

Mortality associated with delays between clinic entry and ART initiation in resource-limited-settings:
results of a transition-state model

Running Head: ART delay and mortality

Authors:

HOFFMANN, Christopher J (1, 2), LEWIS, James J (3), DOWDY, David W (5), FIELDING, Katherine L (3),
GRANT, Alison D (3), MARTINSON, Neil A (1, 6), CHURCHYARD, Gavin J (2, 3, 4), CHAISSON Richard E (1)

Affiliations:

1. Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
2. Aurum Institute, Johannesburg, South Africa
3. London School for Hygiene and Tropical Medicine, London, UK
4. School of Public Health, University of Witwatersrand, Johannesburg, South Africa.
5. Johns Hopkins University School of Public Health, Baltimore, Maryland, USA
6. Perinatal HIV Research Unit, Johannesburg, South Africa

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Correspondence: Christopher J. Hoffmann, MD, MPH, MSc, Division of Infectious Diseases, Johns
Hopkins University School of Medicine, 1550 Orleans Street, CRB II Rm 1M-07, Baltimore, MD 21231
(email: choffmann@jhmi.edu)

Abstract

Objective: Estimate the mortality impact of delay in antiretroviral therapy (ART) initiation from the time of entry-into-care.

Design: A state-transition Markov process model. This technique allows for assessing mortality before and after ART initiation associated with delays in ART initiation among a general population of ART eligible patients without conducting a randomized trial.

Methods: We used patient-level data from three South African cohorts to determine transition probabilities for pre-ART CD4 count changes and pre-ART and on-ART mortality. For each parameter we generated probabilities and distributions for Monte Carlo simulations with one week cycles to estimate mortality 52 weeks from clinic entry.

Results: We estimated an increase in mortality from 11.0% to 14.7% (relative increase of 34%) with a 10 week delay in ART for patients entering care with our pre-ART cohort CD4 distribution. When we examined low CD4 ranges, the relative increase in mortality delays remained similar; however, the absolute increase in mortality rose. For example, among patients entering with CD4 count 50-99 cells/mm³, 12 month mortality increased from 13.3% with no delay compared to 17.0% with a 10 week delay and 22.9% with a 6 month delay.

Conclusions: Delays in ART initiation, common in routine HIV programs, can lead to important increases in mortality. Prompt ART initiation for patients entering clinical care and eligible for ART, especially those with lower CD4 counts, could be a relatively low cost approach with a potential marked impact on mortality.

Key words: ART delay; Africa; CD4 count; mortality; state-transition model

Introduction

Use of combination antiretroviral therapy (ART) dramatically reduces mortality among people living with HIV^{1,2} with maximal benefit when ART is started at higher CD4 counts.³⁻⁵ However, in many sub-Saharan African clinical settings, patients meeting local ART initiation guidelines experience delays of several weeks to several months in initiating treatment.⁶⁻⁹ These delays may occur as a result of health system, provider, and patient-level factors. For example, ART agent shortages and ART waiting lists are health-system factors leading to delay.¹⁰⁻¹³ Pre-ART counseling sessions and investigations for TB and other opportunistic diseases are clinic or provider-level factors that may lead to delay, while failure to return for timely clinic visits or declining ART due to fears of ART side effects are patient-level factors.^{8,14-17} Hesitation by a patient to accept ART may reflect a combination of patient-level and provider-level factors if the patient has not received an accurate and consistent message on the value of ART.

Several recent clinical trials have demonstrated reduced survival with delays in ART initiation in patients with an opportunistic illness or tuberculosis (TB).¹⁸⁻²² These trials highlight the benefit of prompt ART initiation in HIV infected patients with lower CD4 counts (<50 cells/mm³) and raise a question regarding whether ART delay causes a similar increase in mortality among ART-eligible people who do not present with opportunistic disease. If so, then accelerating ART initiation may be a key priority for reducing HIV-associated mortality. To address this question, using patient-level mortality and CD4 count data from three cohorts in South Africa, we developed a Markov state-transition model to simulate one-year mortality from time from entry into HIV care under different scenarios for time to ART initiation.

