Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Table of Content

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Section 2. Contributions to the Design, Conduct and Reporting of the START Study

Dr Babiker et al lead the design of START [1] on behalf of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT). INSIGHT conducted the study including the gathering and quality assurance of the data collected from the participating sites. The three unblinded START statisticians (Drs Grund, Phillips and Ms Sharma) analyzed the data based on a statistical analysis plan written by the START co-chairs and INSIGHT PI . The START leadership team remained blinded to the results until May 15, 2015. The manuscript was written and edited by Dr Lundgren et al (a writing group of 19 persons named on the main publication). The decision to publish these results was based on recommendations from the START data safety and monitoring board at their meeting on May 15, 2015 as detailed in the method section of the manuscript. The writing group vouches for the data, the analysis and the content of the manuscript. No agreements concerning confidentiality of the data exist between the sponsor (University of Minnesota) or the funders, and the writing group members or the institutions they are affiliated with.

Section 3. Recommendations of Antiretroviral Drugs to be Used When Initiating Antiretroviral Treatment in START, As of 26 May 2015 and History

A. Recommendations as of 26 May 2015

Antiretroviral Components Required for the Initial Regimen in START
29 May 2014 [1]

To construct the initial antiretroviral regimen in START, select one component from Column A and one component from Column B		
Column A **NNRTI, PI or INSTI Options** **(alphabetical order)**		**Column B** **Dual-NRTI Options** [2] **(alphabetical order)**
NNRTI: or efavirenz rilpivirine PI: atazanavir + ritonavir (once daily) darunavir + ritonavir (once daily) lopinavir/ritonavir (once or twice daily) or INSTI: dolutegravir elvitegravir + cobicistat [3] raltegravir	+	NRTI: abacavir/lamivudine tenofovir/emtricitabine zidovudine/lamivudine [4]

1. Derived from Table 6 of the Department of Health and Human Services (DHHS) Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (01 May 2014). Use of fixed-dose combinations of components in Columns A and B or of single formulations of NRTIs in Column B is acceptable except as noted in **3** below.
2. Lamivudine may substitute for emtricitabine or vice versa.
3. Only as part of the fixed-dose combination elvitegravir/cobicistat/emtricitabine/tenofovir (e.g., Stribild™ or other approved brand/generic), in individuals with creatinine clearance >70 mL/min
4. As of 01 May 2014, the US DHHS Guidelines no longer recommend zidovudine as part of antiretroviral therapy provided that other and safer alternatives are available. Zidovudine causes excess risk of anemia, neutropenia and lipodystrophy compared with tenofovir and abacavir. Conversely, abacavir is contraindicated in persons with tissue type HLA-B*5701; tenofovir may negatively impact bone physiology and cause renal impairment, and is generally not recommended in individuals with severely impaired kidney function.

Nevirapine (NNRTI) may not be used in the initial antiretroviral regimen in START because it is not recommended for women with a CD4+ cell count > 250 cells/mm^3 or for men with a CD4+ cell count > 400 cells/mm^3 due to increased risk of hepatic toxicity.

Not all of the antiretroviral agents listed above may be available from the START Central Drug Repository.

NRTI: nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI: non-nucleoside reverse transcriptase inhibitor
PI: protease inhibitor
INSTI: integrase strand transfer inhibitor

B. History of Changes to the Recommended Antiretroviral Regimen at Treatment Initiation

When the protocol opened to enrollment in 2009, the following antiretroviral regimens were recommended.

Antiretroviral Components Required for Initial Regimen in START: 13 January 2009[+]

To construct an antiretroviral regimen, select 1 component from Column A and 1 from Column B		
Column A (NNRTI or PI Options – alphabetical order)		**Column B (Dual-NRTI Options – alphabetical order)**
NNRTI: efavirenz or PI: atazanavir + ritonavir (1x/day) fosamprenavir + ritonavir (2x/day) fosamprenavir + ritonavir (1x/day) lopinavir/ritonavir (2x/day) lopinavir/ritonavir (1x/day) darunavir + ritonavir (1x/day)	+	abacavir/lamivudine tenofovir/emtricitabine zidovudine/lamivudine

\+ Derived from Table 6 of the Department of Health and Human Services (DHHS) Guidelines (03 November 2008). Nevirapine is not included in the table as an initial regimen because it is not recommended for women with a CD4+ cell count > 250 cells/mm^3 or men with a CD4+ cell count > 400 cells/mm^3 because of increased risk of hepatic events.

