART initiation tests or ART observed failure confirmatory tests.	CD4TestingIntervalPreARTHighCD4 CD4TestingIntervalPreARTLowCD4 CD4TestingIntervalOnART CD4TestingIntervalOnLastART CD4TestingIntervalPostART
Frequency of CD4, HVL Testing	Mths Between HVL Test	Specifies the number of elapsed patient months from a month with a HVL test before another regularly scheduled HVL test is to be given. The HVL test will be given with the next clinic visit after this time period has elapsed. Note that the regular schedule of CD4 tests may be interrupted by ART initiation tests or ART observed failure confirmatory tests.	HVLTestingIntervalPreARTHighCD4 HVLTestingIntervalPreARTLowCD4 HVLTestingIntervalOnART HVLTestingIntervalOnLastART HVLTestingIntervalPostART
Probability of CD4, HVL Test Errors	HVL Test Higher Error Prob	The risk of an inaccurate HVL test resulting in an observed HVL stratum one higher than the patient's current actual HVL stratum, assessed at the point of the HVL test.	probHVLTestErrorHigher
Probability of CD4, HVL Test Errors	HVL Test Lower Error Prob	The probability of an inaccurate HVL test resulting in an observed HVL stratum one lower than the patient's current actual HVL stratum, assessed at the point of the HVL test.	probHVLTestErrortLower
Probability of CD4, HVL Test Errors	CD4 Test Std Dev (% of curr)	Determines the error in the observed CD4 count, specified as a percentage of the actual CD4 count that will be used as a standard deviation about the mean value of the actual CD4 count.	CD4TestStdDevPercentage
Months between Scheduled Clinic Visits		Specifies the number of elapsed patient months from a month with a clinic visit before another regularly scheduled clinic visit is to occur. Note that in the month of an acute OI event, an unscheduled clinic visit for treatment may be triggered.	clinicVisitInterval
Probability of Detecting OIs in Patient History	Old OI at Prog Entry	Probability that prior OIs in the patient's history are detected in the patient's first clinic visit.	probDetectOIAtEntry
Probability of Detecting OIs in Patient History	OI Since Last Visit	Probability that OIs in the patient's history since the previous clinic visit are detected in the subsequent clinic visit.	probDetectOISinceLastVisit

Probability of Switching to Secondary Prophylaxis at Acute OI Event	Prob stop prim. Proph	Specifies the probability that a patient would stop primary prophylaxis for a particular OI and/or be eligible for secondary prophylaxis in the event of detection of that OI.	probSwitchSecondaryProph
Wait for Regularly Scheduled Clinic Visit to Confirm ART Failure		Specifies whether the special additional HVL or CD4 tests used to confirm observed ART failure could be done outside the context of a regularly scheduled clinic visit.	ARTFailureOnlyAtRegularVisit
Number HVL Tests Outside Clinic Visit At ART Initiation		If specified value is > 0, a HVL test will be given in the month of ART initiation and the subsequent N-1 number of months.	numARTInitialHVLTests
Number CD4 Tests Outside Clinic Visit At ART Initiation		If specified value is > 0, a CD4 test will be given in the month of ART initiation and the subsequent N-1 number of months.	numARTInitialCD4Tests
Emergency Clinic Visits do not count as Scheduled Visits		Specifies whether an emergency clinic visit should affect the regular schedule of clinic visits. If set to true, the OI clinic visit does not reset the number of months until the next clinic visit.	emergencyVisitIsNotRegularVisit
Lag to CD4 Testing Availability		Determines the lag period (in months) before CD4 testing is available	CD4TestingLag
Lag to HVL Testing Availability		Determines the lag period (in months) before HVL testing is available	HVLTestingLag

LTFU worksheet

Monthly Probability of Loss to Follow Up (LTFU)	Use LTFU?	Specifies YES or NO to indicate whether to enable or disable patients becoming LTFU after being linked to care	useLTFU
Pre-ART Propensity to Respond Regression Coefficient	Mean/Std Dev	Distribution of propensity to respond regression coefficient if patient has not started ART Regimen.	propRespondLTFUPreARTLogitMean propRespondLTFUPreARTLogitStdDev
Propensity to Respond LTFU Outcome Function (Monthly prob of becoming LTFU)	L1,L2,L1 Value, L2 Value	Response Table for monthly prob of becoming LTFU.	responseThresholdLTFU responseValueLTFU
Proportion of General Medicine Costs by State	Undetected, Unlinked, In Care, LTFU	Proportion to accumulate to the general medicine cost depending on patient care state.	propGeneralMedicineCost
Behavior While Lost	Probability of remaining on OI Proph	Specifies the probability that the patient will continue taking any OI prophs that they were on at the time they got lost, use once to determine if the continue all or none of their currents prophs	probRemainOnOIProph
Behavior While Lost	Probability of remaining on OI Treatment	Specifies the probability that the patient will continue to be treating for subsequent OIs while LTFU, does not effect their chance of returning to care due to an OI	probReamainOnOITreatment
Monthly Probability of Return to Care (RTC)	Minimum months to remain lost	Specifies the minimum number of months since being lost before the patient may return to care. This can be overridden by an acute OI, in which case there will be a probability of returning to care even if below this number of months.	minMonthsRemainLost
Contributing Regression Coefficients (RTC)	Background	Specifies the baseline logit coefficient for determining RTC probability	regressionCoefficientsRTC
Contributing Regression Coefficients (RTC)	CD4 (if less that threshold)	Specifies a logit to be used if the patients CD4 level is lower than the provided threshold for determining RTC probability	regressionCoefficientsRTC
Contributing Regression Coefficients (RTC)	CD4 Count Threshold	Specifies the CD4 threshold to be used with the above coefficient	CD4ThresholdRTC
Contributing Regression Coefficients (RTC)	Acute Severe OI	Specifies a logit to be used if the patients has a severe acute OI according to the classification for determining RTC probability	regressionCoefficientsRTC
Contributing Regression Coefficients (RTC)	Acute Mild OI	Specifies a logit to be used if the patients has a mild acute OI according to the classification for determining RTC probability	regressionCoefficientsRTC
Contributing Regression Coefficients (RTC)	Severe OIs for RTC	Specifies the classification of OIs as severe or mild for the purposes of determining RTC probability	severeOIsRTC
Contributing Regression Coefficients (RTC)	Probability Checker	Allows user to alter the various parameters and verified that the desired probability of RTC is calculated from the logits, not inputted into the model	
Returning to ART regimen	Max time previously on ART regimen to return to observed failed regimen	Specifies a maximum number of months after observed ART regimen failure before being lost that the patient will return to that line, set to -1 to not allow returning to a failed line	maxMonthsAfterObservedFailureToRestartRegimen
Returning to ART regimen	Probability of returning to failed ART regimen if unobserved failure	Specifies the probability of returning to the previous ART line if failure was never observed. Patient will always return to previous line if they were suppressed on it at the time of being lost.	probRestartRegimenWithoutObservedFailure
If Returning to Previous Regimen	Probability of Suppression	Specifies the overriding probability of suppression that will be used if the patient returns to care on their previous regimen. Stratified by regimen number and efficacy state at the time of becoming lost.	probabilityOfSuppressionWhenReturnToFailed probabilityOfSuppressionWhenReturnToSuppressed

Heterogeneity worksheet

General Propensity to Respond Regression Coefficients	Baseline	Specifies the mean and standard deviation of the individual cohort's logit of propensity to respond. Actual value is drawn from this distribution for each patient at initiation.	propRespondBaselineMean propRespondBaselineStdDev
General Propensity to Respond Regression Coefficients	Age	Specifies the response coefficient to be used for patients based on their age category.	propRespondAge
General Propensity to Respond Regression Coefficients	Peds Age	Specifies the response coefficient to be used for patients based on their pediatric age category.	propRespondAgeEarly propRespondAgeLate
General Propensity to Respond Regression Coefficients	CD4	Specifies the response coefficient to be used for patients based on their true CD4 strata.	propRespondCD4

General Propensity to Respond Regression Coefficients	Gender (if female)	Specifies the response coefficient to be used if the patient is female.	propRespondFemale
General Propensity to Respond Regression Coefficients	History of OIs	Specifies the response coefficient to be used if the patient has a history of any OIs.	propRespondHistoryOIs
General Propensity to Respond Regression Coefficients	Prior ART Toxicity	Specifies the response coefficient to be used if the patient has had a prior ART toxicity.	propRespondPriorARTToxicity
General Propensity to Respond Regression Coefficients	Risk Factor (1 to 5)	Specifies the response coefficients to be used if the patient has each of the generic risk factors.	propRespondRiskFactor

STI worksheet

STI Initiation Policy – First Interruption	CD4 Count	Specifies the observed CD4 range (inclusive) when eligible patients should start the first STI interruption.	firstInterruption.CD4BoundsOnly
STI Initiation Policy – First Interruption	HVL Strata	Specifies the observed HVL range (inclusive) when eligible patients should start the first STI interruption.	firstInterruption.HVLBoundsOnly
STI Initiation Policy – First Interruption	CD4 Count and HVL Strata	Specifies the joint observed CD4 and HVL ranges (inclusive) when eligible patients should start each the first STI interruption	firstInterruption.CD4BoundsWithHVL firstInterruption.HVLBoundsWithCD4
STI Initiation Policy – First Interruption	Observed Acute OI	Specifies the OIs observed in the patient's history since the previous ART regimen was observed to have failed or was stopped to start the subsequent ART regimen. The number of observed OIs needed to start the first STI interruption is subject to the `# OIs to Start STI` input.	firstInterruption.OIHistory
STI Initiation Policy – First Interruption	# OIs to Start STI	Specifies the number of observed OIs in `Observed Acute OI` necessary to start the first STI interruption of ART.	firstInterruption.numOIs
STI Initiation Policy – First Interruption	CD4 Count and Observed Acute OI	Specifies the joint observed CD4 range (inclusive) and observed OIs in patient's lifetime history to start the first STI interruption.	firstInterruption.OIHistoryWithCD4
STI Initiation Policy – First Interruption	Minimum Month # for starting ART	Specifies the minimum month number in the simulation before which each line of ART would not have the first STI interruption start. This month condition is purely a precondition before the other CD4/HVL/OI starting conditions are considered for starting STI on the current line of ART.	firstInterruption.minMonthsNum
STI Initiation Policy – First Interruption	Minimum Mths from ART init for STI	Specifies the number of months since ART initiation before the patient may have the first STI interruption, used purely as a precondition before the other criteria are evaluated.	firstInterruption.monthsSinceARTStart
STI ART Regimen Starting Policy	CD4 Count	Specifies the observed CD4 range (inclusive) when eligible patients on treatment interruption should re-start the corresponding ART regimen.	ARTRestartCD4Bounds
STI ART Regimen Starting Policy	HVL Strata	Specifies the observed HVL range (inclusive) when eligible patients on treatment interruption should re-start the corresponding ART regimen.	ARTRestartHVLBounds
STI ART Regimen Stopping Policy – Subsequent Interruptions	CD4 Count	Specifies the observed CD4 range (exclusive) outside which eligible patients on a treatment interruption regime and currently on an ART regimen should re-stop ART.	ARTRestopCD4Bounds
STI ART Regimen Stopping Policy – Subsequent Interruptions	HVL Strata	Specifies the observed HVL range (exclusive) outside which eligible patients on a treatment interruption regime and currently on an ART regimen should re-stop ART.	ARTRestopHVLBounds
STI Endpoint Definition	CD4 Count	Specifies the observed CD4 range (inclusive) when eligible patients should end the cycle of STI interruptions and be observed to have failed the regimen.	endpoint.CD4BoundsOnly
STI Endpoint Definition	HVL Strata	Specifies the observed HVL range (inclusive) when eligible patients should end the cycle of STI interruptions and be observed to have failed the regimen	endpoint.HVLBoundsOnly
STI Endpoint Definition	CD4 Count and HVL Strata	Specifies the joint observed CD4 and HVL ranges (inclusive) when eligible patients should end the cycle of STI interruptions and be observed to have failed the regimen	endpoint.CD4BoundsWithHVL endpoint.HVLBoundsWithCD4
STI Endpoint Definition	Observed Acute OI	Specifies the OIs observed in the patient's history since the previous ART regimen was observed to have failed or was stopped to end the cycle of STI interruptions and be observed to have failed the regimen. The number of observed OIs needed to end the STI cycle is subject to the `# OIs to Start STI` input.	endpoint.OIHistory
STI Endpoint Definition	# OIs to End STI	Specifies the number of observed OIs in `Observed Acute OI` necessary to end the cycle of STI interruptions and be observed to have failed the regimen.	endpoint.numOIs
STI Endpoint Definition	CD4 Count and Observed Acute OI	Specifies the joint observed CD4 range (inclusive) and observed OIs in patient's lifetime history to end the cycle of STI interruptions and be observed to have failed the regimen.	endpoint.OIHistoryWithCD4
STI Endpoint Definition	Minimum Mths from ART init for STI	Specifies the number of months since the first STI interruption before the patient may end the cycle of STI interruptions and be observed to have failed the regimen, used purely as a precondition before the other criteria are evaluated.	endpoint.monthsSinceARTStart

Prophylaxes worksheet

OI Prophylaxis Efficacy on Primary OIs		Specifies the multiplicative reduction in the probabilities of OIs, assessed in each patient month when the patient is on the given primary prophylaxis. Also used to determine if the proph is a valid one or is unspecified.	primaryOIEfficacy
OI Prophylaxis Efficacy on Secondary OIs		Specifies the multiplicative reduction in the probabilities of OIs, assessed in each patient month when the patient is on the given secondary prophylaxis. Also used to determine if the proph is a valid one or is unspecified.	secondaryOIEfficacy
OI Prophylaxis Resistance	Mth Prob	Probability of developing resistance to a particular prophylaxis, assessed at a fixed number of months since prophylaxis initiation.	monthlyProbResistance
OI Prophylaxis Resistance	% Resist	Specifies decreased multiplicative factor by which prophylaxis efficacy is modified in months when resistance is active.	percentResistance
OI Prophylaxis Resistance	Time Resist	Number of months since prophylaxis initiation at which the probability of prophylaxis resistance is assessed, may be modified by proph compliance.	timeOfResistance

OI Prophylaxis Resistance	Cost Factor	Specifies additional multiplicative factor by which acute OI costs are modified if patient develops prophylaxis resistance for a given OI.	costFactorResistance
OI Prophylaxis Resistance	Mortality Factor	Specifies additional risk to OI death probability if patient develops prophylaxis resistance for a given OI.	mortalityFactorResistance
OI Prophylaxis Toxicity	Minor Prob	Probability of developing minor toxicity while on a particular prophylaxis, assessed at a number of months since prophylaxis initiation. Both minor and major toxicity events cannot occur in the same month.	probMinorToxicity
OI Prophylaxis Toxicity	Major Prob	Probability of developing major toxicity while on a particular prophylaxis, assessed at a number of months since prophylaxis initiation. Both minor and major toxicity events cannot occur in the same month.	probMajorToxicity
OI Prophylaxis Toxicity	Mths to Tox	Number of months since OI prophylaxis initiation when the probabilities of minor and major toxicity are assessed.	monthsToToxicity
OI Prophylaxis Toxicity	Prob Death Major Tox	The probability of mortality from major toxicity, determined in the same month as the toxicity occurs	probDeathMajorToxicity
OI Prophylaxis Costs & QOL	Mth Cost*	OI prophylaxis cost incurred in each month when the patient is on the prophylaxis.	costMonthly
OI Prophylaxis Costs & QOL	MinTox Cost	Cost incurred in the event of minor toxicity from a particular OI prophylaxis.	costMinorToxicity
OI Prophylaxis Costs & QOL	MinTox QOL	Amount of patient QOL multiplier in the month of a minor toxicity event due to a particular prophylaxis.	QOLMinorToxicity
OI Prophylaxis Costs & QOL	MajTox Cost	Cost incurred in the event of major toxicity from a particular OI prophylaxis.	costMajorToxicity
OI Prophylaxis Costs & QOL	MajTox QOL	Amount of patient QOL multiplier in the month of a major toxicity event due to a particular prophylaxis.	QOLMajorToxicity
OI Prophylaxis Switching	Mths from Init	The number of months since prophylaxis initiation after which the current line will be stopped and the patient will be switched to the next line, if one is available	monthsToSwitch
OI Prophylaxis Switching	On MinTox	Indicates whether or not this prophylaxis should require a switch to the next line after a minor toxicity	switchOnMinorToxicity
OI Prophylaxis Switching	On MajTox	Indicates whether or not this prophylaxis should require a switch to the next line after a major toxicity	switchOnMajorToxicity

ART Regimens worksheet

Description		A brief textual description of the ART regimen.	regimenName
Regimen Cost, Startup		Cost incurred as soon as the patient is initiated on an ART regimen. This is a one-time cost incurred only at ART regimen startup. Also used to determine if the ART regimen is a valid one or is unspecified.	costInitial
Regimen Cost, Monthly*		Ongoing cost incurred at the end of patient month if the patient is on the ART regimen. Also used to determine if the ART regimen is a valid one or is unspecified.	costMonthly
Eff Time Horizon		Specifies the number of months after ART regimen initiation constituting the primary, initial efficacy time horizon. Patient will be subject to a monthly probability of late failure or late partial suppression after this time.	efficacyTimeHorizon
Force Fail at Mth		Specifies number of months after ART initiation when all patients still in suppressed or partially suppressed state to transition into failure state, can be set to -1 to disable.	forceFailAtMonth
Mth CD4 change on Suppressed ART	N1, N2	Specifies the month bounds after ART initiation for the CD4 effect of suppressed ART regimens.	stageBoundsCD4ChangeOnART
Mth CD4 change on Suppressed ART	Mean, StdDev	Specifies the slopes of CD4 change for each of the three time stages for patients on suppressed ART. The slope will be drawn once at the beginning of each time period and will remain constant for the remainder of the time period. The specified max patient CD4 level cannot be exceeded. If the nadir CD4 level is reached, the rate of decline cannot exceed the base natural history decline rate.	CD4ChangeOnARTMean CD4ChangeOnARTStdDev
Mth CD4 change on Partially Suppressed ART	N1, N2	Specifies the month bounds after ART initiation for the CD4 effect of partially suppressed ART regimens.	stageBoundsCD4ChangeOnART
Mth CD4 change on Partially Suppressed ART	Mean, StdDev	Specifies the slopes of CD4 change for each of the three time stages for patients on partially suppressed ART. The slope will be drawn once at the beginning of each time period and will remain constant for the remainder of the time period. The specified max patient CD4 level cannot be exceeded. If the nadir CD4 level is reached, the rate of decline cannot exceed the base natural history decline rate.	CD4ChangeOnARTMean CD4ChangeOnARTStdDev
Mth Nat Hist CD4 Multiplier on Failed ART	N1, N2	Specifies the month bounds after ART failure for the CD4 effect of failed ART regimens.	stageBoundsCD4ChangeOnART
Mth Nat Hist CD4 Multiplier on Failed ART	Multiplier	Specifies the multiplicative factors on natural history CD4 decline for patients who have failed but are not taken off the current ART regimen for each of the three stages. If the nadir CD4 level is reached, the rate of decline cannot exceed the base natural history decline rate.	CD4MultiplierOnFailedART
Monthly CD4 Std Dev On ART		Specifies a secondary standard deviation that will be used monthly in addition to the CD4 effect while on ART. Used to create some variability around the constant CD4 slopes. Is applied monthly on for all ART efficacy states.	secondaryCD4ChangeOnARTStdDev
CD4 change multiplier off ART		Specifies the multiplicative factors on natural history CD4 decline for patients who have been taken off the ART regimen. Different multipliers can be specified based on the ART suppression state when they were taken off of ART, and whether or not they have reached their HVL setpoint. If the nadir CD4 level is reached, the rate of decline cannot exceed the base natural history decline rate.	monthlyCD4MultiplierOffArtPreSetpoint monthlyCD4MultiplierOffArtPostSetpoint
HVL Change Rate	Mth Prob	Monthly probability of the patient's HVL moving the specified number strata towards the target HVL for the fully suppressed, partially suppressed, or failed state.	monthlyProbHVLChange
HVL Change Rate	Strata /Mth	Number of strata that patient's HVL is changed in the month when patient's HVL is determined to change.	monthlyNumStrataHVLChange

Toxicity Minor	Prob	Specifies the probability of a minor toxicity occurring after the given number of months from the start of the ART subregimen	toxicity.probToxicity
Toxicity Minor	Time to tox: Mean (mth) Time to tox: Std Dev (mth)	Specifies the distribution of months until toxicity that will be drawn from when the patient initiates the ART subregimen	toxicity.timeToToxicityMean toxicity.timeToToxicityStdDev
Toxicity Minor	QOL mult	Specifies the QOL multiplier to be applied while the toxicity effect is active	Toxicity.QOLMultiplier
Toxicity Minor	QOL duration	Specifies the duration that the QOL multiplier effect is applied each month – 0 is one month, 1 is while on this subregimen, 2 is while on this regimen, and 3 is until death	Toxicity.QOLDuration
Toxicity Minor	Tox cost	Specifies the toxicity cost to be applied while the toxicity effect is active	Toxicity.costAmount
Toxicity Minor	Tox cost duration	Specifies the duration that the toxicity cost will be incurred each month – 0 is one month, 1 is while on this subregimen, 2 is while on this regimen, and 3 is until death	Toxicity.costDuration
Toxicity Minor	On Tox, Swith to sub-regimen	Specifies the subregimen to switch to upon this toxicity occurring, -1 means the patient will not switch subregimens after a toxicity	Toxicity.switchSubRegimenOnToxicity
Toxicity Chronic	Prob	Specifies the probability of a minor toxicity occurring after the given number of months from the start of the ART subregimen	toxicity.probToxicity
Toxicity Chronic	Time to tox: Mean (mth) Time to tox: Std Dev (mth)	Specifies the distribution of months until toxicity that will be drawn from when the patient initiates the ART subregimen	toxicity.timeToToxicityMean toxicity.timeToToxicityStdDev
Toxicity Chronic	QOL mult	Specifies the QOL multiplier to be applied while the toxicity effect is active	toxicity.QOLMultiplier
Toxicity Chronic	QOL duration	Specifies the duration that the QOL multiplier effect will be incurred each month – 0 is one month, 1 is while on this subregimen, 2 is while on this regimen, and 3 is until death	toxicity.QOLDuration
Toxicity Chronic	Tox cost	Specifies the toxicity cost to be applied while the toxicity effect is active	toxicity.costAmount
Toxicity Chronic	Tox cost duration	Specifies the duration that the toxicity cost will be incurred each month – 0 is one month, 1 is while on this subregimen, 2 is while on this regimen, and 3 is until death	toxicity.costDuration
Toxicity Chronic	On Tox, Swith to sub-regimen	Specifies the subregimen to switch to upon this toxicity occurring, -1 means the patient will not switch subregimens after a toxicity	toxicity.switchSubRegimenOnToxicity
Toxicity Chronic	Time to chr dth impact (mth)	Specifies the number of months after the toxicity begins to start applying the effect on the probability of non-AIDS death	toxicity.timeToChronicDeathImpact
Toxicity Chronic	Chr dth incr	Specifies the amount the probability of non-AIDS death occurring should be increased by while this toxicity effect is active	toxicity.chronicDeathIncrease
Toxicity Chronic	Chr dth duration	Specifies the duration that the non-AIDS death increase will be incurred each month – 0 is one month, 1 is while on this subregimen, 2 is while on this regimen, and 3 is until death	toxicity.chronicDeathDuration
Toxicity Major	Prob	Specifies the probability of a minor toxicity occurring after the given number of months from the start of the ART subregimen	toxicity.probToxicity
Toxicity Major	Time to tox: Mean (mth) Time to tox: Std Dev (mth)	Specifies the distribution of months until toxicity that will be drawn from when the patient initiates the ART subregimen	toxicity.timeToToxicityMean toxicity.timeToToxicityStdDev
Toxicity Major	QOL mult	Specifies the QOL multiplier to be applied while the toxicity effect is active	toxicity.QOLMultiplier
Toxicity Major	QOL duration	Specifies the duration that the QOL multiplier effect will be incurred each month – 0 is one month, 1 is while on this subregimen, 2 is while on this regimen, and 3 is until death	toxicity.QOLDuration
Toxicity Major	Tox cost	Specifies the toxicity cost to be applied while the toxicity effect is active	toxicity.costAmount
Toxicity Major	Tox cost duration	Specifies the duration that the toxicity cost will be incurred each month – 0 is one month, 1 is while on this subregimen, 2 is while on this regimen, and 3 is until death	toxicity.costDuration
Toxicity Major	Acute death prob	Specifies the probability of acute toxicity death occurring the month that the toxicity begins	toxicity.probAcuteDeathMajorToxicity
Toxicity Major	Acute dth cost	Specifies the cost incurred due to acute toxicity death	toxicity.costAcuteDeathMajorToxicity
Time to swith (mth)		Specifies the number of months since starting the subregimen after which the patient will be switched to the next subregimen, can be set to -1 to disable.	monthsToSwitchSubRegimen
Heterogeneity	Prob of filling ART prescriptions for Non Responder	The cost for ART Regimen for non responder is the full ART cost multiplied by this probability.	probFillPrescriptionNonResp
Heterogeneity	Probability of Restarting Regimens After Failure	Probability of restarting ART Regimen after failure for each response type	probRestartAfterFail
Heterogeneity	Regimen Specific Propensity to Respond Regression Coefficient	Response Logit for specific ART regimen. Drawn from distribution.	propRespondARTRegimenLogitMean propRespondARTRegimenLogitStdDev
Heterogeneity	L1, L2	Propensity to respond thresholds.	responseTypeThresholds
Heterogeneity	L1 Value, L2 Value	Values of outcomes at L1 and L2	responseTypeValues
Heterogeneity	exponent	Power of function used to interpolate outcomes for partial suppression.	responseTypeExponents
NatHist worksheet			
Chronic AIDS Death Probability	Off ART	Probability of chronic AIDS death assessed in each month that patient is not on a current ART regimen. The probabilities are divided into 2 states: no OI history, and history of OIs including at least one considered severe. There is also a field for the duration since the severe event to apply the multiplier. After the duration the multiplier is not applied.	chronicAIDSDeathProbOffART, chronicAIDSDeathProbOffARTSevereOIDuration
Chronic AIDS Death Probability	On ART	Probability of chronic AIDS death assessed in each month that patient is on a current ART regimen. The probabilities are divided into 2 states: no OI history, and history of OIs including at least one considered severe.	chronicAIDSDeathProbOnART

OI Probability, Off ART	No OI History	Probability of acute OI event assessed in each month that patient is not on a current ART regimen. The probability of each OI is pulled from the No OI History table if the patient does not have a history of that specific OI. Only one acute OI event may occur in a given patient month.	monthlyOIProbOffART
OI Probability, Off ART	OI History	Probability of acute OI event assessed in each month that patient is not on a current ART regimen. The probability of each OI is pulled from the OI History table if the patient has a history of that specific OI. Only one acute OI event may occur in a given patient month.	monthlyOIProbOffART
OI Probability, On ART Multiplier		A rate multiplier used to adjust the acute OI probabilities for those months when the patient is on a current ART regimen. Note that this table is internal to the spreadsheet; the on ART inputs are fed into the program by multiplying the off ART values.	
OI Probability, On ART	No OI History	Probability of acute OI event assessed in each month that patient is on a current ART regimen. The probability of each OI is pulled from the No OI History table if the patient does not have a history of that specific OI. Only one acute OI event may occur in a given patient month.	monthlyOIProbOnART
OI Probability, On ART	OI History	Probability of acute OI event assessed in each month that patient is on a current ART regimen. The probability of each OI is pulled from the OI History table if the patient has a history of that specific OI. Only one acute OI event may occur in a given patient month.	monthlyOIProbOnART
Death from OI Probability	Treated, No OI Hist	Probability of death from acute OI event. This probability is assessed if the patient is treated for the OI (patient is of type that goes to clinic for OIs) and has not had the OI previously.	probDeathFromOITreated
Death from OI Probability	Treated, OI History	Probability of death from acute OI event. This probability is assessed if the patient is treated for the OI (patient is of type that goes to clinic for OIs) and has had the OI previously.	probDeathFromOITreated
Death from OI Probability	Untreated, No OI Hist	Probability of death from acute OI event. This probability is assessed if the patient is not treated for the OI (patient is of type that does not go to clinic for OIs) and has not had the OI previously.	probDeathFromOIUntreated
Death from OI Probability	Untreated, OI History	Probability of death from acute OI event. This probability is assessed if the patient is not treated for the OI (patient is of type that does not go to clinic for OIs) and has had the OI previously.	probDeathFromOIUntreated
Baseline CD4 Decline, Monthly	Mean, Std Dev	Distribution of monthly CD4 decline for patient not on effective ART regimen and not in lag period to baseline CD4 decline after ART failure. Amount of CD4 decline determined each month independently by mean and standard deviation.	monthlyCD4DeclineMean monthlyCD4DeclineStdDev
Baseline CD4 Decline, Monthly	Between Subject Std Dev Perc	Std Deviation of CD4 decline for each specific patient. Applied as a percentage to the mean of monthly cd4 variation each month. Drawn once for each person at start.	monthlyCD4DeclineBtwSubject
Non AIDS Death Probability		Probability of non AIDS death based on age and gender, used monthly to determine mortality from non AIDS causes.	monthlyNonAIDSDeathProb

CHRMs worksheet

Chronic Event Types		Specifies the names for the four possible chronics events. Defaults are CVD, Hepatic, Renal, and Malignancy.	CHRM_STRS
Probability of Chronic Events at Model Entry (Prevalence)	HIV-, all	Specifies the probability of an HIV-negative patient entering the simulation with a prevalent condition of each CHRM. Stratified by gender and age.	probPrevalentCHRMsHIVneg
Probability of Chronic Events at Model Entry (Prevalence)	HIV+	Specifies the probability of an HIV-positive patient entering the simulation with a prevalent condition of each CHRM. Stratified by gender, age, and true CD4 strata.	probPrevalentCHRMs
Prevalence Modifiers	Generic Risk Factors	Logit adjustments that modify the above probabilities when the patient has the corresponding generic risk factors.	probPrevalentCHRMsRiskFactorLogit
Prevalent Chronic Events, Months Since Start	Mean, Std Dev	Specifies the mean and standard deviation for the number of months the patient has already had the CHRM if they are a prevalent case	prevalentCHRMsMonthsSinceStartMean prevalentCHRMsMonthsSinceStartStdDev
Probability of Chronic Events, Monthly (Incidence)	HIV-, all	Specifies the monthly probability of an HIV-negative patient developing an incident condition of each CHRM. Stratified by gender and age.	probIncidentCHRMsHIVneg
Probability of Chronic Events, Monthly (Incidence)	HIV+	Specifies the monthly probability of an HIV-positive patient developing an incident condition of each CHRM. Stratified by gender, age, and true CD4 strata.	probIncidentCHRMs
Incidence Modifiers	On ART Rate Multipliers	Rate multipliers that modify the above probabilities if the patient is currently on ART treatment, stratified by true CD4 strata.	probIncidentCHRMsOnARTMult
Incidence Modifiers	Generic Risk Factors	Logit adjustments that modify the above probabilities when the patient has the corresponding generic risk factors.	probIncidentCHRMsRiskFactorLogit
Incidence Modifiers	History of Chronic Events	Logit adjustments that modify the above probabilities if the patient has any of the other CHRMs conditions. Does not apply to the incidence of other CHRMs in the same month that a CHRM first occurs.	probIncidentCHRMsPriorHistoryLogit
Probability of Death from Chronic Events, Monthly, Months Since Start	N1, N2	Specifies the time boundaries of months since developing each CHRM for its probability of death. Stages are broken up into three time periods – less than or equal to N1, greater than N1 but less than or equal to N2, and greater than N2.	probDeathCHRMsStageBounds
Probability of Death from Chronic Events, Monthly, Months Since Start	HIV-, all	Specifies the monthly probability of death for an HIV-negative patient from each CHRM. Stratified by time period, gender, and age.	probDeathCHRMsHIVneg
Probability of Death from Chronic Events, Monthly, Months Since Start	HIV+	Specifies the monthly probability of death for an HIV-positive patient from each CHRM. Stratified by time period, gender, age, and true CD4 strata.	probDeathCHRMs