Methods

Model Structure

We constructed a Markov state-transition model to simulate mortality while allowing for variation in timing of ART initiation (0 to 52 weeks after clinic entry) and variation in CD4 count state at clinic entry. By simulating thousands of patients, this model can provide an estimate of mortality based on ART delay and CD4 count state at clinic entry. The model allows for transitions between CD4 count states prior to ART initiation and transition between alive and dead, prior to ART initiation and on-ART (Figure 1).

Patient-level data from three cohorts were used to calculate parameters and parameter variance for the model. These cohorts were (i) a study of isoniazid preventive therapy among mine workers with HIV conducted prior to the availability of ART,²³ (ii) data from a large cohort of patients who were provided free HIV care services through a network of community general practitioner HIV providers,²⁴ and (iii) data from a centrally managed ART program in multiple workplace and community clinics.²⁵ Isoniazid preventive study patient-level data were used to calculate CD4 count state transition probabilities, the community general practitioner cohort (the pre-ART cohort) was used to calculate pre-ART mortality, and the ART program cohort (the ART cohort) was used to calculate on-ART mortality. In developing transition probabilities for the state-transition model, we described uncertainty in the CD4 count state transition probabilities using a beta distribution, based on the mean and standard deviation. We also used a beta distribution to describe pre-ART mortality uncertainty generated from the means and standard errors from the primary data. For on-ART mortality, we generated mortality uncertainty distributions following a Normal distribution with a mean centered at the estimated mortality probability and standard deviation of 0.2 (greater detail on the model construction and transition probabilities are provided in a Technical Appendix available as **Supplemental Digital Content**, <http://links.lww.com/QAI/A393>).

We used probabilistic modeling of CD4 state transitions and mortality by sampling from transition distributions in a Monte Carlo micro-simulation (Figure 1). For the purposes of estimating the “whole

cohort” impact of reducing time to ART initiation, we evaluated mortality in a hypothetical cohort of 1000 patients whose CD4 distribution at clinic entry was set to be the same as our patient level data in our pre-ART cohort. We further analyzed a sub-group of the whole cohort, limiting to patients entering care with CD4 counts <150 cells/mm³. In order to allow for comparisons of impact of ART delay by CD4 count at clinic entry we also separately modeled outcomes for each CD4 count state.

We developed the state-transition model using TreeAge Pro 2011 software (TreeAge Software Inc., Williamstown, MA, USA). Monte Carlo micro-simulation of 10,000 cohorts each with 1000 patients was used to estimate mortality probabilities and 95% uncertainty ranges. We performed the following uncertainty analyses: (1) excluding patients with TB disease diagnosed at the time of entry into pre-ART care and (2) separately adjusting CD4 state transition, pre-ART mortality, and on-ART mortality by a relative increase or decrease of 25% while repeating the whole cohort analysis for 0, 10 and 26 week delays in ART initiation.

Data analysis used to populate model

For parameter estimation from each of the three cohorts (CD4 transition, pre-ART, and on-ART) we included all adults (age ≥ 18 years) who were ART naïve and had WHO clinical stage I, II, or III conditions at cohort entry. We excluded patients with WHO clinical stage IV conditions as disease specific management strategies may influence both timing of ART initiation and mortality. For the pre-ART and on-ART cohorts, we maximized ascertainment of deaths using clinic reports and linkage of national civil identification numbers to the South African Department of Home Affairs vital status registry. This linkage provided the date of death for deceased patients among the 65% (pre-ART cohort) to 80% (ART cohort) of patients with valid national ID numbers. Linkage was performed one month after our cohort closure date. We estimated mortality among those lost to follow-up but without identification numbers through inverse probability weighting.^{26;27} To calculate CD4 transitions pre-ART, we stratified all

longitudinal CD4 count values into one of 9 states: <25, 25-49, 50-99, 100-149, 150-199, 200-249, 250-299, 300-349, and ≥ 350 cells/mm³. For each of the nine CD4 states, we calculated the Nelson-Aalen hazards of transition to another CD4 state and expressed these as one-week probabilities. To determine pre-ART mortality, we used survival analysis with cohort entry defined as the first CD4 count. We used time of first CD4 count as time of clinic entry because CD4 count enumeration generally occurs at this time in the South African context. Patients exited at the time of death or were censored at ART initiation; because we could ascertain vital status through national registry linkage, we did not censor based on loss from care. Mortality hazard, stratified by CD4 count, was relatively constant over follow-up time. Thus we converted the six-month Nelson-Aalen survival probability into a one-week mortality probability. We calculated mortality hazard in the on-ART cohort using Nelson-Aalen hazards based on the CD4 count state at ART initiation and time on ART. Because the decline in mortality, by time on ART, approximated the initial slope of an exponential decline, we used an exponential distribution to estimate weekly mortality probabilities by duration on ART.

