Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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WEB ONLY APPENDIX

1. Model Overview

We developed a Markov state-transition model to describe the natural history of HIV disease. We assumed a societal perspective to evaluate health benefits and costs, discounting each at a 3% annual discount rate. We expressed our results in terms of costs, life-years, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios.

The simulation tracks patients' health from the time of entry into the model until death. A patient's health is characterized by distinct health states; the natural history is summarized by the possible transitions between these states. Because each health state has a corresponding cost and quality of life, tracking the transitions between states and counting the accrued costs and quality of life effects yields estimates of the overall costs, life expectancy, and quality-adjusted survival.

The objective of this model is to evaluate the cost effectiveness of screening for HIV. To do so, the model tracks a cohort of individuals, some of whom are already infected with HIV. Those who are HIV uninfected may become HIV-infected and subsequently can be identified. HIV-infected patients can start treatment and progress to an AIDS-related death or death from other causes. The specific focus of this model is the transition from the state of being "HIV infected, unidentified" to "HIV infected, identified" through screening or case finding based on symptoms.

1.1 Strategies

We evaluated two strategies: screening for HIV infection (HIV Screen) and not screening (No Screening). We further adjusted our model to examine strategies of recurrent screening (annual screening to screening every 9 years), including investigation of the optimal screening frequency from a cost-effectiveness perspective.

1.2 Entry into the Model

Patients in both strategies entered the Markov model (**Figure 1**) either as an uninfected patient or as a patient with unidentified HIV infection. Those with unidentified HIV infection were asymptomatic (75%), had symptoms of HIV infection without AIDS (15%), or had experienced an AIDS-defining condition (10%) (**Table 1**). Throughout the model, we defined AIDS according to clinical, rather than laboratory parameters, following the 1987 Centers for Disease surveillance case definition.[1]

2. Definition of Model States

States in the model were characterized by five components:

(1) the health condition of the patient, which classified patients using three characteristics: a) alive or dead; b) HIV infected or not; and c) stage of HIV infection (symptomatic, asymptomatic, or clinical AIDS).

(2) whether the infected patient's HIV status is known or unknown.

(3) the use and type of antiretroviral therapy, which we classified according to the potential to achieve effective virologic suppression, the number of previous regimens discontinued due to inefficacy, and the number of previous regimens discontinued due to intolerance.

(4) the viral load level, which we classified as suppressed or high.

(5) the patient's CD4 count.

Each of these components is described in greater detail below. Although the set of possible health states from combining the components listed above is very large, we simplified the model by not including some states which are improbable (for example, it is very unlikely that an antiretroviral naïve patient would have a suppressed viral load) and by combining some states (for example, we assumed that the distinction between symptomatic and asymptomatic HIV infection was not important after antiretroviral therapy was initiated).

2.1 Health Conditions

We defined five health conditions for the model: uninfected, asymptomatic HIV infection without AIDS, symptomatic HIV infection without AIDS, AIDS, and death. Once a patient started HIV antiretroviral therapy, the distinction between asymptomatic and symptomatic HIV infection was no longer made. We did not distinguish between minor and severe AIDS defining illnesses, nor did we distinguish between single and multiple AIDS defining illnesses. Individuals could transition from having clinical AIDS back to having HIV without AIDS if they experienced virologic suppression to below the limit of quantification after experiencing an AIDS defining condition.

2.2 Knowledge of HIV Status

We classified HIV-infected patients according to whether it was recognized that they had HIV infection or not. The recognition could occur as a result of either screening or symptom-based case finding.

2.3 Antiretroviral Therapy

We assumed that the patient had two consecutive phases of antiretroviral therapy, which we labelled "suppressive therapy" and "non-suppressive therapy" (**Figure 2**).

2.3.1 *Suppressive Therapy*

In suppressive therapy, the goal of therapy was to suppress viral load below the level of quantification of standard assays.[2] We assumed that identified patients started antiretroviral therapy when their CD4 count reached 350 cells/µL and continued treatment throughout the course of their illness. We assumed that patients used three antiretrovirals in combination during the first and second HAART regimens and four antiretrovirals in the third regimens and during non-suppressive therapy. Patients switched regimens either because of inefficacy or intolerance.

Inefficacy was defined as a rebound in viral load levels or the development of a new AIDS defining illness. We assumed that each individual would use three distinct suppressive therapy regimens before progressing to non-suppressive therapy. The probability of achieving a successful virologic response decreased after virologic failure, but not after changing antiretrovirals due to intolerance.[3]

2.3.2 Non-Suppressive Therapy

We assumed that, after intolerance or inefficacy with multiple antiretroviral regimens, suppression to below virologic quantification would not be possible. Patients then started non-suppressive therapy, in which the goal of treatment was to decrease – but not completely suppress – viral load. Partial virologic suppression may still be beneficial because it confers a slower rate of CD4 decline compared to patients not using antiretrovirals and therefore, may delay disease progression.[4-6]

2.4 Viral Load

We modeled viral load levels in four ways in the model: 1) before the initiation of antiretroviral therapy; 2) after successful virologic therapy; 3) during transient virologic rebound; and 4) after suppressive therapy was exhausted.

2.4.1 Set Point Viral Load

We assumed that viral load levels prior to therapy remained stable from shortly after infection until treatment was initiated; that is, viral load was maintained at a "set point",[7,8] meaning it was constant at this level. Our base-case value for this level was 4.6 $\log_{10}$ copies/mL, a typical value for antiretroviral naïve patients in observational and interventional studies.[9-14]

2.4.2 Suppressed Viral Load

After successfully initiating antiretroviral therapy, we classified patients as having a "suppressed viral load." We defined a "suppressed" viral load as 500 copies/mL or less. However, rather than a range of values, our model required a single quantitative level of viremia for patients with suppressed viral loads. To estimate this level, we used data from the INCAS study, in which patients with viral load levels of 500 copies/mL or less underwent further quantification with a more sensitive assay [15]. In that study, the median level was at the limit of quantification for the more sensitive assay, which was 20 copies/mL (1.3 $\log_{10}$). Accordingly, we assumed that patients with suppressed viral loads would have a plasma viral load level of 20 copies/mL and examined lower and higher values (1 to 500 copies/mL) in sensitivity analyses.

Although we assumed that the goal of antiretroviral therapy was to decrease viral load levels to below the limit of quantification, which is 20 to 50 copies/mL with current assays, we included patients with viral load levels less than 500 copies/mL in the "suppressed viral load" state", for three reasons. First, many early HAART studies were conducted when the limit of detection was 400 to 500 copies/mL. Thus, more accurate natural history data relating to this threshold is available on which to base our model. Second, our model incorporated the use of resistance assays, which cannot be used if the viral load level is too low. Third, the clinical management of individuals with viral load levels between 20 and 500 copies/mL is uncertain and some clinicians may elect not to change antiretroviral therapy at these levels.[16] Although such patients are at higher risk for acquiring HIV-resistant viruses than patients with levels below the limit of quantification, the risk of disease progression is low and therapeutic options may be too rapidly expended if treatment changes are initiated at these low levels.[15]

2.4.3 Virologic Rebound

After suppressive therapy fails, we assumed that the viral load level would rebound towards baseline values. Two studies (in which the set point values were 4.5 and 4.6 $\log_{10}$ copies/mL, compared to our value of 4.6) suggest that rebound viral load levels are less than the original levels by 0.2 to 1.2 $\log_{10}$ copies/mL.[13, 14] In our base case, we assumed that the rebound viral load was 4.1 $\log_{10}$ copies/mL, 0.5 $\log_{10}$ copies/mL less than baseline.

