SUPPLEMENTAL DIGITAL CONTENT - TECHNICAL APPENDICES

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Appendix A: Narrative Description of Model Construction

The following text describes, in greater detail, the steps taken in developing the state-transition model. First, we developed a theoretical model, defining the transition states necessary to generate estimates of HIV mortality as a function of ART delay (Figure 1, main manuscript text). Next, we used patient-level data from three South African cohorts to calculate transition probabilities (and associated variability estimates) of transitions between CD4 count states with an *a priori* width of 50 cells/mm^3, starting at 350. We also estimated the within-stratum mortality risk according to CD4 cell state; this process required differentiation between pre-ART mortality and on-ART mortality.

Model Development

Once all state transition probabilities (and estimates of variability) were defined, we used TreeAge 2011 to build a Markov state transition model with a cycle duration of 1 week allowing for transitions from the pre-ART to on-ART and between CD4 states during the pre-ART period. In our primary analysis, we estimated mortality for each of our pre-specified discrete delays (e.g., no delay, 6 weeks, 12 weeks, etc.) within each of our CD4 count states (e.g., 0-24, 25-49, 50-99, etc.), in order to provide a patient-level estimate of the impact of various delays according to entry CD4 count. We also considered a "whole-cohort" analysis, in which we took a population that reflected the distribution of our pre-ART cohort and assigned each individual to a delay using random draws from a log-normal distribution, centered at our pre-specified delay levels (e.g., 6 weeks, 12 weeks, etc.). This analysis was designed to evaluate the population-level effects of reducing delay, accounting for the right-skew in ART delay that may be more reflective of a "real-world" population. For each scenario based on timing in ART initiation and CD4 count and clinic entry we performed a micro-simulation of 1000 patients in 10,000 trials to achieve convergence of results. We used the mean and upper 97.5 and lower 2.5 range to describe the 95% confidence interval.

CD4 count state transition probabilities

Description of cohort from which state transition probabilities were calculated

The cohort was created using patient level data from a clinical trial of isoniazid preventive therapy among gold miners at a single mine site in South Africa. Employees with a prior HIV-positive test were recruited to participate from a workplace wellness clinic. None of the participants received antiretroviral therapy (ART) during the course of the trial because ART was not available at that time in South Africa. 1863 participants were included with a median follow-up time of 1 year (IQR: 0.7, 2.1). CD4 count was enumerated a median of every 6 months. Total mortality was 39/1863 (2%).

Calculation of transition probabilities in the reference case

We calculated transition probabilities between CD4 count states (<25, 25-49, 50-99, 100-149, 150-199, 200-249, 250-299, 300-349, >350) by calculating the Nelson-Aalen hazard function defining a "failure" as

progression to a lower state and separately defining "failure" as a transition to a higher state. We used the four week hazard function and divided by four to arrive at the one week parameter.

Calculation of variability

Since a simple binomial distribution would underestimate the true variability in CD4 transition probabilities across individuals, we estimated the variability in these transition parameters by first performing a linear regression of the instantaneous hazard of transition against the midpoint CD4 cell count in each stratum, excluding the >350 cells/mm^3 stratum and weighted by the number of observations in each stratum. This regression generated an equation for the decline in CD4 count as a function of CD4 count. Second, we constructed a symmetric beta distribution (shape parameter [alpha] pre-specified at 4) around the slope of this regressed line (i.e., predicted change in CD4 count per week, as a function of existing CD4 count), with an upper bound that would provide the probabilities of upward transition seen in our actual data. We chose a beta distribution, rather than a normal distribution, to provide replicability of our transition probabilities while avoiding the potential for unrealistic scenarios (e.g., a CD4 decline of 60 cells/week in a patient with a CD4 count of 55). Third, we took random draws from this beta distribution using Monte Carlo simulation and estimated the probability of transition as (change in CD4 count)/(width of CD4 interval). Thus, a patient with a week-to-week change in CD4 count of 3 cells/mm^3 in a stratum of width 50 cells/mm^3 (e.g., 201-250 cells/mm^3) would have a probability of downward transition of (3/50) = 6%. By simulating thousands of patients until results converged, we were able to estimate the degree of variability in our transition probabilities.

Comparison with the literature

Using our equation for the CD4 count slope, for a CD4 count of 75, the expected slope is -71 cells/mm^3/year. We compared this slope to values reported in the literature (Table B-2 in the Appendix).