History of changes:

14 Jan 2010: Changed after 01 Dec 2009 DHHS guidelines update. Added integrase inhibitors (INSTI) as a class (raltegravir) option in addition to NNRTI and PI.

19 Mar 2012: Changed after 14 Oct 2011 DHHS guidelines update. Added rilpivirine as an NNRTI option.

15 Feb 2013: Changed after 12 Feb 2013 DHHS guidelines update. Added elvitegravir + cobicistat as an INSTI option (only as part of fixed-dose combination with emtricitabine and tenofovir, a.k.a. Stribild, in individuals with creatinine clearance > 70 mL/min).

18 Mar 2013: Changed to allow the substitution of lamivudine for emtricitabine or vice versa in the NRTI backbone combination based on the 12 Feb 2013 DHHS update.

27 Nov 2013: Added dolutegravir as an INSTI option, following the “Recommendations on Integrase Inhibitor Use in Antiretroviral Treatment-Naïve HIV-Infected Individuals from the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents”, released on 30 Oct 2013.

29 May 2014: Changed after 01 May 2014 DHHS guidelines update. Added footnote stating, “the US DHHS Guidelines no longer recommend zidovudine as part of antiretroviral therapy provided that other and safer alternatives are available. Zidovudine causes excess risk of anemia, neutropenia and lipodystrophy compared with tenofovir and abacavir. Conversely, abacavir is contraindicated in persons with tissue type HLA-B*5701; tenofovir may negatively impact bone physiology and cause renal impairment, and is generally not recommended in individuals with severely impaired kidney function.”

Section 4. Methods Used to Readjust Sample Size and Required Number of Primary Endpoints to Maintain Sufficient Power in 2013, and Other Aspects of the START Design

A. Sample Size

The initial sample size for START was estimated as 4000 participants [1]. According to the START protocol, a sample size re-estimation was to be carried out before enrollment was complete to verify some of the key assumptions used in its calculation and ensure that the planned sample size was adequate. Following the sample size re-estimation in January 2013, it was projected that 4,600 participants would be required to reliably address the primary study question. This was based on estimates of the expected event rates for the composite primary outcome and its major components (Serious AIDS and Serious non-AIDS) in the immediate and deferred ART groups. These estimates were obtained using data from a large observational dataset (CASCADE collaboration [2]) and data from START on baseline CD4+ counts and pooled event rates (for both treatment groups combined) obtained at the time of sample size re-estimation, together with computer simulations that account for the distribution of CD4+ cell counts projected for START during follow-up. These estimates and other assumptions used in calculating sample size are summarized below:

a. The primary analysis will be intention to treat using a Cox proportional hazards model with a single indicator for treatment group
b. Type I error is 0.05 (2-sided)
c. Participants are enrolled over a 3-year period and followed for a minimum of 3 years resulting in an average follow-up of 4.5 years and a total study duration of 6 years.
d. Median CD4+ count at entry will be 646 (IQR: 581 – 752) cells per cubic millimeter.
e. The primary endpoint rate in the deferred ART group and the treatment difference (hazard ratio for immediate ART relative to deferred ART) during each year of follow-up are as shown in Table 1 below. The average hazard ratio is 0.64.
f. Serious AIDS events are projected to constitute 23% of the primary event and the average hazard ratio for these events is 0.45. The average hazard ratio for Serious non-AIDS events is 0.70.
g. The estimated treatment differences take into account likely levels of adherence to the immediate ART strategy (e.g., participants followed in CASCADE who started ART were considered “on ART” irrespective of adherence or future discontinuation of their ART).
h. For adherence to the deferred strategy it was assumed that 70% of participants would adhere to the deferral CD4+ count threshold of 350 cells per cubic millimeter and 30% would initiate ART earlier – 10% before the CD4+ count declined to 400 cells per cubic millimeter and 20% while the CD4+ count was between 350 and 400 cells per cubic millimeter.
i. A loss to follow-up rate of 2.7 per 100 person-years (equivalent to a 15% cumulative lost to follow-up after 6 years) is assumed.

j. Based on these assumptions, the estimated sample size of 4,600 participants (2,300 participants in each treatment group) would yield 90% power for the primary comparison and would provide adequate power to address the two major components of the composite endpoint (76% for Serious AIDS and 65% for Serious non-AIDS). The number of primary events required is 213.

