Supplemental Digital Content

Updates of Lifetime Costs of Care and Quality of Life Estimates for HIV-Infected Persons in the United States: Late Versus Early Diagnosis and Entry into Care

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The Progression and Transmission of HIV/AIDS (PATH) model is a Monte Carlo simulation health-state transition model that individually tracks persons (index patients) with human immunodeficiency virus (HIV) infection and their infected partners from the time of infection until death. Because Prabhu et al.[1] described the details of the PATH model, we only give a brief description of the model here, and we discuss recent updates in HIV treatment, costs, and the transmission analysis.

Brief description of PATH

The model initially simulates a first generation of HIV-infected persons (index patients) from the time of infection through the following disease stages: acute infection, asymptomatic infection, symptomatic infection/AIDS (acquired immune deficiency syndrome), and death. We assumed persons entered the model, i.e. were infected, at an average age of 35 years and that HIV was transmitted through injection drug use (IDU) for 12.9% of the persons and through sexual transmission for all others.[2] We did not model behavioral differences in risk groups (men who have sex with men (MSM), high-risk heterosexual or injection drug users (IDU)), but we did include differences by disease stage. We did not stratify by gender or race. We present a schematic flowchart of disease progression for HIV-infected persons in the PATH model in Figure S1. We ran the model with distributions of values for key variables.

The acute phase is characterized by high HIV viral load in the initial weeks of infection. It was modeled to last for one calendar-year quarter, which is the time unit in our model. During the asymptomatic infection phase there are

no AIDS-related symptoms, but the stage is marked by a steady viral load (the HIV viral load set point) and declining CD4 count in the absence of treatment. Symptomatic HIV infection or AIDS is characterized by a drop in CD4 count to below 200 cells/μL or symptoms of an opportunistic infection, determined by a probability of occurrence.

We assumed HIV-infected persons in the model could die from causes either related to HIV/AIDS or other factors. For persons who were not yet on treatment, we used different quarterly probabilities of death for persons infected through sexual transmission[3] or through IDU transmission.[4] These probabilities increased as an individual's CD4 count declined. The maximum number of years of life remaining for a person infected with HIV in the PATH model was limited by life expectancy at the age of infection based on U.S. life tables.

Persons could be tested at any time after the acute phase of infection, followed by initiation of care and treatment, with the exact times determined by the setting under review. For example, in the setting in the main paper, diagnosis and care were categorized by CD4 counts, and treatment was initiated based on a guideline CD4 count for ART initiation. We assumed that HIV testing is conducted using a rapid test followed by a confirmatory Western blot. The natural progression of HIV described above is altered upon initiation of treatment with antiretroviral therapy (ART), which is associated with suppressed viral load, higher CD4 cell counts, improved life expectancy, and improved quality of life.

The PATH model also includes disease progression in a first generation of infected partners arising from transmissions from the index patients. The number of transmissions in each quarter is determined by probabilities defined by the route of transmission, phase of infection and treatment status of the index patient. During the course of the simulation, the model tracks and collects cost and life expectancy measures of the index patient and infected partners. A summary of the input parameters including updated values is provided in Table S1.

Updates to the PATH Model

The PATH model has been updated with recent estimates of HIV-related measures as described below.

Treatment regimen:

In accordance with expert opinion and recent clinical trials,[5-9] we assumed the probability of initial viral load suppression depended on the CD4 count at start of treatment. If initial suppression was obtained, the person continued with the regimen. After some period of time, each person faced a probability of viral load rebound after which the person started on the next line regimen. The duration of time in a regimen was determined by a random number drawn from a geometric distribution. The mean (or rate) of the geometric distribution varied by CD4 count at the start of ART. The rates were derived by calibrating against expected life-expectancies from the Antiretroviral Therapy Cohort Collaboration population.[10] If there was no initial suppression, the person moved to the next line regimen. We considered three lines of suppressive

regimens, which were based on the Department of Health and Human Services (DHHS) guidelines[11] and expert opinion, followed by salvage therapy. The rate of treatment change for the 2nd and 3rd lines of regimen was 1.18 times the rate of the previous regimen.[12]

Cost components:

HIV-infected persons in the model incur costs at different stages of infection. Components include costs for HIV diagnosis, treatment, follow-up CD4 cell count and RNA tests, health care utilization, and opportunistic infection treatment. We updated costs using estimates from Gebo et al.[13] supplemented by data from Schackman et al.[14] adjusted to $US 2011.