Weekly probability of death, pre-ART

Description of cohort from which pre-ART mortality probabilities were calculated

We used patient level data from a community-based HIV management program operated through free-of-charge care provided by general practitioners in three provinces of South Africa. Inclusion criteria were ART-naïve and known date of first CD4 count enumeration in the clinic. We supplemented data from this cohort with a linkage to the South African Department of Home Affairs vital statistics registry to identify unreported deaths. We had national ID numbers for 65% patients allowing for linkage. To reduce bias and underestimated of mortality, we used inverse probability weighting to estimate mortality for those patients who were both lost from care and lacked a valid ID number.

Calculation of transition (mortality) probabilities in the reference case

We used survival time analysis with entry into observation on the date of the first CD4 assay and exit at the date of death with censoring one month prior to the linkage with the vital statistics register or ART initiation. As we were able to ascertain our outcome of interest, death, through means beyond clinic

follow-up, we did not censor patients who were lost from care. We calculated the Nelson-Aalen mortality hazard function by CD4 state using time-updated CD4 count values for the six month period and divided by 26 to obtain a weekly hazard of mortality. We did this after evaluating the mortality hazard by 4 week intervals and not observing a difference over the six month period.

Calculation of variability

We used a beta distribution around the calculated weekly mortality hazard and the standard deviation of the mortality hazard for probabilistic sampling using Monte Carlo simulations.

Comparison with the literature

We simulated mortality, by CD4 state, for 52 weeks without ART to provide pre-ART mortality. We converted raw mortality by week to mortality by 100 person-years for easier comparability with the published literature (Table 2, manuscript).

Weekly probability of death, after initiating ART

Description of cohort from which on-ART mortality probabilities were calculated

We used patient level data from a community-based HIV management program operated through free-of-charge care provided by general practitioners in three provinces of South Africa and a multi-site workplace program. Both programs used similar management algorithms and shared common data collection forms and a relational database. Inclusion criteria were ART-naïve, WHO clinic stage <4, and age ≥18 years old. We supplemented data from this cohort with a linkage to the South African Department of Home Affairs vital statistics registry to identify unreported deaths. We had national ID numbers for 80% of patients allowing for linkage. To reduce bias and underestimation of mortality, we used inverse probability weighting to estimate mortality for those patients who were both lost from care and lacked a valid ID number.

Calculation of mortality probabilities

We used survival time analysis with entry into observation on the date of ART initiation and exit at the date of death with censoring one month prior to vital statistics linkage closure. We calculated the Nelson-Aalen mortality hazard function by CD4 state using time-updated CD4 count values. We used four week probabilities to generate an exponential equation to describe the mortality hazard from the time of ART initiation to 52 weeks on ART. We then calculated the mortality for the midpoint of each one-week interval to generate mortality probabilities.

Calculation of variability in mortality probability

We used a Normal distribution around the calculated weekly mortality hazard and the standard deviation of the mortality hazard for probabilistic sampling during Monte Carlo simulations.

Comparison with the literature

We simulated mortality, by CD4 state, for 52 weeks on ART to provide on-ART mortality. We converted raw mortality by week to mortality by 100 person-years for easier comparability with the published literature (Table 2, manuscript).

Appendix B: CD4 state transitions parameters and CD4 slope

Table B1: CD4 transition probabilities

Starting CD4 state	Probability of transition per week		
	Down 1 state*	No change	Up 1 state*
<25	0	0.998	0.0012
25-49	0.0447	0.941	0.0136
50-99	0.0203	0.972	0.00667
100-149	0.0202	0.973	0.00662
150-199	0.0189	0.974	0.00675
200-249	0.0171	0.976	0.00631
250-299	0.0145	0.979	0.00596
300-349	0.0152	0.978	0.00612
≥350	0.0099	0.99	0

* The mean of the standard deviations for each of the downward transition probabilities was: 0.0055 and for the upward probabilities was 0.0013.