Section 4; Table 1. Annual Primary Event Rate and Hazard Ratio.

Year of Follow-Up	Deferred Group Event Rate (per 100 PY)	Hazard Ratio for Immediate vs Deferred ART
1	1.2	0.66
2	1.3	0.57
3	1.4	0.60
4	1.5	0.65
5	1.5	0.72
6	1.5	0.79

B. Randomization and Blinding

Randomization was stratified by clinical site. Permuted blocks of different sizes were used to generate randomization schedules. Assignments were obtained from a web-based program that verified participant eligibility.

Due to the nature of the study, investigators and participants were not blinded to the treatment group assignment. However, endpoints were reviewed blinded to treatment group.

C. Data Collection and Follow-up of Participants

Prior to randomization, participants underwent a clinical evaluation including history of non-AIDS conditions. Demographic data, HIV-specific data, including likely mode of infection, time since HIV diagnosis, HIV RNA level, and CD4+ and CD8+ counts, and other blood measurements, including lipids, creatinine, glucose, liver function tests, and hepatitis serology were collected. Risk factors for non-AIDS conditions, including smoking status and blood pressure, were assessed; a 12-lead resting electrocardiogram (ECG) was also obtained by the majority of participating sites. These risk factors were used to estimate the Framingham risk of coronary heart disease (CHD)[3].

Follow-up study visits occurred at month 1, month 4, then every 4 months thereafter. At each visit, a targeted health history and examination were conducted, ART changes and adherence (if relevant) were assessed, and CD4+ cell count and HIV RNA levels were obtained. At each annual visit, lipids, liver function tests, glucose and creatinine were measured, non-AIDS risk factors were assessed, and a 12-lead ECG was obtained.

Primary and secondary outcomes, including serious clinical events that were not part of the composite primary outcome, were to be reported as soon as the clinical site became aware of them. Similarly, when participants in the deferred arm initiated ART, this was immediately reported along with the reason for initiating ART.

Section 5. Sensitivity Analyses for the Primary Endpoint.

A. Sensitivity Analyses for Unknown Primary Endpoint Status

In the primary analysis, follow-up was censored on May 26, 2015, the last day of study contact, or when a primary event occurred, whichever occurred earliest. During this time, 6969 person years of follow-up accrued in the immediate ART group (time to primary endpoint), 6932 in the deferred ART group, and event rates were 0.60 and 1.38 per 100 person years, respectively (Table 2 of main manuscript). For 93 (4.0%) participants in the immediate ART group, and 119 (5.0%) in the deferred ART group, the primary endpoint status by May 26, 2015 was unknown (no contact > 10 months, and no primary endpoint during follow-up). For these participants, 202 person-years would have accrued between the last day of study contact and May 26, 2015 in the immediate ART group, and 258 person-years in the deferred ART group ("unobserved follow-up time"). In order to assess the magnitude of potential bias due to missing data during this time, we imputed events for the unobserved follow-up time based on a wide range of assumed event rates for both treatment groups. We added the unobserved and observed person-years of follow-up time, estimated the number of events in each treatment group by adding the imputed expected number of events during the unobserved follow-up time to the observed event counts, and used Poisson regression with a single treatment group indicator to estimate the rate ratios for the immediate versus deferred ART groups with 95% confidence intervals. The Table 1 below shows the assumed event rates for the unobserved follow-up time, the estimated numbers of events, and the estimated rate ratios with confidence intervals and p-values. The actual coverage probability of the confidence intervals is slightly less than 95%, since the methodology does not account for random variability during the unobserved follow-up time.

Section 5; Table 1. Sensitivity Analyses for the Primary Endpoint to Assess the Effect of Unknown Endpoint Status.

