Web Material

The Population Impact of Late Presentation with Advanced HIV Disease and Delayed Antiretroviral Therapy in Adults Receiving HIV Care in Latin America

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Web Appendix 1. Impact of Late Presentation to care (LP), delaying ART initiation among non-LP until development of an AIDS-related event or CD4 decrease to <350cells/mm^3 (LI), and not initiating ART among LP (NI).

Antiretroviral therapy (ART) initiation with advanced HIV-infection is common in Latin America. We assessed the impact that enrolling in care, and initiating ART with advanced stages of HIV-disease, and no-ART initiation (NI) have on mortality of people living with HIV (PLWHIV) receiving medical care in six sites participating in the Caribbean, Central and South American Network for HIV Epidemiology (CCASAnet) cohort. To achieve our aim, we estimated the Attributable Risk (AR) and Population Attributable Fraction (PAF) for all-cause mortality of presentation to care and starting ART with advanced HIV-disease, presenting to care and starting ART late (LI), and not initiating treatment (NI).

In this material, supplementary to the main results report, we present intermediate results and results of secondary analysis, where we repeated analysis for the impact of Late Presentation to care (LP), delaying ART initiation among non-LP until development of an AIDS-related event or CD4 decrease to <350cells/mm^3 (LI), and not initiating ART among LP (NI), and sensitivity analysis. We consider these results as not central to the study, but as information contributing to a better understanding of our main results.

METHODS

We estimated the attributable risk (AR) of death for late presentation with advanced HIV-disease regardless of ART initiation (analysis 1), delaying the start of ART in people enrolled in care

without advanced HIV-disease (analysis 2), and not initiating ART in late presenters with advanced HIV-disease (NI) (analysis 3) using the predicted probabilities of death according to exposure derived from the different models described in the main text. We used the predicted probabilities derived from the models in each set of analysis to compute attributable risks of death as

$$\frac{p_1(t) - p_0(t)}{p_1(t)}$$

where $p_1(t)$ is the probability of death in the exposed group (late presentation, LI and NI) and $p_0(t)$ is the probability of death in patients not exposed in each set of analysis (non-late presenters, non-LI and treatment initiators). This is interpreted as the proportion of deaths among late presenters with advanced HIV-disease (to provide an example) that would have been prevented had these patients presented before developing advanced HIV-disease.

The proportion of patient deaths in the population attributable fraction (PAF) was computed as

$$\frac{p_1(t) \times pE + p_0(t) \times (1 - pE) - p_0(t)}{p_1(t) \times pE + p_0(t) \times (1 - pE)}$$

where $p_1(t)$ is the probability of death over time in the exposed group (advanced-LP, LI and NI); pE is the probability of being exposed to any of the conditions of interest (advanced-LP in analysis 1, at delayed ART initiation in analysis 2, and not initiating ART if presenting with advanced-LP in analysis 3).

Each set of analysis was repeated in secondary analysis for: late presentation to care (analysis 1), delaying the start of ART in non-LP (analysis 2), and not initiating ART in LP (analysis 3).

In all analyses, we modelled continuous variables (Age at enrollment, time from enrollment, year of enrollment, most recent CD4, time since most recent CD4 measurement) using restricted cubic splines to avoid the assumption of linearity of associations. To select the number of knots we used in the models, we a priori looked at the number of events in each analysis and decided on a reasonable number of knots based on the degrees of freedom available for the analyses. For the advanced-LP analyses we could afford more knots so we went with 5; the other analyses permitted fewer knots, so 4 were selected. Then, after performing analyses, we investigated the sensitivity of our results to the choice of the number of knots and we performed likelihood ratio tests to confirm that our choices were reasonable (which they were).

RESULTS

When considering the threshold of CD4<350 cells/μL or AIDS, 74% (n=6,884) of patients were LP in contrast to the 56% of patients with advanced HIV-disease used for primary analysis. (Table 1 and Web Figure 1).

Characteristics of LP, LI and NI

Among the 6,844 LP, 93% started ART before developing AIDS or having a CD4<350 cells/μL, similarly to those with advanced-LP (93%). The median time from enrollment to starting ART for LP was 38 days (p25-p75, 13,84).

