Web Appendix: Technical details

Overview

We estimate the cumulative mortality risk under the observed treatment history (i.e., the "no intervention") and each of the dynamic treatment plans using a Monte Carlo simulation of 50,000 patients sampled from the study sample randomly with replacement at baseline. The densities of covariates measured at baseline were estimated using their empirical distributions in the sampled data, and the densities of time-varying covariates were modeled using parametric regression models in the observed data. The values of these covariates under each dynamic treatment plan were imputed using a draw from a density estimated by the regression models after assigning treatment according to the designated treatment plan in the Monte Carlo sample. The probability of mortality was estimated for each patient in each person-month using a parametric regression model with treatment assignment and covariate history set to what it would have been under the given dynamic treatment plan.

Details

Let patients be indexed from $i = 1, \ldots 3532$, A represent treatment, $\boldsymbol{Z}$ represent a vector of covariates including CD4 cell count, viral load, and baseline covariates, C represent censoring, and Y represent death. Adapting the notation of Young [5], we write the cumulative incidence at time $k+1$ under dynamic treatment regime g using the g-formula:

Equation 1:

$$P\left(Y_{k+1}^{g}=1\right)=\sum_{z_k}\sum_{j=0}^{k}P\left[Y_{j+1}=1\middle|Z_j=z_j,\bar{A}_j=\bar{a}_j,Y_j=C_{j+1}=0\right]\times\prod_{s=0}^{j}P(Y_s=0|Z_{s-1}=z_{s-1},\bar{A}_{s-1}=\bar{a}_{s-1},Y_{s-1}=C_s=0)\times f(z_s|z_{s-1},\bar{a}_{s-1},Y_{s-1}=C_s=0)\times P^{g}(A_s|z_s,a_{s-1},Y_{s-1}=C_s=0)$$

To estimate the cumulative incidence under regime g from the observed data, we follow the steps below:

1. Fit parametric models for component of the density in the observed data.
   a. Fit a logistic model to estimate whether patient *i* has a detectable viral load at time *s.*

$$logit[P\left(dvl_{i,s}=1\right)]=\alpha_0+\boldsymbol{\alpha_1}\boldsymbol{L}_i^T+\alpha_2 dvl_{i,s-1}+\alpha_3 g\left(vl_{i,s-1}\right)+\alpha_4 g\left(cd4_{i,s-1}\right)+\alpha_5 A+\alpha_6 A\times g(age\ group)+\alpha_7 g(s)$$

   Where $\boldsymbol{L}$ is a vector of time-fixed covariates, including sex, race, ethnicity, injection drug use, MSM status, age at baseline, year of study entry, CD4 at study entry, viral load at study entry, the product of year and age at study entry.

   b. Fit linear regression models to estimate viral load at time s among patients who had a detectable viral load at time s.

$$VL_{i,s}=\alpha_0+\boldsymbol{\alpha_1}\boldsymbol{L_i^T}+\alpha_2 dvl_{i,s-1}+\alpha_3 g\left(vl_{i,s-1}\right)+\alpha_4 g\left(cd4_{i,s-1}\right)+\alpha_5 A+\alpha_6 A\times g(age\ group)+\alpha_7 g(s)+\epsilon_i,\qquad \epsilon\sim N(0,\sigma)$$

   c. Fit linear regression models to estimate CD4 cell count at time s stratified by treatment at time $s-1$:

$$CD4_{i,s}=\alpha_0+\boldsymbol{\alpha_1}L_i^T+\alpha_2 dvl_{i,s-1}+\alpha_3 dvl_{i,s}+\alpha_4 g\left(vl_{i,s}\right)+\alpha_5 g\left(vl_{i,s-1}\right)+\alpha_6 g\left(cd4_{i,s-1}\right)+\alpha_7 g(s)+\alpha_8 g(age\ group_i)+\epsilon_i,\qquad \epsilon\sim N(0,\sigma)$$

   d. Fit a logistic regression model to estimate the probability of being treated at time *s.*

$$logit\left[P\left(A_{i,s}=1\right)\right]=\alpha_0+\boldsymbol{\alpha_1}L_i^T+\alpha_2 dvl_{i,s}+\alpha_3 dvl_{i,s-1}+\alpha_4 g\left(vl_{i,s}\right)+\alpha_5 g\left(cd4_{i,s}\right)+\alpha_8 g(s)$$

e. Fit a logistic regression model to estimate the probability of death at time *s*.

