

# Supplementary Appendix

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

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# TECHNICAL APPENDIX

## Introduction

The analysis described in the main manuscript is built upon the foundation of the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) Model, a computer simulation of the clinical management and economics of HIV disease. We have linked this disease simulation to a new model of HIV screening and referral-to-care. In this Technical Appendix, we provide greater detail on the mechanics of both the CEPAC Disease Model and the Screening Model. We also describe our efforts to validate our findings and estimate the impact of expanded HIVCTR on secondary HIV transmission.

## Disease Model

The CEPAC Model [1-7] is a computer-based, state-transition, Monte Carlo simulation model of the progression and outcomes of HIV disease in a hypothetical cohort of patients. “State-transition” means that the model characterizes the natural history of illness in an individual patient as a sequence of monthly transitions from one “health state” to another. “Monte Carlo” refers to a random number generator and set of estimated probabilities that are used to determine the sequence of movements between health states for a particular patient. Each individual patient’s clinical course is followed from the time of entry into the model until death. A running tally is maintained of all clinical events, the length of time spent in each health state, and the costs and quality-of-life associated with each health state. Upon the patient’s death, summary statistics are

recorded and a new patient enters the model. This process is then repeated over a large number of patients (statistical convergence can typically be achieved with cohort sizes of 2 to 5 million), at which point overall performance measures such as average life expectancy, quality-adjusted life expectancy, and cost are computed.

In the Disease Model, health states are chosen to be descriptive of the patient's current health, relevant history, quality-of-life, and resource utilization patterns. They are designed to be predictive of clinical prognosis, including disease progression, immune system deterioration, development and relapse of different opportunistic infections (OIs), toxic reactions to medications, resistance to therapy, and mortality. The model defines three general categories of health states: chronic, acute, and death. Most of the time, patients reside in one of the chronic states, where progression of disease and immune system deterioration (CD4 decline) take place. Patients who develop an acute complication (e.g., an OI or drug-related toxicity) temporarily move to an acute health state, where 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.

The chronic and acute health states are stratified by: current and nadir CD4 cell count (>500 cells/mm<sup>3</sup>; 301–500 cells/mm<sup>3</sup>; 201–300 cells/mm<sup>3</sup>; 101–200 cells/mm<sup>3</sup>; 51–100 cells/mm<sup>3</sup>; and 0–50 cells/mm<sup>3</sup>) and current and set-point HIV-RNA level (>30,000 copies/mL; 10,001–30,000 copies/ mL; 3,001–10,000 copies/ mL; 501–3,000 copies/ mL; 51–500 copies/ mL; 0–50 copies/mL). Upon entry into the model, a patient is randomly assigned to a health state based upon a set of user-specified probability distributions. By permitting the user to define initial population distributions for patient age, sex, CD4 cell

count, HIV-RNA, and other demographic and clinical attributes, the model has the flexibility to explore a broad range of different patient cohorts.

At the start of each one-month cycle, the model records the patient's CD4 cell count, HIV-RNA level, history of acute illness, and current therapies and uses these characteristics to determine the probabilities that indicate movement to a new state in the subsequent month. Monthly probabilities of events are estimated directly from public use datasets and other published sources and translated into risk functions for the model [8-18]. These risk functions embody the key parameters of the natural history of HIV illness, AIDS, and OIs, including: rates of disease progression, OI risks, survival probabilities, and the effects of therapy. The model treats HIV-RNA as the primary driver of immune system deterioration, and thus the assigned viral load level determines the rate at which the patient's CD4 cell count will decline in the absence of ART. Patients with a history of OIs have a higher risk of recurrence, depending on CD4 cell count and current use of antiretroviral therapy [19]. The model's handling of efficacy and durability of antiretroviral therapy are described elsewhere [4]. Briefly, we estimate efficacy from data on viral suppression and CD4 cell count change over time, as reported in randomized trials [20-22]. From these data, we derive a unique "efficacy matrix" for each first-line, second-line, and salvage antiretroviral regimen to be considered. This matrix transitions patients from therapeutic "success" to "failure" with the appropriate change in HIV-RNA and CD4 cell count.