A total of 2,385 patients (26%) enrolled early in care (non-LP). The median CD4 at enrollment was 507 (p25-p75, 421, 658). They were followed-up by a median of 6.5 (p25-p75, 4.2, 8.5) years. A total of 1,587 (67%) of these patients started ART during follow-up: the median time to

starting ART was 18 months (p25-p75, 7, 36 months). The median CD4 at ART initiation was 332 cells/μL (p25-p75, 258, 422). In this group, 1,001 (63%) started ART late (LI); after a median time from enrollment of 24 months (p25-p75, 13, 41). The median CD4 at ART initiation for LI was 276 (p25-p75, 223, 324), and 12% had an ADE. Of the 798 (5%) patients who did not start ART during follow-up, 673 (84%) never reached advanced stages of disease during follow-up. Among all non-LP, there were a high proportion of LI (42%) and NI (33%). Among all non-LP, 75% started late or not started ART at all; in contrast to the 36% among patients without advanced-LP as defined by the 200 CD4 cells/ul or clinical AIDS definition.

Mortality

There were 68 deaths (2.8%) among the subgroup of 2,385 patients who enrolled early in care: 10 (1.7%) among the 586 patients who started ART before developing AIDS or CD4 decrease to <350cells/mm^3, 33 (3.3%) among the 1,001 patients who delayed starting ART, 9 (1.3%) among the 673 patients who never started ART and were never reported to be in advanced disease stages, and 16 (13%) among the 125 patients who never started ART and developed AIDS or CD4 decrease to <350cells/mm^3.

In Web Figure 2, we show the survival probability over 10 years from enrollment for deferring ART until late initiation (LI) (CD4 <350cells/uL or ADE) and for starting before LI. The hazard of death was 1.53 times higher for those who deferred treatment (95% CI: 0.83, 2.83), and very similar when using the primary definition of advanced disease. These results were fairly robust to the choice of winsorization level for the inverse probability weights: 1.52 (95% CI: 0.78, 2.97)

winsorizing at the 1st and 99th percentiles; 1.58 (95% CI: 0.89, 2.82) winsorizing at the 5th and 95th percentiles. (The primary analyses winsorized at the 2.5th and 97.5th percentiles.)
Among the 6,844 LP, there were 632 deaths (9%). The survival probability at 1, 5, and 10 years for LP and non-LP is shown in Web Figure 3.

Among LP, 6,341 (93%) started ART and 503 (7%) did not start ART. Among the 6,341 who started ART, 514 (8%) died. Among the 503 who did not start ART, 118 (23%) died (Web Figure 1). Among LP, starting ART decreased the hazard of death by 63.2% (95%CI: 49.2, 73.3). These results were insensitive to the choice of the winsorizing level for the stabilized inverse probability weights: 66.2% (95%CI: 52.7, 75.9) winsorizing at the 1st and 99th percentiles, and 57.9% (95%CI: 42.5-69.2) winsorizing at the 5th and 95th percentiles. (The primary analysis winsorized at the 2.5th and 97.5th percentiles). The predicted survival probability for up to 5 years after enrollment for late presenters if they started ART versus if they did not start ART is shown in Web Figure 4.

Potentially averted deaths if LP, LI and NI were eliminated

The attributable risk of mortality due to LP over time, and the PAF in the whole cohort are summarized in Web Table 3. The attributable risks of mortality and PAFs of mortality due to LP in this analysis is very similar to that considering the 200cells/ul in CD4 counts or AIDS threshold to define advanced-LP.

Web Table 1. Comparison of baseline sociodemographic and clinical characteristics between patients who enrolled in care at 6 Clinical Care Centers participating in the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) (2000-2014) at advanced disease stage (CD4<200 or previous AIDS defining events) referred as advanced-LP and those enrolled with CD4≥200 and no history of AIDS defining events (not advanced-LP).

Characteristic	Advanced-LP (n=5,162)	Not advanced-LP (n=4,067)	Combined (n=9,229)	P-value[b]
Age (years)	36 (29, 43)	32 (27, 40)	34 (28, 42)	<0.001
Male, n (%)	3,933 (76%)	3,019 (74%)	6,952 (75%)	0.032
CD4 count (cells/uL)	80 (34, 152)	393 (287, 544)	198 (68, 381)	<0.001
Route of HIV transmission, n (%)				
Heterosexual contact	2,560 (50%)	1,600 (39%)	4,160 (45%)	
Homosexual contact	1,409 (27%)	1,605 (39%)	3,014 (33%)	
IDU	89 (2%)	36 (1%)	125 (1%)	<0.001
Other	546 (11%)	425 (10%)	971 (11%)	
Unknown	558 (11%)	401 (10%)	959 (10%)	
Time in follow-up (years)	4 (1, 7)	4 (2, 7)	4 (1, 7)	0.099
Time to start ART after enrollment (months)	1 (0, 2)	7 (2, 22)	2 (1, 6)	<0.001
Started ART	4,809 (93%)	3,119 (77%)	7,928 (86%)	<0.001
Period of enrollment, n(%)				
2001-2005	1,507 (29%)	911 (22%)	2,418 (26%)	
2006-2010	2,414 (47%)	1,990 (49%)	4,404 (48%)	<0.001
2011-2014	1,241 (24%)	1,166 (29%)	2,407 (26%)	

[a] Continuous variables are reported as medians (interquartile range).
[b] P-values computed using chi-square tests for categorical variables and Wilcoxon rank sum tests for continuous variables.