$$logit\left[P\left(Y_{i,s}=1\right)\right] = \alpha_0 + \boldsymbol{\alpha_1} L_i^T + \alpha_2 dvl_{i,s} + \alpha_3 dvl_{i,s-1} + \alpha_4 g\left(vl_{i,s}\right) + \alpha_5 g\left(cd4_{i,s}\right) + \alpha_6 A + \alpha_7 A \times g(age\ group) + \alpha_8 g(s)$$

In all models, continuous variables were modeled using restricted quadratic splines [18], and categorical variables were modeled using indicator variables. Age groups were defined as in the main text (18 – 34, 35 – 44, 45 – 60). Point estimates were nearly identical when models a through e were stratified by age group rather than merely including interaction terms between age group and treatment.

2. Draw a large (N = 50,000) Monte Carlo sample from the observed patients at baseline with replacement.
3. In the Monte Carlo sample, estimate the cumulative incidence under no intervention (as a check on the fit of the parametric models) and each dynamic treatment plan using the g-formula provided in equation 1.
    a. The distribution of $\boldsymbol{L}$ in the large Monte Carlo sample approximates the distribution of $\boldsymbol{L}$ in the observed data.
    b. Estimate CD4 cell count, whether or not viral load is detectable, and viral load for participant i at time s using the coefficients from models a through c above.
    c. Set treatment according to the treatment regime of interest. The value of $A_{i,s}$ drawn from a Bernoulli distribution with probability given below. Specifically, if *x* represents the CD4 cell count threshold for treatment initiation,

$$P^g\left(A_{i,s}=1\right) = \begin{cases} 0 & CD4_{i,s} > x \\ expit\left(\alpha_0 + \boldsymbol{\alpha_1} L_i^T + \alpha_2 dvl_{i,s} + \alpha_3 dvl_{i,s-1} + \alpha_4 g\left(vl_{i,s}\right) + \alpha_5 g\left(cd4_{i,s}\right) + \alpha_8 g(s)\right) & CD4_{i,s} < x, m < 6 \\ 1 & \left(CD4_{i,s} < x\ , m \geq 6\right) \text{ or } A_{i,s-1} = 1 \end{cases}$$

    Where *m* is the number of months that CD4 cell count has been below *x*.

    d. Set $P(C=0) = 1\ \forall\ i,s$
4. Perform steps 1 through 4 in 500 bootstrap samples. The standard deviation of the 500 estimates can be used as the standard error of the point estimate.

Supplementary Table 1: 10-year cumulative incidence of mortality under no intervention and 7 dynamic treatment plans with a 6 month grace period among 3532 patients who entered care at between January 1, 1998 and December 31, 2013 at 8 US clinical sites, followed for death up to 10 years

Treatment plan	Mortality	Risk ratio	Risk difference
No intervention	12.60		
500	10.80	1	0
450	10.81	1.00	0.02
400	11.25	1.04	0.45
350	11.66	1.08	0.87
300	11.93	1.11	1.14
250	12.70	1.18	1.90
200	13.51	1.25	2.71
18 to 34			
500	6.11	1	0
450	5.77	0.95	-0.34
400	6.12	1.00	0.01
350	6.08	1.00	-0.03
300	6.34	1.04	0.23
250	6.69	1.10	0.58
200	6.25	1.02	0.14
35 to 45			
500	11.43	1	0
450	11.94	1.04	0.51
400	11.95	1.05	0.52
350	12.42	1.09	0.99
300	12.14	1.06	0.71
250	12.94	1.13	1.50
200	13.59	1.19	2.15
45 to 65			
500	19.29	1	0
450	18.89	0.98	-0.40
400	20.06	1.04	0.77
350	21.60	1.12	2.30
300	22.84	1.18	3.54
250	24.33	1.26	5.04
200	28.07	1.45	8.78

Supplementary Table 2: 10-year cumulative incidence of mortality under no intervention and 7 dynamic treatment plans with no grace period among 3532 patients who entered care at between January 1, 1998 and December 31, 2013 at 8 US clinical sites, followed for death up to 10 years