In addition to life expectancy, quality-adjusted life expectancy, and total lifetime costs, model outputs may include disaggregated estimates of average cost per patient (e.g., drug, laboratory, hospitalization), performance of therapy (e.g., time on therapy,

time to viral load rebound, rates of toxicity), and morbidity (specific OI incidence rates, and causes of death).

Input data for the Disease Model have been described and published previously [1,4,5]. For the reader's convenience, selected data are reproduced in Table A-1, below.

### **Screening Model**

The purpose of the Screening Model is to simulate the clinical impact of HIVCTR activities in an at-risk population and to convey this information to the Disease Model. The Disease Model combines this information with its own output on the timing of AIDS-defining illnesses (in the absence of treatment) to establish whether, when, and how an individual case of HIV infection is first detected. We use the CDC's 2001 guidelines [23] themselves to specify the parameters of relevance to the analysis, including: the prevalence and incidence of HIV in the population; HIV test attributes such as sensitivity, specificity, cost, and time to results; frequency of screening; and the likelihood of linkage-to-care.

Figure A1 provides a conceptual overview of the Screening Model. Individual members of the population enter the simulation, one at a time. A random-number generator makes use of "time-to-event" probability distributions to assign each incoming person a unique set of four, HIV-related event times: (1) time of HIV infection,  $t_i$ ; (2) time of next HIV test performed within the context of a specific HIV CTR program to be evaluated,  $t_p$ ; (3) time of next HIV test performed within the context of any other "background" screening mechanism (such as an HIV test performed in an office or clinic setting),  $t_b$ ; and (4) time of non-AIDS-related death,  $t_d$ .

We treat the user-specified HIV incidence value as a hazard rate which, in the absence of reliable data, we assume to be constant over time. This rate, in turn, implies a monthly infection probability. Based on this probability, a random number generator within the model determines the individual patient's time to infection. Similar methods are used to determine non-HIV-related mortality based on standard life tables [24]. Instances where a patient's time to non-HIV-related death exceeds the time to infection represent cases of actual infection during one's lifetime.

In the large majority of instances, the assigned time to infection,  $t_i$ , far exceeds the assigned time to death,  $t_d$ , reflecting the reality that most people die uninfected. A simple "IF/THEN" statement (represented by the upper diamond in Figure A-1) makes this determination; such cases will never enter the Disease Model. In a small fraction of cases, however, individuals are assigned values  $t_i < t_d$  and will become HIV-infected during their lifetimes. At their given time  $t_i$ , these patients proceed to the Disease Model, which transcribes their age at the moment of infection and proceeds to simulate the progress of their illness and its associated clinical and economic outcomes. However, these individuals are not eligible to receive any kind of HIV therapy within the Disease Model until and unless their HIV infection is identified. Thus, the Disease Model simulates the progress of disease for all infected individuals, but only detected cases are eligible for antiretroviral therapy and OI prophylaxis. Patients who are successfully detected and linked to care are assumed to receive services (and incur all concomitant costs) that conform to national guidelines. These include CD4 count and HIV-RNA laboratory monitoring every three to four months and both ART and recommended prophylaxis against OIs at the appropriate CD4 cell count thresholds.

Detection of HIV infection can occur via one of three discrete mechanisms: First, an infected individual can receive an HIV-positive test result within the context of a specific CTR program to be evaluated. (In such a case,  $t_b > t_p > t_i$ ). Second, an infected individual can receive an HIV-positive test result within the context of any other background testing mechanism (hence,  $t_p > t_b > t_i$ ). Third, detection of HIV infection can take place because an infected individual seeks medical care for an AIDS-defining illness. The Screening Model determines the time of detection via the first two mechanisms, using a random number generator to combine user-specified assumptions regarding HIV test accuracy, program cost, and rates of test acceptance, return for results, linkage-to-care, and background surveillance, as obtained from publicly available CDC data (see Table 1 in text). This information is conveyed to the Disease Model which, in turn, determines the actual time of detection by comparing the time of screen-detection to the time of the first OI.