Costs of Chronic Events, Monthly, Months Since Start	N1, N2	Specifies the time boundaries of months since developing each CHRM for its associated costs. Stages are broken up into three time periods – less than or equal to N1, greater than N1 but less than or equal to N2, and greater than N2.	costCHRMsStageBounds
Costs of Chronic Events, Monthly, Months Since Start	Costs	Specifies the monthly costs for each CHRM. Stratified by time period, gender, and age.	costCHRMs
Costs of Chronic Events Death		Specifies additional costs in the month of death for each CHRM when it is the cause of death.	costDeathCHRMs
QOL Multiplier of Chronic Events, Monthly, Months Since Start	N1, N2	Specifies the time boundaries of months since developing each CHRM for its associated QOL multiplier. Stages are broken up into three time periods – less than or equal to N1, greater than N1 but less than or equal to N2, and greater than N2.	QOLMultCHRMsStageBounds
QOL Multiplier of Chronic Events, Monthly, Months Since Start	QOL	Specifies the monthly QOL multiplier for each CHRM. Stratified by time period, gender, and age.	QOLMultCHRMs
QOL Multiplier of Chronic Events Death		Specifies additional QOL multiplier in the month of death for each CHRM when it is the cause of death.	QOLMultDeathCHRMs

Cost worksheet

Acute OI Event Costs	Off-ART, Treated	Cost incurred at an acute OI event, when the patient is treated for the OI (patient is of type that goes to clinic for OIs) and is not on a current ART regimen.	acuteOICostTreated
Acute OI Event Costs	Off-ART, Untreated	Cost incurred at an acute OI event, when the patient is not treated for the OI (patient is of type that does not go to clinic for OIs) and is not on a current ART regimen.	acuteOICostUntreated
Acute OI Event Costs	On-ART, Treated	Cost incurred at an acute OI event, when the patient is treated for the OI (patient is of type that goes to clinic for OIs) and is on a current ART regimen.	acuteOICostTreated
Acute OI Event Costs	On-ART, Untreated	Cost incurred at an acute OI event, when the patient is not treated for the OI (patient is of type that does not go to clinic for OIs) and is on a current ART regimen.	acuteOICostUntreated
CD4 Test Costs		Cost incurred at the time of an administered CD4 test.	CD4TestCost
HVL Test Costs		Cost incurred at the time of an administered HVL test.	HVLTestCost
Death Costs	Off-ART, Treated	Cost incurred in the event of an OI death, chronic AIDS death, or non AIDS death. The cost is assessed when the patient is not on a current ART regimen and, for an OI death, when the OI event is treated (patient is of type that goes to clinic for OIs).	deathCostTreated
Death Costs	Off-ART, Untreated	Cost incurred in the event of an OI death, chronic AIDS death, or non AIDS death. The cost is assessed when the patient is not on a current ART regimen and, for an OI death, when the OI event is not treated (patient is of type that does not go to clinic for OIs).	deathCostUntreated
Death Costs	On-ART, Treated	Cost incurred in the event of an OI death, chronic AIDS death, or non AIDS death. The cost is assessed when the patient is on a current ART regimen and, for an OI death, when the OI event is treated (patient is of type that goes to clinic for OIs).	deathCostTreated
Death Costs	On-ART, Untreated	Cost incurred in the event of an OI death, chronic AIDS death, or non AIDS death. The cost is assessed when the patient is on a current ART regimen and, for an OI death, when the OI event is not treated (patient is of type that does not go to clinic for OIs).	deathCostUntreated
Contact/Visit Costs		Cost incurred at the time of each clinical contact/visit with each patient.	clinicVisitCost
General Medicine costs		General medicine cost accrued by everyone each month.	generalMedicineCost
Routine Care Costs	HIV-pos, Off-ART	Routine state cost incurred for HIV-negative patients that are not on ART, stratified by True CD4, gender, and age.	routineCareCostHIVPositive
Routine Care Costs	HIV-pos, On-ART	Routine state cost incurred for HIV-negative patients that are on ART, stratified by True CD4, gender, and age.	routineCareCostHIVPositive

TB worksheet (See appendix 1)

QOL worksheet

Routine Care		QOL multiplier used at the end of each patient month with no acute OI event and not in the month of patient death. If the patient has no history of acute OIs, they will use the No Hist QOL value. If they have history of at least one OI, they will use the lowest QOL value out of all the OIs they have a history of.	routineCareQOL
Acute OIs		QOL multiplier used by each patient in the month of an acute OI event. In any given patient month, this QOL would be used instead of the Routine Care QOL or the Death QOL.	acuteOIQOL
Death		QOL multiplier used in the month of a death from an OI, used instead of the Routine Care QOL or Acute OI QOL for that month.	deathOIQOL
Background Non-AIDS QOL, Monthly		Specifies the monthly base QOL value used each month, determined by the patient's gender and age. All other QOL multipliers will be accumulated with this value.	nonAIDSBackgroundQOL
Enable 20% QOL Decrement		Switch for enabling 20% QOL Decrease for multiple OIs	enableQOLDecreaseMultipleOI

HIVTest worksheet

Enable HIV Testing Module		Enables simulation of population including HIV- and HIV+ individuals. If this is not specified, simulation will start will all patients detected as HIV-positive and in the chronic HIV state.	enableHivTesting
HIV Test Available		Specifies whether HIV tests are available to the population.	HIVTestAvailable
Lab Staging Available		Specifies whether Lab Staging is available to the population	CD4TestAvailable

Use alternate stopping rule		Enable a different target cohort size for the simulation, based on both the number of HIV+ patients and the total cohort size. If not using the alternate stopping rule, the regular cohort size input is used for the total number of HIV+ and HIV- individuals.	useAlternateStoppingRule
HIV+ total limit		Used with the alternate stopping rule. Specifies the total number of patients to run that will be used along with the cohort number of HIV+ patients specified in the RunSpecs input. Simulation will end only when both the number of HIV+ patients and this total number of patients has been reached.	totalCohortsWithHIVPositiveLimit
Cohort total limit		Used with the alternate stopping rule. Simulation will end when this absolute total number of patients has been reached, regardless of how many HIV+ ones have been simulated.	totalCohortsWithoutHIVPositiveLimit
Distribution of Initial HIV Prevalence		Percentage breakdown of the prevalence of HIV- and HIV+ individuals in the population on entry to the simulation, specified as – low risk HIV-, high risk HIV-, acute HIV+, or chronic HIV+	initialHIVDistribution
Distribution of Initial CD4		Mean and standard deviation distribution for acute HIV+ patients, will be used for both prevalent acute HIV+ and incident cases. Prevalent chronic HIV+ patients will have their CD4 level set according to the inputs in the Cohort tab.	initialAcuteCD4DistributionMean initialAcuteCD4DistributionStdDev
Distribution of Initial HVL		Probability distribution of initial HVL strata for acute HIV+ patients, will be used for both prevalent acute HIV+ and incident cases. Prevalent chronic HIV+ patients will have their HVL strata set according to the inputs in the Cohort tab.	initialAcuteHVLDistribution
HIV Incidence		Monthly probabilities of an uninfected individual becoming an incident HIV+ case. These probabilities are stratified by age in years and high/low risk behavior type.	probHIVInfection
Probability of (Prior) OIs for (Prevalent) Patients		Not defined as separate inputs. Prevalent acute HIV+ patients will have no OI history, and prevalent chronic HIV+ patients will use the OI history tables specified in the cohort tab. OI history will then determine if they are chronic symptomatic or asymptomatic	
Probability of HIV Detection for Prevalent HIV+ Patients		Specifies the probability of patients being detected as HIV+ upon model entry, stratified by their HIV state. This allows for the possibility of having some of the population already being detected when evaluating testing strategies.	probHIVDetectionInitial
Probability of HIV Detection on Presentation of OI		Specifies the probability of being detected as HIV positive due to the occurrence of an OI. The above parameter is used for detection from OI history; this will be used only during simulation when an acute OI is observed to determine if they become detected at that time.	probHIVDetectionWithOI
HIV Testing Frequency		Specifies the distribution of testing intervals (in months) between regularly scheduled HIV tests of undetected individuals in the population. An interval of 0 should be used to indicate no testing for those selected patients. All probabilities must sum to 1.	HIVTestingInterval HIVTestingProbability
Cost and QOL for HIV- and Undetected HIV+	HIV-, nonAIDS death	Specifies the monthly cost and base QOL for HIV- patients in the month of death (HIV- have nonAIDS death as their only possible cause of death).	deathCostHIVNegative deathQOLHIVNegative
Cost and QOL for HIV- and Undetected HIV+	Undetected HIV+ month, CD4 VHI–VLO	Specifies the monthly cost and base QOL for HIV+ patients that are undetected, stratified by their current CD4 level.	monthCostHIVUndetected monthQOLHIVUndetected
Cost and QOL for HIV- and Undetected HIV+	Undetected HIV+, chrAIDS or nonAIDS death	Specifies the cost in the month of death from chronic AIDS or non-AIDS causes for undected HIV+ patients, QOL will be set from the standard QOL inputs for that cause of death.	chronicDeathCostHIVUndetected nonAIDSDeathCostHIVUndetected
Acute to Chronic HIV State Transition	Mths from Acute to Chronic HIV	Specifies the number of months from the time of an individual's acute HIV infection to the chronic HIV state.	monthsFromAcuteToChronic
Acute to Chronic HIV State Transition	CD4 Change at Transition	The increase in the individual's CD4, stratified by current HVL before transition occurs, in the month of transition from acute HIV infection to chronic HIV.	CD4ChangeAtChronicHIVMean CD4ChangeAtChroncHIVStdDev
Acute to Chronic HIV State Transition	HVL (Actual & Setpt) Distribution	Probabilities for the individual's HVL setpoint, stratified by current HVL before transition, to move to a different HVL stratum in the month of transition from acute HIV infection to chronic HIV.	HVLDistributionAtChronicHIV
Distribution of Acceptance Rates		Probabilities that HIV- or undetected HIV+ individuals would agree to receive a HIV test. The first 3 rows specify the proportion of patients that will have the acceptance rates specified in the next 3 rows.	HIVTestAcceptDistribution HIVTestAcceptRate
Other Test Inputs	Screening Startup Cost	The one-time cost accrued in the month of an individual starting the HIV screening program, counted for all patients regardless of whether or not they ever accepts a test.	HIVTestInitialCost
Other Test Inputs	Added Cost for Test Non-Return	Additional cost to be accrued for any HIV test administered in which the individual does not return to obtain the test result.	HIVTestNonReturnCost
Other Test Inputs	Additional Cost in Mth of Detection	Additional cost accrued in the month of an HIV+ individual's detection.	HIVTestDetectionCost
Other Test Inputs	Background HIV Testing/Ident Rate	Monthly probability that an undetected HIV+ individual's infection is identified by some background means.	HIVBackgroundDetectionRate
Other Test Inputs	Background HIV Testing Cost	Additional cost accrued in the month of an HIV+ individual being detected via background testing means.	HIVBackgroundTestingCost
HIV Test Characteristics	HIV Test Result Return Rate	Probability assessed at each administered HIV test to determine whether the individual would return to obtain the test results.	HIVTestReturnRate
HIV Test Characteristics	HIV Positive Test Rate for State	Probability that each HIV test would return a positive result depending on the HIV state of the individual. To convert from the test's sensitivity and specifity, the prob of a positive result is for HIV- patients is 1 – specifity, and the prob of positive for HIV+ patients is the test's sensitivity for that particular state.	HIVTestPositiveRate
HIV Test Characteristics	Addit. HIV Test Cost for Pos Result	Added cost accrued at each HIV test which returns a positive result.	HIVTestPositiveCost
HIV Test Characteristics	Addit. HIV Test Cost for Neg Result	Added cost accrued at each HIV test which returns a negative result.	HIVTestNegativeCost

HIV Test Characteristics	HIV Test QOL Mult for Pos Result	QOL multiplier accrued at each HIV test which returns a positive result.	HIVTestPositiveQOLMultiplier
HIV Test Characteristics	HIV Test QOL Mult for Neg Result	QOL multiplier accrued at each HIV test which returns a negative result.	HIVTestNegativeQOLMultiplier
HIV Test Characteristics	HIV Test Cost	Cost of the HIV test, accrued each time the test is administered.	HIVTestCost
Lab Staging Characteristics	CD4 Test Acceptance Rate	Rate of accepting CD4 test	CD4TestAcceptRate
Lab Staging Characteristics	CD4 Test Result Return Rate	Rate of returning for results of CD4 test	CD4TestReturnRate
Lab Staging Characteristics	Screening Startup Cost (@ 1st Test)	Startup cost of CD4 test	CD4TestInitialCost
Lab Staging Characteristics	CD4 Test Cost	Cost of CD4 test	CD4TestCost
Lab Staging Characteristics	Added Cost for Test Non-Return	Cost added if not returning for results	CD4TestNonReturnCost
Lab Staging Characteristics	Added Cost for Test Return (clinic)	Cost added if returning for results	CD4TestReturnCost
Lab Staging Characteristics	CD4 Test Std Dev (% of curr)	The deviation of observed CD4 from true CD4	LabStageStdDev
Lab Staging Characteristics	Linkage to Care	The probability of going into care if return for results	CD4TestLinkRate

E. Additional Model Tools

E1. Sensitivity Analysis Tool

Starting with version cepac30i, an automated linear sensitivity analysis tool has been made available. This tool allows people to quickly create input files for 1-3 way sensitivity analysis. The macro can be invoked by right clicking anywhere on the input spreadsheet and select the 'SensitivityAnalysis' option. The '3 Way Sensitivity Analysis' form will then pop-up –
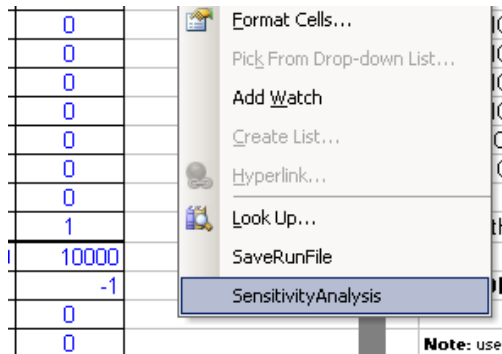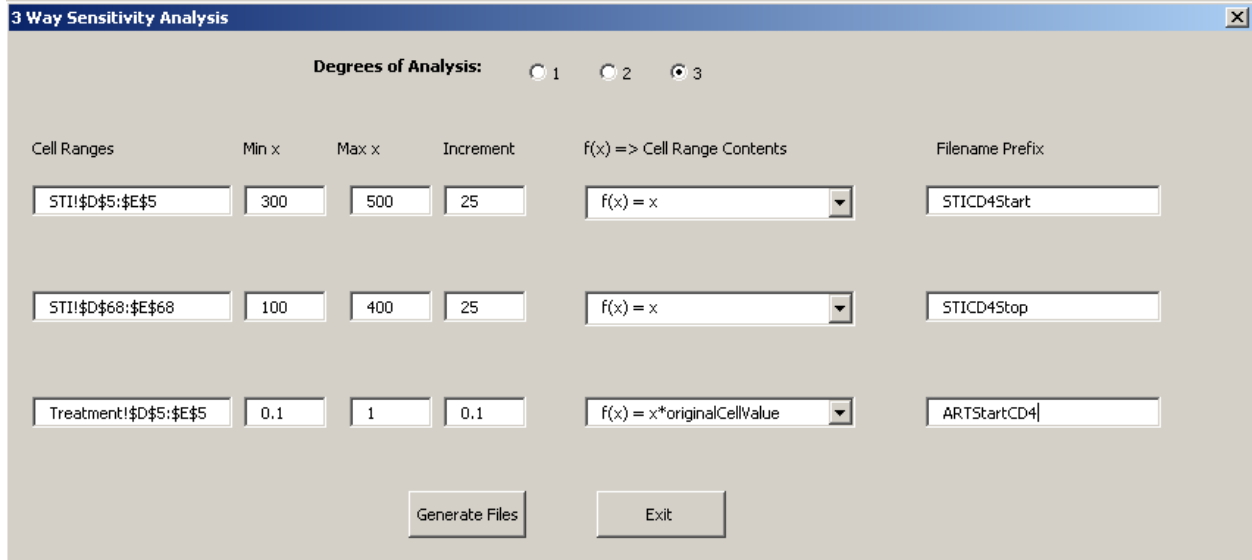
To use this form:
- Select desired degree of analysis. If user selects 1 degree, then the boxes for the 2 – 3 way analyses will be grayed out.
- For each desired degree of analysis
  - Double-click on form Cell Ranges. A pop-up window will allow you to select cells from any sheet within the workbook. If you have already selected those cells for another degree, a user prompt will ask you to pick different cells.
  - Select the f(x) you wish to use to fill in the selected input sheet values
  - Select the min and max value of x that will be used to fill in the selected input sheet values. The increment will determine which values are used between the min and max.
  - Enter a 'Filename Prefix' for the degree of analysis. This prefix will appear in the filenames of the generated input sheet so that you can identify the sensitivity analysis data point.
- Click Generate Files
- A file dialog will ask you to name a directory and base filename for all generated input sheets. Enter a filename and click 'Save'
- The sensitivity analysis tool will now generate the input files that correspond to each data point of the sensitivity analysis. It does this by replacing the selected cells with the value of f(x) for each x that was indicated. It will create input sheets for all combinations of f(x) of each degree of analysis.

For the example inputs on the above file, if we were to choose a base filename of exampleSA, the tool will create files (with the indicated values in the selected input cells) that are named:
> exampleSA,STICD4Start=300,STICD4Stop=100,ARTSTARTCD4=0.1.in
> exampleSA,STICD4Start=300,STICD4Stop=100,ARTSTARTCD4=0.2.in
> exampleSA,STICD4Start=300,STICD4Stop=100,ARTSTARTCD4=0.3.in
> …
> exampleSA,STICD4Start=300,STICD4Stop=125,ARTSTARTCD4=0.1.in
> exampleSA,STICD4Start=300,STICD4Stop=125,ARTSTARTCD4=0.2.in
> exampleSA,STICD4Start=300,STICD4Stop=125,ARTSTARTCD4=0.3.in
> …
> exampleSA,STICD4Start=300,STICD4Stop=150,ARTSTARTCD4=0.1.in
> exampleSA,STICD4Start=300,STICD4Stop=150,ARTSTARTCD4=0.2.in
> exampleSA,STICD4Start=300,STICD4Stop=150,ARTSTARTCD4=0.3.in
> …
> …

This will happen until all combinations of the values of STICD4Start, STICD4Stop, and ARTSTARTCD4 have been generated.

E2. Probabilistic Sensitivity Analysis Tool

The Probabilistic Sensitivity Analysis Tool is a tool outside the model that allows the creation of multiple input files with certain inputs determined from a draw from a specified distribution. This can also enable the use of Value of Information analysis. Check documentation for PSA to learn how to use the Probabilistic Sensitivity Analysis Tool.

E3. Multiple Cohorts Tool

The Multiple Cohorts Tool is a tool outside the model with the capacity to extract, combine, and weigh output from multiple CEPAC runs. It can extract output from many runs at once, even when one does not need to combine the outcomes. The MCT also possesses a time-varying component that allows the user to integrate subcohorts into the composite outcomes at user-defined time points. By simplifying the processes of extracting and combining CEPAC output, this tool reduces the amount of time necessary to compile CEPAC outcomes in analyses that require multiple subcohorts; allows for increased flexibility in the number of sub-cohorts that make up a single population; and streamlines the processes of extracting and weighing cohort-level data. For more information on the tool, including how to use it in analyses, please see the Multiple Cohorts Tool documentation.

F. Program Outputs of the Model

F1. Cohort Summary File

At the end of program execution, the program writes primary outcomes of the batch of runs to the popstats.out file. If the file does not exist, the program creates one with that name; if it already exists, the program appends to that file. It is important not to access the file, especially during program execution. If the file cannot be modified, the program will write the output to a new file, popstats.out-tmp.

The popstats.out file is tab-delimited and uses one line for each completed run. Information for each run includes average projected costs, average expected life months, average expected quality-adjusted life months, and the numbers of primary OI events per thousand patients. The runs are ordered by set, and by cost in ascending order. Incremental cost effectiveness ratios are calculated for runs within the same set. This ratio is defined as the additional cost divided by its additional clinical benefit (i.e. life months or quality-adjusted life months), compared to the next least costly strategy.

The initial columns of the summary file are as follows:

RUN SET	RUN NAME	RUN DATE	RUN TIME	Cohort	TOTAL COHORT					HIV+ PATIENTS		
					COST	LMs	QALMs	COST/LY	Cost/QALY	COST	LMs	QALMs
DefaultSet	noTst-3%dsc	12/17/2001	22:11:55	18347	46870	238.125	231.052			85992	215.574	202.598
DefaultSet	HIVtst-3%dsc	12/17/2001	22:11:46	18538	61475	242.484	235.076	dominated	dominated	111745	223.467	209.735
DefaultSet	noTst-0%dsc	12/17/2001	22:11:51	18347	92477	399.282	386.144	3396	3529	169668	338.864	314.760
DefaultSet	HIVtst-0%dsc	12/17/2001	22:11:40	18538	120022	407.916	394.061	38281	41753	218753	354.772	329.087

The remaining columns are:

PRIMARY OI CASES PER THOUSAND HIV+ PATIENTS							DTHS /1000			MTHS TO DET (PREVAL)	MTHS TO DET (INCID)	AVG CD4 AT DET (INCID)
pcp	mac	toxo	cmv	fungal	bactl	other	chrAIDS	nonAIDS	toxART			
290.2	85.4	35	183.5	134	0	367.4	660.3	203.3	0	16.66	242.898	213.836
235.6	79.6	35.7	188.2	141.4	0	362.2	621.7	244.6	0	8.486	231.623	308.464
290.2	85.4	35	183.5	134	0	367.4	660.3	203.3	0	16.66	242.898	213.836
235.6	79.6	35.7	188.2	141.4	0	362.2	621.7	244.6	0	8.486	231.623	308.464

F2. Run Summary File

At the completion of each run, an output summary file is created with the file extension ".out" describing the results of the run. The output summary file of each run is a tab delimited text file, and can loaded by programs such as Microsoft Excel for viewing. The file contains the results of the cohort simulation, which will be described below.
If the file cannot be modified, the output will instead be written to a file with the extension ".out-tmp"

F2a. Broad Measures

The very first section of the file characterizes broad measures:

POPULATION SUMMARY MEASURES (run completed

```
11/05/09,14:41:27)
[Program version 40a, build 2009-11-03]
  Outcome/Measure          Average      Std Dev      LB              UB
  Costs                     98257        62072        97040           99473
  Life Months               113.9894     66.4215      112.6876        115.2913
  Quality-Adj Life Mths     99.0623      58.739       97.911          100.2135
                            Avg Costs    Avg LMs      Avg QALMs
  Up to 0 ART(s) obsv fail  55271        53.1263      46.62
  Up to 1 ART(s) obsv fail  64815        59.2301      51.8512
  Up to 2 ART(s) obsv fail  69218        62.2393      54.4455
  Up to 3 ART(s) obsv fail  71629        64.2679      56.2187
  Up to 4 ART(s) obsv fail  98257        113.9894     99.0623
  Up to 5 ART(s) obsv fail  98257        113.9894     99.0623
  Up to 6 ART(s) obsv fail  98257        113.9894     99.0623
  Up to 7 ART(s) obsv fail  98257        113.9894     99.0623
  Up to 8 ART(s) obsv fail  98257        113.9894     99.0623
  Up to 9 ART(s) obsv fail  98257        113.9894     99.0623
  Up to 10 ART(s) obsv fail 98257        113.9894     99.0623
  Total Clinic Visits       395471
  Only HIV+ patients        98850        113.9019     98.9393
```

The first and second lines indicate the date and time the run was completed, and the version and build of the executable program. These items are intended to aid in bookkeeping, in particular noting when and how the file was produced.

The first table specifies the mean, standard deviation, and 95% confidence interval (specified by lower and upper bounds) of aggregate cohort costs in discounted dollars and life expectancies in discounted life months and discounted quality-adjusted life months. The second table describes a cross section of costs and life expectancies as the cohort progresses through each line of ART. "Up to 0 ART(s) obsv fail" describes all costs and life months accrued by patients before they are observed to have failed any ART regimen; "Up to 1 ART(s) obsv fail" describes all costs and life months accrued by patients observed to have failed at least one ART regimen; and so on.

The last line indicates the total number of clinic visits made in the cohort simulation.

F2b. HIV Screening

HIV SCREENING MODULE

HIV+ Cases (Preval):	100	HIV- Cases (Preval):	35	
HIV+ Cases (Incident):	0	AvgMths to Inf (Incid):	0	(0.00 SD)
Total HIV+ Cases:	100			

	HIVasym	HIVsymp	HIVacut	HIVneg_loRisk	HIVneg_hiRisk
Init States (Prevalence):	100	0	0	35	0

CD4 at Detection (Preval):	HIVasym	HIVsymp	HIVacut	Total
CD4vhi	37	0	0	37
CD4_hi	20	3	0	23
CD4mhi	5	1	0	6
CD4mlo	2	2	0	4
CD4_lo	2	1	0	3
CD4vlo	2	6	0	8
Total	68	13	0	
Mean CD4 Count:	550.98	160.21	0	488.27

HVL at Detection (Preval):	HIVasym	HIVsymp	HIVacut	Total
HVLvhi	0	0	0	0
HVL_hi	20	4	0	24
HVLmhi	17	2	0	19
HVLmed	15	2	0	17
HVLmlo	8	2	0	10
HVL_lo	8	3	0	11
HVLvlo	0	0	0	0

CD4 at Detection (Incid):	HIVasym	HIVsymp	HIVacut	Total	Total %
CD4vhi	0	0	0	0	0
CD4_hi	0	0	0	0	0
CD4mhi	0	0	0	0	0
CD4mlo	0	0	0	0	0
CD4_lo	0	0	0	0	0
CD4vlo	0	0	0	0	0
Total	0	0	0		
Mean CD4 Count:	0	0	0	0	

HVL at Detection (Incid):	HIVasym	HIVsymp	HIVacut	Total	Total %
HVLvhi	0	0	0	0	0
HVL_hi	0	0	0	0	0
HVLmhi	0	0	0	0	0
HVLmed	0	0	0	0	0
HVLmlo	0	0	0	0	0
HVL_lo	0	0	0	0	0
HVLvlo	0	0	0	0	0

CD4 at Linkage:	HIVasym	HIVsymp	HIVacut		Total	
CD4vhi	9	2	0		11	
CD4_hi	3	6	0		9	
CD4mhi	1	5	0		6	
CD4mlo	1	9	0		10	
CD4_lo	1	3	0		4	
CD4vlo	0	13	0		13	
Total	15	38	0			
Mean CD4 Count:	562.67	189.17	0		294.88	

HVL at Linkage:	HIVasym	HIVsymp	HIVacut		Total	
HVLvhi	0	0	0		0	
HVL_hi	4	11	0		15	
HVLmhi	4	5	0		9	
HVLmed	3	12	0		15	
HVLmlo	1	6	0		7	
HVL_lo	3	4	0		7	
HVLvlo	0	0	0		0	

Avg Mths to Det (Preval):	6.15	(17.36 SD)	Avg Age Mths at Det:	402.15	(17.36 SD)
Avg Mths to Det (Incid):	0	(0.00 SD)	Avg Age Mths at Det:	0	(0.00 SD)
Avg Mths to Det Since Inf (Incid):	0	(0.00 SD)			
Avg Mths to Linkage:	32.11	(29.72 SD)	Avg Age Mths at Linkage:	428.11	(29.72 SD)

	Male	Female
Gender at Detection:	81	0

	initial	HIVscreening	HIVscreening PrevDetected	HIVbackground	presentingBkgd PrevDetected	presentingOI	presentingOI PrevDetected	unidentified
Means of Detection (Preval):	0	68	0	0	0	13	25	19
Means of Detection (Incid):	0	0	0	0	0	0	0	0
Means of Linkage:	0	15	0	0	0	13	25	47
Mean months to linkage:	0	0	0	0	0	38.31	48.16	0
SD(mo to linkage):	0	0	0	0	0	25.43	25.31	0

	PCP	MAC	TOXO	CMV	FUNG	BACT	NONE1	NONE2
Presenting OI:	7	0	0	2	1	0	0	0

	HIVasym	HIVsymp	HIVacut	HIVneg_loRisk	HIVneg_hiRisk
Patient Test Accept Distrib 1:	0	0	0	0	0
Patient Test Accept Distrib 2:	0	0	0	0	0
Patient Test Accept Distrib 3:	100	0	0	35	0

	Accept	Refuse
HIV Test accepts:	97	37
HIV Test returns:	97	0
Lab Staging accepts:	68	0

Lab Staging returns:	68	0					
Linkage To Care (Lab Staging):	15	53					
	[/5000mths]	[/18mths]	[/24mths]	[/36mths]	[/120mths]		
Patient Testing Freq in Prog:	135	0	0	0	0		
	truePos	falsPos	trueNeg	falsNeg	Total		
#s Test Results (Preval):	68	N/A	N/A	0	68		
#s Test Results (Incid):	0	N/A	N/A	0	0		
#s Test Results (HIVneg):	N/A	29	0	N/A	29		
	HIVasym	HIVsymp	HIVacut	HIVneg_loRisk	HIVneg_hiRisk		
#s Tests Done by State:	68	0	0	29	0		
#s Lab Staging Accepts by State:	68	0	0				
#s Lab Staging Return For Results by State:	68	0	0				

#s Lab Staging Num Return For Results		TRUE CD4vlo	TRUE CD4_lo	TRUE CD4mlo	TRUE CD4mhi	TRUE CD4_hi	TRUE CD4vhi	TOTAL
OBSV	CD4vlo	2	0	0	0	0	0	2
OBSV	CD4_lo	0	2	0	0	0	0	2
OBSV	CD4mlo	0	0	2	0	0	0	2
OBSV	CD4mhi	0	0	0	5	0	0	5
OBSV	CD4_hi	0	0	0	0	20	0	20
OBSV	CD4vhi	0	0	0	0	0	37	37
	TOTAL	2	2	2	5	20	37	68

#s Lab Staging Num Link To Care		TRUE CD4vlo	TRUE CD4_lo	TRUE CD4mlo	TRUE CD4mhi	TRUE CD4_hi	TRUE CD4vhi	TOTAL
OBSV	CD4vlo	0	0	0	0	0	0	0
OBSV	CD4_lo	0	1	0	0	0	0	1
OBSV	CD4mlo	0	0	1	0	0	0	1
OBSV	CD4mhi	0	0	0	1	0	0	1
OBSV	CD4_hi	0	0	0	0	3	0	3
OBSV	CD4vhi	0	0	0	0	0	9	9
	TOTAL	0	1	1	1	3	9	15

The next section provides details about the HIV testing module, and will have all zero value if it is not enabled. With the HIV testing module enabled, the program makes a draw at the time of patient initialization of HIV status. Those drawn to be HIV-positive are considered prevalent cases on entry to the model. Initially HIV-negative patients who become HIV-positive during simulation are considered incident cases. The first table specifies the total number of HIV-positive and HIV-negative prevalent cases. The next line specifies the total number of incident cases in the cohort simulation. The average months to infection of the incident cases starting from month 0 is given along with the standard deviation. The total number of HIV-positive cases in the run is simply the sum of prevalent and incident cases, and includes all HIV-positive patients at the time of death.