Treatment plan	Mortality	Risk ratio	Risk difference
No intervention	12.60		
500	10.34	1	0
450	10.49	1.02	0.16
400	10.65	1.03	0.31
350	11.12	1.08	0.78
300	11.28	1.09	0.95
250	11.69	1.13	1.35
200	12.50	1.21	2.16
18 to 34			
500	5.65	1	0
450	5.91	1.05	0.26
400	5.73	1.01	0.08
350	5.85	1.04	0.20
300	5.72	1.01	0.07
250	6.02	1.06	0.36
200	6.19	1.10	0.54
35 to 45			
500	11.47	1	0
450	11.33	0.99	-0.14
400	10.94	0.95	-0.52
350	11.87	1.04	0.41
300	11.73	1.02	0.27
250	11.78	1.03	0.32
200	12.85	1.12	1.38
45 to 65			
500	17.75	1	0
450	18.06	1.02	0.31
400	19.98	1.13	2.23
350	20.28	1.14	2.53
300	21.71	1.22	3.96
250	22.89	1.29	5.14
200	24.72	1.39	6.97

Supplemental table 3. Standardized 10-year cumulative incidence of mortality under no intervention and 3 dynamic treatment plans with a 6-month grace period among 3372 patients who entered care at between January 1, 1998 and December 31, 2013 at 8 US clinical sites *with no prior AIDS diagnosis*, followed for death up to 10 years

Treatment plan	Mortality	Risk ratio	Risk difference
No intervention	12.47		
All ages			
500 cells/mm^3	10.10	1	0
350 cells/mm^3	11.33	1.12	1.23
200 cells/mm^3	13.45	1.33	3.35
18 to 34			
500 cells/mm^3	5.52	1	0
350 cells/mm^3	5.76	1.04	0.24
200 cells/mm^3	6.49	1.18	0.98
35 to 45			
500 cells/mm^3	10.86	1	0
350 cells/mm^3	12.13	1.12	1.27
200 cells/mm^3	13.94	1.28	3.09
45 to 65			
500 cells/mm^3	18.35	1	0
350 cells/mm^3	21.54	1.17	3.19
200 cells/mm^3	27.17	1.48	8.81

Supplemental table 4. Standardized 10-year cumulative incidence of mortality under no intervention and 3 dynamic treatment plans with a 6-month grace period among 3390 patients who entered care at between January 1, 1998 and December 31, 2013 at 8 US clinical sites *with no prior mono or dual therapy use*, followed for death up to 10 years

Treatment plan	Mortality	Risk ratio	Risk difference
No intervention	13.56		
All ages			
500 cells/mm^3	10.92	1	0
350 cells/mm^3	12.37	1.13	1.45
200 cells/mm^3	14.18	1.30	3.26
18 to 34			
500 cells/mm^3	6.31	1	0
350 cells/mm^3	6.55	1.04	0.23
200 cells/mm^3	7.03	1.11	0.72
35 to 45			
500 cells/mm^3	11.62	1	0
350 cells/mm^3	13.42	1.15	1.80
200 cells/mm^3	14.44	1.24	2.81
45 to 65			
500 cells/mm^3	19.18	1	0
350 cells/mm^3	20.79	1.17	3.26
200 cells/mm^3	28.84	1.50	9.66

Supplemental table 5. Standardized 5-year cumulative incidence of mortality under no intervention and 3 dynamic treatment plans with a 6-month grace period among 3390 patients who entered care at between January 1, 1998 and December 31, 2013 at 8 US clinical *sites with censoring after the first 6 and 18 month gaps in care*, followed for death up to 10 years