Web Table 2. Baseline characteristics associated with late presentation with advanced HIV-disease (CD4<200 or AIDS) in patients enrolled in care in 6 HIV-care clinics participating in the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) (2001-2014)

Variable	OR (95% CI)	P-value[b]
Male	1.27 (1.14, 1.41)	<0.001
Age at enrollment [a]		<0.001
20	1	
30	2.53 (2.04, 3.13)	
40	3.41 (2.83, 4.1)	
50	3.98 (3.24, 4.89)	
60	4.41 (3.49, 5.57)	
Site		<0.001
IMTAvH-Peru	1	
FH-Argentina	0.37 (0.32, 0.43)	
FC-Brazil	0.37 (0.33, 0.42)	
FA-Chile	0.33 (0.29, 0.38)	
IHSS/HE-Honduras	1.82 (1.49, 2.22)	
INCMNSZ-Mexico	1.16 (0.97, 1.39)	
Year of enrollment [a]		<0.001
2001	1	
2003	0.86 (0.75, 0.99)	
2005	0.72 (0.58, 0.90)	
2007	0.58 (0.48, 0.71)	
2009	0.56 (0.47, 0.68)	
2011	0.52 (0.43, 0.64)	
2013	0.33 (0.26, 0.42)	

[a] Age and year of enrollment were modelled as continuous variables using splines with 5 knots. The statistics shown in the table are not odds ratios comparing categories, but odds ratios comparing specific age and year of enrollment values with the reference value based on the fitted logistic regression model. Details in Shepherd BE, Rebeiro PF. Assessing and interpreting the association between continuous covariates and outcomes in observational studies of HIV using splines. *JAIDS* 2017; 74: e60-e63. (ref. 20)

[b] p-values based on likelihood ratio tests from the logistic regression model.

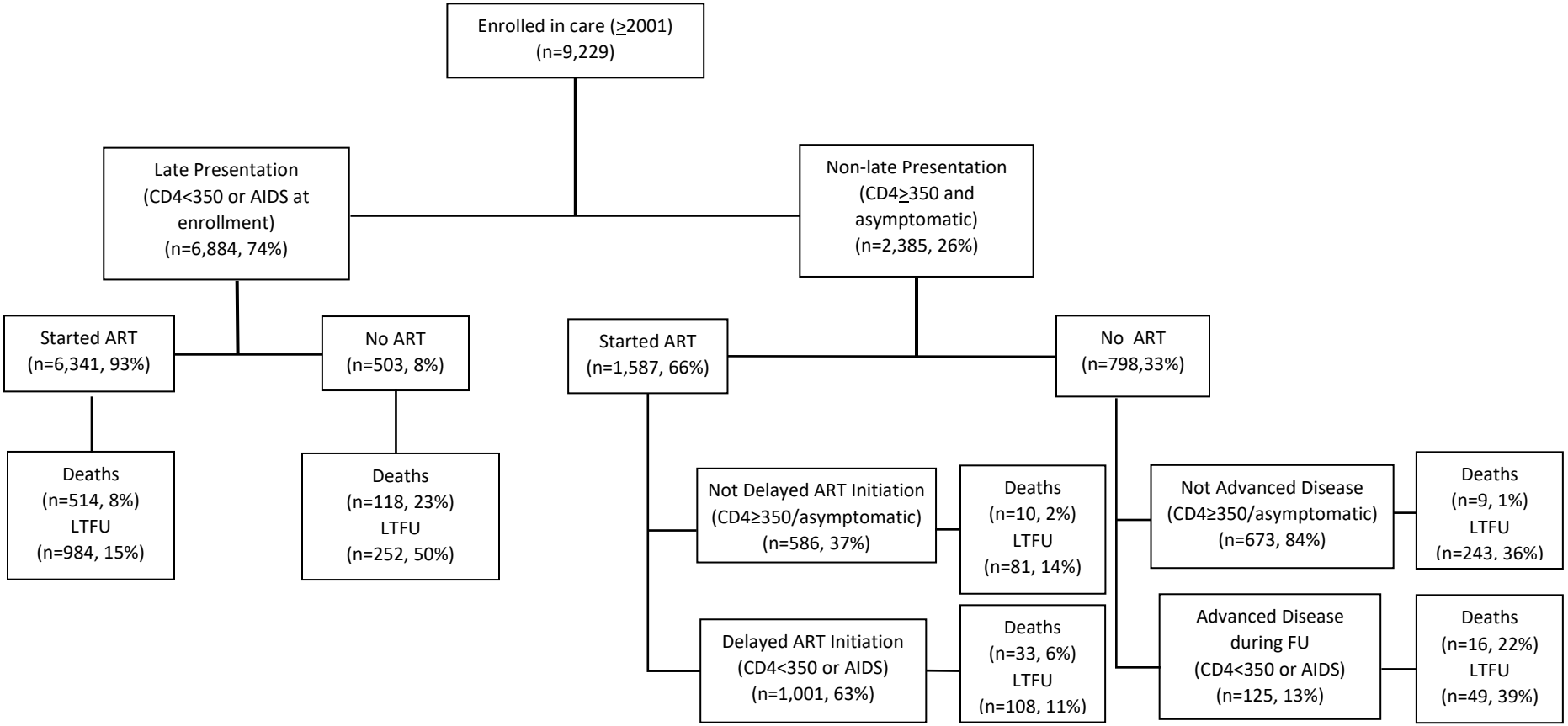
Web Table 3. Attributable deaths and Attributable Population Fraction of deaths due to Late Presentation [a] (LP), delayed antiretroviral initiation [a] (ART) among non-LP (LI), and not initiating ART among LP (NI) at one, five and ten years after enrollment in care in six clinical care centers in Latin America (2001-2014)