Results

Data analysis to populate model:

The CD4 transition cohort had 1,413 ART naïve individuals with a median of 3 (interquartile range; IQR: 2, 4) CD4 assays and median interval between measurements of 196 (IQR: 175, 308) days. The pre-ART cohort consisted of 31,017 individuals contributing 41,724 years of observation. The median CD4 count at care entry was 216 (IQR: 96-376) with none of the 9 CD4 count strata containing less than 9% or more than 15% of the population. Among those meeting an ART eligibility threshold of <350 cells/mm³, the median CD4 count was 143 cells/mm³ and 56% were men. The on-ART cohort consisted of 23,940 individuals contributing 61,374 person years of observation. The median CD4 at ART initiation was 147 cells/mm³ (IQR: 66, 228) and 58% were men.

Markov state-transition model – CD4 count changes

We estimated that patients with CD4 counts of 350 and 75 cells/mm³ would have CD4 cell declines of 48 and 71 cells/mm³/year, respectively. Using the entry CD4 distribution of the pre-ART cohort, we estimated a 10% pre-ART mortality 6 months from clinic entry without ART initiation. Among the survivors at 6 months, 52% remained in the CD4 state in which they entered care, 7.8% increased by one or more states, 22% decreased by one state, and 6.0% decreased by two or more states. During the subsequent 26 weeks of ART, 9% of the pre-ART survivors died for a total 52 week mortality of 19%.

Markov state-transition model - Mortality by delay in ART initiation

Using a hypothetical whole cohort with the same CD4 count distribution as seen in our pre-ART cohort, 11.1% of the population (95% CI: 7.2-15%) were projected to die within 52 weeks, if ART was started immediately on clinic entry. Deaths increased to 13.2% (95% CI: 9.5-17%) with a 6 week delay, 14.7% (95% CI: 11-18%) with a 10 week delay, 19.6% (95% CI: 16-23%) with a 26 week delay, and 24% (95% CI: 20-29%) with a 52 week delay (Table 1). Thus, as compared with immediate ART initiation, delaying ART initiation by 10 weeks resulted in 37 additional deaths (34% increase in one-year mortality) and delaying by 52 weeks resulted in 130 additional deaths (118% increase), per 1,000 patients.

Limiting the simulation to patients entering with CD4 <150 cells/mm³, we observed an increase in mortality from 160 deaths per 1000 patients with no delay, to 210 deaths with a 10 week delay (31% increase) and 340 deaths (112% increase) with a 52 week delay.

The effect of ART delay on mortality within specific CD4 count states at clinic entry is presented in Table 1 and graphically presented in Figure 2. The effect of a 10 week delay among patients with a CD4 count of 50-99 cells/mm³ was an increase of 37 deaths in a cohort of 1000 patients (31% increase). A 26 week delay was associated with an increase of 96 deaths (77% increase).

Excluding patients with TB at clinic entry (5.6% of all patients) gave similar results (results not shown).

To assess the impact of uncertainty on state change probabilities, we performed serial one-way analyses with a relative 25% increase or decrease in probability for each parameter for CD4 state transitions, pre-ART mortality, and on-ART mortality (Figure 3). The ranges for the 52-week mortality for 0, 10, and 26 week delays in ART initiation after these one-way uncertainty analyses all fell within our simulated uncertainty ranges (Table 1).

Discussion

Using data from South African cohorts we modeled a relative 34% increase in 12 month mortality attributable to a 10 week delay in ART initiation. A 10 week delay is consistent with the range reported in the literature of 9 to 125 days^{8,10;28-32} as well as our experience in a hospital-based ART program.³³ Notably, the absolute increase in mortality was highest with lower CD4 count states. For example, a 10-week delay in ART initiation would be expected to result in 15 excess deaths per 1000 patients with CD4 counts at clinic entry between 200-249 cells/mm³, compared to 37 excess deaths among patients entering with CD4 counts between 50-99 cells/mm³. Thus potential gain in survival, if a 10 week delay in ART initiation could be eliminated, is only slightly less than the estimated 40% relative reduction in mortality during the first year of ART through universal use of cotrimoxazole prophylaxis.³⁴⁻³⁶