2.4.4 Viral Load During Non-Suppressive Therapy

We assumed that viral load would increase once suppressive therapy was exhausted and increase even further after developing AIDS.[2, 17, 18] Observational studies have suggested that among patients with detectable viral load levels, levels rose by about 0.05 to 0.16 copies/mL/year.[8, 19-21] To simplify the model, we assumed that this increase happened upon initiating non-suppressive therapy and estimated the total rise to be 0.8 $\log_{10}$ copies/mL (range for sensitivity analysis 0 to 1.5) above the original set-point value.[21] We estimated a further 1 $\log_{10}$ increase with the development of AIDS (range 0 to 2.0).[19, 22, 23] Our model used the viral load to predict the rate of disease progression; however, the predictions may be inaccurate if the model patient's viral load levels are not in the range of the initial data. To avoid this possibility, we set a maximum viral load level of 6.0 $\log_{10}$ copies/mL, based on the observation that by the time viral load levels have reached this level, virtually all patients have died.[24]

We assumed that non-suppressive therapy could decrease viral load levels somewhat and that there were beneficial effects from this decrease, even in the absence of complete suppression.[4, 5] We estimated the magnitude from the pooled average decrease observed with sub-optimal regimens including dual antiretroviral therapy and sequential addition of protease inhibitors in several trials.[15, 25-28] Our base-case estimate was a drop of 0.9 $\log_{10}$ copies/mL and our sensitivity analysis ranges were set at 0 (indicating no effect of anti-suppressive regimens) and 2 $\log_{10}$

copies/mL. The GART study estimated that viral load dropped by 0.37 $\log_{10}$ copies/mL for every active drug (a drug for which the patient does not have a resistant virus) and 0.17 for every inactive drug.[4] Thus, a drop of 0.9 $\log_{10}$ copies/mL is reasonable, reflecting the scenario in which a patient takes a non-suppressive regimen consisting of 1 active and 3 inactive drugs. Because many new antiretroviral medications and drug classes are in development, we assumed that patients would use multiple non-suppressive regimens over time.[29] Thus, we assumed that the drop in viral load levels with non-suppressive therapy was sustained.

2.5 CD4 counts

We modeled CD4 counts in three ways in the model: 1) before the initiation of antiretroviral therapy; 2) after successful virologic therapy; and 3) after suppressive therapy was exhausted. Health states were defined according to the patient's CD4 count, which we classified into 17 strata in intervals of 50 cells/µL ranging from 0-49 cells/µL to 850-900 cells/µL. We assumed that patients within a given stratum had a similar prognosis whether they transitioned into the state from a stratum with a greater CD4 count (such as with a falling CD4 count with ineffective therapy) or from one with a lower CD4 count (such as after immune reconstitution). This assumption is consistent with several natural history studies of patients receiving HAART.[30-34]

3. Transitions Between States

Each month, some patients remained in their current state, others experienced changes in health related to HIV infection, and some died of causes unrelated to HIV, at the rate of a similar age-matched U.S. cohort. We modeled transitions between health states (from HIV uninfected to asymptomatic HIV infection; from asymptomatic to symptomatic HIV infection; from symptomatic HIV infection to experiencing an AIDS complication; and from AIDS to HIV-related death (**Figure 1**)), transitions related to identifying HIV infection, transitions between

antiretroviral therapy states, transitions between viral load level states, and transitions between CD4 states.

3.1 Transitions Between Health Conditions

3.1.1 Transition from Uninfected to HIV Infected

Each month uninfected patients were at risk of becoming infected with HIV. Annual age- and gender-specific incidence of HIV was based on work done by Rosenberg (**Figure 3**).[35] Because these incidences reflected general population incidences, we evaluated the cost-effectiveness of HIV screening in populations with 2- and 3-times the incidence in sensitivity analyses.

3.1.2 Transition Between HIV and AIDS

We estimated the transition of progressing from HIV infection without AIDS to AIDS as rates, in which the numerator is the number of events experienced by a population and the denominator is a product of the number of people in the population and the length of time during which they were observed. We assumed that the rate was constant over time; that is, that the probability could be defined by an exponential distribution. Accordingly, the probability of transitioning from one state to the next in a time interval t, given an annual rate of μ, can be derived by the formula [36]:

$$\text{probability} = 1 - \exp(-\mu \times t)$$

To estimate the probability at any given time in the model, we followed two steps. First, we estimated the baseline hazard rate for fixed CD4 and viral load values. Second, we modified the hazard rate to reflect changes in CD4 and viral load levels over time as a result of both the natural history of HIV and antiretroviral therapy. That is, the rate of disease progression varied across CD4 counts and viral load levels. Accordingly, we adjusted the baseline rate by determining the relative hazard of developing AIDS at different levels of these laboratory tests.

Several studies have indicated that incorporating data from these two parameters accounts for the large majority of the treatment effect of antiretrovirals.[37-42] In all cases, we modeled the risk as changing with continuous levels of the parameters, which provides better model fits than using discrete levels.[2] In deriving these parameters, we gave greatest weight to analyses that modeled viral load as a time-dependent variable (rather than relying solely on baseline values), used multivariable models that combined viral load and CD4 count data, and separated the endpoints of AIDS and death.[22, 43-45] Studies that met only some of these criteria were examined for consistency with the base case estimates and to set limits for the ranges for sensitivity analyses.

3.1.2.1 Baseline Hazard Rate: HIV to AIDS

We based our estimate of the rate of transition from HIV to AIDS on published data from the Multicentre AIDS Cohort Study.[46] In this large observational study, 258 patients had a CD4 count between 351 and 750 cells/µL at baseline with a viral load between 10,001 and 30,000 copies/mL with the bDNA assay, corresponding to 20,442 to 54,894 copies/mL (4.3 to 4.7 $\log_{10}$ copies/mL) with the RT-PCR assay. We assumed that our base case would have a similar risk of progression. At three years, 16.1% of patients had developed AIDS (95% confidence interval [CI] 12 to 21%). Assuming an exponential distribution of transition probabilities and calculating to one significant digit, the transition rate was 6 events per 100 patient years (95% CI 4 to 8). Similar transition rates were observed from smaller studies, albeit with wider confidence intervals.[47, 48] Because these estimates included only baseline values, and did not account for the possibility of declining CD4 counts over time, they may have overestimated the true transition rate. Accordingly, we set the lower bound for the range for sensitivity analysis below that of the lower bound of the 95% confidence interval. Thus, the final range for sensitivity analysis was 2 to 12 new AIDS diagnoses per 100 patient years. We incorporated a small risk of developing

new AIDS illnesses when the viral load was suppressed to account for AIDS-defining conditions, like lymphoma, whose incidence is not related to CD4 counts.