	Attributable deaths Proportion (95% CI)			**Population Attributable Fraction** Proportion (95% CI)		
Time after enrollment	**LP**	**LI among non-LP**	**NI among LP**	**LP**	**LI among non-LP**	**NI among LP**
One year	0.86 (0.76, 0.97)	0.46 (-0.47, 0.82)	0.63 (0.6, 0.85)	0.83 (0.70, 0.95)	0.31 (-0.2, 0.71)	0.14 (0.16, 0.35)
Five years	0.65 (0.54, 0.76)	0.35 (-0.08, 0.64)	0.58 (0.52, 0.80)	0.58 (0.46, 0.69)	0.27 (-0.05, 0.55)	0.03 (0.02, 0.08)
Ten years	0.52 (0.36, 0.68)	0.3 (-0.32, 0.7)	NA [b]	0.44 (0.28, 0.60)	0.24 (-0.24, 0.64)	NA [b]

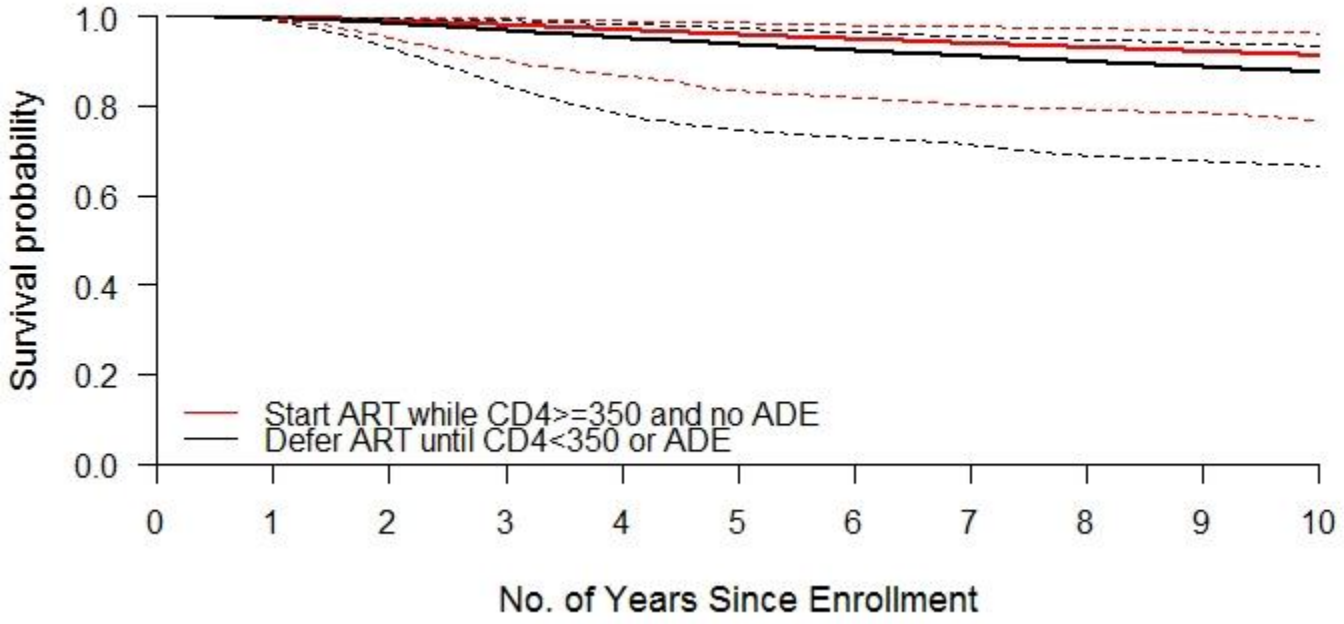
[a] CD4< 350 or AIDS at enrollment or at treatment initiation