While there are no empirical studies of ART delay and mortality from clinic entry and after ART initiation in an unselected population, we can compare estimates from each of our parameters with prior parameter specific reports. Our estimates of pre-ART mortality are similar to prior reports from Africa (Table 2).³⁷⁻³⁹ In this regard, the similarity of our estimates with observational data supports the validity of the pre-ART parameters of our model. In contrast, our parameter-based estimates of on-ART mortality are somewhat higher than previously reported (Table 2)⁴⁰⁻⁴³. This discrepancy in on-ART mortality may be a result of deriving our parameters from data linked to a robust national vital status

registry leading to greater ascertainment of deaths. Such registers are not widely available in sub-Saharan Africa outside of South Africa. Failure to completely ascertain deaths among patients lost to follow-up can markedly reduce mortality estimates.^{27;44-47} Thus, we believe that the on-ART mortality for our cohort is likely reflective of the true mortality experience of other similar settings. Of note, an overestimate of on-ART mortality would lead to an underestimate of the mortality impact of delays in ART initiation. Programs with lower overall pre-ART and on-ART mortality will not achieve as large an absolute reduction in mortality. Nevertheless, the relative reductions in mortality achievable by reducing delays in ART initiation may be similar.

We also compared our findings to three randomized trials of timing of ART initiation for TB patients.¹⁹⁻²² It is notable that although our overall (pre and on-ART mortality combined) mortality predictions were higher than each of the three trials, the absolute increases in mortality were similar when comparing similar entry CD4 counts and durations of delay. The similarity in absolute increases in mortality provides added support to the validity of our model. Our higher overall mortality may reflect the differences in routine clinical practice versus clinical trials, especially clinical trials of TB treatment as a large proportion of mortality in routine care occurs from undiagnosed and untreated TB.⁴⁸

The mortality benefit of accelerating ART initiation should be balanced against potential harms. For example, people started on ART sooner may be less likely to be correctly diagnosed with concurrent opportunistic illnesses (e.g., TB) or adequately prepared for ART initiation. This may increase the risk of immune reconstitution inflammatory reaction (IRIS) and future non-adherence, respectively. However, IRIS is rarely fatal^{21;22;49}, and limited available evidence suggests that adherence counseling during early ART may equal pre-ART counseling.⁵⁰

As with any model-based analysis, our model has several limitations. First, due to limitations of available data, we used primary data with variable duration between CD4 counts to estimate CD4 transition

probabilities. Although this limitation likely introduces the greatest imprecision in our transition probabilities, the findings from our uncertainty analyses are reassuring because even a relatively large change in the CD4 count transition probability (25% increase or decrease) had a small effect on model outcome (Figure 3). The CD4 transition cohort may show a healthy worker bias with a slower decline in CD4 count. However, a calculated decline of 71 cells/mm³/year is consistent with several other studies in which CD4 count decline is 34 to 97 cells/mm³/year.⁵¹⁻⁵⁵ The pre-ART cohort also may not be representative of the natural history of untreated HIV disease, as unmeasured factors may have affected delays in ART initiation (e.g., ill-appearing patients started on ART sooner). However, our analysis is designed to reflect the impact of delays in routine care, not in the abstract situation of untreated natural history. Importantly, we may have underestimated the effect of delay by using the date of the first CD4 test as the date of clinic entry, as delays may occur between clinic entry and CD4 enumeration. However, in our clinical setting, CD4 measurement on the first clinic visit was routine, thereby minimizing the likely effect of this bias. Finally, we did not address delays in diagnosis of HIV or entry into care following diagnosis because our intent was to focus on delays in ART initiation among patients who had already been linked to HIV-specific care. To provide a full spectrum of the impact of delays on HIV-associated morbidity and mortality, future models could also address delays in HIV diagnosis and entry-into-care, as well as modeling the impact of such delays on HIV transmission.