3.1.2.2 Relative Hazard: HIV to AIDS per change in Viral Load Levels

We first estimated how the rates of disease progression would change with changes in viral load levels. Two high-quality studies estimated the time-dependent relative hazard of developing AIDS.[22, 43] Combining these study results (using random-effects meta-analysis methods) yielded an estimate of the relative hazard of 0.43 per 1 $\log_{10}$ drop in plasma viral load, with 95% confidence intervals of 0.28 to 0.65. These values are close to an overview of studies that used a combined endpoint of AIDS or death (0.49, 95% CI 0.23 to 0.76).[44] Similar values have been reported in studies which assessed baseline viral load at only one or two points in time or used combined endpoints.[8, 24, 37-39, 41, 42, 45, 47-55]

3.1.2.3 Relative Hazard: HIV to AIDS per change in CD4 Count

We used a similar process for estimating the relative hazard of AIDS relative to CD4 count changes. One study examined the relative hazard of developing AIDS related to time-dependent changes in absolute CD4 counts and adjusted for viral load levels; the estimate of the relative hazard for every 1 $\log_{10}$ change in the CD4 count was 0.0154 (95% CI 0.0013 to 0.36).[43] However, the range of relative hazards reported in the literature relating to CD4 counts is wider than that for viral load levels; in addition, studies differ as to whether they report absolute or relative changes in CD4 counts. For the latter studies, we estimated the rate per 1 $\log_{10}$ change by applying the relative change to the mean or median baseline count, where available. To reflect these uncertainties, we used a wide range in sensitivity analysis from a low of 0.0002 to a high of 1.00 (indicating that CD4 changes did not influence the relative hazard of disease progression).[8, 22, 24, 37-45, 47-56]

3.1.3 Transition To Death

We assumed that all HIV-related deaths occurred among individuals with AIDS. We used a similar method to estimate the risk of death from AIDS as we did to estimate the risk of transitioning from HIV to AIDS.

3.1.3.1 Non-AIDS Related Death

At all times in the model, patients could die from non-AIDS related causes. Age and sex specific mortality rates for such deaths were calculated from statistical life tables.[57]

3.1.3.2 Baseline Hazard Rate: AIDS to AIDS-related Death

We based these estimates on a cohort study of injection drug users based in Baltimore, MD.[47] In this study, patients with a CD4 count between 200 and 499 cells/µL and a viral load (using the bDNA assay) between 10,000 and 29,999 copies/mL had a 15.6% chance of dying from an infectious disease within 5 years, corresponding to a rate of 3 deaths per 100 patient-years under the assumption of an exponential probability distribution. Assuming no loss to follow-up, the calculated exact binomial confidence interval was 2 to 7 deaths per 100 patient-years. We widened this range for the sensitivity analysis because some infectious disease deaths were not due to AIDS, some patients were likely lost to follow-up, and CD4 counts and viral load levels likely changed over time. Accordingly, the range for sensitivity analysis was 1 to 10 deaths per 100-patient years. We did not model rare deaths from HIV-related causes not due to an AIDS-defining condition.

3.1.3.3 Relative Hazard: AIDS to AIDS-Related Death per change in Viral Load Levels

We next estimated the relative hazard of dying from AIDS with changes in viral load levels. We based our estimate primarily on one study that adjusted for CD4 counts and analyzed viral load as a time-dependent covariate.[45] The relative hazard of dying from this study was 0.64 per 1

log_{10} decrease in plasma viral load with 95% confidence intervals 0.55 to 0.75. Similar values were observed in trials that assessed viral load at only one or two points in time or did not fully control for CD4 counts [8, 24, 38, 47, 49, 50, 55]

3.1.3.4 Relative Hazard: AIDS to AIDS-Related Death per change in CD4 Counts

We based our estimate of the relative hazard for death on a study that examined CD4 counts as a time-dependent covariate and controlled for viral load count; the relative hazard was estimated at 0.118 (95% CI 0.064 to 0.329) per 1 log_{10} change in the CD4 count as calculated in Section 3.1.2.3. Studies estimating the relative hazard from only one or two points in time have yielded similar values [24, 47, 49, 50, 55]

3.2 Transition from Unknown to Known HIV Infection

Patients could transition from having unknown HIV infection to known infection in one of two ways. They could be tested for HIV infection through an HIV screening program when asymptomatic or they could be identified as having HIV when they presented with HIV-related symptoms (case finding).

We assumed that the annual probability of patients being identified through symptom-based case finding was 0% at a CD4 count of 350 cells/µL or more, 80% at a CD4 count of 50 cells/µL or less, and ranged between 0% and 80% at CD4 counts between 50 and 350 cells/µL. We used linear interpolation to estimate symptom-based case finding rates within this range. **Figure 4** demonstrates the relationship between current CD4 count and annual probability of symptom-based case finding in our analysis. Together, these assumptions determined that infected HIV patients in the "No Screening" strategy were identified through symptom-based case finding at an average CD4 count of 175 cells/µL. In sensitivity analysis, we varied both the maximum case finding rate and the threshold at which the maximum rate was reached.

3.3 Transition Between Antiretroviral Regimens

Regimens were changed due to inefficacy or intolerance. Regarding efficacy, we modeled two aspects related to viral load kinetics. First, we estimated the probability of attaining virologic suppression after starting antiretrovirals. Second, we estimated the time to virologic rebound for those patients achieving initial virologic control. We also modeled the concurrent effects on CD4 counts with virologic control (See Section 0 3.5.2 CD4 Counts During Suppressive Therapy).

3.3.1 Initial Virologic Suppression

We based our estimates of the probability of achieving initial virologic suppression on both randomized controlled trials and observational studies. However, the estimates from clinical trials may be too high if trials analyze their results focusing only on those patients without missing data and having complete follow-up.[10] Conversely, using an intent-to-treat analysis and assuming that all missing patients experienced virologic failures may under-estimate the efficacy of antiretrovirals. Observational studies, which have generally reported lower success rates than clinical trials, may under-estimate the efficacy of antiretroviral use if they include a large number of heavily pre-treated patients, include less potent protease inhibitors (such as saquinavir hard-gel capsules), or combine protease inhibitors or non-nucleoside reverse transcriptase inhibitors sub-optimally (or not at all) with other antiretrovirals. Thus, we placed greatest weight on trials that evaluated the proportion of patients achieving a viral load of 500 copies/mL or less with complete follow-up and optimal use of antiretrovirals, in accord with the latest published guidelines.[58, 59]

In the AVANTI trials, the proportion of patients failing to achieve a viral load level of 400 copies/mL or less was variably estimated between 16% and 33%, depending on the type of analysis and the inclusion or exclusion of missing data.[10] An overview of several HAART regimens in predominantly antiretroviral naïve patients estimated that the proportion failing to

achieve a viral load level of 400 copies/mL or less, using a per-protocol analysis and excluding missing data, was 19% (95% CI 5 to 43%).[10] Other trials using a plasma viral load threshold of 400 or 500 copies/mL have yielded estimates commensurate with this overview. While clinical trials have reported probabilities of failure between 2 and 50%, observational trials have reported probabilities between 5 and 60%.[11, 12, 14, 15, 27, 28, 60-88]

In the base case, we assumed that 20% of patients who were tolerant of HAART would fail to suppress viral load levels to 500 copies/mL or less after their initial antiretroviral regimen. To reflect the considerable uncertainty in this estimate, we set the sensitivity analysis rages to be wide (2% to 70%).

Antiretroviral-experienced patients initiating HAART have failure rates of about 20 to 40%.[63, 75, 76, 78, 81, 89-91] Multivariate models suggest that the relative risk is 2 to 3 times higher for experienced, compared to naïve, patients.[67, 70] Accordingly, we evaluated the scenario in which an antiretroviral-experienced patient was initiating HAART and estimated the probability of failing a first HAART regimen as being 2.5 fold higher than that for an antiretroviral naïve patient with each antiretroviral regimen, modeled as an odds ratio.