Assumptions for Event Rates After the Endpoint Status Became Unknown	Assumed Event Rates for Time with Unknown Endpoint Status		Estimated Number of Participants with a Primary Event		Rate Ratio	95% CI	P-value
	Imm. ART Group	Def. ART Group	Imm. ART Group	Def. ART Group			
No. of events	0	0	42	96	0.44	(0.31 – 0.63)	<0.001
Same rate as during the time of known endpoint status	0.60	1.38	43.2	99.6	0.44	(0.30 – 0.62)	<0.001
Rate in the deferred ART group is 2x higher	0.60	2.76	43.2	103.1	0.42	(0.29 – 0.60)	<0.001
Rate in the deferred ART group is 3x higher	0.60	4.14	43.2	106.7	0.41	(0.29 – 0.58)	<0.001
Rate in the deferred ART group is 5x higher	0.60	6.90	43.2	113.8	0.38	(0.27 – 0.54)	<0.001
Rate in the deferred ART group is 10x higher	0.60	13.8	43.2	131.5	0.33	(0.23 – 0.46)	<0.001
Rate in the immediate ART group is 2x higher	1.20	1.38	44.4	99.6	0.45	(0.31 – 0.64)	<0.001
Rate in the immediate ART group is 3x higher	1.80	1.38	45.6	99.6	0.46	(0.32 – 0.65)	<0.001
Rate in the immediate ART group is 5x higher	3.00	1.38	48.0	99.6	0.48	(0.34 – 0.68)	<0.001
Rate in the immediate ART group is 10x higher	6.00	1.38	54.1	99.6	0.54	(0.39 – 0.76)	<0.001

B. Sensitivity Analyses for the Event Adjudication Status

All reported AIDS and Serious non-AIDS events were reviewed by an independent endpoint review committee (ERC) using pre-specified criteria, and blinded to treatment group. As was pre-specified in the protocol, the primary analysis included all events that were adjudicated as confirmed or probable. Table 2 below shows event

counts, rates, and hazard ratios with 95% confidence intervals for all reported events (irrespective of adjudication status), and for only those events that were adjudicated as “confirmed” by the ERC.

Section 5; Table 2. Primary Endpoint and Major Secondary Endpoints, Including All Reported Events, and Including Only Events Adjudicated as “Confirmed”.

	Immediate ART Group (N=2326)		Deferred ART Group (N=2359)			
	No. of Participants with Event	Rate (per 100 Person Years)	No. of Participants with Event	Rate (per 100 Person Years)	Hazard Ratio for Imm. vs. Def. ART groups (95% CI)	P-value
All reported events						
Primary endpoint	51	0.73	121	1.76	0.41 (0.30 - 0.58)	<0.001
Serious AIDS	22	0.32	76	1.10	0.29 (0.18 – 0.46)	<0.001
Serious non-AIDS	30	0.43	48	0.69	0.62 (0.39 – 0.98)	0.04
Confirmed events only						
Primary endpoint	42	0.60	86	1.24	0.48 (0.33 – 0.70)	<0.001
Serious AIDS	14	0.20	42	0.60	0.33 (0.18 – 0.61)	<0.001
Serious non-AIDS	29	0.42	45	0.64	0.64 (0.40 – 1.01)	0.06