Our findings highlight the need to develop approaches to more promptly initiate ART after patients present to care. These approaches must address both clinic-level and patient-level factors. Clinic-level reduction in delays may be achieved through improved turn-around times in obtaining laboratory results, fewer “ART preparation visits”, and streamlined pre-ART assessment protocols. Interventions may include changes in pre-ART counseling, educating staff on the risks of ART delay, and improving access to CD4 count testing, including the use of point-of-care CD4 count assays.²⁸ Patient-level barriers to prompt ART initiation may include barriers to reaching the clinic as well as concerns of ART side

effects, stigma, and coping.^{9;16;41;56-59} Proactive patient-centered approaches (e.g., financial enablers, community-based educational campaigns, home-based care) to overcome these barriers must be advanced if we are to maximize the number of lives saved with ART. Such programs must also address issues of adherence and retention in order to minimize any potential negative consequences of more rapid initiation of ART. Failure to retain patients starting ART would undermine short-term survival benefits.

Our model, based on data from routine programs in South Africa, suggests that the delays in ART initiation which are typical of some existing clinics, may cause substantial excess mortality. Among the most immunosuppressed patients, this absolute mortality increase is substantially higher. Reducing delays to ART initiation for all eligible patients in high-burden settings, especially those with lower CD4 counts and not just those with opportunistic infections, could save thousands of lives every year and should be prioritized if the promise of ART in these populations is to be fully realized.

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FIGURE CAPTIONS:

Figure 1: Markov state transition model with CD4 states and arrows indicating the allowed transitions between states for a cohort followed for 52 weeks from clinic entry and initiating ART at week “k”. Mortality occurs from each state each cycle.

Figure 2: Contour plot of total mortality risk 52 weeks after entering HIV care by duration of delay in ART initiation (x-axis) and CD4 at care entry (y-axis).

CD4 at the time of entry into care is on the y-axis, delay in ART initiation on the x-axis, and contours represent mortality bands by percent of the cohort who died 52 weeks after entering care. The close contour lines at lower entry CD4 represent the more rapid increase in mortality with delays among such patients. The black line represents the increasing mortality with the whole cohort analysis (median CD4

count 143 cells/mm^3) in which mortality increases from 11.0% with no delay to 19.7% with a 26 week delay and 24.2% with a 52 week delay.

Figure 3: Tornado diagram of absolute change in percent mortality at 10 weeks and 26 weeks with a 25% decrease or 25% increase in parameter for CD4 transition, pre-ART mortality, or on-ART mortality.

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Table 1: Total mortality and excess mortality by delay in ART initiation, stratified by CD4 count at care entry

CD4, cells/mm ³	Total: One year mortality risk (%) according to delay from clinic entry to ART initiation (95% uncertainty range)					
	Excess: attributable mortality associated with delay (95% uncertainty range)					
		0 weeks	6 weeks	10 weeks	26 weeks	52 weeks
State-transition model for pre-ART cohort CD4 distribution						
Whole Cohort (median CD4: 143)	Total	11.0 (7.2, 15)	13.2 (9.5, 17)	14.7 (11, 18)	19.7 (16, 23)	24.2 (19, 29)
	Excess	0	2.2 (-3.2, 7.7)	3.7 (-1.8, 9.1)	8.6 (3.4, 14)	13.0 (7.2, 19)
Restricted to CD4 <150 cell/mm ³	Total	15.5 (10, 21)	18.8 (13, 24)	20.8 (16, 26)	27.7 (23, 32)	34.2 (28, 40)
	Excess	0	3.3 (-4.3, 1.1)	5.2 (-2.2, 13)	12.1 (4.8, 19)	18.6 (10, 27)
State transition model for pre-ART CD4 strata at entry into clinic						
300-350	Total	2.8 (1.7, 3.9)	3.2 (1.9, 4.9)	3.5 (2.0, 6.0)	4.3 (2.1, 8.8)	5.1 (1.5, 12)
	Excess	0	0.4 (-1.4, 2.3)	0.7 (-1.6, 3.0)	1.5 (-2.1, 5.2)	2.3 (-3.7, 8.3)
250-299	Total	3.5 (2.2, 4.9)	4.1 (2.6, 6.1)	4.6 (2.7, 7.4)	6.0 (3.2, 11)	7.1 (2.3, 16)
	Excess	0	0.6 (-1.4, 2.3)	1.1 (-1.5, 3.8)	2.5 (-1.8, 6.8)	3.6 (-3.2, 10.5)
200-249	Total	4.7 (2.8, 6.6)	5.6 (3.7, 7.6)	6.2 (4.2, 8.7)	8.4 (5.2, 13)	10.0 (5.0, 17)
	Excess	0	0.9 (-1.8, 3.6)	1.5 (-1.4, 4.5)	3.7 (-0.7, 8.1)	5.2 (-1.2, 12)
150-199	Total	6.6 (4.1, 9.1)	7.9 (5.3, 10)	8.6 (5.9, 11)	11.6 (8.1, 16)	13.9 (9.0, 21)
	Excess	0	1.3 (-2.4, 4.9)	2.0 (-1.8, 5.9)	5.0 (0.37, 10)	7.3 (1.0, 14)
100-149	Total	9.4 (5.5, 14)	11.0 (7.6, 14)	12.2 (8.8, 16)	16.3 (12, 21)	20.0 (14, 27)
	Excess	0	1.6 (-3.7, 6.9)	2.8 (-2.6, 8.3)	6.9 (1.0, 13)	10.6 (2.9, 19)
50-99	Total	13.3 (8.4, 18)	15.6 (10, 21)	17.0 (12, 22)	22.9 (17, 31)	29.2 (21, 40)