Data suggest that patients failing second or third HAART regimens may have higher failure rates. Observational studies indicate that protease inhibitor-experienced patients starting another protease inhibitor based regimen have a probability of failure of 30 to 80%.[6, 12, 14, 65, 76, 80, 81, 83, 86, 92-96] Patients with two HAART regimen failures likely have the greatest risk of failing further HAART regimens. Randomized controlled trials of genotypic or phenotypic resistance testing indicate that 67% to 75% of patients failing their first or second HAART regimen who do not receive a resistance test experience virologic failure, although this number was significantly lower in patients receiving a resistence test.[4, 97, 98] Accordingly, we estimated that the probability

of virologic failure (plasma viral load of 500 copies/mL or higher) with a second HAART regimen was 35% (range 20 to 80%) and with a third regimen was 70% (range 60 to 95%).

3.3.2 *Duration of Viral Load Suppression*

We used interventional and observational data to estimate the short-term rate of virologic rebound. Two trials of maintenance antiretroviral therapy were specifically designed to evaluate the rate of virologic rebound; these studies indicated that about 4 to 6% of patients using indinavir-based triple therapy have virologic rebound at 3 to 6 months.[99, 100] The study with longest follow-up is from a small trial of indinavir, zidovudine, and lamivudine combination therapy in antiretroviral-experienced patients.[28, 101] Approximately 90% of patients achieved initial virologic success (≤500 copies/mL). Of 31 patients from the initial cohort available for evaluation three years after initiating therapy, 68% were still below this threshold; thus, we calculated that 24% ((90-68)÷90) of patients achieving initial virologic suppression had rebounded by 3 years. The study with the largest sample size was reported by the Swiss Cohort Study, in which 20% of treatment naïve patients achieving virologic control had virologic rebound at 2 years. The AVANTI investigators, treating missing patients as treatment failures, found that 15% of patients with nadir viral load levels ≤50 copies/mL had virologic rebound to >5000 copies/mL at one year, compared to 57% of patients with nadir plasma viral load levels between 50 and 400 copies/mL.[10] Other studies have estimated rebound rates consistent with these values.[11, 15, 64, 77, 80, 81, 83, 86, 102-107] Our base-case value of the rate of virologic failure was based on estimates between those observed in interventional and observational trials; we assumed that 15% of patients would experience failure at 2 years and varied this rate in the sensitivity analysis between 6 and 30%. Assuming a constant transition rate, these probabilities correspond to rates of 8 rebounds per 100 patient-years (range 3 to 18).

Second and third HAART regimens may be less durable than initial regimens.[63, 83] We modeled this decreased efficacy by assuming a proportionally increased hazard for virologic rebound with each regimen. A study of maintenance HAART therapy found that less potent regimens (indinavir monotherapy) had a relative hazard for failure of 5.8 compared to a triple drug regimen (95% CI 2.0 to 16.8).[100] An observational study found that antiretroviral-experienced patients were about twice as likely to experience virologic rebound as antiretroviral naïve patients.[91] In the base case, we assumed that each new regimen was associated with a 2-fold increase in the hazard of virologic rebound. In sensitivity analyses, we included the assumption that subsequent regimens were equally durable; thus the range for sensitivity analysis for the relative hazard for virologic rebound was 1.0 to 6.0.

3.3.3 Tolerability of HAART

Many patients discontinue HAART due to side effects, despite good virologic responses.[71, 86] The tolerability of HAART was defined in our model as the proportion that had to discontinue medication due to toxicity (other quality of life effects were modeled with quality of life weights, see below). To estimate the proportion of patients discontinuing their initial HAART regimen, we used both interventional and observational data. We gave less weight to studies that included saquinavir hard-gel capsule or ritonavir in a HAART regimen because of decreased potency and increased toxicity, respectively.[26, 60, 61, 67, 69, 71, 75] Interventional trials, with variable follow-up, indicate that 6 to 38% of patients discontinue therapy due to toxicity.[10, 75, 92, 101, 103] Large observational studies have reported rates of discontinuation of 6 to 35%.[61, 67, 69, 82, 85, 105] Data indicate that patients continue to stop therapy due to toxicity up to 1.5 years after initiating treatment.[85, 105] Indinavir and nelfinavir each had a probability of discontinuation of about 21% in a study with median follow-up of about 15 months.[60] The largest study with the longest follow-up estimated that the cumulative probability of discontinuation at 72 weeks was 26%,

although some patients still stopped thereafter.[105] Longer-term side effects are also likely to occur, although we did not account for these.[108, 109] We estimated that 25% of patients would stop their first HAART regimen, that all would do so within the first two years of initiating therapy, and that the rate of discontinuation was constant over this time. In sensitivity analysis, we varied the proportion discontinuing therapy (from 5 to 40%) and the time over which toxicity developed (from 1 to 4 years).

We assumed that second HAART regimens were associated with equivalent toxicity to initial regimens, but tested this assumption in sensitivity analyses. However, we assumed that 3rd regimens contained both a greater number of drugs and medications with higher toxicities, yielding higher rates of discontinuation. Studies have reported discontinuation rates for ritonavir-based regimens of 21 to 54%.[26, 60, 61, 67, 69, 71, 75] Patients initiating ritonavir-based HAART regimens have approximately 2.2 times the relative hazard of discontinuing treatment.[105] Dual protease inhibitor-based HAART has a similar probability of discontinuation.[63, 80, 110] Thus, we estimated that the discontinuation rate for the third HAART regimen was 1.4-fold higher than that for the initial regimen (sensitivity analysis range 1.0 to 4.0).

3.4 Transition Between Viral Load Levels

3.4.1 Virologic Suppression

In patients who respond to antiretroviral therapy, viral load levels generally start to decline by as early as two weeks.[10] We assumed that patients who had not responded by one month would change antiretroviral regimens. The median time to reach this nadir level varied across studies from 2 to 12 weeks, with a maximum time of 7 to 10 months.[10, 12, 15, 63, 64, 96] We assumed that for patients with successful virologic suppression, the viral load level would drop in a log-linear fashion over 3 months (range 1 to 10 months) until the nadir was reached.

3.4.2 Virologic Rebound

We assumed that patients with virologic suppression had a risk of virologic rebound at every month. We assumed that patients identified as having virologic rebound started a new antiretroviral regimen, we did not model drug holidays or structured interruptions. In some instances, however, there was a lag between when virologic rebound occurred (which could happen at any time) and when it was detected (which occurred at regular intervals when viral load testing was performed). Viral load testing was performed at a frequency of every 3 months, with two exceptions.[2, 16, 111] First, the patients had an additional viral load test 1 month after initiating or changing therapy to assess their responses. Second, a viral load test indicating virologic rebound was confirmed with a repeat test.

3.5 Transition Between CD4 count Levels

3.5.1 CD4 Counts Prior to Initiation of Therapy

We assumed that CD4 counts declined prior to the initiation of therapy. Empirical evidence suggests that the rate of decline is related to the viral load level.[46] Cook and colleagues have estimated the decline in CD4 cell count (cells/µL/year) to be:[112]

$$\Delta CD_4 = -79.2 + 33.5 \times \log_{10} \textit{viral load}$$

We used this model to estimate the change in CD4 counts over time, incorporating the assumption that CD4 counts never increased without therapy (hence, CD4 values were stable if plasma viral load was $\leq 2.36 \log_{10}$ copies/mL).