The next table indicates the distribution of patients by HIV state at initiation time, i.e. the prevalent cases. Note that `HIVasym`, `HIVsymp`, and `HIVacut` constitute the HIV-positive states. The HIV-negative state is divided into the low risk `HIVneg_loRisk` and high risk `HIVneg_hiRisk` states.

The next four tables specify the breakdown of patients' CD4 and HVL in the month of detection and linkage of their HIV-positive status. The first two tables apply only to the prevalent cases, and the second two apply only to the incident cases.

The `Avg Mths to Det` values specify the average number of months (with standard deviation) to detection of HIV-positive status counting from month 0, for the prevalent and incident cases. The average age in months is also given for those detected cases.

The `Gender at Detection` statistic specifies the breakdown of HIV-positive men and women in the cohort who are detected as such in the model.

The next table details the means with which HIV-positive patients are identified and linked, if at all, for the prevalent and incident cases separately. Patients can be detected via a HIV screening program, background HIV testing, or a presenting OI. Patient not detected at the time of death are classified as `unidentified`. For both prevalent and incident cases identified by presenting OI, the next table provides a breakdown of the types of OI events triggering their HIV-positive detection.

Following is a count of the numbers of patients that have each testing acceptance rate. After that, the total numbers of tests that are accepted or refused are listed, followed by the number that return or do not return for results. The initial draw for frequency of HIV testing for each patient is also listed in the next table.

The next table specifies the total number of HIV and lab staging test results given to HIV+ prevalent, HIV+ incident, and HIV- cases. The next table breaks down all HIV tests done by patients' HIV states at the time of the tests.

The last table specifies the number of people who return for lab staging test results and link to care stratified by both observed and true cd4.

F2c. Detailed Life Expectancy

Following the optional HIV testing section is a breakdown of patients' discounted life expectancy:

LIFE MONTH SURVIVAL OF ENTIRE COHORT							
LM bucket (UB, excl):	2	4	6	8	10	12	14
# Patients:	146	144	126	102	78	102	97
LM Min:	0.5		LM Max:	341.5195			
LM Median:	116.7788		LM AvgDev:	54.6104			
LM Mean:	113.9894		LM StdDev:	66.4215		LM AvgDev:	54.6678
LM Variance:	4411.8111		LM Skew:	0.1303		LM Kurtosis:	-0.595
Cost Mean:	98256.66		Cost StDv:	62072.32			
QALM Mean:	99.0623		QALM StDv:	58.739			
LIFE MONTH SURVIVAL EXCLUDING LONGEST 5% (500 patients)							
LMs							

LM bucket (UB, excl):	1	2	3	4	5	6	7
# Patients:	84	62	74	70	66	60	55
LM Min:	0.5		LM Max:	223.7071			
LM Median:	113.1888		LM AvgDev:	50.3534			
LM Mean:	106.804		LM StdDev:	59.8727		LM AvgDev:	50.5885
LM Variance:	3584.7421		LM Skew:	-0.1292		LM Kurtosis:	-1.0044
Cost Mean:	97696.06		Cost StDv:	61224.6			
QALM Mean:	92.4806		QALM StDv:	52.3245			

LIFE MONTH SURVIVAL EXCLUDING SHORTEST 5% (500 patients)
LMs

LM bucket (UB, excl):	9	11	13	15	17	19	21
# Patients:	59	90	100	89	84	88	105
LM Min:	7.44		LM Max:	341.5195			
LM Median:	121.731		LM AvgDev:	51.3866			
LM Mean:	119.8038		LM StdDev:	62.9892		LM AvgDev:	51.4047
LM Variance:	3967.6381		LM Skew:	0.1674		LM Kurtosis:	-0.482
Cost Mean:	102450.74		Cost StDv:	60746.4			
QALM Mean:	104.1193		QALM StDv:	55.8587			

LIFE MONTH SURVIVAL EXCLUDING LONGEST & SHORTEST 5% (1000 patients)
LMs

LM bucket (UB, excl):	8	9	10	11	12	13	14
# Patients:	18	41	37	53	49	51	46
LM Min:	7.44		LM Max:	223.7071			
LM Median:	116.7788		LM AvgDev:	46.9563			
LM Mean:	112.5422		LM StdDev:	56.1964		LM AvgDev:	47.0962
LM Variance:	3158.0327		LM Skew:	-0.1269		LM Kurtosis:	-0.9322
Cost Mean:	102092		Cost StDv:	59790.8			
QALM Mean:	97.453		QALM StDv:	49.1934			

These statistics were intended only for debugging of patient survival. The model keeps track of only the first 1,000,000 HIV-positive patients to avoid excessive memory usage. The number of patients in each LM bucket can be used to produce a histogram of patient survival by life months, as in the following graph of a run with 1 million patients:
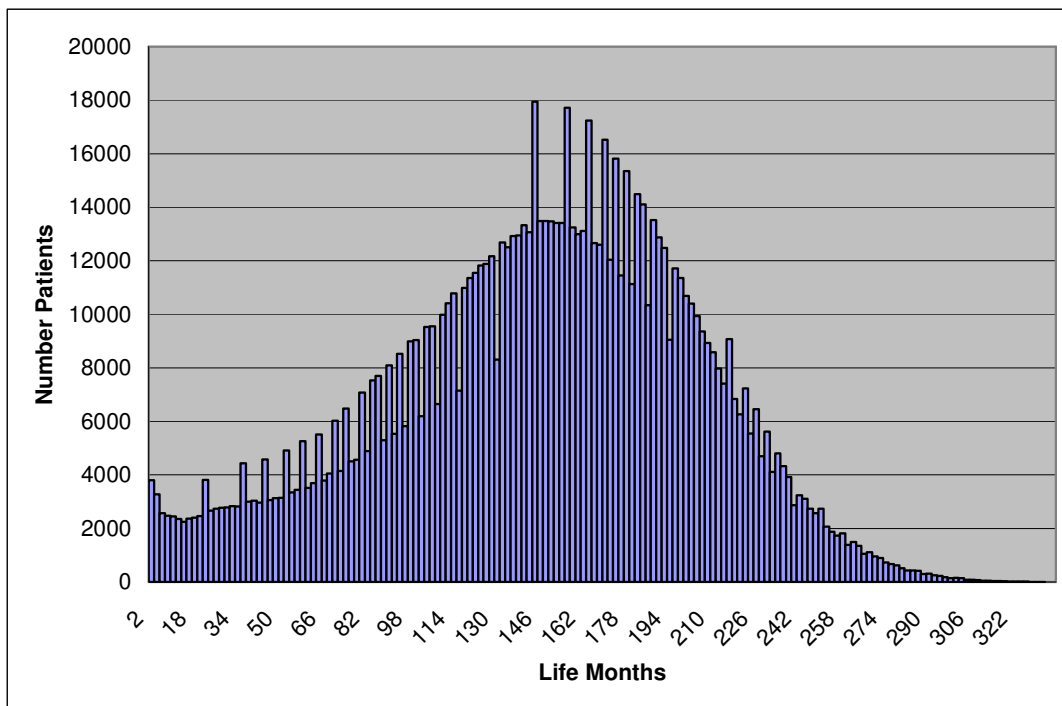
Specific outputs in this section will not be further discussed in this document.

F2d. Initial Characteristics

Next is a section describing the initial characteristics of the cohort:

```
INITIAL DISTRIBUTIONS
   CD4 Count Level      # Patients          HVL Setpt Lvl   # Patients          Curr HVL Lvl    # Patients
   VHI (>500)                6325           VHI (>100k)             0            VHI                     0
   HI (300-500)              1762           HI (30k-100k)        2544            HI                   2544
   MHI (200-300)             1095           MHI (10k-30k)        2516            MHI                  2516
   MLO (100-200)              389           MED (3k-10k)         2451            MED                  2451
   LO (50-100)                123           MLO (500-3k)         1574            MLO                  1574
   VLO (0-50)                 246           LO (20-500)           855            LO                    855
                                            VLO (0-20)              0            VLO                     0
   Avg Init Age(Mths):        417
                                            Female
   Male Patients:            9940           Patients:               0
                         PCP          MAC   TOXO          CMV            FUNG    BACT         NONE1
   Prior OI Histories
   Distrib:                  410    435           435           414     377              0           0
```

The first set of tables here describes the distribution of patients on entry to the model by CD4 strata, HVL setpoints, and actual HVL. The other statistics are the average age (in months), gender breakdown, and numbers of patients with histories of each OI type at the time of initialization.

F2e. Opportunistic Infections and Death Events

The following tables describe the numbers of OI events:

OI SUMMARIES									
Type/OI	PCP		MAC		TOXO		CMV		FUNG
# Primary OIs		2300		796		237		1163	680
# Secondary OIs		286		410		231		8473	51
Primary OIs	PCP		MAC		TOXO		CMV		FUNG
CD4vhi		197		50		27		44	50
CD4_hi		137		67		25		54	53
CD4mhi		273		55		32		115	54
CD4mlo		627		126		27		126	142
CD4_lo		403		107		44		125	113
CD4vlo		663		391		82		699	268
Secondary OIs	PCP		MAC		TOXO		CMV		FUNG
CD4vhi		64		145		131		2462	21
CD4_hi		28		49		47		664	8
CD4mhi		33		45		24		807	4
CD4mlo		53		37		9		727	7
CD4_lo		29		27		4		421	5
CD4vlo		79		107		16		3392	6
Detected OIs	PCP		MAC		TOXO		CMV		FUNG
CD4vhi		500		447		385		2447	304
CD4_hi		226		185		125		720	112
CD4mhi		338		135		100		856	98
CD4mlo		621		169		48		784	150
CD4_lo		414		129		41		502	115
CD4vlo		744		480		89		3717	276
Total		2843		1545		788		9026	1055

The first table details the total number of OI events of the cohort. Primary OIs are defined as the first occurrence of each OI type for each patient. Any subsequent OI event of the same type as one in each patient's history is accrued as a secondary OI. Incidence of primary OIs, secondary OIs, and detected OIs is further broken down by patients' actual CD4 strata in the month of those events.

The following tables provide results of the optional OI history logging mechanism, if not enabled these values will all be N/A. Actual outputs provide results for each program defined OI type – only PCP and MAC are given here for reasons of brevity.

```
PRIOR OI HIST PROB AS PROPORTION OF PATIENTS (LOGGED)
OI: pcp    CD4vhi     CD4_hi     CD4mhi          CD4mlo     CD4_lo     CD4vlo     Total
HVLvhi     N/A        N/A        N/A             N/A        N/A        N/A        N/A
HVL_hi     N/A        0          0.166666667     0          0          0.6        0.16
HVLmhi     N/A        0          0.166666667     0.333333   0          0          0.085714
HVLmed     N/A        0          0.25            0.333333   0.5        1          0.222222
HVLmlo     N/A        0.333333   0               0          0.666667   N/A        0.333333
HVL_lo     N/A        0          0               N/A        0          N/A        0
HVLvlo     N/A        N/A        N/A             N/A        N/A        N/A        N/A
Total      N/A        0.0625     0.15            0.2        0.333333   0.5
OI: mac    CD4vhi     CD4_hi     CD4mhi          CD4mlo     CD4_lo     CD4vlo     Total
HVLvhi     N/A        N/A        N/A             N/A        N/A        N/A        N/A
HVL_hi     N/A        0          0               0          0          0.4        0.08
HVLmhi     N/A        0          0               0          0          0.5        0.028571
HVLmed     N/A        0          0               0.333333   0          0          0.055556
HVLmlo     N/A        0          0               0          0          N/A        0
HVL_lo     N/A        0          0.333333333     N/A        0          N/A        0.142857
HVLvlo     N/A        N/A        N/A             N/A        N/A        N/A        N/A
Total      N/A        0          0.05            0.066667   0          0.375
…
PRIOR OI HIST PROB BY PATIENT MTHS (LOGGED)
OI: pcp    CD4vhi     CD4_hi     CD4mhi          CD4mlo     CD4_lo     CD4vlo     Total
HVLvhi     N/A        N/A        N/A             N/A        N/A        N/A        N/A
HVL_hi     0.293006   0.114973   0.139784946     0.150289   0.233766   0.142857   0.193294
HVLmhi     0.099432   0.05896    0.056372549     0.09611    0.090426   0.009404   0.070524
HVLmed     0.098985   0.141689   0.191836735     0.145833   0.22807    0.235294   0.134284
HVLmlo     0.123649   0.041588   0.15819209      0.068966   0.130435   0.027027   0.095211
HVL_lo     0.097054   0.101907   0.139186296     0.101933   0.151832   0.184211   0.107087
HVLvlo     N/A        N/A        N/A             N/A        N/A        N/A        N/A
Total      0.120502   0.088906   0.12744437      0.108944   0.148479   0.092616
OI: mac    CD4vhi     CD4_hi     CD4mhi          CD4mlo     CD4_lo     CD4vlo     Total
HVLvhi     N/A        N/A        N/A             N/A        N/A        N/A        N/A
HVL_hi     0.166352   0.168449   0               0          0.090909   0.087912   0.114398
HVLmhi     0.008523   0.001156   0               0          0          0.144201   0.018144
HVLmed     0.007614   0.002725   0.204081633     0.140625   0.017544   0.323529   0.057041
HVLmlo     0.010804   0.00189    0.016949153     0.017241   0.021739   0          0.009014
HVL_lo     0.027946   0.015495   0.047109208     0.010545   0.010471   0.105263   0.026119
HVLvlo     N/A        N/A        N/A             N/A        N/A        N/A        N/A
Total      0.033261   0.024128   0.050573163     0.023537   0.019678   0.116395
…
```

The first section details the proportion of patients with a history of each OI type by patients' current actual CD4 and HVL. Note that this proportion represents an arbitrary month for each patient, specifically the first month for each patient in which the OI history logging criteria apply. There are two primary reasons for this. Because the OI history logging mechanism is intended to bootstrap the OI history characteristics of some randomized cohort at some particular point in time, it makes sense to use at most one arbitrary month for each patient and imagine all such selected patient months as concurrent for the desired cohort. Second, picking other specific, non-random points in time may skew cohort characteristics – for example, using the patients' last months of life skews results away from a truly randomized starting cohort.

The second section details the proportion of patient months with a history of each OI type by patients' current actual CD4 and HVL. The actual calculation of this proportion of patient months with a given OI history over the total number of patient months is described in more detail in the *Prior OI History at Entry and Logging Mechanism* description.

The following tables detail statistics about death events:

```
CAUSES OF DEATH
  CD4 Count Level    PCP         MAC        TOXO        CMV        FUNG
  CD4vhi                9          5          28         129          4
```

CD4_hi	4	4	9	41	3
CD4mhi	12	5	8	35	1
CD4mlo	37	10	11	44	5
CD4_lo	13	9	12	23	3
CD4vlo	16	19	18	185	8
# Deaths	91	52	86	457	24
HIVnegs	N/A	N/A	N/A	N/A	N/A
Death Distrib	CD4vhi	CD4_hi	CD4mhi	CD4mlo	CD4_lo
HVLvhi	0	0	0	0	0
HVL_hi	339	188	173	248	154
HVLmhi	422	214	219	250	157
HVLmed	483	223	234	322	175
HVLmlo	408	186	187	232	124
HVL_lo	230	102	106	96	53
HVLvlo	155	30	19	9	2

The total number of deaths is given by each possible cause of death, as well as stratified by CD4 level at the time of death. The possible causes of death include acute OI, chronic AIDS, non AIDS, and ART toxicity. The second table shows the distribution of CD4 and HVL levels at the time of death.

F2f. Aggregate Survival and Costs

The following sections describe the total life months and costs accrued by the simulated cohort:

OVERALL SURVIVAL							
CD4 Strata:	CD4vhi	CD4_hi	CD4mhi	CD4mlo	CD4_lo	CD4vlo	Total
Life Months [woOIHist]	395317	161711	122366	61104	21232	35496	797226
Life Months [w.OIHist]	57224	21321	18733	16720	10443	31416	155858
Life Months [Total]	452541	183032	141099	77824	31674	66912	953084
HVL Strata:	HVLvhi	HVL_hi	HVLmhi	HVLmed	HVLmlo	HVL_lo	HVLvlo
Life Mths, HVL Setpt	0	222985	238981	242141	151236	97741	0
Life Mths, Curr HVL	0	167512	202850	228038	178645	117761	58277
OI:	PCP	MAC	TOXO	CMV	FUNG	BACT	NONE1
Life Mths, no OI hist	906147	927408	936371	933161	930041	953084	953084
Life Mths, with OI hist	46937	25676	16713	19923	23043	0	0
	HIVneg	unidentHIV+	identHIV+	(HIVpos)			
LMs by HIV State:	186810	61553	891531	953084			
	LMs	QALMs					
				LMs in "Reg CEPAC":			
LMs in HIV Scr Module:	186810	172633			953084		

Total discounted life months accrued by all patients in the cohort are broken down by several dimensions. The first table breaks down overall life months by current actual CD4 strata of each patient month, and by whether the patient has a history of any OI. The second table breaks down total life months by patients' HVL setpoints and by patients' current actual HVL strata. The next table breaks down for each OI the total number of patient months spent with and without a history of that OI. The last two tables are useful when the HIV screening module is enabled. Overall discounted life months are broken down by HIV states: HIV-negative, unidentified HIV-positive, identified HIV-positive, and total HIV-positive. The total life months and quality-adjusted life months accrued in the HIV screening module as well as the total life months spent in the cohort simulation outside of the HIV screening module are given at the end.

OVERALL COSTS								
CD4 Strata:	CD4vhi	CD4_hi	CD4mhi	CD4mlo	CD4_lo	CD4vlo	Total	
Costs [woOIHist]	276614259	137953754	119893892	62323143	18461623	53050844	668297515	
Costs [w.OIHist]	95401386	39138830	37013492	31151257	15877097	95686974	314269036	
Costs [Total]	372015646	177092584	156907384	93474399	34338720	148737818	982566551	
HVL Strata:	HVLvhi	HVL_hi	HVLmhi	HVLmed	HVLmlo	HVL_lo	HVLvlo	
Costs, HVL Setpt	0	239856994	242245013	231266408	135547129	133651006	0	
Costs, Curr HVL	0	151179269	184263268	208843649	179905709	165501466	92873190	
Direct Proph Costs	PCP	MAC	TOXO	CMV	FUNG	BACT	NONE1	NONE2
Proph 1	0	0	0	0	0	0	0	0
Proph 2	0	0	0	0	0	0	0	0
Proph 3	0	0	0	0	0	0	0	0

Total Proph Costs	0		0		0		0		0		0		0	0
	ART 1		ART 2		ART 3		ART 4		ART 5	ART 6		ART 7		ART 8
Direct ART Costs:	110315226		86480953		72058628		61572022			0		0		0	0
	CD4 Tests		HVL Tests		ClinicVisits									
Testing Costs:	26843141		39920632		0									
	Tests		Misc											
HIV Screening Costs:	0		0											

	Direct Medical	DirectNon Medical	TimeCosts	Indirect	Unclassified		DrugCosts	Toxicity
Total Undiscounted Costs:	884435835	0	0	0	0		413736214	0

Like total cohort life months, overall discounted costs accrued by all the patients are broken down by current actual CD4 (with and without any history of an OI), and HVL setpoint and current actual HVL strata. The discounted direct costs of drugs and testing incurred by the entire cohort are given for all the possible prophylaxis drugs, ART regimens, both CD4 and HVL testing, HIV tests and program-related costs of HIV screening (only if the HIV screening module is enabled). ART costs are split into initial and monthly costs to enable the use of the Cost adjustment tool. Total undiscounted costs are also given in the final table for the various classifications of total costs, and drug and toxicity costs.

F2g. TB Summary Information

This section summarizes outputs about TB infections and treatments in the patient cohort:

TB SUMMARY EVENTS				
TB State On Entry:	latent	active	treatment	historyActive
dsTB	0	0	0	0
mdrTB	0	0	0	0
xdrTB	0	0	0	0
Start on TB Treatment:	line1	rept1	line2	line3
dsTB	4142	0	482	104
mdrTB	2760	0	762	308
xdrTB	2951	0	1023	656
Dropout TB Treatment:	line1	rept1	line2	line3
dsTB	0	0	0	0
mdrTB	0	0	0	0
xdrTB	0	0	0	0
TB Cure at Treatment Dropout:	line1	rept1	line2	line3
dsTB	0	0	0	0
mdrTB	0	0	0	0
xdrTB	0	0	0	0
Complete TB Treatment:	line1	rept1	line2	line3
dsTB	1837	0	446	95
mdrTB	1303	0	705	281
xdrTB	1388	0	948	612
TB Cure at Treatment Completion:	line1	rept1	line2	line3
dsTB	917	0	206	42
mdrTB	636	0	346	140
xdrTB	708	0	479	301
TB Increase Resistance at Treatment Completion:	line1	rept1	line2	line3
dsTB	438	0	136	27
mdrTB	343	0	187	84
xdrTB	0	0	0	0
	dsTB	mdrTB	xdrTB	
Total TB Latent Infections	2839	1665	1641	
Total TB Active Infections	3470	2094	2035	
Total Reactivations from Latent TB	615	347	357	
Total Reinfections from Latent TB	1400	880	861	
Total Relapses from History Active TB	672	666	916	
Total Reinfections from History Active TB	1014	0	0	
Total TB Spontaneous Resolution	6	23	90	
Total Deaths from TB			95	
	line1	rept1	line2	line3
Total TB Treatment Minor Toxicity	0	0	0	0
Total TB Treatment Major Toxicity	0	0	0	0

	Proph1	Proph2	Proph3
Total TB Proph Minor Toxicity	0	0	0
Total TB Proph Major Toxicity	0	0	0

The first table details the number of patients with each initial TB state upon model entry. The next set of tables describes the TB treatment statistics stratified by each line of treatment. These metrics include the number of patients that start treatment, dropout of treatment, are cured at dropout, complete treatment, are cured at completion, and get increase resistance from failed treatment. The subsequent tables report the number of TB infections, stratified by type if infection and its drug resistance. The number of TB deaths and toxicities are also provided.

F2h. Lost to Follow Up and Return to Care

This section reports the number of patients that become lost to follow up and subsequently return to care:

LOST TO FOLLOW UP AND RETURN TO CARE STATS								
Total persons experiencing LTFU:	0							
Total deaths while LTFU:	0							
	CD4vhi	CD4_hi	CD4mhi	CD4mlo	CD4_lo	CD4vlo	Total	
Total LTFU by CD4	0	0	0	0	0	0	0	
Total RTC by CD4	0	0	0	0	0	0	0	
	ART1	ART2	ART3	ART4	ART5	ART6	ART7	
Total LTFU by ART:	0	0	0	0	0	0	0	
Total RTC by ART continuing on previous ART:	0	0	0	0	0	0	0	
Total RTC by ART switching to next ART:	0	0	0	0	0	0	0	

The statistics show the total number of patients that ever become LTFU and total deaths while LTFU. The next table shows the number of times lost and returned stratified by CD4. The last table shows how many patients were lost on each ART line (or pre-ART or post-ART), and how many were given the previous or next ART line upon return to care.

F2i. Prophylaxis

This section simply summarizes the total number of minor and major toxicity events due to OI prophylaxes:

OI PROPH TOXICITY EVENTS							
Minor Tox Events	pcp	mac	toxo	cmv	fungal	bactl	other
Proph 1	8	0	0	0	0	0	0
Proph 2	0	0	0	0	0	0	0
Proph 3	0	0	0	0	0	0	0
Proph 4	0	0	0	0	0	0	0
Proph 5	0	0	0	0	0	0	0
Total	8	0	0	0	0	0	0
Major Tox Events	pcp	mac	toxo	cmv	fungal	bactl	other
Proph 1	3	0	0	0	0	0	0
Proph 2	0	0	0	0	0	0	0
Proph 3	0	0	0	0	0	0	0
Proph 4	0	0	0	0	0	0	0
Proph 5	0	0	0	0	0	0	0
Total	3	0	0	0	0	0	0

The following section details the number of primary/secondary OI prophylaxis that were initiated, and the true CD4 and observed CD4 at the time of initiation -

PRIMARY OI PROPH MEAN CD4 AT INIT								
	Proph1 True	Obsv CD4	Times Init'd	Proph2 True	Obsv CD4	Times Init'd	Proph3 True	Obsv CD4	Times Init'd
BCIM	0	0	0	0	0	0	0	0	0

```
BCIS    0        0        0        0        0        0        0        0        0
FNGM    0        0        0        0        0        0        0        0        0
FNGS    0        0        0        0        0        0        0        0        0
MLR     0        0        0        0        0        0        0        0        0
ISO     0        0        0        0        0        0        0        0        0
TOXO    0        0        0        0        0        0        0        0        0
MAC     0        0        0        0        0        0        0        0        0
PCP     0        0        0        0        0        0        0        0        0
NONE1   0        0        0        0        0        0        0        0        0
NONE2   0        0        0        0        0        0        0        0        0
NONE3   0        0        0        0        0        0        0        0        0
NONE4   0        0        0        0        0        0        0        0        0
OTHM    0        0        0        0        0        0        0        0        0
OTHS    0        0        0        0        0        0        0        0        0
SECONDARY OI PROPH MEAN CD4 AT INIT
        Proph1 True  Obsv CD4  Times Init'd  Proph2 True  Obsv CD4  Times Init'd  Proph3 True  Obsv CD4  Times Init'd
BCIM    0        0        0        0        0        0        0        0        0
BCIS    0        0        0        0        0        0        0        0        0
FNGM    0        0        0        0        0        0        0        0        0
FNGS    0        0        0        0        0        0        0        0        0
MLR     0        0        0        0        0        0        0        0        0
ISO     0        0        0        0        0        0        0        0        0
TOXO    0        0        0        0        0        0        0        0        0
MAC     0        0        0        0        0        0        0        0        0
PCP     0        0        0        0        0        0        0        0        0
NONE1   0        0        0        0        0        0        0        0        0
NONE2   0        0        0        0        0        0        0        0        0
NONE3   0        0        0        0        0        0        0        0        0
NONE4   0        0        0        0        0        0        0        0        0
OTHM    0        0        0        0        0        0        0        0        0
OTHS    0        0        0        0        0        0        0        0        0
```

F2j. ART Statistics

This first section details the number of months in each suppression state for each ART line, stratified by the patient's true HVL that month -

```
MONTHS IN SUPPRESSED/PARTIALLY SUPPRESSED/FAILED STATES ON ART
                  ART1   ART2   ART3   ART4   ART5  ART6  ART7  ART8  ART9  ART10  Total
Months suppressed 32998  23809  17704  13412  0     0     0     0     0     0      87923
Months partially suppressed
  HVLvhi          0      0      0      0      0     0     0     0     0     0      0
  HVL_hi          5471   4180   2617   2111   0     0     0     0     0     0      14379
  HVLmhi          5920   4428   3205   2294   0     0     0     0     0     0      15847
  HVLmed          6868   5051   3591   2692   0     0     0     0     0     0      18202
  HVLmlo          3512   2782   1842   1353   0     0     0     0     0     0      9489
  HVL_lo          2113   1520   1152   834    0     0     0     0     0     0      5619
  HVLvlo          0      0      0      0      0     0     0     0     0     0      0
  Total           23884  17961  12407  9284   0     0     0     0     0     0
Months failed
  HVLvhi          13221  11575  8232   6237   0     0     0     0     0     0      39265
  HVL_hi          7161   6401   4703   3616   0     0     0     0     0     0      21881
  HVLmhi          5613   4525   3340   2528   0     0     0     0     0     0      16006
  HVLmed          3846   2957   2125   1665   0     0     0     0     0     0      10593
  HVLmlo          2893   2073   1507   1214   0     0     0     0     0     0      7687
  HVL_lo          2059   1498   1068   880    0     0     0     0     0     0      5505
  HVLvlo          0      0      0      0      0     0     0     0     0     0      0
  Total           34793  29029  20975  16140  0     0     0     0     0     0
```

Each line of ART regimen is summarized like the following:

```
ART 1 STATS
              # Total  # Supp       Avg TrueCD4   Avg ObsvCD4   #Drawn Supp   #Drawn Part Supp  #Drawn Fail
At Init:      9989     791          584           584           8458          0                 1531
              # Total  AvgTrueCD4   AvgObsvCD4    MthsToFail(Mean)      MthsToFail(StdDev)
At ART true fail:  9646  1026.45    1013.65       44.46                 43.55
At ART obsv fail:  # Total  # with true fail  AvgTrueCD4   AvgObsvCD4   MthsToObsvFail(Mean)  MthsToObsvFail(StdDev)
Any fail diagnosis 9591     9591              1004.86      1009.82      49.58                 43.73
Virologic          9591     9591              1004.86      1009.82      49.58                 43.73
Immunologic        0        0                 0            0            0                     0
```

Clinical	0	0	0	0	0	0
No fail diagnoses	398					

At ART stop:	# Total	# with true fail	AvgTrueCD4	AvgObsvCD4	MthsToStop(Mean)	MthsToStop(StdDev)
All	8411	8411	474.22	474.79	148.06	109.27
Max Months on ART	0	0	0	0	0	0
On Observed Failure	0	0	0	0	0	0
Fail and CD4	8411	8411	474.22	474.79	148.06	109.27
Fail and Severe OI	0	0	0	0	0	0
Fail and Max Months	0	0	0	0	0	0
LTFU	0	0	0	0	0	0
Never stopped	1578					

	# at Mth 1	# Supp, Mth 1	# at Mth 2	# Supp, Mth 2	# at Mth 6	# Supp, Mth 6
Number Patients:	9982	2201	9974	4308	9339	8497
	Mean, Mth 1	SD, Mth 1	Mean, Mth 2	SD, Mth 2	Mean, Mth 6	SD, Mth 6
HVL Drops:	0.8467	0.3603	1.6266	0.735	3.0964	1.5661

Pat Distrib at Init:	HVLvhi	HVL_hi	HVLmhi	HVLmed	HVLmlo	HVL_lo	HVLvlo
CD4vhi	0	1577	1542	1511	1051	502	0
CD4_hi	0	457	469	491	307	150	0
CD4mhi	0	304	291	295	182	95	0
CD4mlo	0	112	105	106	65	22	0
CD4_lo	0	33	32	38	21	8	0
CD4vlo	0	52	60	60	37	14	0
Minor Tox Cases:	0	0	0	0	0	0	0
Chronic Tox Cases:	0	0	0	0	0	0	0
Major Tox Cases:	0	0	0	0	0	0	0
Death Tox Cases:	0	0	0	0	0	0	0

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5+		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5+		Cycle 1	…
Interruptions:	0	0	0	0	0	Restarts:	0	0	0	0	0	STI Endpoint:	0	…

All numbers in this table represent hard counts of the appropriate items, i.e. are not discounted. The total number of months patients spend on each ART regimen is given, with the counts of patients who get initiated as well as stay on the ART regimen after the specified number of months. The given number of months after initiation can be adjusted via modifying user inputs. At the specified time points, the number of patients actually suppressed is also given. The next table provides the mean and standard deviation of the number of HVL strata that patients on the ART regimen has decreased by from their HVL setpoints. (Therefore the description *HVL Drops* is not entirely accurate in that the difference is calculated from the patients' HVL setpoint, and not current actual HVL strata at the time of ART initiation). Finally the numbers of patients at each different actual CD4 strata, encountering an ART-related minor toxicity event, encountering an ART-related major toxicity event, and encountering death from the major toxicity are given broken down by patients current actual HVL strata.