Linear regression CD4 count slope equation: CD4 count slope: y = 1.486 – 0.0016 * CD4 count + e

Table B-2: Comparison of studies of CD4 slope among ART-naïve individuals

STUDY	POPULATION	Modifying parameter	CD4 decline, cells/mm^3/yr (95% CI)
This study	**South African Miners clinical trial of TB prevention**	**CD4: 75**	**-71 (-79, -63)**
Mellors et al Ann Int Med 1997	US MACS	VL: 10,000-30,000	-64 (-70.0, -59.6)
		VL: >30,000	-76.5 (-70.5, -82.9)
Kiwanuka et al. JAIDS 2010	Uganda		-34.5 (-47, -22)
Mussini et al. AIDS 2011	US Cohort	2-8 years from ART initiation	-39.3 (-44.3, -34.3)
		<2 years from ART initiation	-96.6 (-100.9, -92.6)
Holmes et al. JAIDS 2006	South Africa Clinical cohort (10% received AZT and 31% died during f/u)	CD4 >500	-47.1 (-54, -40)
		351-500	-30.6 (-37, -23)
		201-350	-20.5 (-13.7, -27)
Ding et al. JAIDS 2009	India, Clinical cohort		-97.1 (+/- 11.4)

Appendix C: Pre-ART Mortality Parameters

Table C1: Pre-ART Mortality Transition Probabilities by current CD4 count

	<25	25-49	50-99	100-149	150-199	200-249	250-299	300-349	≥350
Mortality Probability, per week	0.014	0.01	0.00482	0.00346	0.00249	0.00179	0.00128	0.000924	0.000664
Standard Deviation	0.002	0.002	0.002	0.001	0.001	0.001	0.001	0.001	0.0001

Appendix D: On-ART Mortality Parameters

Table D1: On-ART Mortality Transition Probabilities by weeks from ART initiation and CD4 count at ART initiation

Weeks from ART initia-tion	<25	25-49	50-99	100-149	150-199	200-249	250-299	300-349	≥350
1	0.0101	0.0067	0.0049	0.0035	0.0025	0.0017	.0013	0.0009	0.0007
2	0.0098	0.0066	0.0047	0.0034	0.0024	0.0017	0.0012	0.0009	0.0007
3	0.0095	0.0064	0.0046	0.0033	0.0024	0.0016	0.0012	0.0008	0.0007
4	0.0092	0.0062	0.0045	0.0032	0.0023	0.0016	0.0012	0.0008	0.0007
5	0.0089	0.0061	0.0044	0.0031	0.0022	0.0016	0.0011	0.0008	0.0006
6	0.0087	0.0059	0.0043	0.0030	0.0022	0.0015	0.0011	0.0008	0.0006
7	0.0084	0.0058	0.0041	0.0029	0.0021	0.0015	0.0011	0.0008	0.0006
8	0.0082	0.0056	0.0040	0.0029	0.0020	0.0014	0.0010	0.0008	0.0006
9	0.0080	0.0055	0.0039	0.0028	0.0020	0.0014	0.0010	0.0007	0.0006
10	0.0077	0.0053	0.0038	0.0027	0.0019	0.0013	0.0010	0.0007	0.0006
11	0.0075	0.0052	0.0037	0.0026	0.0019	0.0013	0.0009	0.0007	0.0006
12	0.0073	0.0051	0.0036	0.0025	0.0018	0.0013	0.0009	0.0007	0.0006
13	0.0071	0.0049	0.0035	0.0025	0.0017	0.0012	0.0009	0.0007	0.0006
14	0.0069	0.0048	0.0034	0.0024	0.0017	0.0012	0.0009	0.0007	0.0006
15	0.0067	0.0047	0.0033	0.0023	0.0016	0.0011	0.0008	0.0006	0.0006
16	0.0065	0.0046	0.0033	0.0023	0.0016	0.0011	0.0008	0.0006	0.0005
17	0.0063	0.0044	0.0032	0.0022	0.0015	0.0011	0.0008	0.0006	0.0005
18	0.0061	0.0043	0.0031	0.0021	0.0015	0.0010	0.0008	0.0006	0.0005
19	0.0060	0.0042	0.0030	0.0021	0.0014	0.0010	0.0007	0.0006	0.0005
20	0.0058	0.0041	0.0029	0.0020	0.0014	0.0010	0.0007	0.0006	0.0005
21	0.0056	0.0040	0.0028	0.0020	0.0014	0.0010	0.0007	0.0006	0.0005
22	0.0055	0.0039	0.0028	0.0019	0.0013	0.0009	0.0007	0.0006	0.0005
23	0.0053	0.0038	0.0027	0.0018	0.0013	0.0009	0.0007	0.0005	0.0005
24	0.0051	0.0037	0.0026	0.0018	0.0012	0.0009	0.0006	0.0005	0.0005
25	0.0050	0.0036	0.0025	0.0017	0.0012	0.0009	0.0006	0.0005	0.0005
26	0.0049	0.0035	0.0025	0.0017	0.0012	0.0008	0.0006	0.0005	0.0005
27	0.0047	0.0034	0.0024	0.0016	0.0011	0.0008	0.0006	0.0005	0.0005
28	0.0046	0.0033	0.0024	0.0016	0.0011	0.0008	0.0006	0.0005	0.0004
29	0.0045	0.0033	0.0023	0.0016	0.0011	0.0008	0.0006	0.0005	0.0004
30	0.0043	0.0032	0.0022	0.0015	0.0010	0.0007	0.0005	0.0005	0.0004
31	0.0042	0.0031	0.0022	0.0015	0.0010	0.0007	0.0005	0.0005	0.0004