[b] Not Applicable. Not estimated because most LP not initiating ART did not reached 10 years of follow-up

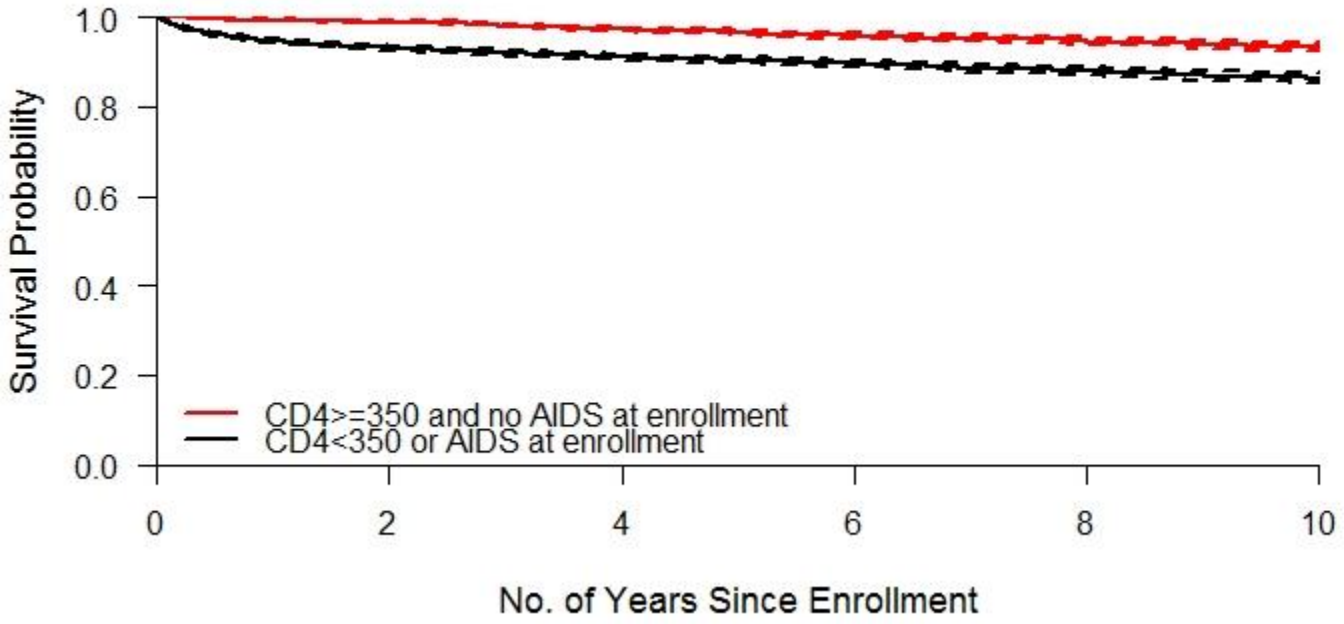
Web Figure 1. Distribution and cumulative mortality of people living with HIV enrolled in care in 6 centers participating in the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) (2001-2014) according to stage of disease at enrollment and to stage of disease at antiretroviral therapy initiation.