For individuals not in care, we applied only costs of medications for conditions not directly related to treatment of HIV.[13] For individuals in care we added the costs of non-HIV medication, opportunistic infection (OI) prophylaxis, and outpatient, inpatient, and emergency department utilization. These costs were determined by the CD4 cell count category of a person during a given quarter.[13] We also included the costs of CD4 cell count and HIV viral load testing each quarter and HIV genotype testing at the beginning of each ART regimen. We applied the costs of treating an OI[14] during any quarter the model predicted an occurrence. When patients began treatment with ART, we added the costs of drugs corresponding to each regimen as initiated and for salvage therapy.[13,14] We used current ART guidelines[11] and expert opinion to select the combination of drugs for each regimen.

Transmission of HIV to sexual and needle sharing partners:

An infected index person can transmit HIV infection through sexual contact or injection drug use (IDU) at a rate dependent on the infection phase. Previous analyses[15,16] have estimated sexual transmission rates as a ratio of incidence to prevalence in each of three transmittable populations: acute unaware, non-acute unaware, and non-acute aware. In our model we subdivided the aware population further to differentiate between persons on and not on ART and the success of viral load suppression from treatment. Modifying the model of Pinkerton[15] and Prabhu et al.,[16]

I = total number of sexual transmissions on any given day,

γ_k = daily transmission rate in group k,

N_k = number of persons living with HIV/AIDS in group k, and

I_k = proportion of new infections transmitted by group k, where,

$k = \{1,2,3,4,5\}$ constitute the HIV transmittable populations grouped according to their stage of infection, i.e., 1= acute unaware; 2= non-acute unaware; 3= non-acute aware not on treatment; 4= non-acute aware on treatment with viral load not suppressed; 5 = non-acute aware on treatment with suppressed viral load. Then,

$$\mathrm{I} = \sum_{k=1}^{5} \gamma_k N_k$$

$$I_1 = \frac{\gamma_1 N_1}{I} = \frac{\frac{\gamma_1}{\gamma_3} N_1}{\frac{\sum_{k=1}^{5} \gamma_k N_k}{\gamma_3}} = \frac{\mu_{12}\mu_{23} N_1}{\mu_{12}\mu_{23} N_1 + \mu_{23} N_2 + N_3 + \frac{1}{\mu_{34}} N_4 + \frac{1}{\mu_{35}} N_5},$$

where, $\mu_{12} = \frac{\gamma_1}{\gamma_2}$; $\mu_{23} = \frac{\gamma_2}{\gamma_3}$; $\mu_{34} = \frac{\gamma_3}{\gamma_4}$; $\mu_{35} = \frac{\gamma_3}{\gamma_5}$; and $\mu_{12}\mu_{23} = \frac{\gamma_1}{\gamma_3}$.

In general, μ_{ij} is the ratio of daily transmission rate in group i (i.e., γ_i) to the daily transmission rate in group j (i.e., γ_j). For example, $\mu_{12} = \frac{\gamma_1}{\gamma_2}$ = the daily transmission rate in acute unaware group divided by the daily transmission rate in non-acute unaware group.

Denoting the denominator

as $D = \mu_{12}\mu_{23}N_1 + \mu_{23}N_2 + N_3 + \frac{1}{\mu_{34}}N_4 + \frac{1}{\mu_{35}}N_5$, we can write:

$I_2 = \frac{\mu_{23}N_2}{D}$; $I_3 = \frac{N_3}{D}$; $I_4 = \frac{\frac{1}{\mu_{34}}N_4}{D}$; $I_5 = \frac{\frac{1}{\mu_{35}}N_5}{D}$. Let n_k be the total number of unprotected sex acts across all partners, and α_k be the average per-act transmission probability for persons in group k. Pinkerton[15] estimated $\mu_{12} =$ 8.1 and, under the assumption that the risk of transmission from condom-protected acts is zero, estimated $\gamma_2 \sim n_2\alpha_2$ since α_2 is a relatively small value. Similarly, we use $\gamma_k \sim n_k\alpha_k$ for $k = \{3,4,5\}$, $\mu_{ij} = \frac{n_i\alpha_i}{n_j\alpha_j}$ for $ij = \{23, 34, 35\}$, and estimate values of μ_{ij} by assuming a 57% [range 52-59%] reduction in the prevalence of UAV (unprotected anal or vaginal intercourse) with at-risk partners in the aware group compared to unaware group,[17] no change in virology across groups 2, 3, and 4 ($i.e., \alpha_2 = \alpha_3 = \alpha_4$), no change in behavior across groups 3, 4, and 5 (i.e., $n_3 = n_4 = n_5$), and a 90% [range 80-99%] reduction in infectivity due to viral load suppression from treatment.[18] Therefore, we can write $\mu_{23} = \frac{1}{1-0.57} = 2.33$, $\mu_{34} = 1$, and $\mu_{35} = \frac{1}{1-0.9} = 10$. Note that, although we assumed an equal transmission rate between groups 3 and 4 (i.e., $\mu_{34} = 1$), we separated the groups to allow for future consideration of partial reduction in

transmission arising from treatment even when viral load is not completely suppressed.