Figure S1. START Study Design and CONSORT Flow Diagram

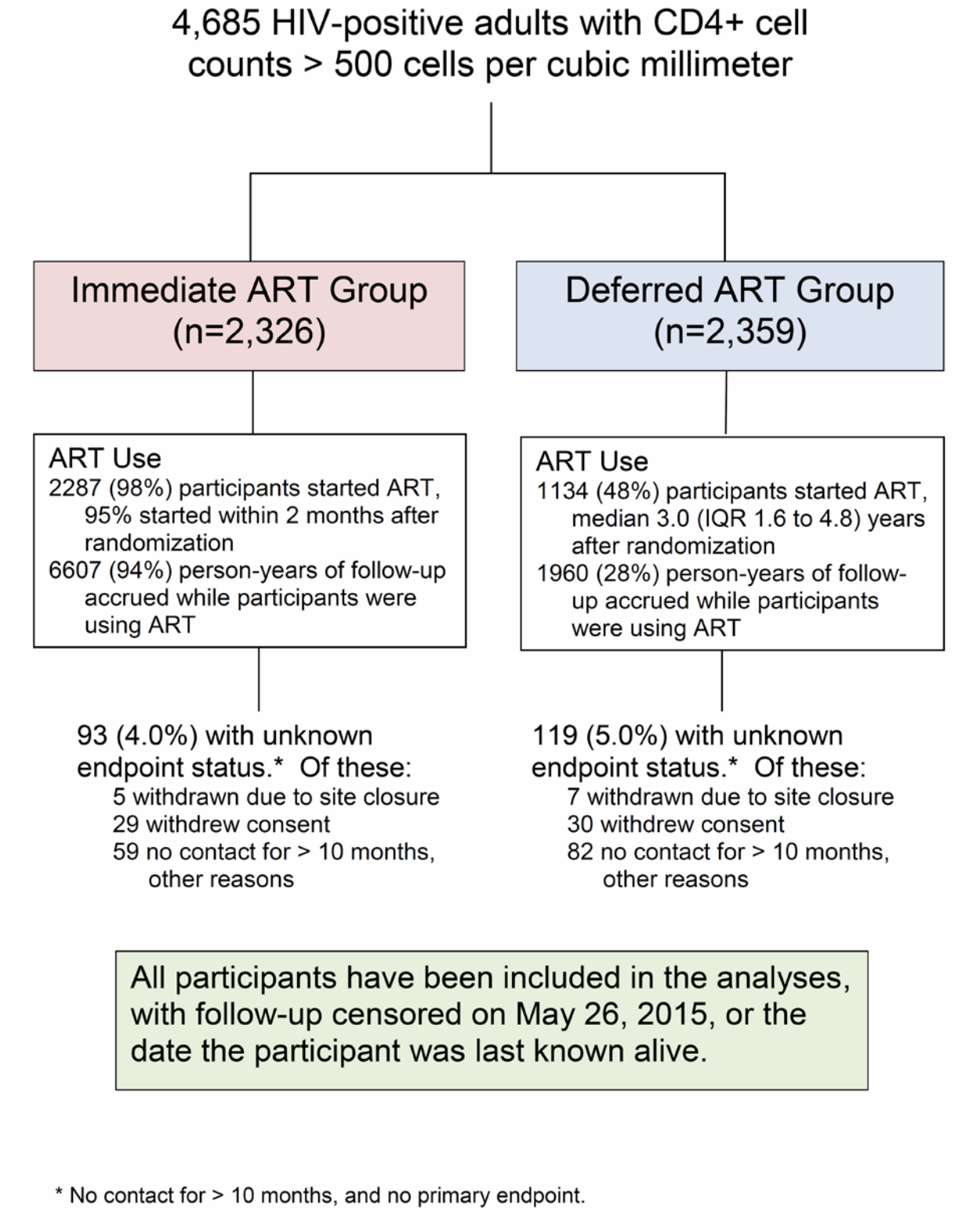


Figure S2. Time to