3.5.2 CD4 Counts During Suppressive Therapy

We assumed that CD4 counts remained stable while receiving suppressive therapy because, even if virologic rebound occurred, antiretroviral therapy was changed before CD4 counts fell. We estimated that CD4 cell counts increased after successful initiation of therapy. Studies

suggest that it is rare for CD4 counts to remain stable with large drops in viral load.[113] It is also uncommon for patients to have an improvement in CD4 counts without a large change in viral load levels.[6, 113, 114] Thus, we made the simplifying assumption that CD4 counts did not change if virologic suppression was not achieved, that is, we only modeled concordant CD4 and viral load responses.

Several studies have indicated that, after significant drops in viral load levels, the rise in CD4 is strongly related to the baseline CD4 level but only weakly to the initial viral load level.[88, 115, 116] Drusano and colleagues found an excellent fit between the increase in CD4 count and the baseline CD4 count; the viral load level improved the model slightly.[115] In our model, we used a simplification of the Drusano equation:

$$\Delta CD_4 \ when\,starting\ therapy = 110 + 535 \times \left(\frac{initial\ CD_4^{\ 0.98}}{initial\ CD_4^{\ 0.98} + 260} \right)$$

and modified it further to assume that the minimal rise in CD4 counts was 60 cells/μL. This estimate yielded increases consistent with those seen in clinical trials.[68, 73]

We assumed the CD4 count increased rapidly in the first 2 months, more slowly thereafter until the maximum level was reached, and then stabilized while viral load levels were suppressed. CD4 counts declined again when virologic rebound occurred. The rates of increase and decline were estimated from previous regression models and observational data (**Table 1**).[46, 68, 73, 88, 112, 115, 116]

3.5.3 CD4 Counts During Non-Suppressive Therapy

During non-suppressive therapy, we assumed that CD4 again fell according to the Cook formula described above. In this part of the model, we tracked the CD4 count continuously from the time non-suppressive therapy was initiated until it reached a nadir value, which we set at 20 cells/μL, in order to avoid over-estimating the risk of death and AIDS.

4. Quality of Life

When unidentified as being HIV infected, we assumed individuals had reduced quality of life, with a quality-of-life weight of 0.91, consistent with data we have collected.[117] Once identified, we assumed that quality-of-life weight decreased initially to 0.84 for the first year after identification and then increased to 0.89 until symptoms of HIV developed, as was the case in formal quality of life assessments we performed in 66 patients.[117] Patients with symptomatic and untreated HIV infection had a quality of life weight of 0.79. Once HAART was initiated, this weight increased to 0.83. With the occurrence of AIDS, we assumed quality of life declined, with a weight of 0.73 (**Table 1**). [118-121] We varied these assumptions extensively in sensitivity analyses.

To model the quality of life associated with dose-limiting side effects, we assumed that there was a transient decrease in quality of life, which lasted for one month. The value for this was assumed to be equivalent to that of side effects related to *Myobacterium avium* prophylaxis, 0.53.[122]

These studies used time trade-off [117, 118] and standard gamble [119, 120] methods to elicit HIV infected patients' estimates of utility for the following health states: asymptomatic HIV infection, symptomatic HIV infection, and AIDS.

5. Costs of Care

The annual cost of care for HIV infected patients with CD4 counts greater than 500, 200-500, and less than 200 cells/µL was $2,978, $5,096, and $7,596, respectively ($2004) (**Table 1**). The annual cost of care of a patient with AIDS was $10,998. Patients using non-suppressive therapy cost $16,230 annually. [16, 59, 98, 123-125] Patients who experienced a dose-limiting side effect were given a one-time cost of $148 representing the cost of a typical out-patient visit.[126-128]

We updated all costs to 2004 U.S. dollars using the gross domestic product (GDP) deflator.[129, 130] Unlike the medical component of the Consumer Price Index (CPI), the GDP deflator accounts for improvements in productivity. In addition, the GDP deflator considers all domestic economic activity, while the CPI only includes spending by households.

6. Transmission of HIV to Sexual Partners

Transmission from an HIV infected patient to their sexual partner(s) depended on the infected patient's sex, type of sexual activity, number of sexual partners, knowledge of HIV status, and viral load.

We assumed that, on average, heterosexual men and women each had one sexual partner at risk of acquiring HIV over the course of a lifetime, while men-who-have-sex-with-men had two. At baseline viral load levels, and without antiretroviral therapy, we assumed that the annual rate of transmitting HIV for heterosexual men, heterosexual women, and men-who-have-sex-with-men were 3%,[131-135] 1%,[131-134] and 4%[136-140] respectively.

Based on randomized-controlled trials of counseling to prevent transmission of HIV by increasing condom use,[141-143] we assumed a 20% reduction in transmission for patients with identified HIV infection (range 0-60%). Based on studies of transmission and treatment,[144] we assumed that reductions in viral load further reduced transmission. Based on the work by Quinn and colleagues, we assumed that infectivity fell by a factor of 2.45 for each 1 $\log_{10}$ copies/mL decrease in viral load.

Therefore the infected patient's sex, type of sexual activity, number of sexual partners, knowledge of HIV status, and viral load combined to give the probability of transmission each cycle using the following equation:

Probability of Transmission =

$$(\text{Number of Sexual Partners})*(\text{Relative Risk of Infectivity})^{(\text{viral load}-(\text{starting viral load}))}*(\text{Transmission Rate})*(1-\text{Effectiveness of Counseling})$$

To calculate the costs and loss of life to the infected partner, we assumed that partners infected by an index patient with identified HIV infection would be identified at an earlier time than those infected by an undiagnosed patient. Infected partners of an identified HIV patient would begin HAART treatment when their CD4 count reached 350 cells/µL and thereby gain the life expectancy benefit from early identification and treatment. The partner's loss of life was calculated to be their age-specific life expectancy minus the life expectancy if they became infected with HIV and received treatment at 350 cells/µL. This latter age-specific life expectancy was calculated by our model. This loss in life expectancy would thus reduce the overall life expectancy of the index patient. Similarly, partners who were infected by an undiagnosed HIV patient would begin treatment only when identified through symptom-based case finding and therefore their loss of life would be their age-specific life expectancy minus the life expectancy if they became infected with HIV and did not receive treatment until identified through symptom-based case finding (on average at a CD4 count of 175 cell/µL). Again, the loss of life expectancy attributed to the HIV-infected partner would be taken into account in the index patient's life expectancy.

7. Transmission of HIV by Injection Drug Users

In a sensitivity analysis we incorporated the costs and benefits of transmission of HIV by injection drug users. We made the following assumptions in this analysis: we assumed that 2.5% of the population are injection drug users, and that the prevalence of HIV in this population is 10%.[145] Therefore 0.25% of the HIV prevalence was accounted for by injection drug users (2.5% x 10% = 0.25%). Thus, in our base-case analysis with a prevalence of 1%, 25% of these HIV

infected patients would be injection drug users. We assumed that the injection drug users have 40 risky injections per year,[145] and that the risk of infection per risky injection is 0.5%.[145] We varied this infectivity based on viral load: a 1 $\log_{10}$ decrease in viral load results in a factor of 2 change in infectivity.[146]

Because 10% of the injection drug user population is assumed to already be infected with HIV, these users can not be re-infected. Therefore, we assumed that an HIV infected patient has 36 injections with uninfected partners per year (40 risky injections – [10% of 40 = 4 to account for the partners already infected with HIV]). The risk of transmitting HIV to a partner through injection drug use is 16.5% (=1-(1-risk of infection)$^{\text{number of partners at risk}}$ = 1-(0.995)^{36}). In our analysis we assume that if a patient's HIV status is identified then they will receive counseling regarding the risks of injection drug use and that such counseling reduces risky injections by 25%.[147] Therefore, patients with identified HIV have 27 injections with uninfected partners per year (40 risky injections reduced by 25% = 30 – [10% of 30 to account for the partners already infected with HIV]). For these identified patients therefore, the risk of transmitting HIV to a partner through injection drug use was 12.6% (=1-(0.995)^{27}).