The Screening Model defines four, distinct HIV states: HIV-negative, HIV-acute, HIV-asymptomatic, and HIV-symptomatic. Patients newly infected with HIV are immediately moved from the HIV-negative state to the transient, HIV-acute state. Following their acute HIV infection, patients transition from the HIV-acute state to the chronic, HIV-asymptomatic state [6]. The time for that transition is a user-specified option whose value in the current analysis is set to two months. Users can specify both pre- and post-seroconversion test sensitivities and specificities, thus capturing the “window” properties of alternative test protocols.

Each individual’s experience in the Screening Model is tracked from the time of entry until either death or transition to the Disease Model. A running tally is maintained

of all test offers and acceptances, success/failure to return for test results, success/failure to link to care, and all costs and quality-of-life effects associated with these events. Upon the patient's departure from the Screening Model, summary statistics are recorded and a new patient simulation begins. Stable estimates of overall performance are obtained by aggregating large numbers of patient simulations. Sample size requirements depend upon user-specified assumptions of population prevalence, incidence, and testing program performance. Outputs of the screening model include: total program enrollment by HIV status; test acceptance and return rates by HIV status; frequency of testing and total number and type of tests performed; total true- and false-positive tests and true- and false-negative tests; CD4 cell count and HIV-RNA at the time of detection; time from HIV infection to diagnosis; mechanism of detection (program screening, background surveillance, or AIDS-defining illness); and total testing-related costs.

### **External Validation**

For purposes of external validation, we compare our model's predictions of CD4 counts at detection in the "CDC Threshold" population scenario (mean 316 cells/mm<sup>3</sup>) to those observed from population-based surveillance data reported to the CDC through June 2003 from 33 states that receive name-identified notifications of new HIV diagnoses [25]. Median (and interquartile range) CD4 cells were: 474/mm<sup>3</sup> (351 to 657/mm<sup>3</sup>) among patients who remained without AIDS for at least 12 months after the HIV diagnosis; 115/mm<sup>3</sup> (39 to 186/mm<sup>3</sup>) among patients who progressed to AIDS within a year following diagnosis; and 58/mm<sup>3</sup> (20 to 142/mm<sup>3</sup>) among patients who were diagnosed with both HIV and AIDS within the same calendar month. While overall

mean CD4 count at detection was not reported, the weighted average of reported median CD4 cells was 328/mm<sup>3</sup>.

### **Estimating Secondary Infections**

The success of ART and behavioral counseling in reducing transmission of HIV infection can be gauged by the reductions they produce in the reproductive number,  $R_0$ , a widely used measure of the state of an epidemic.  $R_0$  can be interpreted as the average number of secondary cases attributable to a single, infected person during his or her infectious period in a susceptible population. We rely upon published sources to assign values of  $R_0$  to infected individuals in the Screening Model based upon a) the mechanism by which their infection is detected and b) assumptions regarding the virologic and behavioral impact of ART [26,27]. Given the uncertainty surrounding the effect of ART on secondary transmissions, we consider a range of plausible scenarios, ranging from “no ART impact” to “high impact” (see Table A-2). We combined this information with output from the Screening Model on the distribution of detection mechanisms in order to compute a weighted average value of  $R_0$  – and, from there, an estimated number of downstream, secondary infections – for a given population under a given screening strategy.