As in Prabhu et al.,[16] we estimated values of N_k using the 2006 U.S. estimates of incidence and prevalence, i.e., the total number of persons living with HIV is 1,106,300,[19] incidence of HIV infections is 56,300, of which 47,207 infections are from sexual transmission [2], the number of undiagnosed HIV cases is 232,700,[19] and the number of diagnosed cases of HIV is 873,600. N_1 was estimated by assuming that the acute phase of infection lasts for 49 days,[15] and during this phase, the person was assumed to remain serostatus-unaware. N_3, N_4, and N_5 were estimated by assuming that 65% of the aware population is linked to care of which 80% are on ART, and 80% of people on ART have a suppressed viral load [expert opinion][20]. Values for $I_k$were estimated by applying the estimates of $N_k$and μ_{ij} in the formulation for I_k presented earlier. The number of new infections from group k per year was estimated as I_k X 47,207 and the annual transmission rates as incidence divided by prevalence, i.e., $\frac{I_k \times 47,207}{N_k}$.

We assumed IDUs contributed 12.9% of new HIV infections and that the transmission rate from the non-acute unaware population was 0.165 per year [21,22]. We estimated IDU transmission rates for all other groups using the proportion of sexual transmission rates across the groups.

Figure S1. Schematic overview of the PATH disease progression model

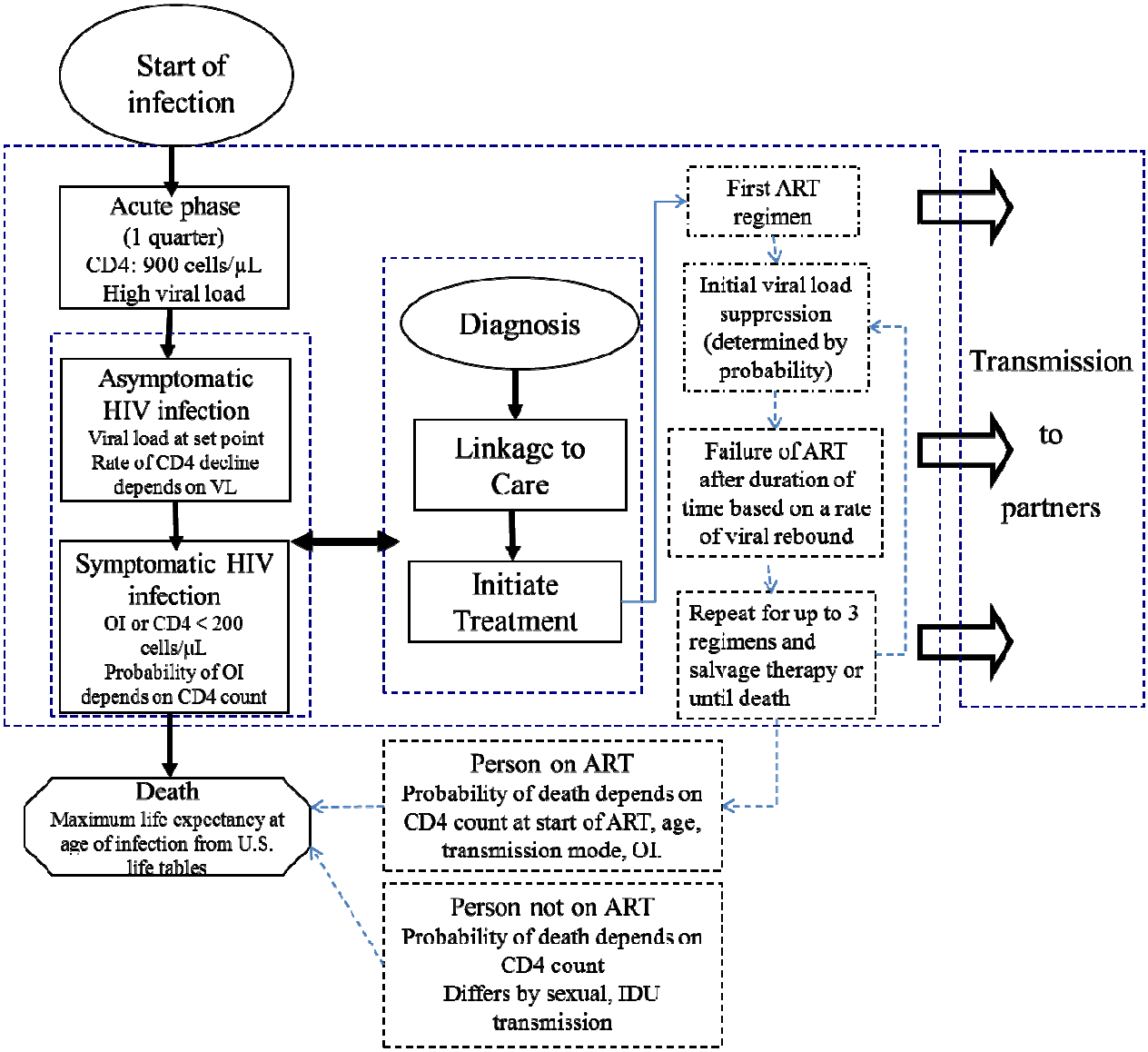

Table S1: Complete List of Input Parameters

Variable	Base Case Value	Range[a]	Source
Age at infection (years)	35	30 - 40	[b,23]
Discount rate for costs and quality-adjusted life years (QALYs)	3%		[24]
Natural Disease Progression			
CD4 cell count when infected (cells/μL)	900	750 - 900	[25]
Acute phase HIV viral load (log_{10} copies/ml)	5.3	4.4 – 6.2	[26,27]
HIV viral load set point (log_{10} copies/ml)	4.5	4.0 – 5.0	[28,29]
Natural rate of CD4 count decline (cells/μL/quarter) as a function of HIV viral load stratum (log_{10} copies/ml)			[30]