	Excess	0	2.2 (-4.9, 9.3)	3.7 (-3.3, 11)	9.6 (1.1, 18)	15.8 (5.2, 26)
<50	Total	21.3 (14, 29)	26.2 (19, 33)	29.2 (22, 36)	38.8 (33, 44)	47.4 (39, 55)
	Excess	0	4.8 (-5.3, 15)	7.8 (-2.1, 18)	17.4 (7.9, 27)	26.1 (15, 37)

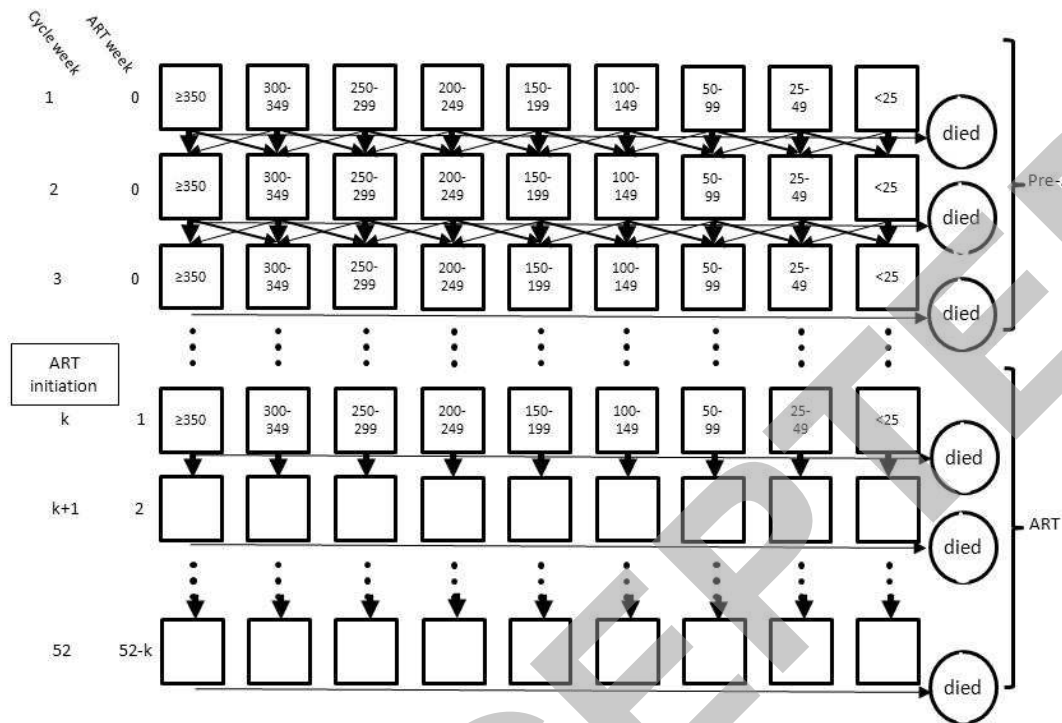
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Table 2: Pre- and on-ART 52 week mortality estimates (per 100-person-years) from the model simulation and the published literature