**Table A-1: Selected Disease and Screening Model Input Data\***

<b>Mean monthly decline in CD4 cell count according to HIV-RNA level †</b>		<b>Source</b>
<u>HIV RNA</u>	<u>Decline in CD4 cell count (cells/mm<sup>3</sup>)</u>	
30,001-100,000 copies/ml	6.375	19
10,001-30,000 copies/ml	5.400	19
3,001-10,000 copies/ml	4.600	19
501-3,000 copies/ml	3.733	19
≤ 500 copies/ml	3.025	19

<b>Opportunistic infections, % monthly risk by CD4 stratum</b>							
	<u>0-</u>	<u>51-</u>	<u>101-</u>	<u>201-</u>	<u>301-</u>		
	<u>50/mm<sup>3</sup></u>	<u>100/mm<sup>3</sup></u>	<u>200/mm<sup>3</sup></u>	<u>300/mm<sup>3</sup></u>	<u>500/mm<sup>3</sup></u>	<u>&gt;500/mm<sup>3</sup></u>	
PCP‡	0.037	0.031	0.0096	0.00373	0.00085	0.00041	8
MAC‡	0.0122	0.00375	0.00101	0.00022	0.000055	0.000059	8
Toxoplasmosis	0.0027	0.0014	0.00067	0.00042	0.000092	0.000029	8
Cytomegalovirus	0.01857	0.00523	0.00214	0.00058	0.000129	0.000059	8
Fungal infection	0.01123	0.00591	0.00135	0.00029	0.000276	0.000088	8
Other§	0.0394	0.0246	0.00716	0.00224	0.00087	0.00047	8

**Annual cost of antiretroviral regimens and tests ||**

First-line	\$12,178	28
Second-line	\$13,464	28
Third-line	\$16,927	28
Fourth-line therapy	\$15,505	28
Genotypic resistance test (per test)	\$400	¶
CD4 cell count cost (per test)**	\$83	¶
HIV RNA cost (per test)**	\$110	¶

**Health-related quality of life score according to CD4 cell count**

>500 cells/mm <sup>3</sup>	0.870	29
200-500 cells/mm <sup>3</sup>	0.860	29
50-200 cells/mm <sup>3</sup>	0.850	29
0-50 cells/mm <sup>3</sup>	0.832	29

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\* This table is adapted from previously published material. See references 1 and 4.

† Mellors (1997) and the Multicenter AIDS Cohort Study public use data set (1995) report viral load measurements performed on frozen heparinized plasma.

‡ Abbreviations: PCP: *Pneumocystis jirovecii* pneumonia; MAC: *Mycobacterium avium* complex

§ Other infections included bacterial infections, tuberculosis and Kaposi's sarcoma. Data are estimated directly from the Multicenter AIDS Cohort Study public use data set 1995 and have been validated in three other HIV-infected populations [30,31,32].

|| Data on the costs of antiretroviral regimens are computed from average wholesale prices, less 12% to reflect actual government reimbursement rates (as described in the *Red Book* [28]).

¶Office of Payment, Boston Medical Center, Boston, MA. (unpublished data)

\*\* CD4 cell count and HIV RNA tests performed every three months.

**Table A-2: Reproductive Numbers Stratified by Mechanism of Detection**

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	<b>No ART</b>	<b>Minimal ART</b>	<b>High ART</b>
<b>Mechanism of Detection</b>	<b>Impact Scenario*</b>	<b>Impact Scenario†</b>	<b>Impact Scenario†</b>
<b>Testing program</b>	1.44	1.27	0.9
<b>Background screening</b>	1.44	1.27	0.9
<b>Opportunistic infection</b>	1.44	1.44	1.27
<b>Never detected</b>	1.44	1.44	1.44