Enrolled in care (≥2001)
(n=9,229)
Late Presentation
(CD4<350 or AIDS at enrollment)
(n=6,884, 74%)
Non-late Presentation
(CD4≥350 and asymptomatic)
(n=2,385, 26%)
Started ART
(n=6,341, 93%)
No ART
(n=503, 8%)
Started ART
(n=1,587, 66%)
No ART
(n=798,33%)
Deaths
(n=514, 8%)
LTFU
(n=984, 15%)
Deaths
(n=118, 23%)
LTFU
(n=252, 50%)
Not Delayed ART Initiation
(CD4≥350/asymptomatic)
(n=586, 37%)
Deaths
(n=10, 2%)
LTFU
(n=81, 14%)
Not Advanced Disease
(CD4≥350/asymptomatic)
(n=673, 84%)
Deaths
(n=9, 1%)
LTFU
(n=243, 36%)
Delayed ART Initiation
(CD4<350 or AIDS)
(n=1,001, 63%)
Deaths
(n=33, 6%)
LTFU
(n=108, 11%)
Advanced Disease during FU
(CD4<350 or AIDS)
(n=125, 13%)
Deaths
(n=16, 22%)
LTFU
(n=49, 39%)

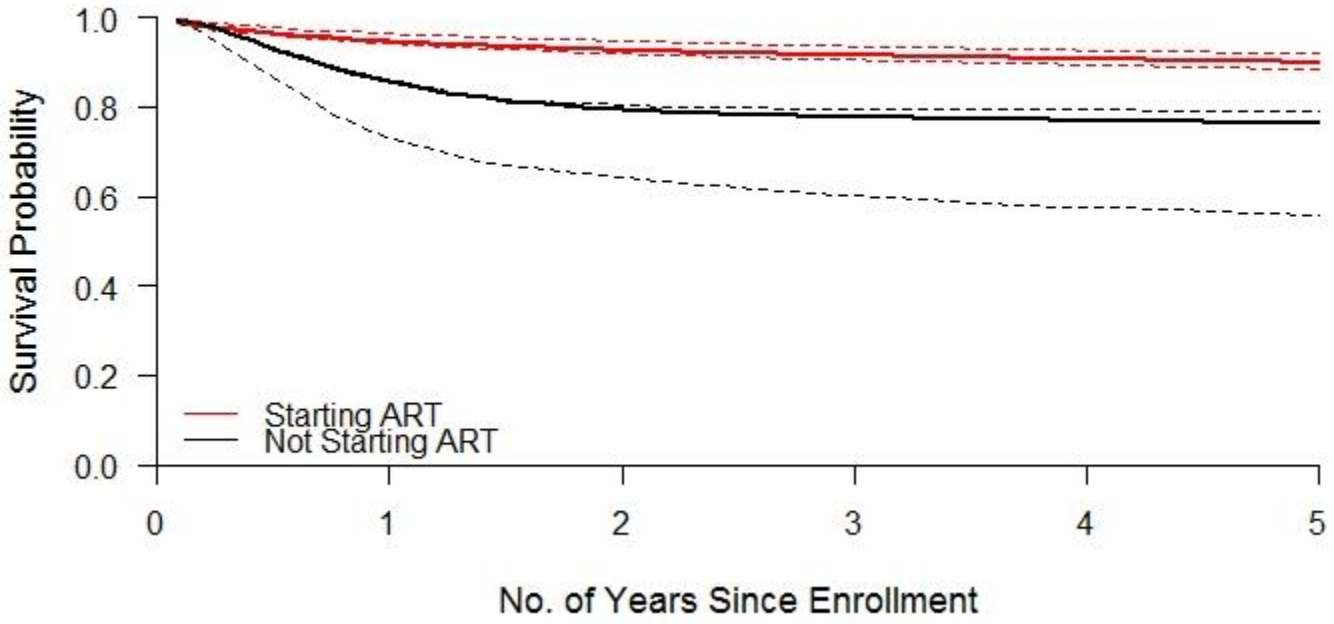
Web Figure 2: Estimated survival probability over 10 years from enrollment for deferring ART until late initiation (CD4 <350cells/uL or ADE) and for starting before this stage among people receiving care for HIV in 6 HIV-care centers participating in the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) (2001-2014)



Web Figure 3. Adjusted probability of death in people with HIV who were late presenters (CD4<350cells/ul or and AIDS defining event) and non-late presenters up to 10 years after enrollment in 6 HIV-care centers participating in the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) (2001-2014)



Web Figure 4. Adjusted probability of death in late presenters (CD4<350cells/ul or and AIDS defining event) enrolled in 6 HIV-care centers participating in the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) (2001-2014) and started ART in comparison to those that not started ART.



Abbreviations: ART antiretroviral therapy