Each year we therefore assumed that HIV-infected patients who were injection drug users and were undiagnosed would transmit HIV to 16.5% of their partners. Similarly, each year we assumed that HIV-infected patients who were injection drug users and had been identified with HIV would transmit their infection to 12.6% of their partners. We assumed partners infected through injection drug use would be identified through symptom-based case finding.

We did not analyze the effects of maternal-to-fetal transmission.

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WEB ONLY APPENDIX FIGURE LEGENDS

Figure 1. Schematic Representation of the Decision Model. In panel A, the square node at the left represents the decision to screen for HIV or not. The patient's health thereafter is simulated by a Markov model. Patients may enter the model with prevalent HIV infection (asymptomatic or symptomatic HIV or AIDS) or they may be uninfected. Each month, uninfected patients are at risk of developing HIV infection. Patients who have asymptomatic disease may progress to symptomatic HIV or remain in the asymptomatic health state. Patients that have symptomatic HIV infection may progress to an AIDS defining condition, or may remain with symptomatic HIV. Patients with AIDS may either die from their infection or remain with AIDS. Each month all patients may be identified either through a voluntary screening program in the HIV screen arm, or through symptom-based case finding in the symptomatic HIV and AIDS health states in both the HIV screen arm and the No Screening arm. Throughout the patients' lifetime, all patients are at risk for non-HIV related mortality. Panel B shows the possible paths of patients identified with HIV and started on highly active antiretroviral therapy (HAART). Each month a patient on HAART may experience toxicity from their regimen or tolerate the drugs. Those who experience toxicity are switched to a new regimen. Those patients without toxicity may have their viral load suppressed or not. Once an unsuppressed viral load is identified through viral load testing, the patient is switched to a new drug regimen. Each month, all HIV patients are at risk for progression to AIDS. Such progression is considered a treatment failure and once identified the patient is switched to a new drug regimen.

Figure 2. Transition Between Antiretroviral Regimens. Patients initially used suppressive therapy (top box). When no further suppressive regimens were available, patients used non-

suppressive therapy (bottom box). Within suppressive therapy, patients could change regimens due to intolerance (horizontal arrow) or after experiencing inefficacy (vertical arrow). Each patient used three suppressive therapy regimens before starting non-suppressive therapy.

Figure 3. Age- and Gender-Specific Incidence. Based on work by Rosenberg[35] our model incorporated age- and gender-specific incidence of HIV throughout the patient's lifetime.

Figure 4. Relationship Between CD4 Count and Annual Probability of Symptom-Based Case Finding. The probability of a patient being identified through symptom-based case finding was based on their CD4 count. For patients with a CD4 count above 350 cell/µL we assumed that the probability of being found through symptom-based case finding was 0. At a CD4 count of 50 cell/µL we assumed that 80% of patients would be found annually based on their symptoms.