F2k. Longitudinal Log of Cohort

The program allows for longitudinal snapshots of overall cohort characteristics over time. Such longitudinal logs can be done on a monthly or yearly basis. When done on a monthly basis, outputs can be in detailed or in shortened form. The type of logging enabled is specified in the user inputs.

Below is an example of one year's cohort summary:

```
COHORT SUMMARY FOR YEAR 1 END
                   HIVneg        unidentHIV+   identHIV+     Total
# Alive:           179           5             3             187
Mean True CD4 (/infd):  335  (145 SD)   Mean True CD4 (/cohort):  14  (74 SD)   Mean Obsv CD4 (/infd):  356  (142 SD)
Mean True HVL (/infd):  9219 (9295 SD)  Mean True HVL (/cohort): 394 (2598 SD)  Mean Obsv HVL (/infd):  9219 (9295 SD)
CD4 Strata Distrib    CD4vlo   CD4_lo   CD4mlo   CD4mhi   CD4_hi   CD4vhi
True CD4:             0        1        0        2        5        0
Obsv CD4:            0        1        0        2        5        0
HVL Strata Distrib    HVLvlo   HVL_lo   HVLmlo   HVLmed   HVLmhi   HVL_hi   HVLvhi
True HVL:             0        3        0        2        3        0        0
Obsv HVL:            0        3        0        2        3        0        0
OIs Distrib           pcp      mac      toxo     cmv      fungal   bactl    other
Prim OI evts:         0        0        0        0        0        0        0
Sec OI evts:          0        0        0        0        0        0        0
# w/ OIhist:          0        0        0        0        0        0        0        # None OI hist:  187
                      CD4&HVL      HIVtests     HIVmisc
Testing costs:        2863         0            0
Total Cohort Mth costs:   139408.4
```

```
Proph Costs        pcp      mac      toxo     cmv      fungal     bactl     other
Proph 1            65       0        336      0        0          0         0
Proph 2            0        0        0        0        0          0         0
Proph 3            0        0        0        0        0          0         0
Proph 4            0        0        0        0        0          0         0
Proph 5            0        0        0        0        0          0         0
                            ART 1             ART 2             ART 3             ART 4
ART Costs:                  34014             0                 0                 0
```

Year Summary (yearly detail)

```
COHORT SUMMARY FOR MONTH 1
              HIVneg         unidentHIV+   identHIV+     Total                     Total QOL applied
# Alive:      0              0             1000          1000                      1000
Mean True CD4 (/infd): 335  (145 SD)      Mean True CD4 (/cohort): 14  (74 SD)    Mean Obsv CD4 (/infd):  356  (142 SD)
Mean True HVL (/infd): 9219 (9295 SD)     Mean True HVL (/cohort): 394 (2598 SD)  Mean Obsv HVL (/infd):  9219 (9295 SD)
CD4 Strata Distrib   CD4vlo   CD4_lo   CD4mlo   CD4mhi   CD4_hi   CD4vhi
True CD4:            0        0        0        999      1        0
Obsv CD4:           0        0        0        1000     0        0
HVL Strata Distrib   HVLvlo   HVL_lo   HVLmlo   HVLmed   HVLmhi   HVL_hi   HVLvhi
True HVL:           0        694      167      82       39       18       0
Obsv HVL:           0        66       164      274      245      251      0
OIs Distrib    pcp     mac      toxo     cmv      fungal  bactl    other
Prim OI evts:  5       0        3        2        1       0        5
Sec OI evts:   0       0        0        0        0       0        0
# w/ OIhist:   5       0        3        2        1       0        5            # None OI hist:   984
                       CD4&HVL           HIVtests          HIVmisc
Testing costs:         0                 0                 0
Total Cohort Mth costs:   1761424.82
Proph Costs    pcp     mac      toxo     cmv      fungal  bactl    other
Proph 1        0       0        0        0        0       0        0
Proph 2        0       0        0        0        0       0        0
Proph 3        0       0        0        0        0       0        0
Proph 4        0       0        0        0        0       0        0
Proph 5        0       0        0        0        0       0        0
               ART 1   ART 2    ART 3    ART 4
ART Costs:     956742  0        0        0
```

Month Summary (monthly detail)

```
COHORT SUMMARY FOR MONTH 1
           HIVneg   unidentHIV+   identHIV+   Total
# Alive:   0        0             1000        1000      MeanTrueCD4 (/infd): 266    MeanTrueHVL (/infd): 2949
OIs Distrib    pcp     mac     toxo    cmv     fungal bactl   other
Tot OI evts:   5       0       3       2       1      0       5
# w/ OIhist:   5       0       3       2       1      0       5                   # None OI hist:  984
```

Month Summary (short monthly)

F3. Trace Output File

The following are examples of traces produced by the program. Note that life months (LMs), quality adjusted (QA) life months, and patient costs are cumulative, discounted values.

Each line in the patient trace is preceded by a month number – this is the number of months since the hypothetical patient has enterred the model.

Here is an example of such a trace file –

```
BEGIN PATIENT 2                                         init VisitType sched, Implement proph YES art YES;
  gender: male, init age: 396 mths (33.00 yrs)          HIV state: HIVneg
```

**0 HIV SCREENING STARTUP, $ 0
**0 HIV TEST ACCEPT, RETURN, TRUE NEGATIVE, $ 0
 0 mth: LM 1.00 QA 0.00, $ 0;
 1 mth: LM 2.00 QA 1.00, $ 0;
 2 mth: LM 2.99 QA 1.99, $ 0;
 3 mth: LM 3.99 QA 2.99, $ 0;
 4 mth: LM 4.98 QA 3.98, $ 0;
 5 mth: LM 5.96 QA 4.96, $ 0;
 6 mth: LM 6.95 QA 5.95, $ 0;
 7 mth: LM 7.93 QA 6.93, $ 0;
 8 mth: LM 8.91 QA 7.91, $ 0;
 9 mth: LM 9.89 QA 8.89, $ 0;
 10 mth: LM 10.87 QA 9.87, $ 0;
 11 mth: LM 11.84 QA 10.84, $ 0;
**12 HIV TEST ACCEPT, RETURN, TRUE NEGATIVE, $ 0
 12 mth: LM 12.81 QA 10.84, $ 0;
 13 mth: LM 13.78 QA 11.81, $ 0;
 14 mth: LM 14.74 QA 12.77, $ 0;
 15 mth: LM 15.71 QA 13.74, $ 0;
 16 mth: LM 16.67 QA 14.70, $ 0;
 17 mth: LM 17.63 QA 15.66, $ 0;
 18 mth: LM 18.59 QA 16.61, $ 0;
 19 mth: LM 19.54 QA 17.57, $ 0;
 20 mth: LM 20.49 QA 18.52, $ 0;
 21 mth: LM 21.44 QA 19.47, $ 0;
 22 mth: LM 22.39 QA 20.42, $ 0;
 23 mth: LM 23.33 QA 21.36, $ 0;
**24 HIV TEST ACCEPT, RETURN, TRUE NEGATIVE, $ 0
 24 mth: LM 24.28 QA 21.36, $ 0;
 25 mth: LM 25.22 QA 22.30, $ 0;
 26 mth: LM 26.15 QA 23.24, $ 0;
**27 HIV INFECTION;
 27 init CD4: 266;
 27 init HVL: HVLmlo, setpt: HVLmlo;
 27 upd: true CD4 262, true HVL HVLmlo;
 27 mth: LM 27.09 QA 24.18, $ 0;
 28 upd: true CD4 258, true HVL HVLmlo;
 28 mth: LM 28.02 QA 25.11, $ 0;
**29 HIV ACUTE TO CHR: CD4 258, HVLsetpt HVLmlo;
 29 upd: true CD4 254, true HVL HVLmlo;
 29 mth: LM 28.95 QA 26.04, $ 0;
 30 upd: true CD4 251, true HVL HVLmlo;
 30 mth: LM 29.88 QA 26.97, $ 0;
 31 upd: true CD4 247, true HVL HVLmlo;
 31 mth: LM 30.81 QA 27.90, $ 0;
 32 upd: true CD4 243, true HVL HVLmlo;
 32 mth: LM 31.73 QA 28.82, $ 0;
 33 upd: true CD4 240, true HVL HVLmlo;
 33 mth: LM 32.66 QA 29.74, $ 0;
 34 upd: true CD4 236, true HVL HVLmlo;
 34 mth: LM 33.58 QA 30.66, $ 0;
 35 upd: true CD4 232, true HVL HVLmlo;
 35 mth: LM 34.49 QA 31.58, $ 0;
**36 HIV TEST ACCEPT, RETURN, FALSE NEGATIVE, $ 0
 36 upd: true CD4 228, true HVL HVLmlo;
 36 mth: LM 35.41 QA 31.58, $ 0;
 37 upd: true CD4 224, true HVL HVLmlo;
 37 mth: LM 36.32 QA 32.49, $ 0;
 38 upd: true CD4 221, true HVL HVLmlo;
 38 mth: LM 37.23 QA 33.40, $ 0;
 39 upd: true CD4 217, true HVL HVLmlo;
 39 mth: LM 38.14 QA 34.31, $ 0;
 40 upd: true CD4 213, true HVL HVLmlo;
 40 mth: LM 39.05 QA 35.22, $ 0;
 41 upd: true CD4 210, true HVL HVLmlo;
 41 mth: LM 39.95 QA 36.12, $ 0;
 42 upd: true CD4 206, true HVL HVLmlo;
 42 mth: LM 40.85 QA 37.02, $ 0;
 43 upd: true CD4 203, true HVL HVLmlo;
 43 mth: LM 41.75 QA 37.92, $ 0;

 44 upd: true CD4 198, true HVL HVLmlo;
 44 mth: LM 42.65 QA 38.82, $ 0;
 45 upd: true CD4 195, true HVL HVLmlo;
 45 mth: LM 43.54 QA 39.71, $ 0;
 46 upd: true CD4 191, true HVL HVLmlo;
 46 mth: LM 44.44 QA 40.61, $ 0;
 47 upd: true CD4 187, true HVL HVLmlo;
 47 mth: LM 45.33 QA 41.50, $ 0;
**48 HIV TEST ACCEPT, RETURN, TRUE POSITIVE, $ 0
 48 CD4 TEST: obsv CD4 184, $ 74;
 48 HVL TEST: obsv HVL HVLmlo, $ 172;
**48 CLINIC VISIT, $ 172;
**48 INIT NEW ART 1, $ 172;
**48 ART DRAW suppressed;
 48 upd: true CD4 184, true HVL HVLmlo;
 48 mth: LM 46.22 QA 41.50, $ 1707;
 49 CD4 TEST: obsv CD4 194, $ 1781;
 49 HVL TEST: obsv HVL HVL_lo, $ 1878;
 49 upd: true CD4 194, true HVL HVL_lo;
 49 mth: LM 47.10 QA 42.25, $ 3409;
 50 upd: true CD4 205, true HVL HVLvlo;
 50 mth: LM 47.99 QA 43.01, $ 4937;
 51 CD4 TEST: obsv CD4 224, $ 5010;
 51 HVL TEST: obsv HVL HVLvlo, $ 5107;
**51 CLINIC VISIT, $ 5107;
 51 upd: true CD4 224, true HVL HVLvlo;
 51 mth: LM 48.87 QA 43.77, $ 6705;
 52 upd: true CD4 244, true HVL HVLvlo;
 52 mth: LM 49.75 QA 44.53, $ 8299;
 53 upd: true CD4 262, true HVL HVLvlo;
 53 mth: LM 50.62 QA 45.28, $ 9888;
 54 CD4 TEST: obsv CD4 286, $ 9961;
 54 HVL TEST: obsv HVL HVLvlo, $ 10058;
**54 CLINIC VISIT, $ 10058;
 54 upd: true CD4 286, true HVL HVLvlo;
 54 mth: LM 51.50 QA 46.03, $ 11643;
**55 ART LATE PARTIAL;
 55 upd: true CD4 315, true HVL HVLvlo;
 55 mth: LM 52.37 QA 46.79, $ 13225;
 56 upd: true CD4 344, true HVL HVL_lo;
 56 mth: LM 53.24 QA 47.53, $ 14803;
**57 ART LATE FAIL;
 57 CD4 TEST: obsv CD4 372, $ 14876;
 57 HVL TEST: obsv HVL HVLmlo, $ 14971;
**57 CLINIC VISIT, $ 14971;
 57 upd: true CD4 372, true HVL HVLmlo;
 57 mth: LM 54.11 QA 48.28, $ 16225;
 58 HVL TEST: obsv HVL HVLmlo, $ 16320;
 58 upd: true CD4 365, true HVL HVLmlo;
 58 mth: LM 54.98 QA 49.03, $ 17571;
 59 HVL TEST: obsv HVL HVLmlo, $ 17666;
 59 upd: true CD4 356, true HVL HVLmlo;
 59 mth: LM 55.85 QA 49.77, $ 18913;
 60 CD4 TEST: obsv CD4 345, $ 18985;
 60 HVL TEST: obsv HVL HVLmlo, $ 19080;
**60 CLINIC VISIT, $ 19080;
**60 ART 1 FAIL OBSV BY HVL;
**60 TAKEN OFF ART 1 by NEXT_REGIMEN_TO_START;
**60 INIT NEW ART 2, $ 19080;
**60 ART DRAW failure;
 60 upd: true CD4 345, true HVL HVLmlo;
 60 mth: LM 56.71 QA 50.51, $ 20643;
 61 CD4 TEST: obsv CD4 337, $ 20714;
 61 HVL TEST: obsv HVL HVLmlo, $ 20809;
 61 upd: true CD4 337, true HVL HVLmlo;
 61 mth: LM 57.57 QA 51.25, $ 22368;
 62 HVL TEST: obsv HVL HVLmlo, $ 22462;
 62 upd: true CD4 330, true HVL HVLmlo;
 62 mth: LM 58.43 QA 51.99, $ 24017;
 63 CD4 TEST: obsv CD4 320, $ 24088;

63 HVL TEST: obsv HVL HVLmlo, $ 24183;
**63 CLINIC VISIT, $ 24183;
**63 ART 2 FAIL OBSV BY HVL;
**63 TAKEN OFF ART 2 by NEXT_REGIMEN_TO_START;
**63 INIT NEW ART 3, $ 24183;
**63 ART DRAW partial_suppressed;
 63 upd: true CD4 320, true HVL HVLmlo;
 63 mth: LM 59.28 QA 52.73, $ 25734;
 64 CD4 TEST: obsv CD4 349, $ 25805;
 64 HVL TEST: obsv HVL HVLmlo, $ 25899;
 64 upd: true CD4 349, true HVL HVLmlo;
 64 mth: LM 60.14 QA 53.46, $ 27446;
 65 HVL TEST: obsv HVL HVLmlo, $ 27540;
 65 upd: true CD4 383, true HVL HVLmlo;
 65 mth: LM 60.99 QA 54.20, $ 29083;
 66 CD4 TEST: obsv CD4 413, $ 29154;
 66 HVL TEST: obsv HVL HVLmlo, $ 29247;
**66 CLINIC VISIT, $ 29247;
**66 ART 3 FAIL OBSV BY HVL;
**66 TAKEN OFF ART 3 by NEXT_REGIMEN_TO_START;
**66 INIT NEW ART 4, $ 29247;
**66 ART DRAW partial_suppressed;
 66 upd: true CD4 413, true HVL HVLmlo;
 66 mth: LM 61.84 QA 54.93, $ 30474;
 67 CD4 TEST: obsv CD4 443, $ 30544;
 67 HVL TEST: obsv HVL HVLmlo, $ 30637;
 67 upd: true CD4 443, true HVL HVLmlo;
 67 mth: LM 62.69 QA 55.66, $ 31861;
 68 HVL TEST: obsv HVL HVLmlo, $ 31954;
 68 upd: true CD4 472, true HVL HVLmlo;
 68 mth: LM 63.53 QA 56.38, $ 33174;
 69 CD4 TEST: obsv CD4 502, $ 33244;
 69 HVL TEST: obsv HVL HVLmlo, $ 33337;
**69 CLINIC VISIT, $ 33337;
**69 ART 4 FAIL OBSV BY HVL;
**69 TAKEN OFF ART 4 by STOP_ON_FAIL;
 69 upd: true CD4 502, true HVL HVLmlo;
 69 mth: LM 64.38 QA 57.12, $ 33543;
 70 upd: true CD4 472, true HVL HVLmlo;
 70 mth: LM 65.22 QA 57.84, $ 33748;
 71 upd: true CD4 443, true HVL HVLmlo;
 71 mth: LM 66.06 QA 58.56, $ 33953;
 72 CD4 TEST: obsv CD4 412, $ 34023;
 72 HVL TEST: obsv HVL HVLmlo, $ 34115;
**72 CLINIC VISIT, $ 34115;
 72 upd: true CD4 412, true HVL HVLmlo;
 72 mth: LM 66.90 QA 59.28, $ 34383;
 73 upd: true CD4 385, true HVL HVLmlo;
 73 mth: LM 67.73 QA 60.00, $ 34651;
 74 upd: true CD4 354, true HVL HVLmlo;
 74 mth: LM 68.56 QA 60.72, $ 34919;
 75 CD4 TEST: obsv CD4 325, $ 34988;
 75 HVL TEST: obsv HVL HVLmlo, $ 35079;
**75 CLINIC VISIT, $ 35079;
 75 upd: true CD4 325, true HVL HVLmlo;
 75 mth: LM 69.40 QA 61.43, $ 35652;
 76 upd: true CD4 295, true HVL HVLmlo;
 76 mth: LM 70.22 QA 62.15, $ 36224;
 77 upd: true CD4 263, true HVL HVLmlo;
 77 mth: LM 71.05 QA 62.86, $ 36794;
 78 CD4 TEST: obsv CD4 233, $ 36863;
 78 HVL TEST: obsv HVL HVLmlo, $ 36954;
**78 CLINIC VISIT, $ 36954;
 78 upd: true CD4 233, true HVL HVLmlo;
 78 mth: LM 71.88 QA 63.57, $ 37523;
 79 upd: true CD4 202, true HVL HVLmlo;
 79 mth: LM 72.70 QA 64.27, $ 38090;
 80 upd: true CD4 184, true HVL HVLmlo;
 80 mth: LM 73.52 QA 64.97, $ 38657;
 81 CD4 TEST: obsv CD4 180, $ 38725;

 81 HVL TEST: obsv HVL HVLmlo, $ 38815;
**81 CLINIC VISIT, $ 38815;
 81 upd: true CD4 180, true HVL HVLmlo;
 81 mth: LM 74.34 QA 65.67, $ 39311;
 82 upd: true CD4 176, true HVL HVLmlo;
 82 mth: LM 75.16 QA 66.36, $ 39806;
 83 upd: true CD4 173, true HVL HVLmlo;
 83 mth: LM 75.97 QA 67.06, $ 40300;
 84 CD4 TEST: obsv CD4 170, $ 40368;
 84 HVL TEST: obsv HVL HVLmlo, $ 40457;
**84 CLINIC VISIT, $ 40457;
 84 upd: true CD4 170, true HVL HVLmlo;
 84 mth: LM 76.79 QA 67.75, $ 40950;
 85 upd: true CD4 166, true HVL HVLmlo;
 85 mth: LM 77.60 QA 68.44, $ 41441;
 86 upd: true CD4 162, true HVL HVLmlo;
 86 mth: LM 78.41 QA 69.12, $ 41931;
 87 CD4 TEST: obsv CD4 158, $ 41998;
 87 HVL TEST: obsv HVL HVLmlo, $ 42087;
**87 CLINIC VISIT, $ 42087;
 87 upd: true CD4 158, true HVL HVLmlo;
 87 mth: LM 79.21 QA 69.81, $ 42576;
 88 upd: true CD4 155, true HVL HVLmlo;
 88 mth: LM 80.02 QA 70.50, $ 43064;
 89 upd: true CD4 151, true HVL HVLmlo;
 89 mth: LM 80.82 QA 71.18, $ 43550;
 90 CD4 TEST: obsv CD4 147, $ 43617;
 90 HVL TEST: obsv HVL HVLmlo, $ 43705;
**90 CLINIC VISIT, $ 43705;
 90 upd: true CD4 147, true HVL HVLmlo;
 90 mth: LM 81.62 QA 71.86, $ 44190;
 91 upd: true CD4 143, true HVL HVLmlo;
 91 mth: LM 82.42 QA 72.54, $ 44674;
 92 upd: true CD4 139, true HVL HVLmlo;
 92 mth: LM 83.22 QA 73.22, $ 45157;
 93 CD4 TEST: obsv CD4 136, $ 45223;
 93 HVL TEST: obsv HVL HVLmlo, $ 45311;
**93 CLINIC VISIT, $ 45311;
 93 upd: true CD4 136, true HVL HVLmlo;
 93 mth: LM 84.01 QA 73.89, $ 45793;
 94 upd: true CD4 132, true HVL HVLmlo;
 94 mth: LM 84.81 QA 74.57, $ 46273;
 95 upd: true CD4 128, true HVL HVLmlo;
 95 mth: LM 85.60 QA 75.24, $ 46753;
 96 CD4 TEST: obsv CD4 125, $ 46818;
 96 HVL TEST: obsv HVL HVLmlo, $ 46905;
**96 CLINIC VISIT, $ 46905;
 96 upd: true CD4 125, true HVL HVLmlo;
 96 mth: LM 86.39 QA 75.91, $ 47383;
 97 upd: true CD4 121, true HVL HVLmlo;
 97 mth: LM 87.18 QA 76.58, $ 47860;
 98 upd: true CD4 117, true HVL HVLmlo;
 98 mth: LM 87.96 QA 77.25, $ 48336;
 99 CD4 TEST: obsv CD4 113, $ 48401;
 99 HVL TEST: obsv HVL HVLmlo, $ 48488;
**99 CLINIC VISIT, $ 48488;
 99 upd: true CD4 113, true HVL HVLmlo;
 99 mth: LM 88.74 QA 77.91, $ 48962;
**100 PRIMARY OI OTHEROI;
**100 OBSV OI OTHEROI;
**100 CLINIC VISIT, $ 53332;
 100 upd: true CD4 110, true HVL HVLmlo;
 100 mth: LM 89.53 QA 78.45, $ 53806;
 101 upd: true CD4 106, true HVL HVLmlo;
 101 mth: LM 90.31 QA 79.11, $ 54278;
 102 upd: true CD4 102, true HVL HVLmlo;
 102 mth: LM 91.08 QA 79.78, $ 54749;
 103 CD4 TEST: obsv CD4 98, $ 54814;
 103 HVL TEST: obsv HVL HVLmlo, $ 54899;
**103 CLINIC VISIT, $ 54899;

```
 103 upd: true CD4 98, true HVL HVLmlo;              109 HVL TEST: obsv HVL HVLmlo, $ 56366;
 103 mth: LM 91.86 QA 80.44, $ 55096;             **109 CLINIC VISIT, $ 56366;
 104 upd: true CD4 94, true HVL HVLmlo;              109 upd: true CD4 77, true HVL HVLmlo;
 104 mth: LM 92.63 QA 81.09, $ 55291;               109 mth: LM 96.48 QA 84.36, $ 56559;
 105 upd: true CD4 91, true HVL HVLmlo;              110 upd: true CD4 74, true HVL HVLmlo;
 105 mth: LM 93.41 QA 81.75, $ 55487;               110 mth: LM 97.24 QA 85.01, $ 56752;
 106 CD4 TEST: obsv CD4 88, $ 55551;                111 upd: true CD4 70, true HVL HVLmlo;
 106 HVL TEST: obsv HVL HVLmlo, $ 55635;            111 mth: LM 98.00 QA 85.65, $ 56945;
**106 CLINIC VISIT, $ 55635;                        112 CD4 TEST: obsv CD4 67, $ 57008;
 106 upd: true CD4 88, true HVL HVLmlo;             112 HVL TEST: obsv HVL HVLmlo, $ 57091;
 106 mth: LM 94.18 QA 82.40, $ 55830;             **112 CLINIC VISIT, $ 57091;
 107 upd: true CD4 84, true HVL HVLmlo;             112 upd: true CD4 67, true HVL HVLmlo;
 107 mth: LM 94.94 QA 83.06, $ 56024;              112 mth: LM 98.76 QA 86.30, $ 57283;
 108 upd: true CD4 81, true HVL HVLmlo;           **113 DEATH chrAIDS;
 108 mth: LM 95.71 QA 83.71, $ 56218;              LMs 99.14 QA 86.62 $ 64524 ;
 109 CD4 TEST: obsv CD4 77, $ 56282;               END PATIENT
```

F4. Generalized Data Extraction

Starting in version cepac40c, the Generalized Data Extraction executable, "data_extraction_*xx*.exe", was created to help pull out useful information from multiple CEPAC output files (*.out). When run, this program will first scan the current directory for any data extraction parameter "*.gde-in" files. These files describe which data to extract and how to format the output. For each of these parameter files, the program will then extract the specified data from all of CEPAC "*.out" files in that directory and generate corresponding data extraction output "*.gde-out" files. The format for the data extraction parameter files is described below –

Examples for specifying which data to extract are shown below. These can be specified anywhere in the file, as long as they are specified on their own lines and have the correct format. There are two main types of data extraction that can be used - individual data and repeating data. The possible calculations that can be done are the ICER calculation or the user defined individual one. There is also a parameter for specifying the format of the output table.

The following TABLE_FORMAT parameter can be set to specify if the outputs should be organized by rows or columns. If "orientation" is set to "row", the filenames will appear in the first column with all outputs for that file will be in its row. If set to "column", the filenames will appear in the first row and all outputs will be in its column. If unspecified, the default is "row". The value specified for "sort" will be the label of extracted data that the output files should be ordered by, will default to alphabetical by "filename".

TABLE_FORMAT: orientation="row", sort="filename"

The SINGLE_DATA type indicates a single data entry. The "label" value is the label that will be used in the output file and for calculated entries. The "section" value is the section header in the output file under which the desired date will be found. The entire section name does not need to be listed, a shortened prefix that distinguishes it from other sections is sufficient. The "rowoffset" and "column" values are the number of rows down from the section header and the column of the desired cell.

SINGLE_DATA: label="Costs", section="POPULATION SUMMARY", rowoffset="3", column="C"
SINGLE_DATA: label="LMs", section="POPULATION SUMMARY", rowoffset="4", column="C"

If ICERs should be calculated, use the CALC_ICER type with the specified labels of extracted data for the costs, "costs_label", and time period, "time_label". This should only be specified once and will also override the "sort" value and cause the outputs to be sorted by the "costs_label".

CALC_ICER: costs_label="Costs", time_label="LMs"

Single calculated entries can be specified with type SINGLE_CALC. The "label" value is the label that will be used in the output file. The "equation" value is an equation that uses the labels of the single data values and can have any basic math functions: +,-,*,/,(,). An example is shown below after some additional single data values.

SINGLE_DATA: label="chrAIDSDth", section="CAUSES OF DEATH", rowoffset="8", column="R"
SINGLE_DATA: label="nonAIDSDth", section="CAUSES OF DEATH", rowoffset="8", column="S"
SINGLE_CALC: label="percChrAIDSDth", equation="chrAIDSDth / (chrAIDSDth + nonAIDSDth)"

Repeated data entries can be specified with type REPEAT_DATA. The "label" value is the base label that will be used in the output file, it will be followed by the iteration number. The "section", "rowoffset", and "column" values specify how far off from the repeating section header the data can be found. The "repeatnum" label specifies how many times to repeat this data extraction. The following example extracts the number alive values for each month for a year.

REPEAT_DATA: label="numAlive", section="COHORT SUMMARY", rowoffset="2", column="F", repeatnum="12"

G. Programming Notes

The code, which is developed with Microsoft Visual Studio, is mostly written in standard ANSI C++, to support compilation and execution on both MS Windows PCs, Mac OS X, and Unix workstations. Compilation with both Windows Visual C++ and Linux G++ compiler is currently supported.

Microsoft Excel has been retained as the primary user interface for data input. Its advantages over, say, custom modal dialogs include reduced code modification to support data changes, more flexibility in manipulating data inputs as the operator sees fit, and the leveraging of common user proficiency in Excel. Its primary disadvantage is the manual nature of manipulating inputs into the format required by the program. There is the possibility of changing to a custom graphical user interface within the next few years.

G1. Random Numbers

In the simulation, random draws determine the occurrence of acute events and transitions between patient health states. In general, event risks and state transitions are assumed to be stochastic, or near-stochastic, in nature. Random number generators work by repeatedly performing mathematical operations to generate a series of numbers that appear to be random. This process can be thought of as black box, with the only input being the initial seed to start the sequence. Anytime the model needs to perform a random draw, it will use the next number in the sequence coming out of this black box.