Initiation of ART, Kaplan-Meier Estimates

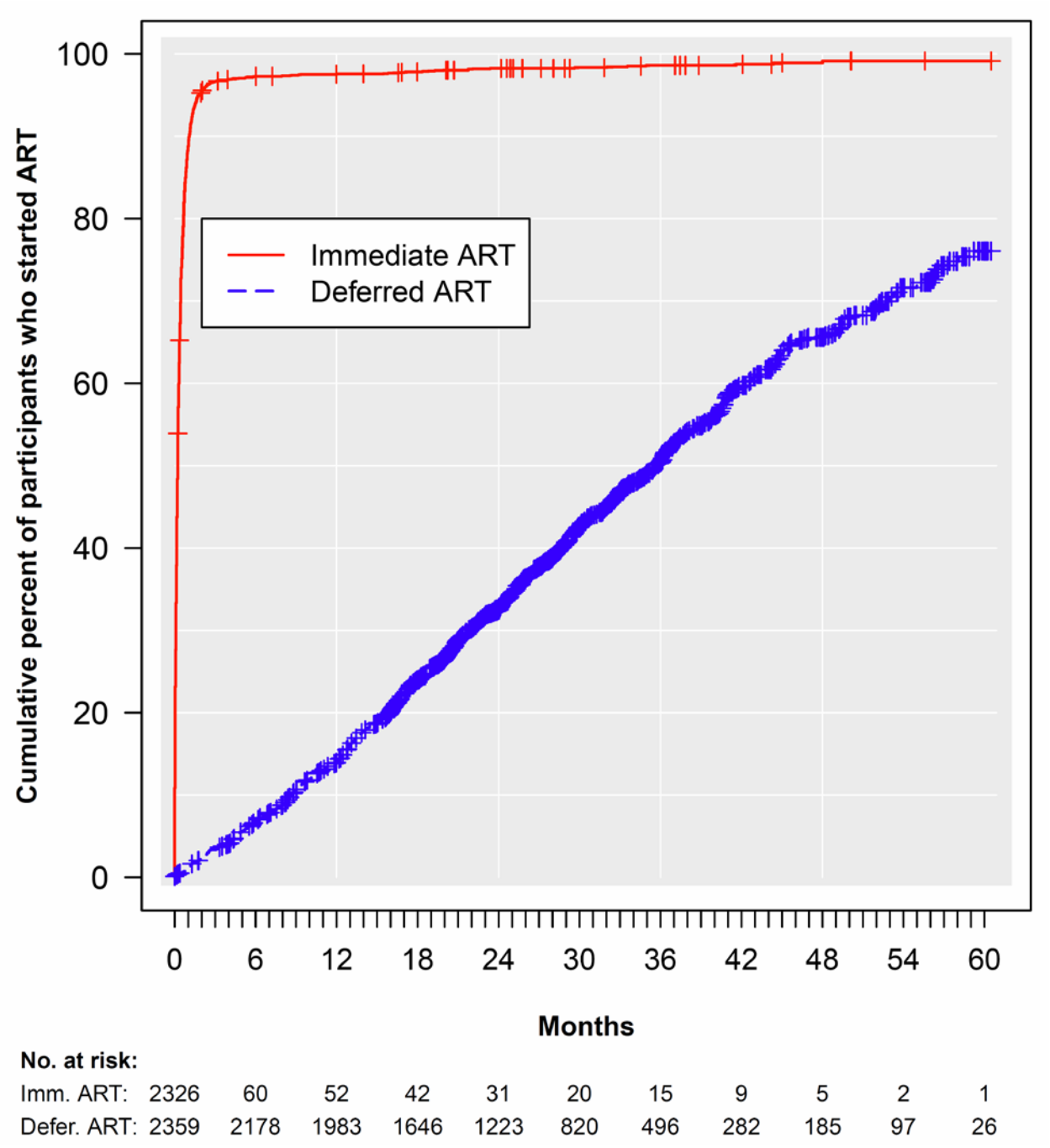
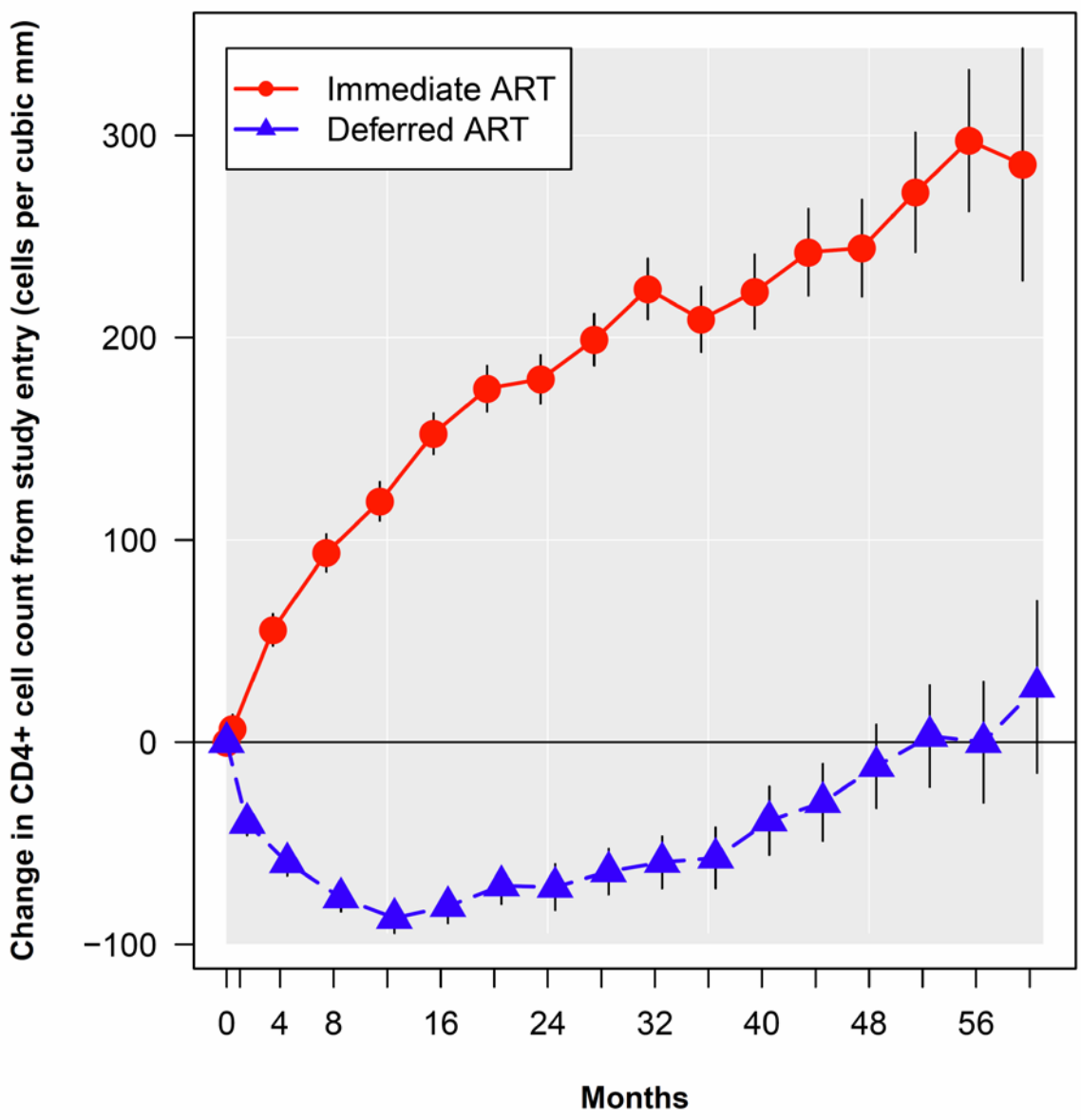