≤ 2.7	5.1	2.4 – 7.8	
2.7 – 3.3	9.9	7.2 – 12.3	
3.3 – 4.0	12	9.9 – 13.8	
4.0 – 4.6	14.1	11.7 – 16.2	
≥ 4.6	19.5	17.1 – 21.9	
Quarterly Probability of Developing an Opportunistic Infection (OI) (%)			[31,32]
Pneumocystis pneumonia (PCP)	0.1 – 10.7[c]		
Mycobacterium avium complex	0.0 – 3.6		

Toxoplasmosis	0.0 – 0.8		
Cytomegalovirus infection	0.0 – 5.5		
Fungal infection	0.0 – 3.3		
Other	0.1 – 11.4		
Cumulative probability for all OIs	0.3 – 35.3		
Quarterly Probability of Death for Antiretroviral Therapy (ART)-Naïve Individuals (%)			
Sexual transmission: CD4 count (cells/μL)			[3]
≥ 650	0.043		
500 – 649	0.05		
350 – 499	0.08		
200 – 349	0.145		
50 – 199	0.767		
< 50	4.9		
Injection drug use (IDU) transmission: CD4 count (cells/μL)			[4]
≥ 350	1.069		
200 – 349	1.486		
< 200	4.068		
ART Regimens			
Suppressed HIV viral load level (log_{10} copies/ml)	1.3	1.0 – 2.7	[33]
Rebound HIV viral load level (log_{10} copies/ml)	3.7	3.1 – 4.5	[34]
Maximum number of ART regimens and regimen drug composition	3 + Salvage Therapy (I. EFV/TDF/FTC; II. ATV/r+ABC/3TC; III. RAL+TDF/FTC)		[d,11]

Probability of virologic suppression in ART regimens 1 – 3 by CD4 count (cells/μL)			[5,6]
>200	0.84		
50 - 200	0.79		
< 50	0.774		
Rate of HIV viral load rebound (% experiencing rebound after one year on first regimen) by CD4 count (cells/μL)	5 - 1.45 [e]		[10,35]
Percent increase in rate of HIV viral load rebound for each successive regimen compared to its previous regimen	18		[12]
HIV viral load above set-point during salvage therapy (log_{10} copies/ml)	0.8	0.0 – 1.5	[21]
HIV viral load above set-point during salvage therapy after onset of AIDS (log_{10} copies/ml)	1	0.0 – 2.0	[21]
Quarterly increase in CD4 count during HIV viral load suppression (cells/μL/quarter)			[36]
Quarters 1 – 2	68		
Quarters 3 – 12	40		
Quarters 12+	0		
Maximum CD4 count achieved based on CD4 count at initiation of ART (cells/μL)			[36]
< 50	410		
50 – 200	548		
201 – 350	660		
351 - 500	780		