The CEPAC treatment program utilizes the Mersenne Twister random number generator algorithm developed by Takuji Nishimura and Makoto Matsumoto. The implementation used in the model is based on MT19937, and was ported to C++ by Jasper Bedaux. For more information about this algorithm and implementation, see http://www.bedaux.net/mtrand/.The algorithms produce random numbers uniformly distributed from 0 to 1. In multiple contexts, the model utilizes normal, or Gaussian, probability distribution functions (PDFs) – normally distributed deviates with 0 mean and unit variance. These Gaussian deviates are obtained by transforming uniformly distributed deviates by the polar form of the Box-Muller transform.

The model can be specified to either use a fixed seed or current time seed for initializing the random number generator. A description of the functionality of each of these options and when they should be used is described below -

Fixed seed:
Fixed seed initializes the random number generator using a constant number. This results in a sequence of numbers that will be identical between different runs of the model. Using this option will cause the exact same outputs to be generated for any set of input files. In prior versions, if an input file was changed at all then the outputs would be completely different. Even though the model was generating the same sequence of random numbers, the model would request them in a different order. For example, if toxicity was disabled in one run and then enabled in the next, there would need to be an extra random number draw every month in the second run to determine if toxicity occurred. In month 1, patient 1 would use the next random number for its toxicity draw and the subsequent random number draw for OIs would not be consistent with the run that did not have toxicity.
Starting in cepac42a, this fixed seed behavior has been changed to fix such problems. Now, for every random number that the model needs, it will reseed the random number generator based on what part of the model is running, the patient number, and the month number. This will guarantee that at the same point in the model for patient X in month Y, the same random number will be used across different runs. For example, when determining if patient 25 gets PCP in month 47, the same result will occur across different runs. This will even hold true across different model versions, given that that specific component of the model was not modified.
Fixed seed should only be used for debugging and consistency checking. Due to the reseeding, this new functionality greatly slows down the model. It will allow the user to make changes to the inputs of certain modules and verify that these do not have unpredictable consequence for other modules. If the same set of inputs are imported to the next model version, the effects of the model changes on the outputs can be analyzed. Both of these features should be very useful for debugging and validation.
Starting with cepac45c the fixed seed has been changed so that the seed is only reset when a new patient is created and not before every draw. This will decrease the runtime of fixed seed runs. This will also increase consistency and correlation between similar runs that are slightly different.

Current time seed:
Current time seed initializes the random number generator based on the system time of the computer. This results in a sequence of numbers that will be more "random" and will vary between different runs of the model.
Current time seed should be used for ALL analysis. If there is a large amount of variability between model runs, it means that the cohort size is too small and that there is a lot of noise. The results from fixed seed are no more accurate than any single run

using random seed. Final results for publication should be verified as being sufficiently accurate by performing multiple random seed runs or by calculating confidence intervals.

G2. Compilation Flags

-DCEPAC_CONSOLE	Include this flag to make a console only version of CEPAC (currently the GUI is only supported on Windows, all other platforms should use this flag)

G3. Log of Model Program Changes

Program Version	Program Date	Input Version	Description
5.0a	06/22/2016	201020873	Added new TB model and Early Infant Diagnosis Model (EID). Can now support resuppression regimens. Added Community Viral Load transmission calculation. Can use CHRMS as a proxy for modeling orphans. Added a way to stop CD4 monitoring upon reaching CD4 threshold. Added Bias to CD4 tests. Added many outputs to monthly outputs. Option to generate a new detailed costs file. Added costs for HIV neg and HIV pos undetected patients.
4.5c	07/25/2014	201020614	Added multiple discount rates and subcohort modules. Initial CD4 can now be specified s a square root transform. Routine Care costs use true rather than observed CD4. Added max month ART as starting criteria. Changed method of fixed seed to reset seed only on patient initialization. OI's now have a time limit to affect Chronic AIDS death probabilities. Tools: PSA, cost adjustment, subcohort icers.
4.5b	08/22/2013	201020603	Added outputs for lab staging based on care state. Changed how between subject nat hist cd4 decline works. Added general medicine costs. Changed contact visit costs. Added exposed, uninfected in pediatrics module.
4.5a	07/24/2012	201020594	Added Heterogeneity, Lab Staging. Added Cost, Proph, ART Start/Fail/Stop policies for Peds. Added Lag to CD4/HVL test availability. Added Initial start age distribution for peds.
4.4f	11/4/2011	201020583	Enable 20% QOL Decrement for Multiple OIs, Multiple bug fixes in PEDS,QOL, and TB
4.4d	2/9/2011	201020571	Three substates were added to TB history of active: history of active after true cure, history of active after false cure, and history of active after self cure. These states vary based on their probability of relapse, new inputs to the model added in cells J75:Q133 in the TB sheet. New inputs were added to cells AE38:AJ42 to distinguish a true cure from a false cure.
4.4c_2	11/19/2010	201020560	Multiple TB bugs fixed relating to prophylaxis and treatment behaviors which weren't working as specified previously: TB state at entry is now correctly tallied, not all cells in the spreadsheet were being correctly written to the .in file (namely, initial history of active prevalence), minor toxicity to TB treatment probability is now correctly attributed, the order of skipping and repeating lines of treatment has been fixed, TB prophylaxis starting policy now correctly distinguishes between AND and OR, TB prophylaxis stopping policy has been fixed, some clarification was added to the input Excel spreadsheet.
4.4c	10/18/2010	201020560	Basic monthly costs added to simplified Peds model
4.4b	9/16/2010	201020550	Age Categories for CHRMs switched to include more granularity at the later ages BUG FIX: In the peds model, breast feeding now stops when the mother dies
4.4a	8/11/2010	201020540	Pediatric ART Treatments added
4.3b	7/28/2010	201020530	Add LTFU fixes for suppression prob after RTC, regimen based CD4 envelope, no efficacy time horizon after RTC, and lag to CD4 decline only on late failure Calculation corrections for ART resistance penalty, and heterogeneity ART effect and late failure Add background routine care costs for HIV-negative patients CD4 envelope bug fix
4.3a	5/14/2010	201020520	Add CHRMs functionality and background QOL Heterogeneity fixes – probabilities instead of rates and thresholds by regimen New version of data extraction script - multiple parameter files and ICER calculation
4.2b	4/22/2010	201020510	Eliminate data file, all inputs are now user defined Add .in file upgrade script and input sheet import macro
4.2a	3/30/2010	201020500	Introduce heterogeneity(adherence) response for ART regimens ART resistance penalty can be set for each prev regimens effect on each new one Major ART toxicity can be specified to cause the regimen to stop New fixed seed behavior for better reproducibility
4.1a	3/19/2010	201020490	Initial beta version of Pediatrics model, natural history only Fix issues with TB module – extended mortality, treatment for prevalent cases, treatment/prophylaxis toxicity mortality Add separate classification of severe/mild OIs for RTC Fix issue with negative CD4 envelope

4.0f	2/4/2010	201020480	Add prophylaxis toxicity mortality and switching options Switch to Mersenne Twister random number generator Fix bug with reading in Boolean inputs Fix scheduling of CD4/HVL tests and changes to ART failure confirmatory testing Fix attributable cause of death – attributable cause calculated using rates Additional monthly logging output for QOL Multiplier Fix bug in applying extended TB mortality
4.0e	1/27/2010	201020470	TB underspecification fixes Better integration of parameters for HIV testing module New ART observed failure and stopping criteria New prophylaxis stop at month and switch at month criteria Correct probability combinations to use independent calculation Change ART next regimen start to be evaluated after previous stop
4.0d	12/14/2009	201020460	Fix changes to CD4 effects on ART, use natural history multipliers for failing ART Move all treatment changes into the clinic visit, special events trigger emergency visits Convert all probability multipliers to rate multipliers
4.0c	11/24/2009	201020450	Changes to the CD4 effects on ART – patient response type and discordant responses
4.0b	11/16/2009	201020440	Changes to the LTFU module, dealing with restarting previous regimens and criteria for return to care
4.0a	11/03/2009	201020430	C++ reimplemention of entire model, the model in the shop project Maintained compatibility with cepac32b inputs/otputs Revamped GUI using wxWidgets platform Reordering of functionality – disease progression now before clinical Integration of HIV Screening module into main loop
3.2a	6/27/2009	201020420	Added LTFU, improved performance of ART toxicity
3.1i	2/1/2008	201020412	Added separation of observed ART failure, stopping, and restarting criteria.
3.1h	1/3/2008	201020400	Added new toxicity module and age stratified risk of HIV infection. Fixed mean months on ART for STI regimens and number of observed OI(s).
3.1b	7/31/2007	201020382	Added mean # STI interruptions and the average duration to the summary statistics
3.0i	7/01/2007	201020389	Stratified the HIV incidence for non-infected individuals generated in the testing module by age. Added an indicator to the patient traces to indicate whether patient's CD4 level has reached the CD4 envelope. Added a 3 way sensitivity analysis tool to input spreadsheet.
3.1g	06/20/2007	201020392	Added summaries of TB events in output file. Implemented prior latent and active TB cases on entry to model. Discontinue TB prophylaxis at active TB infection. Implemented weighted cure probability at TB treatment dropout.
3.1g	05/30/2007	201020391	Replaced older chronic OI structure with TB mechanism.
3.1f	05/12/2007	201020390	Added user specified CD4 bounds for strata. Added CD4 envelope for subsequent ART regimens. Fixed off-by-one month for maximum months on ART policy option. Fixed off ART CD4 multiplier to be based on most recent suppressed state before failure on regimen, instead of most recent state at ART stop. Added limit of off ART CD4 decline multiplier to 1 if reached patient's CD4 nadir. Fixed uninitialized routine care cost for month for history of OI(s) when history costs are all 0.
3.0h	04/15/2007	201020388	Fixed off-by-one month for maximum months on ART policy option. Fixed off ART CD4 multiplier to be based on most recent suppressed state before failure on regimen, instead of most recent state at ART stop. Added limit of off ART CD4 decline multiplier to 1 if reached patient's CD4 nadir. Fixed uninitialized routine care cost for month for history of OI(s) when history costs are all 0.
3.0h	03/12/2007	201020388	Added CD4 envelope for subsequent ART regimens.
3.0g	02/12/2007	201020387	Added user specified CD4 bounds for strata.
3.0f	01/28/2007	201020386	Added back routine/chronic cost and QOL stratification by OI history. Added rate of HVL change based on full suppression, partial suppression, or failure of ART.
3.1e	01/27/2007	201020385	Added back routine/chronic cost and QOL stratification by OI history. Added rate of HVL change based on full suppression, partial suppression, or failure of ART.
3.1d	01/06/2007	201020384	Added criteria to stop ART by toxicity or maximum number of months (ported from 3.0e 2006-12-01 version). Swapped incorrect reading of partial suppression late failure probability with probability of late partial suppression from suppressed state. Switched to use VC++ 2005 compiler.
3.0e	01/05/2007	201020379	Swapped incorrect reading of partial suppression late failure probability with probability of late partial suppression from suppressed state.
3.0d	12/30/2006	201020378	Swapped incorrect reading of partial suppression late failure probability with probability of late partial suppression from suppressed state.
3.0e	12/01/2006	201020379	Added criteria to stop ART by toxicity or maximum number of months.
3.1c	10/29/2006	201020383	Add resistance penalty for each ART regimen. Add tracking of months spent on partially suppressed or failed ART regimens.
3.1b	09/19/2006	201020382	Vary CD4 change on STI (on and off ART) by CD4 nadir, HVL setpoint, and interruption cycle. Added late failure and late partial suppression probabilities to STI regimens by interruption cycle.
3.1a	08/29/2006	201020381	Added chronic OI histories to start/stop ART and OI prophylaxis regimens. Added number interruptions/restarts on each ART to summaries.
3.1	08/09/2006	201020380	Added chronic OI type with extended mortality and (treatment) cost periods. Added STI option of each ART regimen. (CD4/HVL response as function of interruption is not implemented in this version.)
3.0d	05/25/2006	201020378	Added log output of patient's "first" OI (first from set of user-specified OIs).

3.0c	03/02/2006	201020377	Fixed OI history criteria for starting/stopping prophylaxis when "OR" condition used. Allow CD4/HVL tests outside clinic visits.
3.0b	01/23/2006	201020376	Fix reset of CD4 slope stages in transition from full to partial suppression on ART.
3.0a	11/28/2005	201020376	Back-ported confirmation of ART observed failure by same means and other tweaks from A2.6c version. Modified month stages of CD4 effect on and off ART regimens. Added option to force failure of ART at specified month. Added option to stop ART regimen at specified month after regimen initiation.
A2.6c 2.6c	11/9/2005	201020371	Fix on-ART scheduling frequency of CD4/HVL tests in the month that 1st regimen is initiated.
A2.6c 2.6c	9/26/2005	201020371	Require confirmation of ART observed failure by same means (i.e. by OI event, CD4 test, or HVL test). Added summary outputs at time of true and observed ART failure. Split testing costs by CD4, HVL, and clinic costs.
3.0	8/8/2005	201020375	Removed ART efficacy matrix; implemented new ART efficacy mechanism with suppressed, partial suppression, and failure states. Increased number of OIs to 15. Added time and absolute CD4 criteria to stopping ART regimens. Removed old US version of program from future builds. Removed previous STI mechanism.
2.5l	4/13/2005	201020366	Added monthly percentage decrease to number of acts for HIV transmission estimates. Separated late stage HIV transmission estimates into separate category independent of HVL.
2.5l	4/6/2005	201020365	Added minimum month numbers for starting/stopping proph/ART regimens.
2.5l	3/28/2005	201020364	Back-ported HIV transmission estimate based on monthly distribution of patients in cohort by joint CD4 and HVL (including late stage bucket for transmission probabilities).
A2.6b 2.6b	2/28/2005	201020371	Stratified longitudinal output of cohort distribution by joint true CD4 and HVL in addition to on/off ART.
A2.6b 2.6b	2/21/2005	201020371	Added HIV transmission estimate based on monthly distribution of patients in cohort by joint CD4 and HVL. Modified longitudinal output of cohort distribution to joint true CD4 and HVL. Modified initial HVL distribution to be dependent on CD4 stratum.
A2.6a 2.6a	2/15/2005	201020370	Reformated inputs to new spreadsheet structure. Added names to prophylaxis and ART regimen inputs. Split costs into 4 components.
A2.5l 2.5l	9/26/2004	201020363	Added on/off ART separation of tables for OI monthly probability and chronic AIDS death tables. Fixed for cases where no CD4/HVL test(s) given.
A2.5k 2.5k	8/29/2004	201020362	Added (multiple) count of OIs in patient's recent history to start and/or stop ART. Added back independent HVL criteria for starting ART. Removed "Force OI Event to Start New ART in Subsequent Month" option.
A2.5j 2.5j	8/16/2004	201020361	Added on/off ART stratification for state costs (routine, acute OI, post-acute OI, death).
A2.5i 2.5i	7/19/2004	201020360	Changed CD4 drop for ART fail diagnosis to percentage basis.
A2.5i 2.5i	7/18/2004	201020360	Removed separate ART starting criteria for acute HIV patients. Removed independent HVL criteria for starting ART. Added OI history critieria and joint CD4 and OI history criteria for starting ART.
A2.5h 2.5h	6/8/2004	201020359	Changed total numbers of OIs, deaths from acute OIs, detected OIs, and clinic visits in popstats.out to per 1000 patients. Added numbers patients on OI prophylaxis to run outputs. Fixed detection of OIs (LDC only) in the month of death from acute OI. Revised draw of OIs.
A2.5h 2.5h	5/18/2004	201020359	Added total numbers of OIs (primary and secondary), total numbers of deaths from acute OIs, total number of detected OIs (LDC only), and total number of clinic visits (LDC only) to popstats.out summary file. Fixed ART stopping rule based on observed acute OIs in LDC version. Made sure all clinic visit patient types visit clinic if on ART/prophylaxis in LDC version.
A2.5h 2.5h	11/17/2003	201020359	Added CD4/HVL transition information output for dynamic transmission model input. Added MT algorithm for randomization. Moved to VC++ 7.1. Revised OI prophylaxis start criteria: to start, patients must not have any OI history for cells marked 0, and if there is at least one 1, prophylaxis would be started at the first occurrence of any of those OIs.
A2.5g 2.5g	8/10/2003	201020359	Added stop prophylaxis criteria by specific type of OI history.
A2.5f 2.5f	7/27/2003	201020358	Modified OI history trigger for prophylaxis start: start when any of the specified OI types are in patient's history.
A2.5f 2.5f	7/23/2003	201020358	Added all OI types as trigger for each OI prophylaxis start. Allow prophylaxis negative efficacies (but not -1).
A2.5f 2.5f	7/21/2003	201020357	Integrated fix for resetting of current true HVL at STI effect limit when patient starting new ART regimen from 7/14/2003 version. Added average true and observed CD4 at ART and prophylaxis initiation. Added probability of switching primary prophylaxis to secondary OI prophylaxis at acute OI event.
2.5	7/14/2003	201020351	Fixed resetting of current true HVL at STI effect limit when patient starting new ART regimen from 11/24/2002 version.
2.5b	7/8/2003	201020352	Fixed prior OI history at initialization in 1/22/2003 version.
A2.5e 2.5e	7/3/2003	201020356	Added additional count of patients on each ART including those with observed failure but continued costs in longitudinal output.
A2.5e 2.5e	6/29/2003	201020356	Fixed number of patients count on each ART in longitudinal output.
2.5e	6/26/2003	201020356	Added numbers of patients on each ART in longitudinal output.
A2.5e	5/05/2003	201020356	Added primary and secondary OI effects for primary and secondary prophylaxes. Fixed

2.5e			prior OI history at initialization.
A2.5d	4/16/2003	201020355	Added distributions of clinic visit and implement ART/proph patient types. Added probabilities for detecting OI histories of patient at program entry and since last clinic visit. Added schedule of clinic visits wrapping both CD4 & HVL testing. Added unknown observed CD4 and HVL. Removed toll costs. Added explicit secondary prophylaxis for Africa/LDC version; removed post-acute OI state for costs from Africa/LDC version. Added gender and age dimensions to CD4 state costs and death costs. Added treated and untreated dimension to acute OI costs and death from acute OI probabilities.
2.5c	3/6/2003	201020353	Reduced number of OI prophylaxis options from 5 to 3. Removed special PCP/MAC prophylaxes effect on TOXO/BACT; generalized multiple OI effects to every prophylaxis. Added CD4 test result standard deviation. Increased cost/QOL inputs for OI history by CD4 and treated/detected dimensions. Added (unused) inputs for probability of switching to post-acute OI care when OI observed.
2.5b	1/22/2003	201020352	Fixed draw non-AIDS death time in HIV testing to not exceed MAX_RAND_ATTEMPTS. Moved MAX_RAND_ATTEMPTS out to 3000 months.
2.5b	1/19/2003	201020352	Added classification of OIs by mild/severe. Added chronic AIDS mortality stratification by mild/severe OI history.
2.5a	1/19/2003	201020351	Fixed off by one in # patients simulated per chunk. Added user controls to Win32 UI.
2.5	11/24/2002	201020351	Removed `stderr` file references from source code. Returned to MS VC++ 6 compiler.
2.5	11/17/2002	201020351	Modified accumulation of run summary costs and life months by chunks. Replaced console UI with W32 dialog UI. Re-built with Intel compiler 6.0.1-305, and profiling enabled.

Appendix 1: CEPAC TB Module Specifications

Overview

This tuberculosis (TB) module is designed to capture the natural history, diagnosis, treatment, and associated costs of TB for both HIV-infected and HIV-uninfected individuals in resource-limited settings using the framework of the CEPAC model.

This document describes the components of the module chronologically in the order that patients flow through the model. Flowchart sections are noted in parentheses (e.g., 10a) where appropriate for reference. Accompanying variable definitions and equations are provided where applicable.

Begin Month Updater (10a)

In the first month of the simulation, the module will evaluate a toggle (yes/no) to use the TB module, ignoring all of the module's functions if the toggle is set to 0. The module will also evaluate whether the TB clinic is integrated with the HIV Clinic; if toggle is set to 1 ("yes"),the diagnosis and treatment of TB will occur within the setting of an HIV clinic.

Enable TB Module	0	**0** = no, **1** = yes
TB and HIV Clinic Integrated?	0	**0** = no, **1** = yes

In the first month, patients will be distributed to one of the sixnatural history health states:
- Uninfected
- Latent TB
- Active Pulmonary TB
- Active Extrapulmonary TB
- Previously Treated TB
- TB Treatment Default

This initial distribution will depend on HIV status (HIV-infected or HIV-uninfected) and, for HIV-infected patients, CD4 count.

Distribution of TB states at model entry

Probability	Uninfected	Latent TB	Active Pulr	Active Extr	Prev Treat	TB Treat Default	
HIV -	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 VHI	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 HI	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 MHI	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 MLO	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 LO	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 VLO	1.0000	0.0000	0.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0

For all patients who are not in the Uninfected state, the strain of TB will be drawn as one of three variables: drug-susceptible TB (*dsTB*), multidrug-resistant TB (*MDR-TB*), or extensively drug-resistant TB (*XDR-TB*). This distribution will not depend on HIV status, CD4 count, or distribution of TB states.

Distribution of TB Strain

	dsTB	MDR-TB	XDR-TB	
	0.9000	0.0000	0.1000	**Note**: row must sum to 1.0

Each patient will then be evaluated for 3separate binarytracker variables based on their TB state:

1. TB sputum bacillary load (*sputumbacloadhi*/*sputumbacloadlo*)
2. Immune reactivity (*immreactyes*/*immreactno*)
3. Symptoms consistent with TB (*symptomyes*/*symptomno*)

This distribution is dependent upon HIV status, CD4 count, and TB state.

TB Sputum Bacillary Load: Sputum bacillary load is a clinical characteristic that is a surrogate for smear status and is representative of infectivity.

- Sputum bacillary load will be "low" for all Uninfected, Latent TB, Active Extrapulmonary TB, Previously Treated TB, and TB Treatment Default states.
- Sputum bacillary load can be"high" or "low" for patients in the Active Pulmonary TB state.

Immune Reactivity: Immune reactivityis a clinical characteristic that is a surrogate for tuberculin skin test (TST) and Quantiferon blood test results. It represents whether a person has mounted an immune response to tuberculosis bacterium (indicating TB exposure).

- Note that "Immune reactivity" can be falsely positive for some patients who have received the BCG vaccine or have been exposed to non-tuberculous mycobacteria, and falsely negative for patients with compromised immune systems (e.g., low CD4) and, thus, can be positive or negative in any of the health states.

Symptoms consistent with TB (which can be defined by the user and parameterized according to available data) can be present for patients in any of the health states. Patients with Active Pulmonary TB will keep their symptom flag until successfully treated for TB; patients in any other health state will keep their symptom flag for one month only.

Sputum Bacillary Load Hi at entry

Prob positive	Uninfected	Latent TB	Active Pulm	Active Ext	Prev Treat	TB Treat Default	
HIV -	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 VHI	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 HI	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 MHI	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 MLO	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 LO	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 VLO	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0

Immune Reactive at entry

Prob positive	Uninfected	Latent TB	Active Pulm	Active Ext	Prev Treat	TB Treat Default	
HIV -	0.0000	1.0000	1.0000	1.0000	1.0000	0.0000	**Note**: row must sum to 1.0
CD4 VHI	0.0000	1.0000	1.0000	1.0000	1.0000	0.0000	**Note**: row must sum to 1.0
CD4 HI	0.0000	1.0000	1.0000	1.0000	1.0000	0.0000	**Note**: row must sum to 1.0
CD4 MHI	0.0000	1.0000	1.0000	1.0000	1.0000	0.0000	**Note**: row must sum to 1.0
CD4 MLO	0.0000	1.0000	1.0000	1.0000	1.0000	0.0000	**Note**: row must sum to 1.0
CD4 LO	0.0000	1.0000	1.0000	1.0000	1.0000	0.0000	**Note**: row must sum to 1.0
CD4 VLO	0.0000	1.0000	1.0000	1.0000	1.0000	0.0000	**Note**: row must sum to 1.0

TB symptoms at entry

Prob symptom	Uninfected	Latent TB	Active Pulm	Active Ext	Prev Treat	TB Treat Default	
HIV -	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 VHI	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 HI	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 MHI	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 MLO	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 LO	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0
CD4 VLO	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000	**Note**: row must sum to 1.0

TB Disease Updater (50a-50e)

This section of the module describes the natural history transitions between the 6 TB natural history states (described below). This section will appear after the HIV Infection Updater and CHRMS Updater and before the Drug Toxicity Updater. Each natural history state will have a subroutine, and the order of the subroutines will be as follows: Uninfected, Latent TB, Active Pulmonary TB, Active Extrapulmonary TB, Previously Treated TB, and TB Treatment Default.

TB Natural History States (See diagram below, next page)
All states in the model are based on the true state of the patient, rather than on diagnostic test result or clinical management/observation.

Uninfected: The patient is not infected with *Mycobacterium tuberculosis* and thus cannot develop active TB without first becoming infected.

Latent TB: The patient is infected with *Mycobacterium tuberculosis* but does not have active TB disease. This is also referred to as "latent TB infection" or "LTBI." There are no symptoms or morbidity associated with LTBI itself, and no transmission risk to others.

Active Pulmonary TB: The patient has active TB disease in the lungs. Morbidity and mortality can result from untreated or ineffectively treated active TB disease. This can be a first episode of active TB or a subsequent episode, which would be marked by a flag and would confer a different probability of drug resistance, treatment success, and death, and possibly trigger a different treatment regimen. This state also will include patients who have both active pulmonary and active extrapulmonary TB, as most diagnostic strategies assess for pulmonary TB.

Active Extrapulmonary TB: Similar to "Active Pulmonary TB," but the patient does not have active TB disease in the lungs and instead has active disease elsewhere. The patient may have symptoms but does not pose a transmission risk to others, and standard pulmonary tests (e.g., sputum culture) will be negative.

Previously Treated TB: The patient does not have active TB currently (and consequently no TB-associated morbidity, TB-associated mortality, or transmission risk to others) but has had active TB in the past and successfully completed TB treatment.

TB Treatment Default: The patient has been treated for TB but did not complete the entire course or treatment. Those who have rolled for success will go to the TB Treatment Default state after at least 2 consecutive months of being LTFU. Those who rolled for failure will return to an Active TB state. Those in this state can experience either Relapse or Reinfection.

Dead: The patient is dead due to TB or non-TB causes. Patients can transition to this state from any other state (not shown in the diagram below for simplicity). This is an absorbing state.

Figure 1. A simplified schematic of the natural history states and monthly transitions in the proposed CEPAC TB module. Arrows indicating remaining in the current state are omitted for clarity. Patients can transition from any of the shown states to the Deadstate (not shown for simplicity).
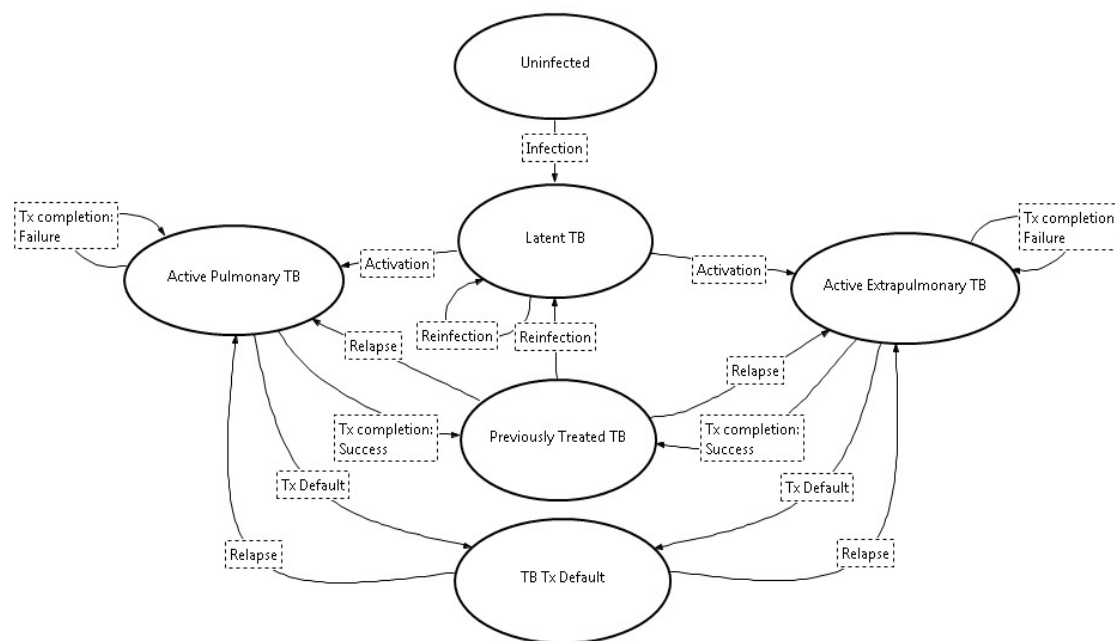
Relapse = Active disease from the same strain that caused the previous active disease. Patient will draw for becoming *sputumbacloadhi.*

Reinfection = Exposure to, and infection by, another strain of *Mycobacterium tuberculosis* in a patient who has been infected previously. Patient will draw for a strain, which will replace the prior strain.

Notable Flags

Infecting TB Strain (*dsTB*, *MDR-TB*, *XDR-TB*)

Observed TB Strain (*ObserveddsTB, ObservedMDRTB, ObservedXDRTB*)

PriorActiveTBn (where n is the number of previous active TB episodes since model entry)

PriorTreatmentDefault

OnTBProphylaxisX (where X is the number of the prophylaxis regimen)

OnTBTreatmentX (where X is the number of the treatmentregimen)

TBTreatmentFail

TBTreatmentSuccess

Transitions between TB States (monthly)
A: Uninfected → Uninfected (50b)
This "transition" involves remaining in the current Uninfected state. The probability will effectively be the product of one minus each of the other transition probabilities (i.e., the default is to remain in the current state).

B: Uninfected → Latent TB (50f)
This event is infection. The probability will be defined according to published data from South Africa or another setting of interest and will be independent of HIV status and CD4. Upon this state transition, a flag will be assigned describing the strain of TB with which the patient has been infected, drawn from a

distribution of drug-susceptible TB (dsTB), multidrug-resistant TB (MDR-TB), and extensively drug-resistant TB (XDR-TB). Uninfected patients who are on prophylaxis or treatment for TB (either due to a false positive diagnostic result or because they receive empiric therapy) will have a marked reduction in infection probability. Patients who undergo this transition will roll for becoming either *immreactyes* or *immreactno*, which depends on HIV status and CD4. If the patient is on TB prophylaxis (*onTBprophylaxisX*) when infected, the patient can roll for a more resistant strain.