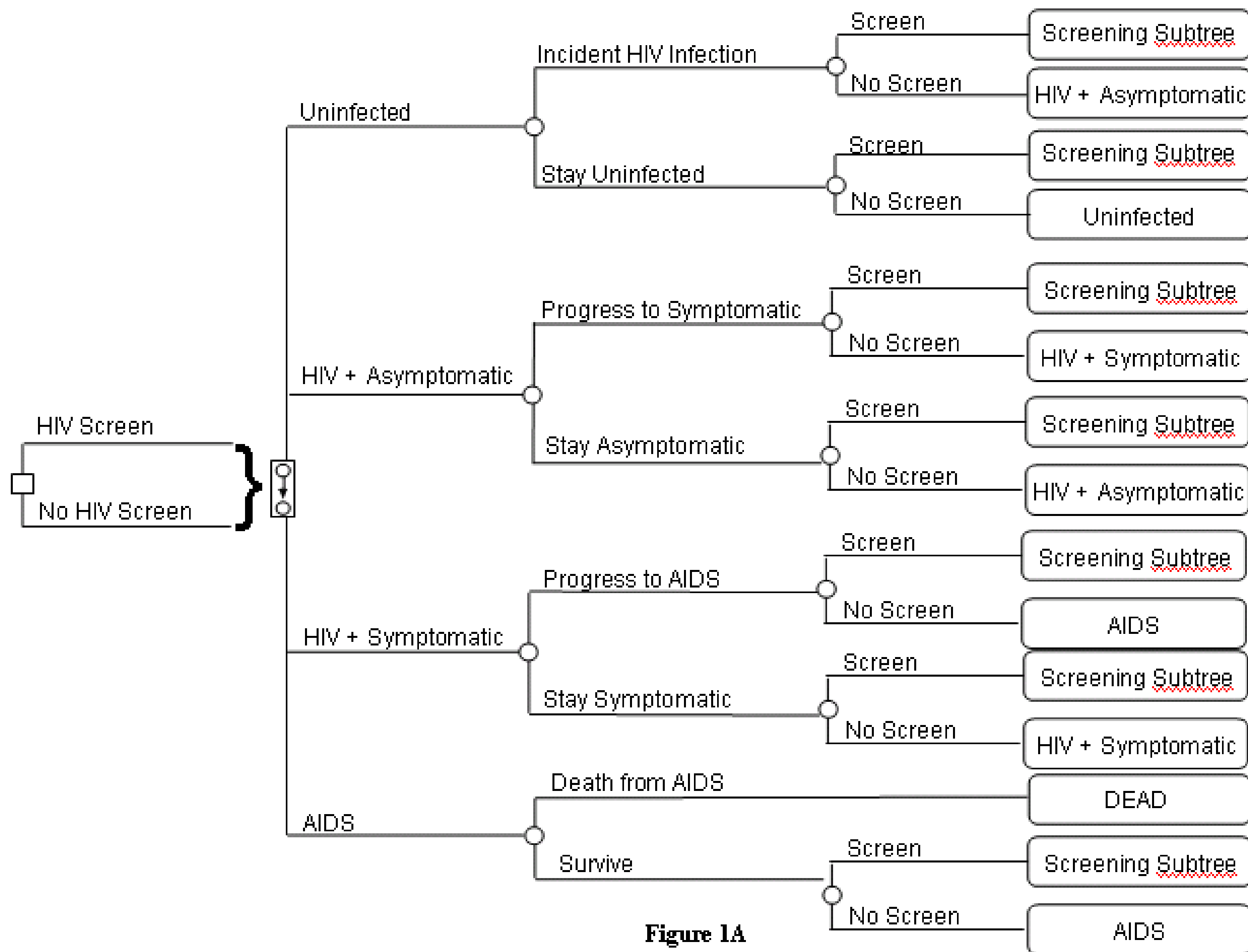

Figure 1A

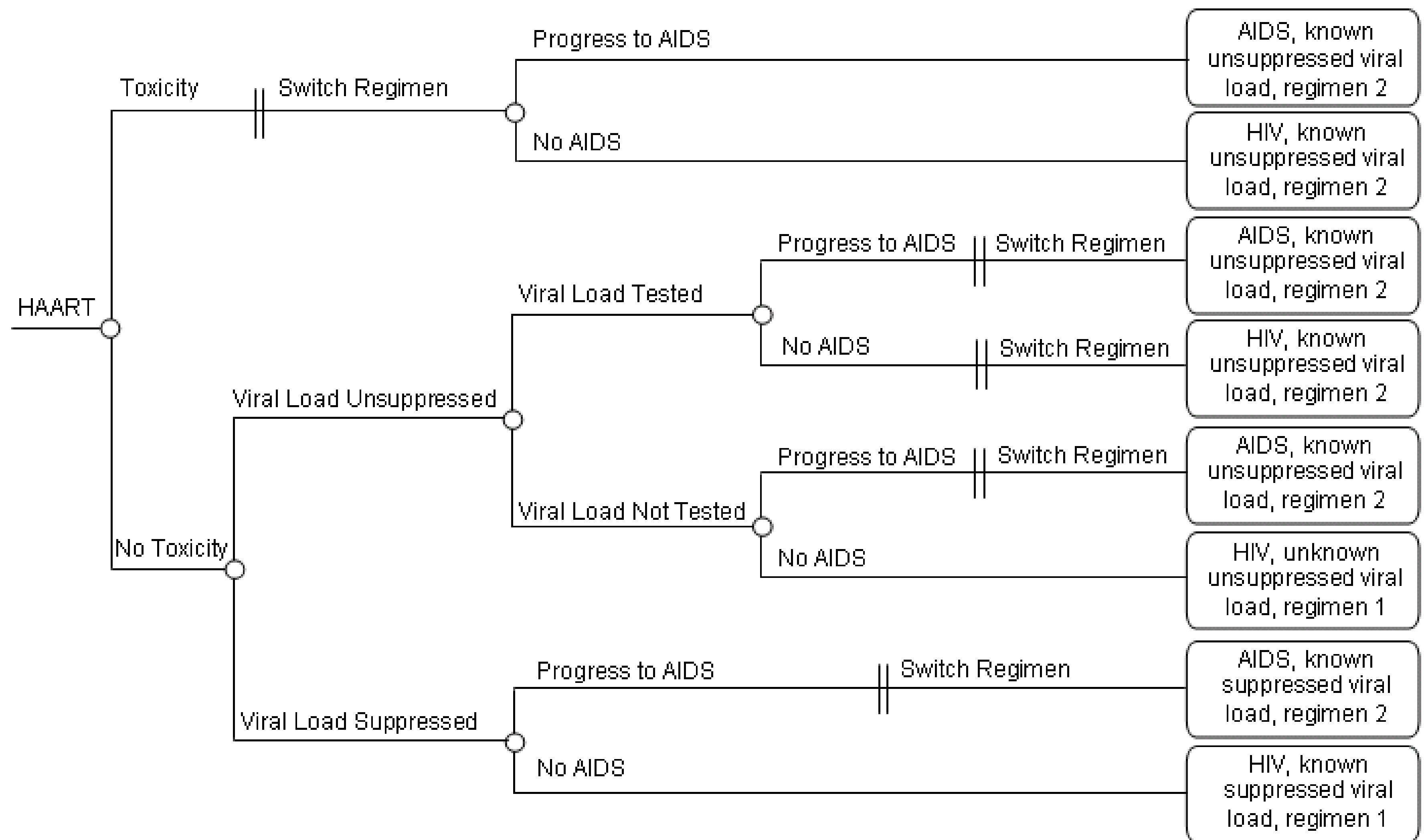

Figure 1B

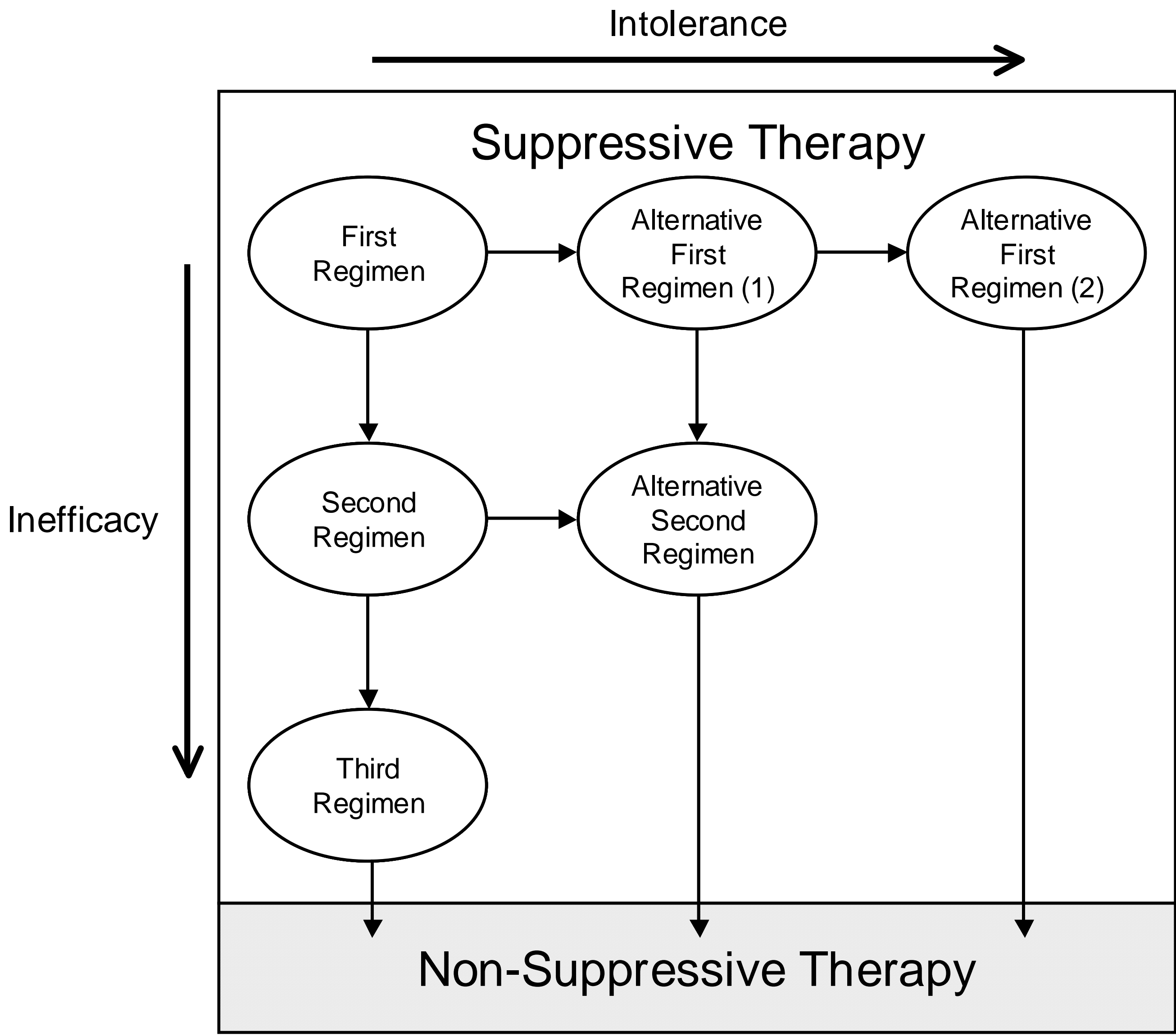