32	0.0041	0.0030	0.0021	0.0014	0.0010	0.0007	0.0005	0.0004	0.0004
33	0.0040	0.0029	0.0021	0.0014	0.0009	0.0007	0.0005	0.0004	0.0004
34	0.0038	0.0029	0.0020	0.0013	0.0009	0.0006	0.0005	0.0004	0.0004
35	0.0037	0.0028	0.0019	0.0013	0.0009	0.0006	0.0005	0.0004	0.0004
36	0.0036	0.0027	0.0019	0.0013	0.0009	0.0006	0.0005	0.0004	0.0004
37	0.0035	0.0026	0.0018	0.0012	0.0008	0.0006	0.0004	0.0004	0.0004
38	0.0034	0.0026	0.0018	0.0012	0.0008	0.0006	0.0004	0.0004	0.0004
39	0.0033	0.0025	0.0017	0.0012	0.0008	0.0006	0.0004	0.0004	0.0004
40	0.0032	0.0024	0.0017	0.0011	0.0008	0.0005	0.0004	0.0004	0.0004
41	0.0031	0.0024	0.0017	0.0011	0.0007	0.0005	0.0004	0.0004	0.0004
42	0.0031	0.0023	0.0016	0.0011	0.0007	0.0005	0.0004	0.0004	0.0004
43	0.0030	0.0023	0.0016	0.0010	0.0007	0.0005	0.0004	0.0003	0.0004
44	0.0029	0.0022	0.0015	0.0010	0.0007	0.0005	0.0004	0.0003	0.0003
45	0.0028	0.0021	0.0015	0.0010	0.0006	0.0005	0.0004	0.0003	0.0003
46	0.0027	0.0021	0.0014	0.0009	0.0006	0.0005	0.0003	0.0003	0.0003
47	0.0026	0.0020	0.0014	0.0009	0.0006	0.0004	0.0003	0.0003	0.0003
48	0.0026	0.0020	0.0014	0.0009	0.0006	0.0004	0.0003	0.0003	0.0003
49	0.0025	0.0019	0.0013	0.0009	0.0006	0.0004	0.0003	0.0003	0.0003
50	0.0024	0.0019	0.0013	0.0008	0.0006	0.0004	0.0003	0.0003	0.0003
51	0.0023	0.0018	0.0013	0.0008	0.0005	0.0004	0.0003	0.0003	0.0003
52	0.0023	0.0018	0.0012	0.0008	0.0005	0.0004	0.0003	0.0003	0.0003

Appendix E: Whole cohort analysis with lognormal distribution around ART delay

The table (Table E1) represents results of whole cohort simulations when using a distribution around the delay duration. We used a lognormal distribution with the mean the "delay" and the median 25% lower than the mean. This distribution provides a long tail of delay in ART initiation.

Table E1: Mortality by ART delay using a beta distribution around the duration of the delay

Weeks to ART	0	6	10	26	52
Total mortality	11 (7.4, 15)	13 (8.8, 17)	14 (10. 18)	18 (14, 21)	22 (19, 26)
Excess mortality	0	1.5 (-4.1, 7.1)	2.6 (-2.9, 8.1)	6.5 (1.3, 12)	11 (5.7, 16)