INFECTION

Monthly Incidence of TB Infection (Primary and Reinfection)

	<18	18-25	26-30	31-35	36-40	41-45	46+
HIV -	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 VHI	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 HI	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 MHI	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 MLO	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 LO	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 VLO	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

C: Uninfected → Dead (60a)

Death occurs from a non-TB cause as defined in the remainder of the CEPAC model for HIV-infected patients (chronic AIDS death, OI acute mortality, ART toxicity, non-AIDS death, etc.), or as defined in the monthly non-AIDS death probability in the Natural History tab for HIV-negative patients. Also, death can occur from toxicity of prophylaxis or treatment of TB, though the number of cases is expected to be quite small.

D: Latent TB → Latent TB (50c)

There are two pathways for this "transition":
1) Similar to **A**, this pathway is the default for patients with latent TB infection. Factors that will effectively increase the likelihood of no transition include the *OnTBProphylaxisX* or *OnTBTreatmentX* (due to false positive diagnostic result or empiric treatment) flag, HIV-negative status, and high CD4 count for HIV-infected patients.
2) Reinfection: In this pathway, a patient with latent TB infection has a monthly probability of becoming infected with a different strain of *Mycobacterium tuberculosis*. The new infecting strain will always replace the previous infecting strain, as it is believed that relapse is most likely to occur with the newest strain. [**Note:** It was decided that the newest infecting strain should trump the previous infected strain instead of the more resistant strain trumping the less resistant strain; 3/17/15] Patients will first draw for reinfection from the same probabilities for infection as described in **B**. If reinfected, the patient will draw from the distribution of TB strains. If patients are reinfected and were previously *immreactno*, they will draw again for either *immreactyes* or *immreactno*.
   Note: although reinfection can technically occur in any infected or active TB state, we simplify and assume that only those in the Latent TB, Previously Treated TB, or TB Treatment Default states can become reinfected.

E: Latent TB → Active Pulmonary TB (50c)

There are two pathways for this transition:
1) Activation of latent TB: There is a monthly probability of activation (termed "reactivation TB" in most literature) dependent on the following factors:
   a. For HIV-negative patients: duration of latent TB infection

   For HIV-negative patients, we have:
   $$p(transition\ at\ time\ t) = LtoARateMultiplier * e^{-\chi LtoA t}$$

where $-x_{LtoA}t$ is determined from the literature of HIV-negative patients from the rate at which transitions decrease over time, while the $LtoARateMultiplier$ is included so that the integrated value from t=0 to t=life expectancy of ($LtoARateMultiplier * e^{-x_{LtoA}t}$) equals the estimated proportion of individuals with latent TB who will develop active pulmonary TB over their lifetime.

b. For HIV-infectedpatients: duration of latent TB infection, CD4 count

Although there arenot data showing that the duration of latent TB infection matters for HIV-infectedpatients, we believe that this factor should also be included in HIV-infected patients for consistency.

For HIV-infected patients, we will include an additional multiplier $F_{LtoA,CD4_y}$ reflecting the current CD4 value:

$$p(transition\ at\ time\ t, current\ CD4 = y) = F_{LtoA,CD4_y} * LtoARateMultiplier * e^{-x_{LtoA}t}$$

The set of values $F_{LtoA,CD4_y}$ (for the different CD4 strata in the model) can be determined from the annual TB rate in HIV-negative individuals and various CD4 strata of HIV-infected individuals. When data is available only for a range of CD4 (e.g., an annual rate in HIV-negative, and an annual rate in HIV-infected individuals with CD4 < 200), we will calculate $F_{LtoA,CD4_y}$ so that (a) $F_{LtoA,CD4_y}$ is strictly increasing as the CD4 count goes down; (b) that the sum of the proportion of the population at a level times $F_{LtoA,CD4_y}$ equals the estimated ratio from the population data; and (c) so that the changes in $F_{LtoA,CD4_y}$ with increasingly lower CD4 levels is increasing. We recognize that there may not be a unique solution to this, and willconsider variations as part of a sensitivity analysis.

c. For all patients: presence of *onTBprophylaxisX* or *onTBtreatmentX* flags will offer a reduction in the monthly probability

2) Primary progressive TB: This transition to active disease occurs in the same month of either infection or reinfection; thus the patient enters the Latent TB state in that month but essentially bypasses it and moves directly on to Active Pulmonary TB or Active Extrapulmonary TB within the same month. [**Note:** The ordering of the Uninfected, Latent TB, and Active Pulmonary TB and Active Extrapulmonary TB subroutines allows a person to go from Uninfected to Active Pulmonary TB or Active Extrapulmonary TB in the same month; this is primary progressive TB.] The probability of primary progressive TB will equal the probability of activation in the first month and will be higher than activation probabilities in subsequent months (see equations above).

After this transition, patients will draw for becoming *sputumbacloadhi*, which will depend on CD4 status. [**Note**: In the future, this distribution may depend on age for pediatric-related analyses]

ACTIVATION

Incidence of TB Activation

probActivation=F(CD4)*Multiplier*e^(-xt)

	Multiplier	x		Distribution of Pulmonary and Extra Pulmonary		
	0.0000	0.0000				
					Pulm	ExtraPulm
		F(CD4)		HIV -	1.0000	0.0000
CD4 VHI	1.0000			CD4 VHI	1.0000	0.0000
CD4 HI	1.0000			CD4 HI	1.0000	0.0000
CD4 MHI	1.0000			CD4 MHI	1.0000	0.0000
CD4 MLO	1.0000			CD4 MLO	1.0000	0.0000
CD4 LO	1.0000			CD4 LO	1.0000	0.0000
CD4 VLO	1.0000			CD4 VLO	1.0000	0.0000

Sputum Bacillary Load Hi Once Activated (Pulm only)

	Probability
HIV -	0.0000
CD4 VHI	0.0000
CD4 HI	0.0000
CD4 MHI	0.0000
CD4 MLO	0.0000
CD4 LO	0.0000
CD4 VLO	0.0000

F: Latent TB → Active Extrapulmonary TB (50c)

There are two pathways for this transition, essentially the same as those described in **E**. The ratio of active extrapulmonary to pulmonary TB cases rises as CD4 falls. Patients will not draw for *sputumbacloadhi* after this transitionas patients with extrapulmonary TB do not have high bacillary load in their sputum (and in fact are sputum smear-negative).

G: Latent TB → Dead (60a)

Death occurs from a non-TB cause, toxicity from TB prophylaxis, or toxicity from TB treatment.

H: Active Pulmonary TB → Active Pulmonary TB (50f)

This is the default for this state. A patient will remain in this state while on treatment, andcurrent treatment will be marked with a time-counted flag (*onTBtreatmentX*). A patient who draws treatment failure (defined clinically as positiveculture at end of treatment course)or who is lost to follow-up (having initially rolled for failure) will remain in this state. Those who fail from treatment will be flagged as such and will have a higher probability of acquiring drug resistance (i.e., developing MDR-TB or XDR-TB). Patients who fail and are flagged as *sputumbacloadhi* will keep this flag.

I:Active Pulmonary TB → TB Treatment Default

Patients who are on TB treatment and who roll for TB treatment default will transition to the TB Treatment Default state, unless they roll for failure in which case they will remain in the Active TB state.

J: Active Pulmonary TB →Previously Treated TB (50d)

Patients who achieve treatment success (completion of appropriate treatment for strain and negative culture at end of treatment course) undergo this transition. They will be flagged as having successfully completed treatment. Patients who default on treatment will have a probability of success weighted by the proportion of their treatment that they complete. Those who default and roll for success will transition to the Previously Treated TB state and will be considered treatment successes, though they will have flagged as having defaulted. Patients who undergo this transition will lose their *sputumbacloadhi* tracker variable if it is present.*(Refer to "TB clinic treatment subroutine" section below for details on treatment success/failure.)*

K: Active Pulmonary TB → Dead (60a)

Death occurs from active pulmonary TB, including untreated or undertreated TB (e.g. treatment for ds TB when the patient in fact has MDR-TB), toxicity from TB treatment, or a non-TB cause.

L: Active Extrapulmonary TB → Active Extrapulmonary TB (50f)

Similar to the description provided in **H**.

M: Active Extrapulmonary TB →Previously Treated TB (50d)

Similar to the description provided in **J**.

N: Active Extrapulmonary TB → Dead (60a)

Similar to the description provided in **K**.

O: Previously Treated TB→Previously Treated TB (50d)

This is the default for this state. A patient will remain in this state as long as he/she does not die, develop reinfection, or relapse.

P: Previously Treated TB→ Latent TB (50f)

This transition involves reinfection with any strain of *Mycobacterium tuberculosis*. The probability of reinfection will be defined as that described for infection in **B**. The patient can then go on to develop active TB disease via the two pathways described in **E**. The reinfecting strain will replace the prior strain (e.g., if a patient completed treatment for MDR-TB in the past and now becomes infected with dsTB, then they will be flagged as having only dsTB, and potential subsequent activation will reflect dsTB).If patients are reinfected and were previously *immreactno*, they will draw again for either*immreactyes* or *immreactno.*

Q: Previously Treated TB→ Active Pulmonary TB (50g)

This direct transition involves relapse of active disease from the same strain of *Mycobacterium tuberculosis* that caused the previous active disease. The incidence of relapse depends on months since completion of successful TB treatment (relapse incidence declines over time and is CD4-dependent). After this transition, patients will draw for becoming *sputumbacloadhi*, which will depend on CD4 status. This will follow the approach outlined in section E (Latent TB to Active Pulmonary TB) with the following change:

As data suggests that the transition rate stabilizes at approximately 5 years (60 months), for HIV-negative patients, we will have:

$$p(transition\ at\ time\ t) = PTtoARateMultiplier * e^{-x_{PTtoA}(\min[t, 60])}$$

where $-x_{PTtoA}$ is determined from the literature of HIV-negative patients from the rate at which relapse decrease over time, while the PTtoARateMultiplier is included so that the integrated value from t=0 to t=life expectancy of

$(PTtoARateMultiplier * e^{-x_{PTtoA}(\min[t, 60])})$ equals the estimated proportion of individuals with previously treated TB who will relapse to active pulmonary TB over their lifetime.

This change will also be used in the monthly relapse rate for HIV-infected individuals.Patients who relapse will face a probability of increasing strain resistance.

RELAPSE
Incidence of TB Relapse

probRelapse=F(CD4)*Multiplier*e^(-x*(min[t,threshold]))/(propTxComp)

	Multiplier	x	threshold (months)	Distribution of Pulmonary and Extra Pulmonary		
	0.0000	0.0000	60			
					Pulm	ExtraPulm
		F(CD4)		HIV -	1.0000	0.0000
	CD4 VHI	1.0000		CD4 VHI	1.0000	0.0000
	CD4 HI	1.0000		CD4 HI	1.0000	0.0000
	CD4 MHI	1.0000		CD4 MHI	1.0000	0.0000
	CD4 MLO	1.0000		CD4 MLO	1.0000	0.0000
	CD4 LO	1.0000		CD4 LO	1.0000	0.0000
	CD4 VLO	1.0000		CD4 VLO	1.0000	0.0000

Sputum Bacillary Load Hi Once Relapsed (Pulm only)

		Probability
	HIV -	0.0000
	CD4 VHI	0.0000
	CD4 HI	0.0000
	CD4 MHI	0.0000
	CD4 MLO	0.0000
	CD4 LO	0.0000
	CD4 VLO	0.0000

R: Previously Treated TB→ Active Extrapulmonary TB(50g)
Similar to the description provided in **Q**, adjusted for probability of developing extrapulmonary rather than pulmonary TB.

S: Previously Treated TB→ Dead (60a)
Death occurs from a non-TB cause or toxicity from TB treatment.

T: TB Treatment Default → Active Pulmonary (27e) or Active Extrapulmonary TB(50g)
This transition represents relapse to the either the Active Pulmonary TB state or the Active Extrapulmonary TB state, dependent upon CD4 and time.

Upon defaulting, those who had initially rolled for treatment success now roll again for success vs. failure: this time, the probability of success is proportional to the number of months of treatment completed before defaulting (e.g., if the patient completed 2 months of the planned 6 months of treatment, then the probability of success is 0.33).Those who roll for failure this time go to one of the "Active TB" states (whichever one they were in previously). They have a probability of increased resistance (i.e., a more drug-resistant strain of TB) after defaulting, as defined in the TB treatment tab. Those who again roll for success go to the "Default" state; they do not have active TB, but they are at higher risk for relapse.

If a patient who defaults subsequently becomes reinfected, then they are flagged with the new strain.

U: TB Treatment Default → Latent TB (50f)
Patients who have defaulted can get reinfected with Latent TB and will be flagged with *PriorTreatmentDefault* and will have an increased risk of developing Active TB.

After evaluating each natural history subroutine, all patients will be evaluated for the symptom flag (*symptomyes/symptomno*), which indicated the presence of symptoms consistent with TB and can be defined by the user.

TB SYMPTOMS

Monthly Incidence of TB symptom occurence

Prob symptoms	Uninfected	Latent TB	Active Pul	Active Extr	Prev Treat	TB Treat Default
HIV -	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 VHI	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 HI	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 MHI	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 MLO	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 LO	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
CD4 VLO	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

- If a patient is not symptomatic (*symptomno*), he/ she will roll for acquiring symptoms this month, which will depend on TB state and CD4.
- If a patient is currently symptomatic (*symptomyes*), he/ she will clear that flag and roll again if not in the Active Pulmonary TB or Active Extrapulmonary TB state. If the patient is in one of those two states, he/she will keep the *symptomyes* flag (assumption).

Drug Toxicity Updater (30a)

TB prophylaxis and treatment toxicities will be evaluated in CEPAC in the same section as ART toxicities and other OI prophylaxis toxicities. Patients who are currently on prophylaxis or treatment (described later in the specifications) will be flagged with the variables *onTBprophylaxisX* or *onTBtreatmentX*, respectively, where *X* refers to the prophylaxis or treatment regimen that the patient is receiving. Currently, this module does not consider interactions between TB drugs and *specific* HIV drugs, but it does allow for a higher likelihood of toxicity if a patient is on both TB and HIV regimens.

TB Prophylaxis Toxicity (30d)

Each month that a patient carries the *onTBprophylaxisX* flag, he/she will roll for toxicity, stratified by on/off ART to simulate increased toxicity for patients on ART (e.g., hepatotoxicity). If the toxicity is rolled for, the patient will accrue a cost (*TBprophtoxcost*) and quality of life (QOL) modification (*TBprophtoxQOL*).

The patient will also accrue a mortality risk (*TBprophtoxmortality*) to be added and evaluated in the Mortality Updater (60a).

TB Prophylaxis Toxicity

	Number	Prophylaxis Name	Minor Tox Monthly Prob		Major Tox Monthly Prob		Prob Dth (Maj)
			Off ART	On ART	Off ART	On ART	
	0	Isoniazid	0.000000	1.0000	0.000000	1.0000	0.000000
	1	Rifampin	0.000000	1.0000	0.000000	1.0000	0.000000
	2	User Proph 1	0.000000	1.0000	0.000000	1.0000	0.000000
	3	User Proph 2	0.000000	1.0000	0.000000	1.0000	0.000000
	4	User Proph 3	0.000000	1.0000	0.000000	1.0000	0.000000

Patients who are HIV-uninfected will be scheduled for an Emergency TB Clinic Visit in the same month that they experience a toxicity event. Patients who are HIV-infected will be scheduled for an Emergency TB Clinic Visit this month in both HIV/TB integrated clinic settings and non-integrated settings.

TB Treatment Toxicity (30d)

Similar to TB prophylaxis toxicity, each month that a patient carries the *onTBtreatmentX* flag, he/she will roll for toxicity. If the toxicity is rolled for, the patient will accrue a cost (*TBtreatmenttoxcost*) and quality of life (QOL) decrement (*TBtreatmenttoxQOL*).

Toxicity

| | Minor Tox Monthly Prob | | Major Tox Monthly Prob | | |
	Off ART	On ART	Off ART	On ART	Prob Dth (Maj)
HIV -	0.000000	0.000000	1.000000	1.000000	0.500000
HIV +	0.000000	0.000000	1.000000	1.000000	0.500000

	Minor Tox Cost	Minor Tox QOL Mult	Major Tox Cost	Major Tox QOL Mult	
HIV -	0.00	1.0000	0.00	1.0000	
HIV +	0.00	1.0000	0.00	1.0000	

The patient will also accrue a mortality risk (*TBtreatmenttoxmortality*) to be added and evaluated in the Mortality Updater (60a).

Patients who are HIV-uninfected will be scheduled for an Emergency TB Clinic Visitin the same month that they experience a toxicity event. Patients who are HIV-infected will be scheduled for an Emergency TB Clinic Visit this month in both HIV/TB integrated clinic settings and non-integrated settings.

General Mortality Updater (60a)

The General Mortality Updater is already a framework within the CEPAC module which accrues all of the mortality probabilities in the Disease section of CEPAC and evaluates whether a patient dies in that month. This TB module will not change this structure at all, but will need: untreated TB mortality (*untreatedTBmortalityCD4xxx*, where xxx denotes CD4 stratum [e.g., vhi, hi, mhi, etc.]), TB prophylaxis toxicity mortality (*TBprophtoxmortality*), and TB treatment toxicity mortality (*TBtreatmenttoxmortality*).Those who rolled for treatment success (*TBTreatmentSuccess*) will have no mortality risk while on treatment (the probability of treatment success depends on the appropriateness of the regimen for that strain)while those who rolled for treatment failure (*TBTreatmentFail*) will have a mortality risk equivalent to that of those with untreated TB.

MORTALITY

Mortality from TB (Active, untreated TB)

Prob death		Active Pulm TB	Active Extrapulm TB
	HIV -	0.0000	1.0000
	CD4 VHI	0.0000	1.0000
	CD4 HI	0.0000	1.0000
	CD4 MHI	0.0000	1.0000
	CD4 MLO	0.0000	1.0000
	CD4 LO	0.0000	1.0000
	CD4 VLO	0.0000	1.0000

Multiplier by Tx and fail/success draw:

If on successful treatment	0.0000
If on failed treatment	0.0000

Behavior Updater (90a/b)

The Behavior Updater in CEPAC handles loss to follow-up (LTFU) and return to care (RTC). The default is to assume that HIV care and TB care are not integrated (i.e., they operate independently of each other), though we plan to allow for integration of HIV care and TB care, designated by a toggle (yes/no).

If HIV care and TB care are not integrated, HIV-infected patients who are LTFU in HIV care are not automatically LTFU in TB care.Patients who are LTFU will be moved into the "TB Treatment Default" state if

they have not attended a TB clinic for a user-defined number of months (usually 2 months). Patients who are LTFU for less than the user-defined number of months for defaulting will remain in the TB state they were in upon LTFU. Note that HIV-uninfected patients will skip the Behavior Updater (as they currently do)since they cannot beLTFU to HIV care.

When HIV care and TB care <u>are</u> integrated, being LTFU in HIV care will automatically signify being LTFU in TB care. When a patient rolls for LTFU in HIV care, the module will evaluate if the patient is on TB prophylaxis (*onTBprophlyaxisX*) or on TB treatment (*onTBtreatmentX*), and will clear these flags, thus stopping both TB prophylaxis and treatment for patients who are LTFU. Patients who were destined to fail treatment will still fail and remain in the Active TB state. Patients who were destined to complete treatment successfully will draw for treatment failurebased on the proportion of their treatment they completed before going LTFU upon defaulting. Patients who fail will draw for *sputumbacloadhi*.

HIV Clinic Visit Updater (130a)

The Clinic Visit Updater currently describes the HIV clinic visit and all of its subroutines. We propose to add a TB Treatment Program Subroutine and a TB Proph Program Subroutine (identical to the TB Treatment and TB Proph subroutines, respectively, in the TB Clinic Visit Updater) when the TB Module is enabled and when HIV care and TB care are integrated at the HIV Clinic.

TB Testing at HIV Clinic Updater (135b)

The TB Testing at HIV Clinic Updater is used to simulate the diagnosis and treatment of TB within the setting of anHIV clinicand to ultimately link patients to TB treatment via the TB linkage subroutine (130p).Patients receiving TB testing at an integrated HIV/TB clinic will always link to TB treatment and care.

Attendance at HIV clinic this month will be evaluated. These specifications are already in use in CEPAC and, thus, are not described here. Patients not attending clinic in this month skip the rest of the TB Testing at HIV Clinic Updater.

Patients who attend HIV clinic this month will be evaluated for Active Pulmonary TB or Extrapulmonary TB. As a simplifying assumption, patients who are on successful TB therapy will not be subject to further diagnostic testing.

Patients who are not on TB therapy will be tested for TB if: a) they are due for scheduled TB screening this month, or b) they meet the criteria to be tested. Other criteria for the timing of screening will include:

1. Upon HIV diagnosis
2. Presentation with TB symptoms
3. At HIV clinic visit with CD4<200 (or other CD4 criterion)
4. With any OI
5. At month X in model simulation (one-time)
6. Every Y months (recurring)

Initiation Policy for TB Testing					
	Use Policy?				
	0	NO	Upon HIV Diagnosis		OR
	1	YES	With TB Symptoms		OR
	0	NO	With any OI		OR
	0	NO	0 < CurrCD4 <	350	OR
	0	NO	Calendar month	0	OR
	0	NO	Months between testing	1	OR

If any of these criteria are met, the patient will be subject to diagnostic testing. If not, the patient will skip the rest of the TB Testing at HIV Clinic Updater.

Patients will be eligible for up to 4diagnostic tests (which can include combinations of chest X-ray, sputum smear, sputum culture, sputum GeneXpert, and urine LAM, though the fourtests can be parameterized to represent any type, number, or order of tests). All test results, except for sputum culture, will be evaluated in the month of screening, and the results will be drawn in that month.

Each test will be associated with a "Time to results" parameter, signifying the delay to result associated with each test (i.e., sputum smear results are available immediately whereas sputum culture results require up to 2 months, and longer for conventional drug-susceptibility testing). This parameter will be a probability distribution with mean month and standard deviation. If the test results are positive and available in that month, the patient will be flagged as diagnosed with TB, which will inform TB treatment decisions later that month in the module. If a test result is not available in that month, the patient will receive the test result in a subsequent month, and that test result can inform clinical decisions only after it has been received.

The tests will be ordered and performed according to the test matrix below. A value of "1" indicates that the test should be performed, and a value of "0" indicates that the test should not be performed. For example, if Test 1 is sputum smear, and the result is positive, one may forgo additional diagnostic tests.

Test Sequence Matrix

If 2 tests				
Perform test 1 when	Test 0 +		1	0 = no, 1 = yes
	Test 0 -		0	0 = no, 1 = yes

If 3 tests		Test 1 +	Test 1 -	
Perform test 2 when	Test 0 +	0	1	0 = no, 1 = yes
	Test 0 -	1	1	0 = no, 1 = yes

If 4 tests	**Test 2 +**			**Test 2 -**		
Perform test 3 when		Test 1 +	Test 1 -		Test 1 +	Test 1 -
	Test 0 +	0	1	0 = no, 1 = yes	Test 0 +	1	1	0 = no, 1 = yes
	Test 0 -	1	1	0 = no, 1 = yes	Test 0 -	1	1	0 = no, 1 = yes

Each test will have a defined sensitivity (the probability of apositivetest result for those in the Active Pulmonary TB and Active Extrapulmonary TB states) and specificity (the probability of a negative test result for those who truly do not have active TB).

TB Test 0

Test Name:	Test 0					

Test characteristics						
TB Positive Test Rate	Uninfected	Latent TB	Active Pulm TB	Active Extrapulm TB	Prev Treat TB	TB Treat Default
HIV -	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000
CD4 VHI	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000
CD4 HI	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000
CD4 MHI	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000
CD4 MLO	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000
CD4 LO	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000
CD4 VLO	0.0000	0.0000	1.0000	0.0000	0.0000	0.0000

Each test will also have a probability of test acceptance, probability of result pick-up, and time to result pick-up.Patients will rollfor a one-time probability of picking up the results of each diagnostic test. For patients who roll to pick up their results, they roll for a "time to result pick up". If these patients pick up the results before the time defined in the "repeat all tests if not picked up by n months" cell, then they move onto the next test (if available) or receive a diagnosis. If these patients pick up the results after the time defined in the "repeat all tests if not picked up by n months," then they will repeat all diagnostic tests when they "show up" to pick up their results.

For patients who roll to **not**pick up their results, they then roll for a "time to wait before re-testing" time (defined by mean and SD). If they "show up" before the time defined by the "repeat all tests if not picked up by n months" cell, then they will simply have to repeat the current test. If they show up after that time frame, they will have to repeat all diagnostic tests.

Probability of test acceptance	1.0000	
Probability of result pick-up	1.0000	
Repeat all tests if not picked up by n months:	6	
	Mean	SD
Time to result pickup (mth)	6.0000	0.0000
Time to wait before re-testing if not picking up results	6.0000	0.0000

Drug Resistance Testing Subroutine (135c')

Tests that include drug resistancetesting will enter the "Drug Resistance Testing Subroutine" via a yes/no toggle under the Test Ordering section. The user will define the resistance test based on the type of diagnostic test (either conventional drug susceptibility test [DST]or GeneXpert rifampin resistance testing) being performed.

If this is a **conventional DST** performed after a positive sputum culture result, there should be resistance testing for the 3 strains (ds-TB, MDR-TB, XDR-TB) of TB.

Drug Resistance Positive Test Rate	dsTB	MDR	XDR	Time to Result (mo.)	Upon positive result, switch to treatment:
ds-TB Positive Test Rate	1.0000	0.0000	0.0000	2	Line 0
MDR-TB Positive Test Rate	0.0000	1.0000	1.0000	2	Line 0
XDR-TB Positive Test Rate	0.0000	0.0000	1.0000	2	Line 0

Note: column and row must sum to 1.0 for all strains

The sensitivities and specificities of the drug resistance tests will be used to populate the cells. Those testing positive for MDR-TB will receive the tracker variable *ObservedMDRTB*. Those testing positive for XDR-TB will receive the tracker variable *ObservedXDRTB*. Like the result of a test without DST, the result of DST will be evaluated in that month but will be made available only after a user-specified amount of time. Patients who receive the diagnosis of MDR-TB or XDR-TB in a given month will begin treatment or switch treatment that month.

If this is a **GeneXpert** test, there should be two user-defined test rates for RIF-sensitive TB and RIF-resistant TB. Time to result will generally be 0 months as results can be obtained on the same day in some settings.

Drug Resistance Positive Test Rate	ds-TB	MDR-TB	XDR-TB	Time to Result (mo.)	Upon positive result, switch to treatment:
RIF-sensitive Test Rate	1.0000	0.0000	0.0000	0	Line 0
RIF-resistant Test Rate	0.0000	1.0000	1.0000	0	Line 0
User defined resistance test rate 2	0.0000	0.0000	1.0000	2	Line 0

Note: columns must sum to 1.0 for all strains

If the drug resistance test is not linked to the diagnostic test result, patients will roll for a probability of results pick-up for each drug susceptibility test.

Is DST linked to diagnostic test?	1	0 = no, **1** = yes
If not linked, probability of DST result pick-up:	0.5000	

Each test also has associated costs and QOL multipliers.

Initial TB test cost	0.00
Initial TB test QOL multiplier	0.00
Addit. Cost for drug sensitivity testing	555.00

Because we are including the possibility of multiple diagnostic assays, we will also need to include a diagnostic "Result Interpretation Matrix" to determine the clinical diagnosis based on the combination of results from the test sequence matrix. For example, if two tests are performed, we are likely to consider the patient diagnosed with TB if both tests are positive, or if one of the tests is positive, but not if neither test is positive. In each case, the user must specify the clinical diagnosis.

Result Interpretation Matrix

If 1 test
Diagnosed TB when	Test 0 +	1	0 = no, 1 = yes
	Test 0 -	0	0 = no, 1 = yes

If 2 tests
Diagnosed TB when		Test 1 +	Test 1 -	
	Test 0 +	1	1	0 = no, 1 = yes
	Test 0 -	1	0	0 = no, 1 = yes

If 3 tests
Diagnosed TB when	Test 2 +				Test 2 -			
		Test 1 +	Test 1 -			Test 1 +	Test 1 -	
	Test 0 +	1	1	0 = no, 1 = yes	Test 0 +	1	1	0 = no, 1 = yes
	Test 0 -	1	1	0 = no, 1 = yes	Test 0 -	1	0	0 = no, 1 = yes

If 4 tests
Diagnosed TB when	Test 3 +							
	Test 2 +				Test 2 -			
		Test 1 +	Test 1 -			Test 1 +	Test 1 -	
	Test 0 +	0	0	0 = no, 1 = yes	Test 0 +	1	1	0 = no, 1 = yes
	Test 0 -	0	1	0 = no, 1 = yes	Test 0 -	1	1	0 = no, 1 = yes

	Test 3 -							
	Test 2 +				Test 2 -			
		Test 1 +	Test 1 -			Test 1 +	Test 1 -	
	Test 0 +	1	1	0 = no, 1 = yes	Test 0 +	1	1	0 = no, 1 = yes
	Test 0 -	1	1	0 = no, 1 = yes	Test 0 -	1	1	0 = no, 1 = yes

A patient can be given empiric treatment for active TB, even in the absence of a definitive diagnosis of active TB. Scenarios in which this can occur include: 1) no additional diagnostic testing is done; 2) the clinician is waiting for the result of a diagnostic test (especially sputum culture); or 3) the clinician believes that the patient has active TB despite negative or inconclusive diagnostic test results.

Regimen
The majority of patients who are given empiric treatment for active TB are presumed to have dsTB, and accordingly will be given a first-line multidrug treatment regimen for dsTB. The only patients who may be given an empiric treatment regimen targeting MDR-TB or XDR-TB will be those who have a known history (flag) of active TB disease with either of these strains; these patients will have a probability of being given an empiric treatment regimen for MDR-TB or XDR-TB. The empiric treatment regimens to be given for presumed dsTB, MDR-TB, or XDR-TB are defined by the user.

Probability of empiric MDR-TB treatment for those with known history of MDR-TB	0.0000
Probability of empiric XDR-TB treatment for those with known history of XDR-TB	0.0000

Initiation of empiric treatment
Empiric treatment can be *initiated* in the following scenarios, dependent on HIV status and CD4 count:
1) Patient is symptomatic; awaiting result of TB Text X
2) Patient is asymptomatic; awaiting result of TB Test X
3) Patient is symptomatic; TB Test X comes back positive (a non-definitive test such as chest x-ray) and clinician is still awaiting the result of TB Test Y

4) Patient is asymptomatic; TB Test X comes back positive (a non-definitive test such as chest x-ray) and clinician is still awaiting the result of TB Test Y

Probability of initiating empiric treatment				
	While Awaiting Results		Upon Positive Result	
	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic
HIV -	0.0000	0.0000	0.0000	0.0000
CD4 VHI	0.0000	0.0000	0.0000	0.0000
CD4 HI	0.0000	0.0000	0.0000	0.0000
CD4 MHI	0.0000	0.0000	0.0000	0.0000
CD4 MLO	0.0000	0.0000	0.0000	0.0000
CD4 LO	0.0000	0.0000	0.0000	0.0000
CD4 VLO	0.0000	0.0000	0.0000	0.0000

If modeling a scenario where all symptomatic patients are given empiric treatment and no additional diagnostic tests are performed, the user can specify that a clinician's "detection" of symptoms is a positive test result (TB Test 0), and the probability of symptomatic patients starting empiric treatment given this positive test result is 1.