Figure 2

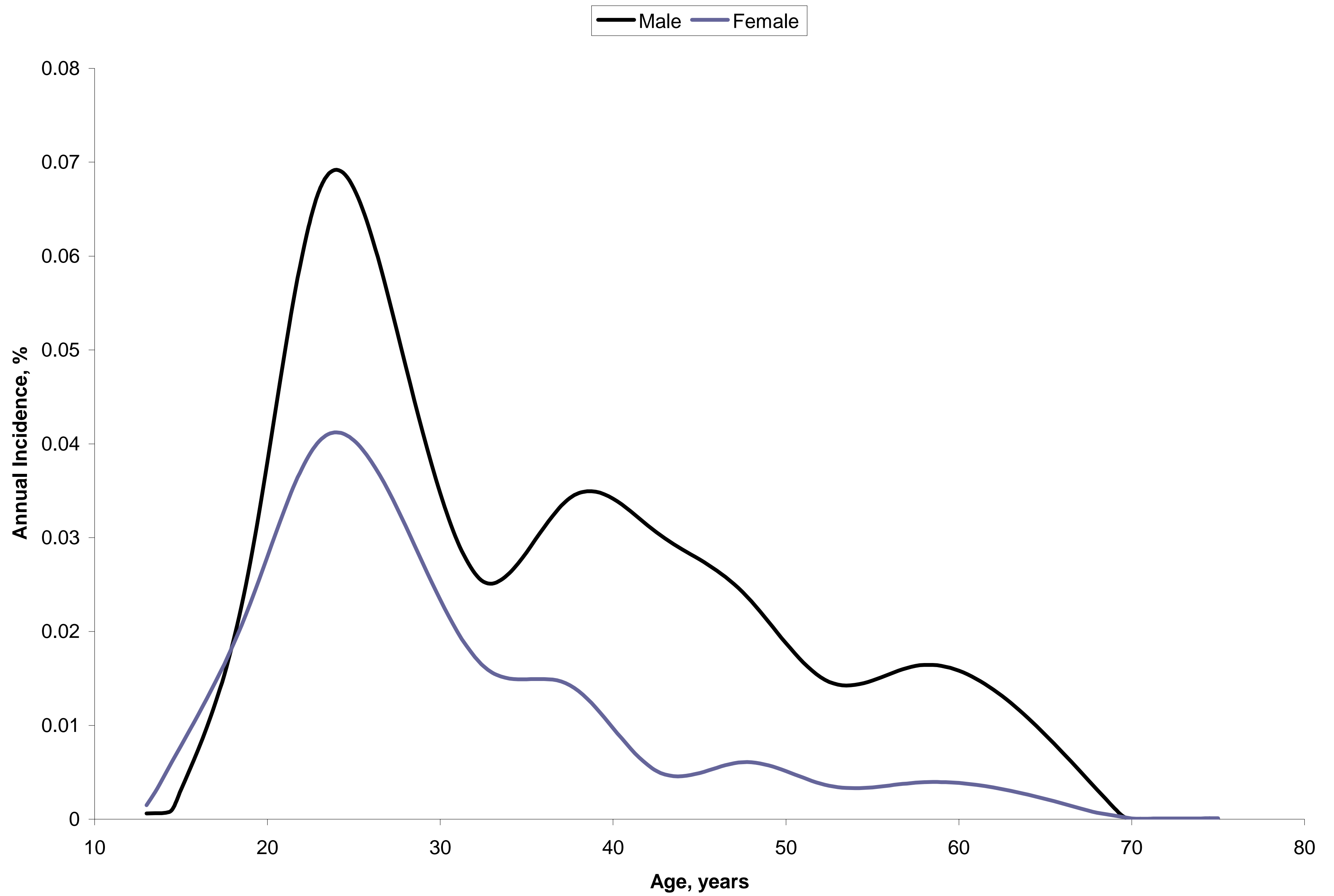

Figure 3

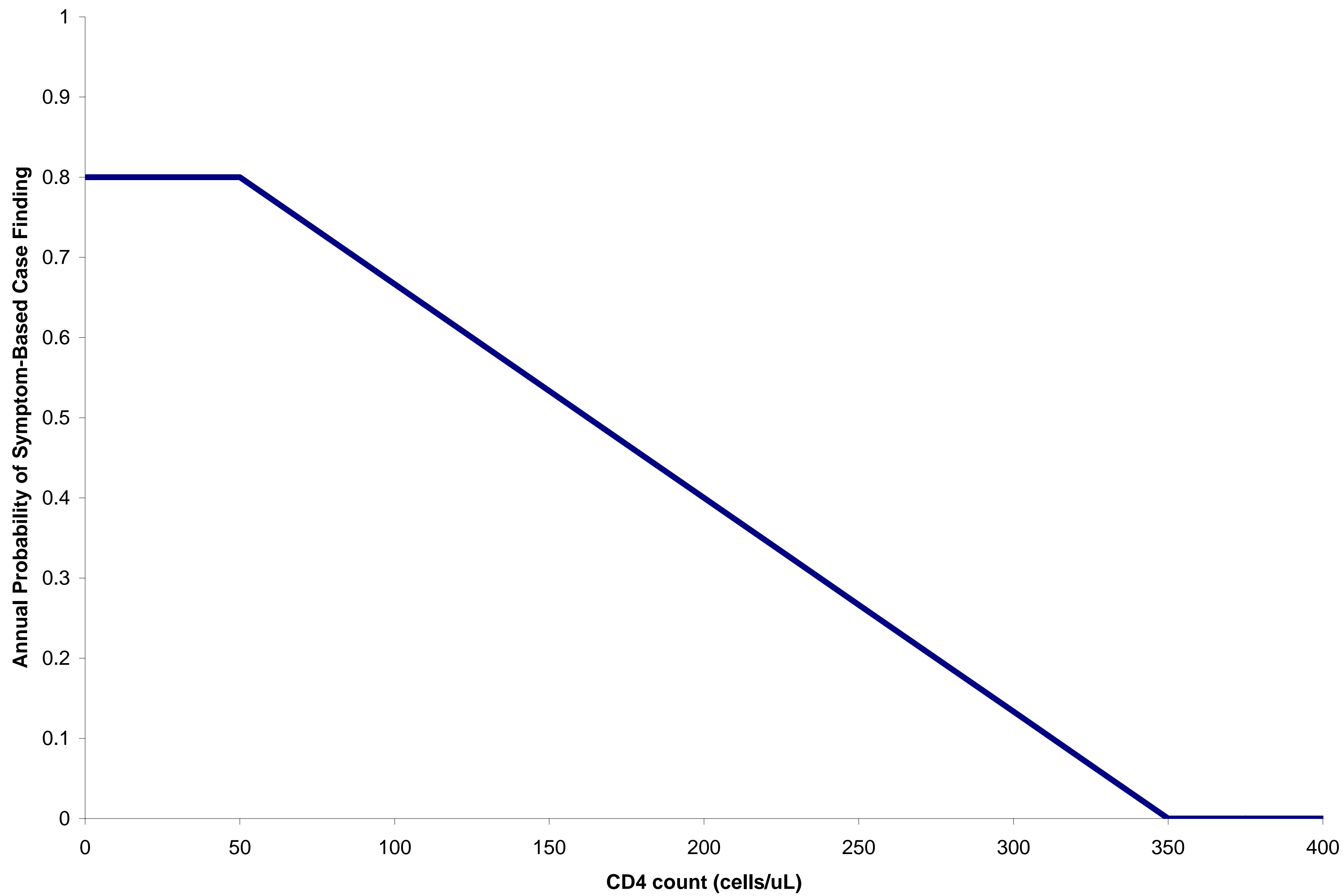

Figure 4