	CD4 strata (cells/mm ³)								
Mortality per 100 person-years	<25	25-49	50-99	100-149	150-199	200-249	250-299	300-349	≥350
<i>Pre-ART</i>									
Model	72	56	34	22	15	11	7.7	7.6	3.8
Anglaret	69		32		17		4.2		0.6
Fielding	43			11			3.3		0.6
Badri			27				8		NR
Amuron*	80%		50%			31%			NR
<i>On-ART</i>									
Model	29	20	14	9.9	6.9	4.8	3.6	2.8	2.8
May	24	16	8.7		5.5			5.1	
Brinkhof	17	11	7.3		4.8			3.8	
Mills		13	6.4	4.4	3	3.3	2.2		2.8

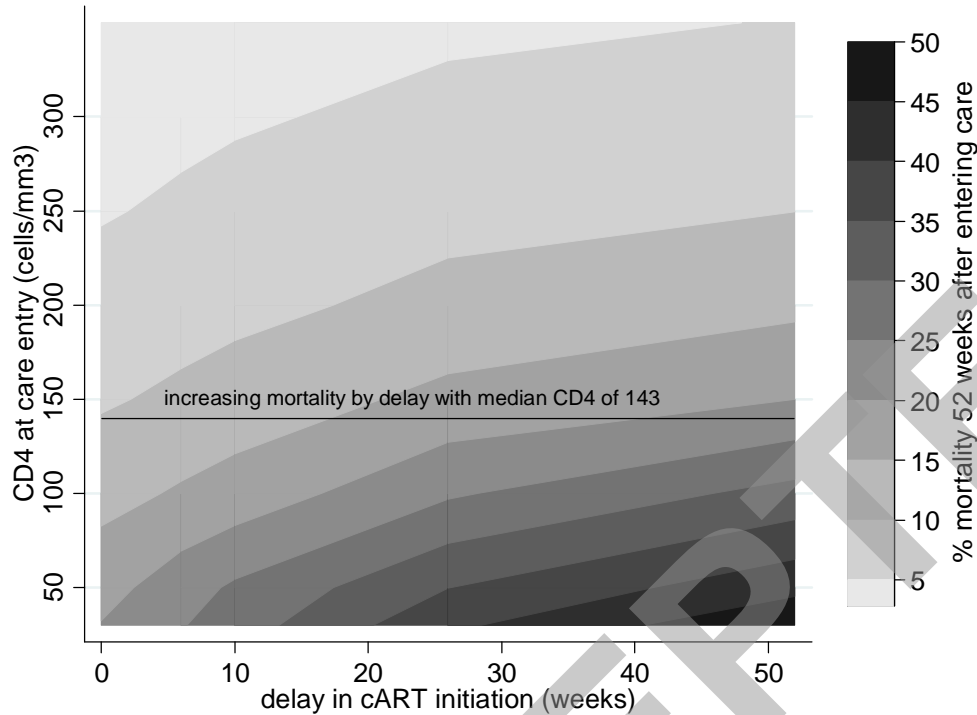
* mortality risk over a 12month time period; NR not reported

Figure 1: Markov state transition model with CD4 states and arrows indicating the allowed transitions between states for a cohort followed for 52 weeks from clinic entry and initiating ART at week “k”. Mortality occurs from each state each cycle.



Before ART initiation, transitions can occur between adjacent CD4 count states. After ART initiation, mortality is estimated as a function of CD4 count state at ART initiation and weeks since ART initiation, and thus there are no transitions between CD4 count states and the boxes are blank because individual patients may have a wide range of CD4 counts.

Figure 2: Contour plot of total mortality risk 52 weeks after entering HIV care by duration of delay in ART initiation (x-axis) and CD4 at care entry (y-axis).



CD4 at the time of entry into care is on the y-axis, delay in ART initiation on the x-axis, and contours represent mortality bands by percent of the cohort who died 52 weeks after entering care. The close contour lines at lower entry CD4 represent the more rapid increase in mortality with delays among such patients. The black line represents the increasing mortality with the whole cohort analysis (median CD4 count 143 cells/mm³) in which mortality increases from 11.0% with no delay to 19.7% with a 26 week delay and 24.2% with a 52 week delay.

Figure 3: Tornado diagram of absolute change in percent mortality at 10 weeks and 26 weeks with a 25% decrease or 25% increase in parameter for CD4 transition, pre-ART mortality, or on-ART mortality.