Cessation or continuation of empiric treatment
Empiric treatment can be *stopped* in the following scenarios:
1) Patient is symptomatic; pending TB Test X comes back negative
2) Patient is asymptomatic; pending TB Test X comes back negative
The probability of each of these is defined by the user in the input sheet ("probability of stopping empiric therapy upon negative result").

Probability of stopping empiric therapy upon negative result		
	Symptomatic	Asymptomatic
	0.0000	0.0000

Empiric treatment can be *continued* in the following scenarios:
1) Patient is symptomatic; pending TB Test X comes back negative
2) Patient is asymptomatic; pending TB Test X comes back negative
The probability of each of these is defined in the input sheet as 1 minus the "probability of stopping empiric therapy upon negative result."

Duration of treatment
If a patient is on empiric treatment and a subsequent test result (e.g., sputum culture) returns positive, then the same treatment will be continued assuming that it's for the same strain; e.g., if normal treatment duration for dsTB is 6 months and the patient received empiric dsTB treatment for 2 months before getting a positive sputum culture, then dsTB treatment will be continued for an additional 4 months. However, if the patient's observed strain turns out to be different from the strain targeted by empiric treatment (e.g., patient received 2 months of empiric dsTB therapy but then is observed to have MDR-TB by a test result indicating such), then the patient will start an MDR-TB treatment regimen from scratch; the 2 months of dsTB treatment do not count.

Costs and toxicities

While on an empiric treatment regimen, the patient accrues costs and toxicity probabilities defined for that regimen, identical to those defined for those on non-empiric treatment. If a patient experiences minor toxicity from empiric treatment, the treatment will be continued. If a patient experiences major toxicity while on empiric treatment, the treatment will be stopped; the patient will not be switched to a different regimen. However, if a pending test results subsequently returns positive, the patient can start "non-empiric" treatment with the next regimen.

Empiric treatment as prophylaxis
Empiric treatment, when the full duration is completed, should also be considered as effective prophylaxis; in other words, it will reduce the risk of infection, reinfection, and activation in a manner similar to prophylaxis.

Once all test results for a month have been evaluated, if the patient is diagnosed with TB (*ObservedxxxTB*) he/she will be flagged to begin treatment in that month if not already on treatment. Patients flagged to begin treatment will roll for linking to TB clinic if HIV/TB care is not integrated (schedule Emergency TB Clinic Visit).

Probability of Linking to TB Treatment Upon TB-positive diagnosis:	
Integrated HIV/TB Clinic	1.0000
Non-integrated HIV/TB Clinic	1.0000

Patients who are HIV-infected but undetected (and not linked to HIV care) and receive a TB-positive diagnosis will also roll for becoming detected as having an HIV infection upon linking to TB care.

Probability of HIV Detection Upon Linkage to TB Care	
Integrated HIV/TB Clinic	1.0000
Non-integrated HIV/TB Clinic	1.0000

TB Clinic Visit Updater (135a)
The TB Clinic Visit Updater is used to simulate the diagnosis and treatment of TB within the setting of a TB clinic that is not integrated with the HIV clinic in the CEPAC model. Thus, patients can be in or out of care at either clinic independently. Additionally, HIV-negative patients who do not cycle through the HIV clinic in CEPAC are able to cycle through the TB Clinic Visit Updater to manage their TB care. HIV-infected individuals who are diagnosed with TB during their HIV clinic visit (see previous section "TB Testing at HIV Clinic Updater") can link to the TB Clinic Visit updater.

Will Attend TB Clinic This Month (135b)
As with the HIV Clinic in CEPAC, patients will be evaluated for attendance at a TB clinic visit this month.
- Patients who are TB LTFU and who do not return to care will not attend clinic.
- Patients who are HIV-uninfected will attend TB clinic only if they are symptomatic and roll to present to TB clinic. HIV-uninfected patients can also have a probability of showing up to TB clinic via a screening intervention (this will allow us to model TB-screening interventions in HIV-negative patients and how wide of a "net" the intervention must cast.) Patients who are HIV-uninfected will enter directly into the TB Clinic Diagnostics Subroutine.
- HIV-infected patients will not attend TB clinic if HIV/TB care is integrated. If HIV/TB care is not integrated, patients who link to TB clinic from the "TB Testing at HIV Clinic Updater" will skip the diagnostic portion of the TB Clinic Visit updater, so as not to cycle twice through the diagnostic algorithm. HIV-infected patients who have not been linked to TB clinic from the HIV clinic will cycle through the TB Clinic Diagnostics Subroutine.

- All patients awaiting a TB diagnosis, on TB treatment, scheduled to start or stop prophylaxis, or experiencing a treatment or prophylaxis toxicity this month will attend TB clinic, unless they are LTFU.

TB Clinic Diagnostics Subroutine (135c)

The TB Clinic Diagnostics Subroutine and drug resistance testingsubroutine will function almost identically to the "TB Testing at HIV Clinic" subroutine with the following exceptions:
1. No evaluation of "Will attend HIV Clinic this month?"
2. No linking to TB care after positive diagnosis (patient is already in TB care).

TB Clinic Treatment Subroutine (135g)

The TB Clinic Treatment Subroutine links patients who have been diagnosed with TB to TB treatment. It deals with the clinical management of TB and the efficacy of treatment. All patients can receive TB treatment, regardless of true TB natural history state. This will allow treatment of those who do not truly have TB (false positives).

Users can specify a time lag to the start of treatment initiation. Each line of treatment will have a user-specified intended duration.

Months Lag to Treatment Initiation	Mean	Std Dev
	0.00	0.00

Based on the presence of the diagnosed drug strain tracker variables ($ObserveddsTB$, $ObservedMDRTB$, $ObservedXDRTB$), patients will have a probability of receiving each line of therapy as initial treatment. The probabilities for each strain must sum to one. Patients not identified as having drug-resistant TB will be assumed to have drug-susceptible TB.

Probability of Receiving Each line as initial treatment

TB Treatment #	Name of Treatment	Prob Initial Observed ds-TB	Observed MDR-TB	Observed XDR-TB
0	Treatment 0	1.0000	0.0000	0.0000
1	Treatment 1	0.0000	1.0000	0.0000
2	Treatment 2	0.0000	0.0000	1.0000
3	Treatment 3	0.0000	0.0000	0.0000
4	Treatment 4	0.0000	0.0000	0.0000
5	Treatment 5	0.0000	0.0000	0.0000
6	Treatment 6	0.0000	0.0000	0.0000
7	Treatment 7	0.0000	0.0000	0.0000
8	Treatment 8	0.0000	0.0000	0.0000
9	Treatment 9	0.0000	0.0000	0.0000
		Must sum to 1	Must sum to 1	Must sum to 1

When starting a line of treatment, a patient will roll for a destined treatment outcome. The two options will be *TBTreatmentSuccess* and *TBTreatmentFailure*. The distribution will be dependent upon HIV status, CD4 count, and the true TB strain.

Overall Probability of Treatment Success

	ds-TB	MDR-TB	XDR-TB
HIV -	1.0000	1.0000	1.0000
CD4 VHI	0.0000	0.0000	0.0000
CD4 HI	0.0000	0.0000	0.0000
CD4 MHI	0.0000	0.0000	0.0000
CD4 MLO	0.0000	0.0000	0.0000
CD4 LO	0.0000	0.0000	0.0000
CD4 VLO	0.0000	0.0000	0.0000

Patients with Active Pulmonary TB or Active Extrapulmonary TB who roll for treatment success will not face monthly probabilities of TB mortality; these patients will lose their *sputumbacloadhi* flag if present. Patients in the Active Pulmonary TB or Active Extrapulmonary TB states who successfully complete treatment will move to the Previously Treated TB health state.

Those who roll for treatment failure (*TBTreatmentFail*)will continue to face monthly TB mortality equal to that ofthose with untreated TB.

Patients in the Uninfected, Latent TB, Previously Treated TB, or TB Treatment Default states who are treated due to false positive diagnostic results or empiric therapy will remain in their respective health states upon treatment completion. However, their risks of infection and reinfection will be reduced while on TB treatment. Also,for those in the Latent TB state, completion of a full course of TB treatment without default will count as "prophylaxis," thereby reducing their risk of subsequent activation in a manner similar to that if they had completed a course of prophylaxis.

Patients who roll for treatment failure will have a probability of experiencing observed early failure before the end of a treatment regimen. Patients who are observed to experience early failure will have a probability of switching to the next user-defined treatment regimen.

Monthly Probability of Observed Early Failure		0.0000
Probability of Switching Treatment Lines Upon Observed Early Failure		0.0000
Next Treatment Upon Observed Early Failure		
	TB Treatment #	Name of Treatment
	-1	N/A

Patients who completed a treatment line but failed can move to the next regimen.

Next Treatment Upon Failure (Non early)		
	TB Treatment #	Name of Treatment
	-1	N/A
-1=N/A		

Patients who fail treatment can also have a probability of repeating the same regimen that they had just failed.Patients can have a probability of increased drug resistance upon treatment failure or default (i.e.,*dsTB* changing to *MDR-TB* or *MDR-TB* changing to *XDR-TB;* for simplification, patients cannot directly change from dsTB to XDR-TB).

Repeating line as retreatment after failure					Probability of Increased Resistance	
	TB Treatment #	Name of Treatment	Prob Repeat	Max # of Repeats	After Failure	After Treatment Default
	0	Treatment 0	0.0000	0	0.0000	1.0000
	1	Treatment 1	0.0000	0	0.0000	0.0000
	2	Treatment 2	0.0000	0	0.0000	0.0000
	3	Treatment 3	0.0000	0	0.0000	0.0000
	4	Treatment 4	0.0000	0	0.0000	0.0000
	5	Treatment 5	0.0000	0	0.0000	0.0000
	6	Treatment 6	0.0000	0	0.0000	0.0000
	7	Treatment 7	0.0000	0	0.0000	0.0000
	8	Treatment 8	0.0000	0	0.0000	0.0000
	9	Treatment 9	0.0000	0	0.0000	0.0000
			0=No repeat			

If the patient experienced a toxicity associated with TB treatment in this month, the module will evaluate the treatment decision here.

- If there is no subsequent line of TB treatment available, the module will evaluate whether a patient should stop this line of TB treatment upon experiencing toxicity. If no, the patient will remain on the current line of therapy. If yes, the patient will stop TB treatment and will lose the *onTBtreatmentX* flag. The patient will roll for treatment success, weighted by the proportion of time spent on treatment compared to the intended duration.

- If there is a subsequent line of TB treatment available, the patient *will switch to* the next line of treatment and will receive a new *onTBtreatmentX* flag (where X designates the line of therapy) and will update the treatment efficacy.

TB Clinic Proph Subroutine (135f and 135f')

The user can specify the order of prophylaxis administration and define the duration of each prophylaxis line.

Order of Administering Prophylaxes

	Proph #	Proph Name	Proph Duration (Mths)
Line 0	0	*Isoniazid*	6
Line 1	-1	N/A	6
Line 2	-1	N/A	6
Line 3	-1	N/A	6
Line 4	-1	N/A	6

Note: use "-1" to indicate unused proph.

TB Prophylaxis initiation criteria will be evaluated and will include: CD4 count, known history of active TB, presence of *immreactyes* tracker variable, or at ART initiation. If either or all of these criteria (and/or evaluated by a toggle) are met, the patient will start the next line of prophylaxis and will gain the *onTBprophylaxisX* time-counted flag.

Prophylaxis Starting Policy for HIV+

		0	Note: use 0="AND", 1="OR"
	All on proph	1	0 = no, **1** = yes
AND	CurrCD4 <=	350	
	CurrCD4 >=	0	
AND	ART Initiation	0	0 = no, **1** = yes
AND	History of Active TB	0	0 = no, **1** = yes
AND	Immune Reactive	0	0 = no, **1** = yes

Prophylaxis Starting Policy for HIV -

		0	Note: use 0="AND", 1="OR"
	All on proph	1	0 = no, **1** = yes
AND	History of Active TB	0	0 = no, **1** = yes
AND	Immune Reactive	0	0 = no, **1** = yes

Patients who qualify for prophylaxis will experience a probability of actually receiving treatment based on HIV status and whether they are on or off ART. There can be a user-defined time delay in starting prophylaxis treatment, characterized by months (mean and standard deviation) of lag.

Proportion of Patients who Qualify for Proph to Receive Proph:

HIV-	Off ART	On ART
1.0000	1.0000	1.0000

	Mean	Std Dev
Lag to Start	0	0

Patients already on prophylaxis who experience toxicity this month will be evaluated for availability of a second line of prophylaxis, as defined by the order of prophylaxis administration.

Move onto next line of prophylaxis upon toxicity:

0	0=no, 1=yes

If so, the patient will switch to that line (*onTBprophylaxisX*), and the prophylaxis efficacy will be updated. If another line of prophylaxis is not available, the patient will lose the *onTBprophylaxisX* flag and will no longer be conferred the benefit, toxicity risks, or costs of being on prophylaxis. Patients will also experience continued protection against TB infection or activation for a user-defined period of time after stopping prophylaxis treatment.

Patients with Uninfected Status

Efficacy of prophylaxis against TB infection

Number	0	1	2	3	4
Prophylaxis Name	Isoniazid	Rifampin	User Proph 1	User Proph 2	User Proph 3
HIV-	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 VHI	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 HI	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 MHI	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 MLO	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 LO	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 VLO	1.0000	1.0000	1.0000	1.0000	1.0000
Months of Efficacy after stopping	0	0	0	0	0

Patients in Latent state

Efficacy of prophylaxis against activation

Prophylaxis Name	Isoniazid			Rifampin			User Proph 1		
	ds-TB	MDR-TB	XDR-TB	ds-TB	MDR-TB	XDR-TB	ds-TB	MDR-TB	XDR-TB
HIV-	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 VHI	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 HI	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 MHI	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 MLO	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 LO	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 VLO	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Months of Efficacy after stopping	0	0	0	0	0	0	0	0	0

Patients in Latent, Prev Treated, or Default states

Efficacy of prophylaxis against reinfection

Prophylaxis Name	Isoniazid			Rifampin			User Proph 1		
	ds-TB	MDR-TB	XDR-TB	ds-TB	MDR-TB	XDR-TB	ds-TB	MDR-TB	XDR-TB
HIV-	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 VHI	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 HI	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 MHI	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 MLO	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 LO	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
CD4 VLO	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
Months of Efficacy after stopping	0	0	0	0	0	0	0	0	0

TB Prophylaxis Cost and QOL

Number	Prophylaxis Name	Mth Cost	MinTox Cost	Min Tox QOL	Maj Tox Cost	Maj Tox QOL
0	Isoniazid	0.00	0.00	0.00	0.00	0.00
1	Rifampin	0.00	0.00	0.00	0.00	0.00
2	User Proph 1	0.00	0.00	0.00	0.00	0.00
3	User Proph 2	0.00	0.00	0.00	0.00	0.00
4	User Proph 3	0.00	0.00	0.00	0.00	0.00

TB Prophylaxis Toxicity

		Minor Tox Monthly Prob		Major Tox Monthly Prob		
Number	Prophylaxis Name	Off ART	On ART	Off ART	On ART	Prob Dth (Maj)
0	Isoniazid	0.000000	1.0000	0.000000	1.0000	0.000000
1	Rifampin	0.000000	1.0000	0.000000	1.0000	0.000000
2	User Proph 1	0.000000	1.0000	0.000000	1.0000	0.000000
3	User Proph 2	0.000000	1.0000	0.000000	1.0000	0.000000
4	User Proph 3	0.000000	1.0000	0.000000	1.0000	0.000000

Each month on prophylaxis, the patient will roll to default, or 'drop off', from TB prophylaxis.

Of Patients who are Taking Proph	
Monthly Probability of Drop Off	1.0000

If the patient does not default from prophylaxis, he/she will be evaluated for whether TB prophylaxis should be stopped (criteria based on HIV status, CD4 count, number of months since prophylaxis initiation, ART initiation, and a major toxicity event). If none of the criteria are met, the patient will

continue the same line of prophylaxis until the duration of prophylaxis is complete. If the stopping criterionis met, the patient will stop TB prophylaxis and will lose the *onTBprophylaxisX* flag.

Prophylaxis Stopping Policy for HIV+			
		0	Note: use 0="AND", 1="OR"
	CurrCD4 <=	350	
	CurrCD4 >=	0	
AND	# Months on Proph	10000	
AND	Major Toxicity	0	0 = no, 1 = yes

Prophylaxis Stopping Policy for HIV-			
		0	Note: use 0="AND", 1="OR"
	# Months on Proph	100000	
AND	Major Toxicity	0	0 = no, 1 = yes

Patients who have completed prophylactic therapy can have a probability of increased drug resistance (i.e.,*dsTB* changing to *MDR-TB* or *MDR-TB* changing to *XDR-TB)*upon activating, though the probability of activating may be reduced by the prophylactic therapy.

TB Prophylaxis Increase Resistance After Activation			
	Number	Prophylaxis Name	Prob Resist
	0	Isoniazid	0.000000
	1	Rifampin	0.000000
	2	User Proph 1	0.000000
	3	User Proph 2	0.000000
	4	User Proph 3	0.000000

TB Clinic LTFU Subroutine (135d)

The TB Clinic LTFU Subroutine will be used to simulate TB treatment defaultwhen HIV and TB clinics are not integrated, for TB-infected, HIV-negative patients, and for TB-infected, HIV-positive but undetected (not linked to HIV care) patients.

Those who are LTFU do not incur treatment or toxicity costs when they are LTFU. For patients who are on treatment and not already LTFU, there will be a monthly probability of beingLTFU based on TB state; those who roll to be LTFU can then again roll for treatment success vs. failure:

- Patients who initially rolled for destined treatment failure (*TBTreatmentFail*) will automatically fail upon becoming lost to follow-up.
- Patients who initially rolled for destined treatment success (*TBTreatmentSuccess*) will roll again (after being loss to follow-up for the minimum number of months required to be defined as default (2 months) using a treatment success probability weighted by the proportion of time spent on treatment. If Y is the intended duration of treatment and X is the number of months on treatment prior to becoming LTFU, then the probability of success will be (X/Y)**ProbTBTreatmentSuccess*. Patients who roll for success the second time will lose their *sputumbacloadhi* flag and will go to the Default state; patients who roll for failure the second time will redraw for the *sputumbacloadhi* flag and will remain in the Active TB state.
- Patients in the Uninfected, Latent TB, or Previously TreatedTB states who are unnecessarily receiving treatment will automatically stay in their respective states upon beingLTFU.

Use TB LTFU?		0	0=no, 1=yes

Monthly Probability of Going LTFU	
Uninfected	1.0000
Latent TB	1.0000
Active Pulm TB	0.5000
Active Extrapulm TB	1.0000
Prev Treat TB	1.0000
TB Treat Default	1.0000

Patients who are currently LTFU from TB treatment will face a monthly probability of returning to care based on TB state, HIV status, and CD4 count. We will assume that patients in the Uninfected, Latent TB, and Previously Treated TB states who areLTFU from TB treatment will not return to TB treatment. However, patients in the Uninfected, Latent TB, and Previously Treated TBstates who default from TB prophylaxis will have a monthly probability of returning to TB care to recommence prophylaxis.

Patients with Active Pulmonary TB, Active Extrapulmonary TB, and TB Treatment Default states who return to care will be placed on a treatment regimen based on the time spent LTFU.They can reinitiate the original treatment regimen from the beginning, resume the original treatment regimen according to the month during which they were LTFU, roll to be re-tested for active TB, or initiate the next treatment line if available.

Monthly Probability of Return to Care (RTC)

	Uninfected	Latent TB	Active Pulm TB	Active Extrapulm TB	Prev Treat TB	TB Treat Default
HIV -	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
HIV +	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

Returning to TB care (Active State only)

	Number of months since LTFU				
	0-2 months	2-4 months	4-6 months	6-8 months	8+ months
Reinitiate original treatment regimen	0.0000	0.0000	0.0000	0.0000	0.0000
Resume original treatment regimen	0.0000	0.0000	0.0000	0.0000	0.0000
Re-testing for new regimen	0.0000	0.0000	0.0000	0.0000	0.0000
Move onto next treatment regimen	1.0000	1.0000	1.0000	1.0000	1.0000
	must sum to 1.0	must sum to 1.0	must sum to 1.0	must sum to 1.0	must sum to 1.0

End Month Updater (140a/b/c)

In the end month updater, which handles the majority of costing in CEPAC, we propose to add the costs of TB prophylaxis, TB prophylaxis toxicity, TB treatment, TB treatment toxicity, and TB diagnostic tests. We will include the option of an HIV/TB integrated care multiplier, which will allow us to examine the effects of cost reductions and/or increases associated with integrated care.We will include an option to increase or decrease TB care cost by a specified dollar amount or percentage until a specified month, after which TB care costs can be increased or decreased by another specified dollar amount or percentage. This functionality will allow us to examine cost reductions or increases associated with coordinated care.

We will also include TB-specific death costs and QOL in the End Month Updater if the patient dies of TB in that month.
Model Output

TB SUMMARY EVENTS							
TB State upon Entry:	dsTB	mdrTB	xdrTB				
uninfected	0	0	0				
latent	0	0	0				
active pulm	0	0	0				
active extrapulm	0	0	0				
prev treated TB	0	0	0				
Start on TB Treatment:	dsTB Tx	dsTB Tx rpt	MDR-TB Tx	XDR-TB Tx			
uninfected	0	0	0	0			
latent	0	0	0	0			
active pulm	0	0	0	0			
active extrapulm	0	0	0	0			
prev treated TB	0	0	0	0			
Start on TB Treatment:	dsTB Tx	dsTB Tx rpt	MDR-TB Tx	XDR-TB Tx			
dsTB	0	0	0	0			
mdrTB	0	0	0	0			
xdrTB	0	0	0	0			
	dsTB	mdrTB	xdrTB				
Total TB Primary Infections	0	0	0				
Total Activations (Pulm) from Latent TB	0	0	0				
Total Activations (Extrapulm) from Latent TB	0	0	0				
Total Activations (All) from Latent TB	0	0	0				
Total Reinfections from Latent TB	0	0	0				
Total Treatment Failures (Pulm) from Active TB	0	0	0				
Total Treatment Failures (Extrapulm) from Active T	0	0	0				
Total Treatment Failures (All) from Active TB	0	0	0				
Total Treatment Defaults (Pulm) from Active TB	0	0	0				
Total Treatment Defaults (Extrapulm) from Active T	0	0	0				
Total Treatment Defaults (All) from Active TB	0	0	0				
Total Successful Treatments (Pulm) from Active TB	0	0	0				
Total Successful Treatments (Extrapulm) from Activ	0	0	0				
Total Successful Treatments (All) from Active TB	0	0	0				
Total Relapses (Pulm) from Prev Treated TB	0	0	0				
Total Relapses (Extrapulm) from Prev Treated TB	0	0	0				
Total Relapses (All) from Prev Treated TB	0	0	0				
Total Reinfections from Prev Treated TB	0	0	0				
Total Treatment Initiation Latent TB	0	0	0				
Total Treatment Initiation Uninfected	0	0	0				
Total Deaths from TB (excluding drug toxicity)	0	0	0				
Total Deaths from Untreated TB	0	0	0				
	dsTB Tx	dsTB Tx rpt	MDR-TB Tx	XDR-TB Tx			
Total TB Treatment Toxicity Events	0	0	0	0			
Total Deaths from TB Treatment Toxicity	0	0	0	0			
	Proph1	Proph2					
Total TB Proph Toxicity Events	0	0					
Total Deaths from TB Proph Toxicity	0	0					
	Test 1	Test 2	Test 3	Test 4	Test 5	Algorithm	
Average time correct TB Dx	0	0	0	0	0	0	
	Test 1	Test 2	Test 3	Test 4	Test 5	Algorithm	
TB cases missed (false negatives)	0	0	0	0	0	0	
	Test 1	Test 2	Test 3	Test 4	Test 5	Algorithm	
Non-TB cases diagnosed as TB (false positives)	0	0	0	0	0	0	

Costs					
	dsTB Tx	dsTB Tx rpt	MDR-TB Tx	XDR-TB Tx	
TB Treatment costs	0	0	0	0	
TB Treatment toxicity costs	0	0	0	0	
	Proph1	Proph2			
TB Proph costs	0	0			
TB Proph toxicity costs	0	0			
	Test 1	Test 2	Test 3	Test 4	Test 5
Diagnostics	0	0	0	0	0

TB MONTH EVENTS

	uninfected	latent	active pulm	active extrapulm	prev treated TB
TB State	0	0	0	0	0
On Treatment					
dsTB Tx	0	0	0	0	0
dsTB Tx rpt	0	0	0	0	0
MDR-TB Tx	0	0	0	0	0
XDR-TB Tx	0	0	0	0	0
On Prophylaxis					
Proph 1	0	0	0	0	0
Proph 2	0	0	0	0	0

	dsTB	mdrTB	xdrTB
TB Primary Infections	0	0	0
Activations (Pulm) from Latent TB	0	0	0
Activations (Extrapulm) from Latent TB	0	0	0
Activations (All) from Latent TB	0	0	0
Reinfections from Latent TB	0	0	0
Treatment Failures (Pulm) from Active TB	0	0	0
Treatment Failures (Extrapulm) from Active TB	0	0	0
Treatment Failures (All) from Active TB	0	0	0
Treatment Defaults (Pulm) from Active TB	0	0	0
Treatment Defaults (Extrapulm) from Active TB	0	0	0
Treatment Defaults (All) from Active TB	0	0	0
Successful Treatments (Pulm) from Active TB	0	0	0
Successful Treatments (Extrapulm) from Active TB	0	0	0
Successful Treatments (All) from Active TB	0	0	0
Relapses (Pulm) from Prev Treated TB	0	0	0
Relapses (Extrapulm) from Prev Treated TB	0	0	0
Relapses (All) from Prev Treated TB	0	0	0
Reinfections from Prev Treated TB	0	0	0
Treatment Initiation Latent TB	0	0	0
Treatment Initiation Uninfected	0	0	0
Deaths from TB treatment toxicity	0	0	0
Deaths from TB prophylaxis toxicity	0	0	0
Deaths from TB (excluding drug toxicity)	0	0	0
Deaths from Untreated TB	0	0	0

Appendix 2: EARLY INFANT DIAGNOSIS (EID)

Individual Virologic Test Cascade

HIV Test 71

Dependent upon maternal status

Show up to Clinic

Dependent upon maternal status

Offered Testing

Dependent upon maternal status

Accept testing

Cost of Performing Test

HIV Test Specificity

HIV Test Sensitivity

Positive Result Cost

Negative Result Cost

Next specified testing opportunity (6 wks, 10 wks, etc)

Start ART per starting policy

Clinical Care

(Delay) Confirm with Test 73

(Possible Delay) Confirm with Test 72

Dependent upon maternal status

If test is positive

Average time (±SD) of Result Return

Dependent upon maternal status

Result Return Rate

Note: This involves both the Lab → Clinic rate and the Clinic → Patient rate

Note: *Each confirmatory test has the preceding cascade of test offer, acceptance probability, etc.*

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Overall Testing Program Cascade

Simulate Pediatric Patient (Month 0):
[1] Draw Maternal Status
[2] Draw own HIV transmission status
[3] Draw CD4% and HVL (if infected)
Each month, draw for:
[1] Opportunistic Infection (if infected)
[2] Mortality
[3] HIV test this month (if in strategy)

The probability of parameter **NOT** happening	The probability of parameter happening

** Choice of which test is used depends upon whether the mother is known to be positive or not and the provider-determined age of seroreversion. Each confirmatory test has a similar testing cascade as the one below.

** All patients going through this cascade are still subjected to monthly natural history probabilities of OIs and death if infected. HIV-exposed/uninfected children face PP infection risks, and HEU mortality if exposed in utero. HIV-unexposed children face background mortality risks.

** If patients become lost at a certain point, then when they return there is a probability that the provider will know where they left off in the cascade, and will continue where they left off. Otherwise, they will begin at the start of that testing window's cascade.

Birth Test

Prob. of parent showing up → *Dependent upon maternal status*

Testing Offer** → Acceptance → Result Receipt → Confirmatory Test** → HIV care

Or miss result / Or decline / miss test

6 week visit

If patient does not enter HIV care then they enter next testing window.

Prob. of parent showing up → *Dependent upon maternal status*

Testing Offer** → Acceptance → Result Receipt → Confirmatory Test** → HIV care

Or miss result / Or decline / miss test

10 week visit

If patient does not enter HIV care then they enter next testing window.

Prob. of parent showing up → *Dependent upon maternal status*

Testing Offer** → Acceptance → Result Receipt → Confirmatory Test** → HIV care

Or miss result / Or decline / miss test

6 month visit

If patient does not enter HIV care then they enter next testing window.

Provider-determined age of seroreversion? → *Dependent upon maternal status*

Testing Offer** → Acceptance → Result Receipt → Confirmatory Test** → HIV care

Or miss result / Or decline / miss test

12 month visit

If patient does not enter HIV care then they enter next testing window.

Etc.

§§ Non-maternal caregivers have differential probabilities of offer/acceptance of tests, but use baseline probabilities (unmodified by multipliers) for result return and confirmatory tests

Dependent upon maternal status

OI at any time can lead to presentation to care → Confirmatory Test**

CEPAC: clinical care; ART per specified starting policy --LTFU begins to apply at this stage

Non-Maternal Caregiver

Simulate Pediatric Patient (Month 0):
[1] Draw Maternal Status
[2] Draw own HIV transmission status
[3] Draw CD4% and HVL (if infected)
Each month draw for:
[1] Opportunistic Infection (if infected)
[2] Mortality
[3] HIV test this month (if in strategy)

The probability of parameter *NOT* happening / The probability of parameter happening

++Choice of which test is used depends upon whether the mother is known to be positive or not and the provider-determined age of seroreversion.

++All patients going through this cascade are still subjected to monthly natural history probabilities of OIs and death if infected. HIV-exposed/uninfected children face PP infection risks, and HEU mortality if exposed in utero. HIV-unexposed children face background mortality risks.

++If patients become lost at a certain point, then when they return there is a probability that the provider will know where they left off in the cascade, and will continue where they left off. Otherwise, they will begin at the start of that testing window's cascade.

Birth Test

Prob. of parent showing up

Dependent upon maternal status

Testing Offer++ → Acceptance → Result Receipt → Confirmatory Test++ → HIV care

Or miss result / Or decline/miss test

If patient does not enter HIV care then they enter next testing window

6 week visit

Non-maternal caregiver§§ shows up

Testing Offer and Acceptance++ → Result Receipt → Confirmatory Test++ → HIV care

Or miss result / Or decline/miss test

If patient does not enter HIV care then they enter next testing window

10 week visit

Prob. of parent showing up

Dependent upon maternal status

Testing Offer++ → Acceptance → Result Receipt → Confirmatory Test++ → HIV care

Or miss result / Or decline/miss test

If patient does not enter HIV care then they enter next testing window

6 month visit

Provider-determined age of seroreversion?