> 500	870		
Quarterly Probability of Death After Initiation of ART (%)			[37,38]
Sexual transmission			
No AIDS symptoms			
Age 16 – 29 years	0.09 – 0.26[f]		
Age 30 – 39 years	0.12 – 0.32		
Age 40 – 49 years	0.15 – 0.43		
Age ≥ 50 years	0.29 – 0.81		
Clinical symptoms of AIDS			
Age 16 – 29 years	0.19 – 0.53		
Age 30 – 39 years	0.25 – 0.69		
Age 40 – 49 years	0.32 – 0.93		
Age ≥ 50 years	0.64 – 1.77		
Injection drug use transmission			
No AIDS symptoms			
Age 16 – 29 years	0.27 – 0.75		
Age 30 – 39 years	0.35 – 0.99		
Age 40 – 49 years	0.46 – 1.30		
Age ≥ 50 years	0.87 – 2.44		
Clinical symptoms of AIDS			
Age 16 – 29 years	0.58 – 1.63		
Age 30 – 39 years	0.75 – 2.06		
Age 40 – 49 years	0.99 – 2.77		
Age ≥ 50 years	1.84 – 5.11		
Utility Weights to Estimate Quality Adjusted Life Years (QALYs)[g]			[39]
OI or CD4 count < 200 cells/μL	0.702		
CD4 count ≥ 200, < 350 cells/μL	0.818		
CD4 count > 350 cells/μL	0.935		
Quarterly Costs ($US 2011)			

Individuals in care: additional cost components include non-HIV medication, inpatient, outpatient, and emergency department resource utilization, and opportunistic infection prophylaxis	1,330-6,808 [h]	[i]	13
Individuals not in care: non-HIV medication costs only	577[j]		13
Additional costs of opportunistic infections (each occurrence)	4,247 – 21,890[k]		14
Per Person Cost of ART (each quarter) (3 Regimen + Salvage I. EFV/TDF/FTC; II. ATV/r+ABC/3TC; III. RAL+TDF/FTC)	3,597; 5,006; 4,819; 7,628 [l]		13,14
CD4 count test (one each quarter)	45		13
HIV viral load test (one each quarter)	107		13
HIV genotype test (beginning of each regimen)	452		13
Program cost per positive HIV test (emergency department scenario)	2,573		1,40
Annual Rates of Transmission (# events per year per person)			
Sexual transmission			Derived from 15,16
Acute[m]	0.733		
Non-acute unaware	0.091		
Non-acute aware, not on ART	0.039		
Non-acute aware, on ART but viral load not suppressed	0.039		
Non-acute aware, on ART with suppressed viral load	0.004		

IDU transmission			Derived from [15,16,21,22]
Acute	1.337		
Non-acute unaware	0.165		
Non-acute aware, not on ART	0.071		
Non-acute aware, on ART but viral load not suppressed	0.071		
Non-acute aware, on ART with suppressed viral load	0.007		

[a]We assigned truncated normal distributions based on the ranges of these variables to reflect individual variability in disease progression.
[b]Written communication, R. Song, Centers for Disease Control and Prevention, June, 2008.
[c]The lower and upper bounds for various types of OIs reflect probabilities for CD4 counts of > 500 cells/μL and 0 – 50 cells/μL respectively. Probabilities of an OI at intermediate CD4 counts lie within these bounds.
[d]Expert opinion; EFV/TDF/FTC = efavirenz/tenofovir/emtricitabine, ATV/r = atazanavir/ritonavir, ABC/3TC = abacavir/lamivudine, RAL = raltegravir
[e]Upper and lower bound for CD4 counts at start of ART of <100 and >500 cells/μL respectively. Rate of rebound at intermediate CD4 counts lie within these bounds
[f]The lower and upper bounds reflect the probability of death for CD4 counts ≥ 350 cells/μL and < 25 cells/μL, respectively. Probabilities of death at intermediate CD4 counts lie within these bounds.
[g]We applied the utility weights from Tengs and Lin[39] as follows: 0.935, asymptomatic, for CD4 count > 350 cells/μL; 0.818, symptomatic, for CD4 count ≥ 200, < 350 cells/μL; 0.702, AIDS, for CD4 count < 200 cells/μL or for presence of an opportunistic infection.
[h]The lower and upper bounds for costs reflect costs for CD4 counts > 500 cells/μL and ≤ 50 cells/μL, respectively. Costs for intermediate CD4 counts lie within these bounds.
[i]The means and ranges for each cost category are drawn from Gebo et al.[13]
[j]Reflects average cost over all CD4 count ranges.
[k]Numbers represent costs for different opportunistic illnesses.
[l]Costs for the three ART regimens and salvage therapy.
[m]We derived a quarterly probability of HIV transmission per infected person from the annual transmission rates, and we assumed the acute phase of infection lasted one quarter.

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