	Censor after 6 month gap in care [a]			Censor after 18 month gap in care [b]		
Treatment plan	Mortality	Risk ratio	Risk difference	Mortality	Risk ratio	Risk difference
All ages						
500 cells/mm^3	5.27	1	0	5.19	1	0
350 cells/mm^3	5.64	1.10	0.36	5.62	1.08	0.43
200 cells/mm^3	5.79	1.10	0.51	6.07	1.17	0.88
18 to 34						
500 cells/mm^3	1.97	1	0	2.20	1	0
350 cells/mm^3	1.89	0.96	-0.08	2.29	1.04	0.09
200 cells/mm^3	2.10	1.10	0.14	2.28	1.04	0.08
35 to 45						
500 cells/mm^3	4.37	1	0	5.65	1	0
350 cells/mm^3	4.87	1.11	0.49	6.00	1.06	0.35
200 cells/mm^3	4.38	1.00	0.01	6.50	1.15	0.86
45 to 65						
500 cells/mm^3	12.94	1	0	9.88	1	0
350 cells/mm^3	14.08	1.09	1.14	11.21	1.13	1.32
200 cells/mm^3	15.13	1.17	2.19	12.46	1.26	2.58

[a] When censoring was performed after a 6 month gap in care, 82% of the patients were censored by 10 years after study entry (likely due to the more common acceptance of longer visit intervals).

[b] When censoring was performed after an 18 month gap in care, 47% of patients were censored by 10 years after study entry.

Note that mortality estimates, risk ratios, and risk differences in this table are reported for 5-year mortality rather than 10 –year mortality as data became sparse when patients were censored after a 6 month gap in care

Supplemental table 6. Percentage of patients who initiated therapy in each CD4 cell count category and median CD4 cell count at therapy initiation by year of study entry among eligible patients *who initiated antiretroviral therapy during the study period* in CNICS.

Year at study entry	n	Category	Percentage in each category	Median CD4 cell count at therapy initiation
1998	88			566
		Under 200	9.09	
		Between 200 and 350	10.23	
		Between 350 and 500	12.50	
1999	96			513
		CD4 under 200	4.17	
		CD4 between 200 and 350	16.67	
		CD4 between 350 and 500	26.04	
2000	83			496
		Under 200	12.05	
		Between 200 and 350	24.10	
		Between 350 and 500	14.46	
2001	103			407
		Under 200	10.68	
		Between 200 and 350	28.16	
		Between 350 and 500	27.18	
2002	80			397
		Under 200	17.50	
		Between 200 and 350	25.00	
		Between 350 and 500	18.75	
2003	113			409
		Under 200	11.50	
		Between 200 and 350	29.20	
		Between 350 and 500	21.24	
2004	91			394
		Under 200	8.79	
		Between 200 and 350	30.77	
		Between 350 and 500	25.27	
2005	104			373
		Under 200	5.77	
		Between 200 and 350	34.62	
		Between 350 and 500	27.88	
2006	111			442
		Under 200	5.41	
		Between 200 and 350	22.52	
		Between 350 and 500	29.73	
2007	131			486

		Under 200	5.34	
		Between 200 and 350	15.27	
		Between 350 and 500	34.35	
2008	150			528
		Under 200	4.00	
		Between 200 and 350	14.00	
		Between 350 and 500	26.67	
2009	157			552
		Under 200	0.64	
		Between 200 and 350	12.74	
		Between 350 and 500	21.66	
2010	177			594
		Under 200	1.13	
		Between 200 and 350	3.39	
		Between 350 and 500	18.08	
2011	143			610
		Under 200	0.00	
		Between 200 and 350	4.90	
		Between 350 and 500	13.29	
2012	148			641
		Under 200	0.00	
		Between 200 and 350	2.03	
		Between 350 and 500	5.41	
2013	43			667
		Under 200	0.00	
		Between 200 and 350	0.00	
		Between 350 and 500	2.33	

Supplemental table 7. Number and percentage of patients initiating 4 classes of antiretroviral therapy regimens by age group at study entry in CNICS between 1998 and 2013.

Regimen	Ages 18 – 34		Ages 35 – 44		Ages 45 – 65	
	n	%	n	%	n	%
Did not start therapy	776	47	538	47	323	44
Integrase inhibitors	39	2	46	4	36	5
Non-nucleoside reverse transcriptase inhibitors	514	31	316	27	218	30
Protease inhibitors	284	17	225	19	134	18
Nucleoside reverse transcriptase inhibitors	22	1	27	2	17	2

Supplemental table 8. Number and proportion of patients lost to follow-up over the 10-year study period by age group

Age group	n	%
Between 18 and 34	970	59
Between 35 and 44	637	55
Between 45 and 65	304	41

Supplemental table 9. Standardized 10-year cumulative incidence of mortality under no intervention and 3 dynamic treatment plans with a 6-month grace period among 3532 patients who entered care at between January 1, 1998 and December 31, 2013 at 8 US clinical sites *stratified by year at study entry*, followed for death up to 10 years.