Dependent upon maternal status

Testing Offer++ → Acceptance → Result Receipt → Confirmatory Test++ → HIV care

Or miss result / Or decline/miss test

If patient does not enter HIV care then they enter next testing window

12 month visit

Etc.

§§Non-maternal caregivers have differential probabilities of offer/acceptance of tests, but use baseline probabilities (unmodified by multipliers) for result return and confirmatory tests

OI at any time can lead to presentation to care

Dependent upon maternal status

Confirmatory Test++

CEPAC: clinical care; ART per specified starting policy
--LTFU begins to apply at this stage

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Modeling Loss-to-Follow Up

Simulate Pediatric Patient (Month 0):
[1] Draw Maternal Status
[2] Draw own HIV transmission status
[3] Draw CD4% and HVL (if infected)
Each month, draw for:
[1] Opportunistic Infection (if infected)
[2] Mortality
[3] HIV test this month (if in strategy)

The probability of parameter *NOT* happening

The probability of parameter happening

**Choice of which test is used depends upon whether the mother is known to be positive or not and the provider-determined age of seroreversion.

**All patients going through this cascade are still subjected to monthly natural history probabilities of OIs and death if infected. HIV-exposed/uninfected children face PP infection risks, and HEU mortality if exposed in utero. HIV-unexposed children face background mortality risks.

**If patients become lost at a certain point, then when they return there is a probability that the provider will know where they left off in the cascade, and will continue where they left off. Otherwise, they will begin at the start of that testing window's cascade.

Birth Test

Dependent upon maternal status

Prob. of parent showing up

Testing Offer++ → **Acceptance** → **Result Receipt** ✚ **Confirmatory Test++**

6 week visit

Did not return for confirmatory test

Patient LTFU

6 month visit

If the provider does not know...

Provider has a probability of knowing patient had a positive initial test.

If the provider knows..

Dependent upon maternal status

Testing Offer++ → **Acceptance** → **Result Receipt** ✚ **Confirmatory Test++** ✚ **HIV care**

12 month visit

Or miss result

Or decline/miss test

If patient does not enter HIV care, then they enter next testing window.

Etc.

‡Non-maternal caregivers have differential probabilities of offer/acceptance of tests, but use baseline probabilities (unmodified by multipliers) for result return and confirmatory tests

OI at any time can lead to presentation to care

Dependent upon maternal status

Confirmatory Test++

CEPAC: clinical care; ART per specified starting policy
--LTFU begins to apply at this stage

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PEDIATRIC TESTING/EID Phase II: New PedsHIVTest Tab

Proposed Specifications: Phase II of Pediatric testing/Early Infant Diagnosis

The specifications proposed below represent "Phase II" of our incorporation of Pediatric HIV testing and Early Infant Diagnosis (EID) into the CEPAC model. It provides the capacity for the model user to specify test characteristics for antibody-based and virologic diagnostic assays, as well as the capability to specify different testing algorithms for children who are known to be exposed to HIV and those whose exposure is unknown.

PEDS HIV TESTING PANEL

[C2]

This cell will activate the Peds HIV Testing tab (i.e., the EID tab) for simulations.

[C3:C5]

The alternate stopping rule has two purposes: (1) ensuring that enough HIV-positive people run through both the Peds HIV Testing module and the main model that the results are not influenced by a few outliers, and (2) if we specify a high percentage of HIV-negative individuals, that the simulation will not cycle for hours attempting to find enough HIV-positive individuals to satisfy the main model's cohort size requirement. Let's look at an example of how a run would be affected if this did not exist. If we specify that the HIV prevalence in a cohort is 1% and only run 100,000 people in the simulation, then we will have (on average) 1,000 HIV-positive individuals who enter the main CEPAC model. Cost and life expectancy for the cohort will only be based on those 1,000 patients, so there will be a lot of noise from outliers. The alternative stopping rule ensures that a sufficient number of HIV-positive individuals enter the main model.

[E3:G12]

These cells are not modifiable by the user – they simply serve as a reminder of the assays that are currently being used within the tab.

[B9]

Prevalence of HIV among the pediatric cohort at birth (intrauterine and intrapartum infection) is already specified in the Peds tab stratified by maternal status and transmission type – this is where the pediatric testing/EID module will pull prevalence information from.

[B11]

Similarly, the monthly probability that an uninfected infant's mother becomes infected with the virus is specified already in the Peds tab, and the pediatric testing/EID module will pull this value as well in order to flag previously non-exposed infants who now are at risk to become infected through breastmilk (particularly while the mother is acutely infected).

[B20:G72]

These tables with six columns are used to specify the testing algorithm that will be used in the pediatric testing /EID simulation. Cells B20:B74 allow the user to specify the test that will be used in the clinic visit at a particular age. Users will specify an assay (ranging from number "70" (corresponding to the first test input by the user) to "79," the 10th assay, as we do for ART regimens 70-89. Cells C20:C72 will automatically fill in with the associated name of the specified test that is input into that test's individual panel, provided that the panel is filled in already with the appropriate name. For example, if Test 70 is a "Point-of-Care EIA," then the user would specify "70" in cell B20 and "Point-of-care EIA" would automatically appear in C20.

Specifying whether an EID test will be offered if a child misses a planned EID opportunity:
In our analyses, we are often modeling a sequence of testing opportunities, each with their own probabilities of patients presenting to the visit. If a patient misses a test (i.e. presents but is not offered or does not accept, or does not present), then presents at a subsequent "well-child" appointment (not an EID visit) that has no test already scheduled, there is the ability in the model to specify that the provider at the well-child visit will offer them the most recently scheduled assay that they missed.
- The reason that this only happens at a subsequent well-child (rather than EID) visit is that a patient presenting for a subsequent EID visit will be tested regardless of prior missed tests–

(e.g., a 3-month visit does not coincide with any scheduled vaccination, and so the only purpose of the visit is EID). However, a well child visit includes birth and vaccinations. If a patient presents to a well-child visit <u>where they weren't already going to get a test</u>, then they will be offered the most recent test they missed.

- An example of this situation is shown here:

		If maternal HIV status is NOT known to be positive			0="well-child", 1=EID	-1="No", 1="Yes"
Assay	Name of assay	Age at time of visit (months)	Baseline probability of presenting	Probability that child who presents is brought by non-maternal caregiver	Is this a "well-child" (0) (eg vaccination) visit or an EID visit (1)?	A child with a "missed test" flag can be reoffered testing at this visit?
-1	NONE	-1	0.950000	0.150000	0	1
71	POC EIA test	1	0.300000	0.200000	0	1
-1	NONE	-1	0.850000	0.250000	0	1
71	POC EIA test	3	0.800000	0.300000	1	1
-1	NONE	-1	0.000000	0.000000	1	-1
-1	NONE	-1	0.000000	0.000000	1	-1
-1	NONE	-1	0.000000	0.000000	0	-1
-1	NONE	-1	0.000000	0.000000	1	-1
-1	NONE	-1	0.000000	0.000000	1	-1
-1	NONE	9	0.500000	0.500000	0	1
-1	POC EIA test	10	0.500000	0.500000	1	-1

In the screenshot above, we are simulating a "Test only at 6 weeks and 14 weeks (i.e., 1 month and 3 months)" scenario. In the above table, no test should occur in Month 0 (i.e., birth) because (a) there is no assay specified for that age, and (b) there was no prior test that could have been missed. Thus, patients can show up and get a visit *cost*, but there's no diagnostic value to that testing window. In Month 1, there is a POC EIA test scheduled at a "well-child" visit. Thus, if the patient were to attend they would get the visit cost *and* any diagnostic value of the test if the assay is indeed administered. Let's say in this scenario, a patient either did not present to the Month 1 visit or they didn't receive the test when they did present. At that point, the patient would receive the label **MissedTest.** This label will follow the patient throughout EID until they are administered another EID assay. This can occur at a scheduled test (i.e., if the patient gets tested at a "well-child" visit where an EID test was scheduled to be administered, or at a scheduled EID visit) or at a "well-child" visit where no EID test was scheduled to be administered. In the event that the latter occurs, the patient will have the last scheduled assay in the algorithm table to be performed at the "well-child visit." In order to have repeat testing occur at a "well-child" visit that has no tests scheduled, three things are necessary:

(a) The assay number is set to -1
(b) The visit is classified as a "well-child" visit by a 0 in the penultimate column.
(c) There is a 1 in the final column indicating that a patient may be reoffered testing at that visit.

Thus, after a test is reoffered and accepted, or a scheduled test occurs, the **MissedTest** flag will disappear. It should also be noted that should a patient have the flag, and they present to a visit but still do not receive a test, then they will retain that flag. Additionally, flags do not accumulate – a patient cannot possess multiple **MissedTest** flags. Finally, the flag doesn't expire until after 24 months – therefore a patient may have the flag issued at 0 months, and if there is a testing opportunity at 9 months and they still have not been tested at that point in a previous window, they will receive the most recently scheduled assay, not the original test they missed (even though they did not receive the most recently scheduled test, this is done to reduce the likelihood that a post-seroreversion child will receive a PCR test when they could have received a cheaper antibody assay instead).

If you do not want retesting performed in your run, you can set the number in the final column of the testing algorithm table to "-1" to indicate that "a child with a missed test flag WON'T be reoffered testing at the visit."

| | | | | | 0="well-child", 1=EID | -1="No", 1="Yes" |
| | | | If maternal HIV status is NOT known to be positive | | | |
Assay	Name of assay	Age at time of visit (months)	Baseline probability of presenting	Probability that child who presents is brought by non-maternal caregiver	Is this a "well-child" (0) (eg vaccination) visit or an EID visit (1)?	A child with a "missed test" flag can be reoffered testing at this visit?
-1	NONE	-1	0.350000	0.150000	0	-1
71	POC EIA test	1	0.900000	0.200000	0	-1
-1	NONE	-1	0.850000	0.250000	0	-1
71	POC EIA test	3	0.800000	0.300000	1	-1
-1	NONE	-1	0.000000	0.000000	1	-1
-1	NONE	-1	0.000000	0.000000	1	-1
-1	NONE	-1	0.000000	0.000000	0	-1
-1	NONE	-1	0.000000	0.000000	1	-1
-1	NONE	-1	0.000000	0.000000	1	-1
-1	NONE	9	0.500000	0.500000	0	-1
-1	POC EIA test	10	0.500000	0.500000	1	-1
-1	POC EIA test	11	0.500000	0.500000	1	-1
-1	POC EIA test	12	0.500000	0.500000	0	-1
-1	POC EIA test	13	0.500000	0.500000	1	-1
-1	POC EIA test	14	0.500000	0.500000	1	-1
-1	POC EIA test	15	0.500000	0.500000	1	-1
-1	POC EIA test	16	0.500000	0.500000	1	-1
-1	POC EIA test	17	0.500000	0.500000	1	-1
-1	POC EIA test	18	0.500000	0.500000	0	-1
-1	POC EIA test	19	0.500000	0.500000	1	-1
-1	POC EIA test	20	0.500000	0.500000	1	-1
-1	POC EIA test	21	0.500000	0.500000	1	-1
-1	POC EIA test	22	0.500000	0.500000	1	-1
-1	POC EIA test	23	0.500000	0.500000	1	-1
-1	POC EIA test	24	0.500000	0.500000	1	-1

This allows a child to still present and get the cost of the well-child visit (as specified in the table below) without having any potential diagnostic value assigned to the test.

Cost of visit

Age at clinic visit	Cost of Visit
0	$15.00
1	$10.00
2	$10.00
3	$10.00
4	$0.00
5	$0.00
6	$0.00
7	$0.00
8	$0.00
9	$10.00
10	$0.00
11	$0.00
12	$0.00
13	$0.00
14	$0.00
15	$0.00
16	$0.00
17	$0.00
18	$0.00
19	$0.00
20	$0.00
21	$0.00
22	$0.00
23	$0.00

Rows 19 and 47
Within the model, the user is capable of specifying alternate testing algorithms if the child's mother is known to be HIV+. When the child's mother is known to be HIV+, the child will have the label "MotherKnownHIV+" associated with him/her. In order for a child to have this label, they must (1) be born with the label (based upon the probabilities specified in the Peds tab), (2) the label can switch from MotherNotKnownHIV+ to MotherKnownHIV+ during breastfeeding, or (3) if a child receives the result of a positive EIA prior to seroreversion (reflecting maternal antibody), the maternal status will switch to MotherKnownHIV+ (this is a simplification; in reality a provider would also need to interpret this correctly). If maternal status is known positive, for example, a testing algorithm might specify that PCR tests be used, rather than antibody-based tests.

[D20:D72]
The user specifies in these cells the ages (in months) at which each diagnostic test is administered. Only one test should be specified per age – confirmatory tests will be specified in the individual test panels. However, the same test can be used for multiple ages. These ages will be in months.

Please change the header of this column to "Age at time of visit (months)." Also, a -1 in this column should indicate that no testing whatsoever should be performed, and will override any presentation probabilities or assays input into the table.

[E20:E24]

At each clinical visit (age), there will be a probability the infant (by way of their mother or a non-maternal caregiver) presents to the clinic for testing. The baseline probability specified here applies to a maternal caregiver. It can then be modified by a multiplier based on whether the child has missed any previous visits.

[F20:F72]

At each clinical visit (age), there is a probability that the guardian bringing the child to get tested is not the mother. This may have implications for whether the provider offers the child testing and whether the child (by way of the non-maternal caregiver) receives the result of the test. If maternal mortality occurs, then there is a 100% probability that the non-maternal caregiver is the one who brings the child to the visit. – THIS IS NOT BEING IMPLEMENTED AT THE PRESENT TIME; this will be incorporated into a later phase. Please just gray this out in the input sheet.

[G20:G72]

In the event that a child is diagnosed as HIV+, but does not link to care, they will exit the pediatric testing/EID portion of the model. However, the child will still be able to link to care through emergency visits (i.e., if they get an OI), as well as routine "well-child" clinic visits (e.g., vaccination visits). Thus, the user is capable of specifying for each clinic visit whether it is a "well-child" visit (e.g., a vaccination visit) or explicitly for pediatric testing/EID purposes.

[B74:B75]
This cell specifies the average age, and standard deviation, at which a child seroreverts (i.e., maternal antibodies have waned from circulation and an antibody test in an uninfected child will no longer be positive).

Multipliers:
Both multipliers are designed to <u>reduce</u> probabilities of receiving care (i.e., to be <1).
Multiplier on probability of presenting for each clinical visit:
[D78]
This multiplier applies to the child's probability of presenting to any given and all future clinical visits, for all visits except the first possible visit. If the child did not present for the visit prior to the current visit, this multiplier will reduce their probability of presenting from the baseline value. It resets the baseline probability, such that baseline*multiplier becomes the new upper bound on probability of presentation for all subsequent visits, i.e., the probability of presentation can continue to decrease, but cannot increase again.

> Example: The baseline probability is 80%, and the multiplier in cell D78 is 95%. The child attends visit 1, but misses visit 2. The probability of presenting to visit 3 is 0.80*0.95=0.76. The child attends visit 3. The probability of presenting to visit 4 is still 76% (i.e., it does not go back up to 80%). The child misses visit 4. Now the probability of presenting to visit 5 is 0.76*0.95=0.72. *Thus the probability continues to decrease over time.*

Note that this multiplier applies regardless of prior visit type and current visit type (e.g. "well-child" vs pediatric testing/EID visit).

Multiplier on probability of offering HIV testing, given presentation at a clinical visit:
[D81]
For a child who presents at any given visit, this multiplier is applied if the child's mother is alive, but the child is brought by a non-maternal caregiver (e.g., mom is ill, or mom has gone back to work), based on cells E20-72. If a non-maternal caregiver is offered and accepts testing, then the baseline (i.e., maternal caregiver) probabilities for result return, confirmatory tests, and linkage to care will apply, as specified for each assay 70-79. If maternal mortality occurs, causing the non-maternal caregiver to become the primary caregiver, then the maternal caregiver probabilities for presenting and test offer will apply (even though the probability of a non-maternal caregiver now is 100%).

Note that a non-maternal caregiver may also have a different probability of PRESENTING for a visit compared to a maternal caregiver, but we have excluded this for simplification, and to allow us to simulate a scenario where a non-maternal caregiver PRESENTS for a vaccination visit (high likelihood), but is not OFFERED HIV testing due to concerns about divulging maternal HIV status.

In summary, the logic will be:
To determine if child presents:
--What is baseline probability of presenting?
* *Is maternal status known positive? If no, use E20-44. If yes, use E48-72.*
--Did the child present for previous clinical visit (not applicable to the first visit/age specified)?
* *If no, apply D78; if yes, no multiplier*
To determine if test is offered after child presents:
--Who brings child - mom or other caregiver?
If mom: no change.
If not mom: is mom alive? If mom alive, apply D81. If mom not alive, apply baseline probability (E20-72) , with multiplier D78 if relevant.

Note that maternal status label can change over time from MotherNotKnownHIV+ to MotherKnownHIV+.

Example: baseline probability 80% (E20-45), 40% (E49-74)
   * Mom known positive. Probability of attending visit 1 = 80%. Same for all subsequent visits, provided that the child doesn't miss any clinic visits.
   * Mom not known positive. Probability of attending visit 1 = 40%. Attend visit 1, test EIA negative. Probability of attending visit 2 = 40%
   * Mom not known positive. Probability of attending visit 1 = 40%. Then the child attends visit 1 and tests EIA positive and PCR negative. Maternal status flag now transitions to MotherKnownHIV+. Probability of attending visit 2 = 80%.

AGAIN THIS WILL BE INCORPORATED IN A LATER PHASE!

[D85]
If a child receives a positive test result, but becomes lost before a confirmatory test is done (or is diagnosed, but doesn't link, and then presents with an OI at an emergency visit), then this cell specifies the probability that the provider will know of the prior positive test result when the child returns at the next visit (i.e., where they left off in the cascade, and where to continue them from). If the provider doesn't know the prior positive result, the child will start at the beginning of the testing sequence at the next clinic visit. If a child returns to care, and the provider knows of the previous positive result, but the testing algorithm has changed for the current visit (i.e., a different test is specified), then the child will proceed to the confirmatory test that should have followed the positive test at the prior visit.

Example:
Child with a MotherNotKnownHIV+ label attends a clinic visit at 9 months of age, receives an EIA with a positive result, but does not come back for the confirmatory test which would have been an RNA PCR. The child shows up at 15 months, but now the algorithm says to test only with an EIA. If the physician knows the previous test result, the physician will not test the child with an EIA again, but will proceed to give the child the RNA PCR that he/she missed. If the physician does not know the previous result, then he/she will test the child with an EIA again and if it positive, diagnose the child as HIV+.

*Note: if an RNA PCR is used as a confirmatory test, the user should disable the "VL at entry to care" parameter in the treatment model (to avoid repeating the RNA PCR unnecessarily).

[A89:B112]
Visit cost for clinic visit at each specified age. These costs exclude assay costs, phlebotomy costs, offer costs, and result return costs (specified for each assay 70-79) and do not include routine HIV-related or OI care.

PEDIATRIC HIV TEST COHORT CHARACTERISTICS panel

[L15:L29]
An HIV-infected child who experiences an opportunistic infection will have a user-specified probability of detection of HIV, which will lead to entry into HIV care in CEPAC (an emergency clinic visit), unless a confirmatory test is required for diagnosis.

[L31, L34:O35]
If HIV is detected, the user can specify whether a laboratory test will be done to confirm the diagnosis upon entry to car. In many settings, HIV-unexposed children and HIV-exposed but uninfected children can experience clinical events, such as recurrent bacterial infections, that mimic opportunistic infections. The user can specify which assay will be used to confirm infection, based on maternal status (known to be infected vs. not known to be infected) and child age.

Notably, one key reason to include confirmatory testing after OI is to reduce the rate of false-positive HIV diagnoses. In some settings, it has been reported that a large proportion of children without HIV infection start ART after clinical events that appear to be OIs. After starting ART, it is difficult to discover whether HIV was incorrectly diagnosed, because both antibodies and RNA can be negative in truly infected children if the virus is suppressed with ART. False positive tests may therefore lead to a lifetime of expensive ART, without any benefit, and potentially with any toxicities associated with the medication.

Lifelong (incorrect) ART after false-positive HIV diagnosis is therefore important to include. However, in CEPAC, HIV-uninfected children cannot experience OIs or start ART. While we cannot address the limitation of incorrect HIV diagnosis after OI, we can address false positive diagnostic tests for HIV. Life expectancy for HIV-uninfected children will be correctly included in the cohort tally. To approximate costs of ART given "incorrectly," the model will output the number of false positive HIV test results. For each incorrectly diagnosed child, we can multiply the average HIV-uninfected LE by a (discounted or undiscounted) stream of ART costs based on yearly costs for HIV-infected children on first-line ART.

[L38]
The tests chosen for confirmation of HIV infection after observed OI may differ depending upon whether a provider believes the child has seroreverted. Here the user can specify the value of N1 to separate the use of two different confirmatory tests by age of the child (in months).

SPECIFIC HIV ASSAY Panels (Assays 70-79)
[V5]
This cell indicates if this assay is a confirmatory test. If it is a confirmatory test, the test itself will not have any subsequent confirmatory tests (since confirmatory tests are specified in the primary assay panel). If possible, answering 1 here will lead the confirmatory test section below (V73-X75) to become grayed out.

[W8]
Given that a child/caregiver presents to a clinical visit (from first panel), this cell reflects the probability that they will be offered the assay described in this panel.

[W9]
Upon being offered a test, this is the probability of accepting the offer.

[W10]
This is the value that the model will use to determine if the child is actually tested. It is the product of the OFFER and ACCEPT probabilities, and is shown here for the user's information.

[W13]
The cost of performing the test will be put into this cell. This cost also includes any costs associated with pre-test counseling or the offer of the test itself.

[W14]
If there is a cost associated with the return of the result from lab to clinic, this is where it is to be specified.

[W15]
If there is a cost of a negative result (e.g., nurse time to meet with the patient), this cost is specified here.

[W16]
If there is an additional cost associated with a patient receiving a positive test result (e.g., nurse time for counseling of the patient), this cost is specified here.

[W18:W19]
The probability that the result is returned between the lab and the clinic, and the clinic to the patient, are specified in these cells. Note, if this is a point-of-care test, then the probability that the result will be returned from lab-to-clinic may be 100% (or may be slightly less, to reflect uninterpretable specimens, capacity concerns, etc).

[W20]
The probability that the result of the test is successfully transmitted from lab to patient is the product of the two probabilities specified above. This is the value the model will use to determine whether the patient receives their diagnosis, and is shown here for user information.

[W21:W22]
The time it takes for the patient to receive test results will be specified here, as well as a standard deviation. Note, for rapid point-of-care testing, the average time will likely be 0 months, though due to capacity issues a standard deviation greater than 1 month may still be applied in cell W24 in this scenario (the distribution of result-return time will be bounded at 0).

[V29:AE46]
The sensitivity (i.e., the ability to detect disease when it is present) of the HIV test for true infection (not exposure) is specified in these cells. Sensitivity values apply only to children with true HIV infection. The sensitivity inputs are stratified by:
1. Whether the mother was infected before or after pregnancy (and thus whether the baby will have maternal antibody when born)
2. When the baby was infected: intrauterine, intrapartum, or postpartum.

3. For infants at risk for or with postpartum infection, whether the test is performed before or after seroreversion.

In some cases, the months represent time since birth, and in others, time since infection, as noted. While some input are not pertinent to one kind of assay (antibody-based or virologic), this single structure is designed to include all parameters needed to accommodate either type of assay.

[AF29:AF46]

If the mother or baby receives ARVs for PMTCT, the sensitivity of some assays may be reduced because even though true infection is present, the viral load may be "suppressed" to the point where it is not detectable. The multiplier for ART to reduce sensitivity is indicated in these cells. This will be assumed to incorporate the impact of both maternal ART and any infant prophylaxis regimens given to a child in addition to maternal ART (e.g., 6 weeks of AZT or NVP). This will apply only to a child born to a mother on ART in pregnancy (Peds tab, G15:I15); it will not apply to a child whose mother is on ART during breastfeeding (although the concomitant infant regimen, if given, could falsely "suppress" viral load, we do not model this infant regimen explicitly). *NOTE: It is important to keep in mind that if you have a birth strategy with a CONFIRMATORY test that occurs in Month 1, and you have set a month 1 reduction in sensitivity multiplier, this will also be affected. So birth testing outcomes will be lower across the various values tested, even though you are focusing on a 6 week multiplier (i.e., would expect just the 6 week testing runs to change). It is also important to note that for PP infections, a 6 week multiplier would apply 6 weeks AFTER infection, not the age. So a 10 week testing strategy could also be affected by this input, if a 6 week multiplier is used.*

[V53:AE70]

The specificity (i.e., the ability to detect the absence of the disease when there is no infection) is specified in these cells. Specificity is stratified by the same parameters as sensitivity above, but there is no multiplier for receipt of maternal or infant ARVs.

[V74:X75]

If the primary assay described in this panel is meant to be confirmed with a subsequent test or tests, these confirmatory tests are specified here. A delay to the time at which the confirmatory test is performed may also be specified. Any confirmatory tests associated with the primary test of the test panel will be put into these cells, with any appropriate delays specified in cells X74-X75.

[W77]

This cell represents the probability of linking to care. It is assumed that those who link to care start ART based upon the ART start criteria listed in the Peds tab. Thus, the value of (1-probability in this cell) reflects the proportion of children who are diagnosed with HIV, but do not link to an HIV/ART clinic to initiate HIV-related care.

Children who have positive confirmatory tests, but do not link to care, can come to HIV care in two ways:
1. Develop an OI (i.e., have an emergency clinic visit). If the provider is aware that the patient has been diagnosed as HIV+, then the patient will not require additional confirmatory tests. If the provider is not aware (according to the probability in cell D87) that the patient has already been diagnosed, then they will follow the confirmatory testing algorithm specified by the user in cells L34-O35 of the Pediatric HIV Test Cohort Characteristics panel.

2. Return for a well-child, non- pediatric testing/EID visit (i.e., vaccination visit). This is specified in cells G20:G74. Again, the provider will have a probability of knowing that the child has already been diagnosed. If the provider is aware that the child has been diagnosed, then the child will bypass the pediatric testing /EID testing cascade and will be immediately subjected to a probability of linkage again from the primary test associated with that clinic visit. If the provider does not know the child was already diagnosed, then the child will proceed through the pediatric testing/EID testing cascade, and if they make it all the way to the end of the cascade they will subjected to the new probability of linkage – again, this only occurs at routine clinic visits. Diagnosed children will not present to explicit pediatric testing/EID visits again.

OUTPUTS NEEDED FOR PEDIATRIC TESTING/EID MODEL:

Monthly updater/traces:

To include monthly:
Maternal tags:
    -- MotherALIVE, MotherDECEASED
    -- MotherNotOnART, MotherOnART
    -- MotherNotKnownHIV+, MotherKnownHIV+
True maternal HIV status (uninfected, acute infection, chronic infection)
True infant HIV status (unexposed, exposed/uninfected, infected)
Infant feeding status (exclusive BF, mixed or complementary BF, replacement feeding)

To include at each testing visit:
Presented to testing visit
Whether "non-maternal caregiver" or mother brings to visit
Visit cost
Test X offered
Test X accepted
Test X result (true/false, negative/positive)
Test X result returned
Test X cost incurred (test and result return cost)
Confirmatory test Y offered
Confirmatory test Y accepted
Confirmatory test Y result (true/false, negative/positive)
Confirmatory test Y result returned
Test Y cost incurred (test and result return cost)
If applicable: is provider aware of prior test results?
Diagnosis status: True negative, true positive_unlinked, true positive_linked, false negative, false positive_unlinked, false positive_linked.
- • False negative: these children remain in the EID module and have opportunities to be re-tested, if testing is specified for subsequent age visits.
- • False positive: If a child is diagnosed as HIV-infected but is truly HIV- and does NOT link to care, then they will be flagged with the label **FalsePositive_unlinked**. Within the EID module, they will be treated in the same way a true positive patient who does not link to care is treated in the model, as described on Page 18 of this handout: that is, they can return to well-child visits, and if the physician knows their diagnosis they will immediately be given the opportunity to link again, otherwise they will go through the EID testing cascade. Once the FalsePositive_Unlinked patient does link to care, their status will change to **FalsePositive_Linked**. Because a truly HIV-uninfected patient cannot enter CEPAC, they will then exit the EID portion of the model and will be subjected to nonAIDS death probabilities. If at some point before age 24 months, the patient does become truly HIV infected (i.e., postpartum infection from breastfeeding), then the patient will become **TruePositive_Linked** and will be assigned a CD4, HVL and be subjected to OI and ChrAIDS probabilities.

To include once (in the month in which it occurs):
Seroreversion has/has not occurred

Outfiles:

1. Number of IU, IP, PP infected infants alive each month.
2. Number of new PP infections each month.

3. Number of detected and undetected infections each month (does not need to be stratified into IU, IP, and PP unless easier to do this way).

4. Of newly detected infant infections each month, number with unknown maternal status in that month. This will allow us to quantify the number of mothers who are identified as HIV-infected through testing of their infants; that is, of newly identified HIV-infected children, how many have the Mother_NotKnown HIV+ tag. (We could then model the impact of HIV diagnosis on these women in the CEPAC-Adult model if desired.)

5. Number of false-negative and false-positive results for first and confirmatory tests. This is an important output from a policy/implementation perspective.

6. Additional information for false-positive results. In the model, it is not possible for HIV-uninfected children to receive ART or accrue HIV-related care costs. We need to keep track of how many people are identified as false-positive in order to estimate their care/ART costs outside the model. To do this, we need two outputs:

a) Number of <u>people</u> who are FalsePositive_linked AND TrueNegative and remain in this category lifelong. We will use this to calculate:
   --Undiscounted lifetime costs of care/ART: as monthly cost * average LM for HIV-uninfected people
   --Discounted lifetime costs of care/ART: as a stream of monthly discounted costs, over the average
      lifetime of HIV-uninfected people

b) Number of <u>life-months</u> spent in the FalsePositive_linked state before a patient obtains a TruePositive state as well (from postpartum infections through breastfeeding). This is likely a small number, but because their costs only accrue for a short period of time in the FalsePositive_linked state, we need to count them separately from the group in #1 above. We will calculate:
   --Undiscounted costs for these LM: monthly cost of care/ART * number of LM in this state
   --Discounted costs: assume equal to undiscounted costs above (this is a reasonable assumption
      because all of these costs accrue in the first 24 months, so we are only omitting discounting for
      months 12-24. Since we don't want to keep track of exactly in which month of the simulations these
      LM accrue, this is a reasonable simplification).