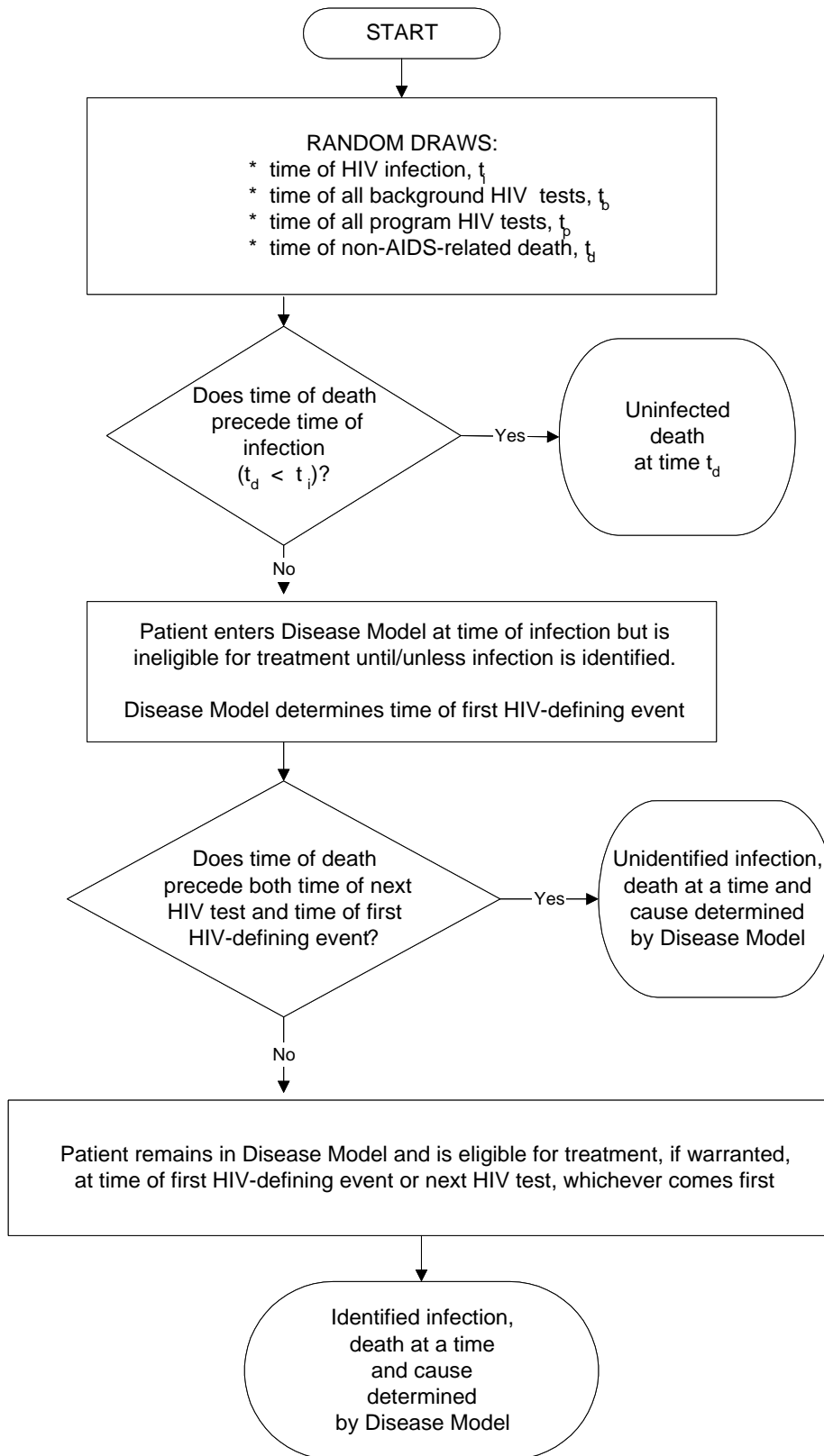
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\* ART impact is restricted to viral suppression and disease progression in the treated patient. There is no direct impact on secondary transmission of HIV infection.

† ART impact extends beyond the treated patient to reductions in secondary transmission of HIV infection via both virologic and behavioral effects.

**Sources:** 26,27



## **FIGURE LEGEND**

### **Figure A1: Conceptual framework for the Screening Model**

A random number generator assigns each incoming member of the population four, HIV-related event times. A series of “IF/THEN” statements reconciles the sequencing of these events and determines if and when HIV infection takes place, the time and frequency of all HIVCTR activities, and times of HIV screen detection and patient eligibility for therapy. For HIV-infected individuals, this information is conveyed to the Disease Model, which then simulates the progress of HIV disease, clinical care, and all associated costs. For all individuals, the Screening Model records cost and performance data on HIVCTR services.

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