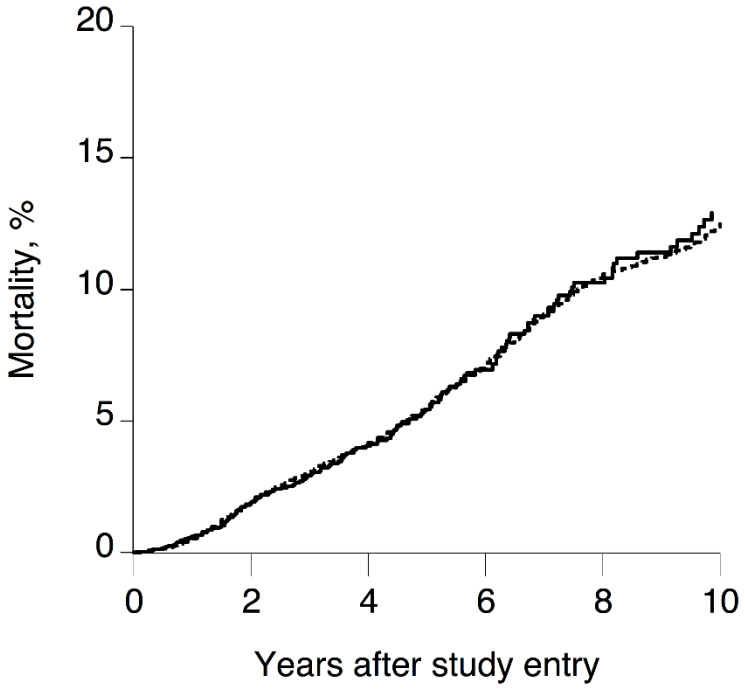
Treatment plan	Mortality	Risk ratio	Risk difference
No intervention	12.60		
All years			
500 cells/mm^3	10.80	1	0
350 cells/mm^3	11.66	1.08	0.87
200 cells/mm^3	13.51	1.25	2.71
1998 – 2002			
500 cells/mm^3	12.75	1	0
350 cells/mm^3	13.32	1.05	0.57
200 cells/mm^3	15.42	1.21	2.67
2003 - 2007			
500 cells/mm^3	11.55	1	0
350 cells/mm^3	13.23	1.15	1.68
200 cells/mm^3	14.24	1.23	2.69
2008 to 2013			
500 cells/mm^3	6.02	1	0
350 cells/mm^3	6.60	1.10	0.58
200 cells/mm^3	9.42	1.56	3.40

Supplemental table 10. Crude 5-year cumulative incidence of mortality by age and CD4 cell count at therapy initiation 1811 patients who initiated therapy at between January 1, 1998 and December 31, 2013 at 8 US clinical sites, followed from therapy initiation to death up to 5 years [a].

Age group	CD4 cell count at ART	5-year mortality	Risk ratio	Risk difference
18 – 34	0 – 200	6.9%	3.7	5.1
	201 – 350	5.2%	2.8	2.7
	351 – 500	4.6%	2.5	3.3
	>500	1.8%	1	0
35 – 44	0 – 200	17.5%	2.1	9.4
	201 – 350	6.0%	0.7	-2.2
	351 – 500	5.9%	0.7	-2.3
	>500	8.2%	1	0
45 – 65	0 – 200	24.1%	5.8	20.0
	201 – 350	8.9%	2.1	4.7
	351 – 500	12.2%	2.9	8.1
	>500	4.2%	1	0

[a] These crude results may be subject to lead time bias in addition to confounding.

Supplementary figure 1: Observed cumulative incidence of mortality (solid line) and cumulative incidence of mortality estimated under no intervention (dashed line) among 3532 patients who entered care at between January 1, 1998 and December 31, 2013 at 8 US clinical sites with a CD4 cell count over 500 cells/mm^3, followed for death up to 10 years



Supplementary figure 2. Cumulative incidence of combination antiretroviral therapy initiation by time since enrollment in CNICS among patients with HIV between 1998 and 2013