Figure S3. Change in Mean CD4+ Count from Study Entry



No. of participants:

Imm. ART:	2326	2236	2205	1853	1075	574	157
Defer. ART:	2359	2274	2190	1829	1077	549	162

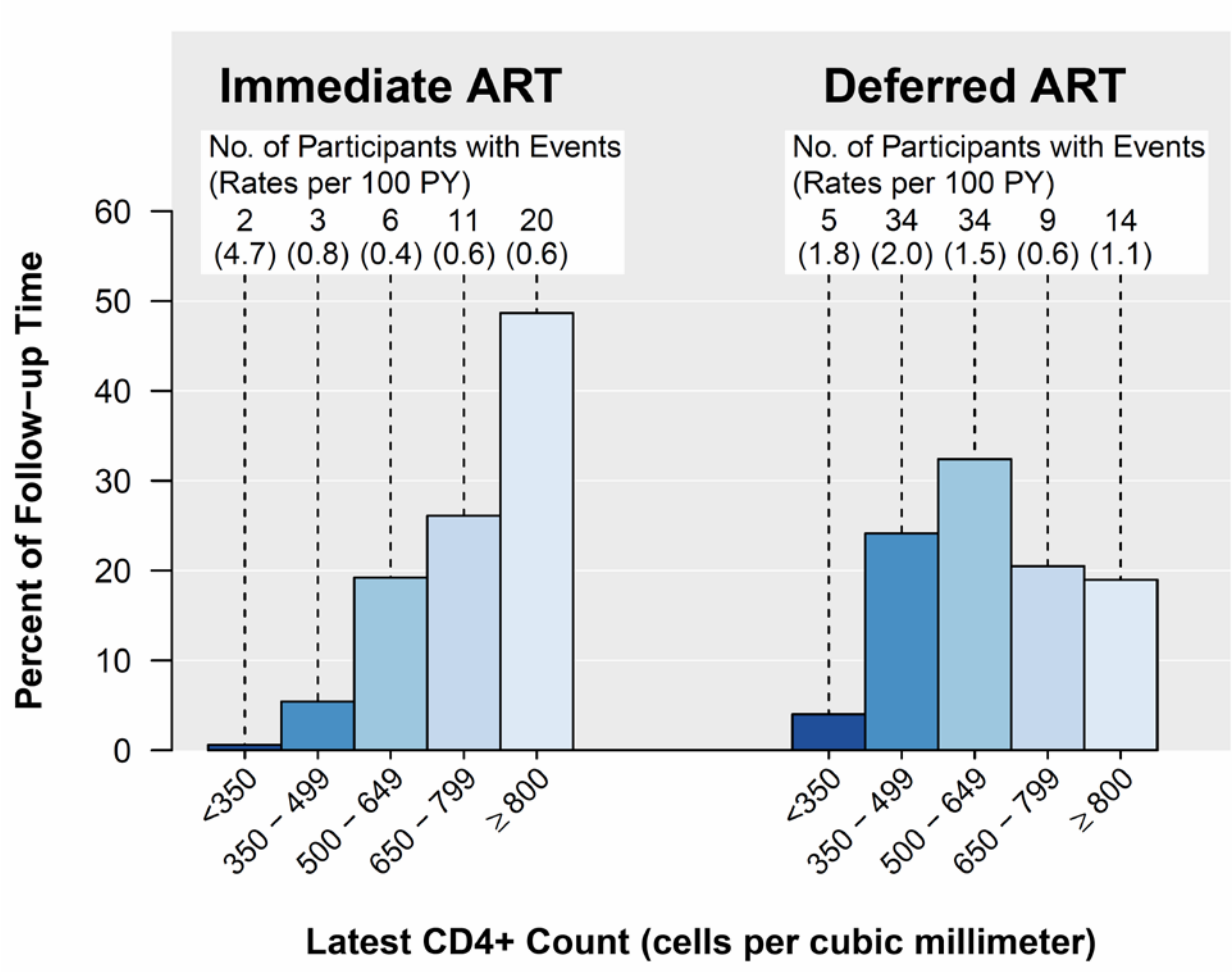
P−values, t−tests, unadj.:

<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Longitudinal mixed model, adj. for baseline CD4 and visit:

Est. diff.: 194.2 95% CI: 185.1 − 203.3 P−value: <0.001

Figure S4. Follow-up Time, Primary Endpoint Counts and Rates by Latest CD4+ count



During follow-up, CD4+ counts tended to be higher in the immediate ART group compared with the deferred ART group. The bars show person-years that were accumulated in each of five strata of latest (time-updated) CD4+ counts, as percent of total follow-up time. In addition, the CD4+ count immediately preceding each primary event was determined. Above each bar, the number of events in each stratum is shown, with the event rate calculated per 100 person-years accumulated in that CD4+ count stratum.

Table S1. Reasons for Initiating ART in the Deferred ART Group

Reasons for ART Initiation	N	%	Latest CD4+ Prior to ART Initiation (cells per cubic mm) Median (5^{th}, 25^{th}, 75^{th}, 95^{th} Percentile)
Latest CD4+ count < 350 cells/mm^3 prior to ART initiation	422	37.2	300 (178, 262, 329, 346)
Latest CD4+ count $\geq$ 350 cells/mm^3 prior to ART initiation [1]	712	62.8	514 (362, 422, 639, 941)
Earlier CD4+ < 350	60		
Progression of disease (AIDS-related), or conditions/symptoms indicative of HIV progression	118		
Serious non-AIDS event	10		
Other clinical event/diagnosis	93		
Rapidly declining CD4 or low CD4%	104		
Elevated HIV RNA	106		
Reduce risk of HIV transmission	124		
Pregnancy or breastfeeding	46		
Clinician-directed, none of the above	71		
Patient wish, none of the above	116		
Other or reason unknown, none of the above	3		
Number of participants who started ART	1134		408 (225, 319, 563, 832)

[1] Reasons not mutually exclusive.

Table S2. Type of Initial ART Used in the Immediate and Deferred Groups

	Nucleos(t)ide Reverse Transcriptase Inhibitor Combinations (# Participants)										Total	
3rd	ABC/3TC		TDF/FTC		ZDV/3TC		TDF/3TC		NPP			
drug:	Imm	Def	Imm	Def	Imm	Def	Imm	Def	Imm	Def	Imm	Def
EFV	24	10	1463	525	173	29	1	10	0	0	1661	574
RPV	2	2	95	139	0	0	0	0	0	0	97	141
ATV/r	22	12	199	81	8	2	0	1	0	1	229	97
DRV/r	14	18	149	105	0	0	0	0	0	0	163	123
FPV/r	0	0	9	6	2	0	0	0	0	0	11	6
LPV/r	1	3	15	6	2	11	0	0	0	0	18	20
RAL	7	10	91	77	1	1	0	0	1	0	100	88
EVG/c	0	0	1	49	0	0	0	0	0	0	1	49
DTG	1	9	0	8	0	0	0	0	0	1	1	18
NPP	0	6	3	6	1	3	0	0	2	3	6	18
Total	71	70	2025	1002	187	46	1	11	3	5	2287	1134

A total of 2287 and 1134 participants initiated ART in the immediate (Imm) and deferred (Def) groups, respectively. Drugs from the following antiretroviral medicines classes were used: Nucleos(t)ide reverse transcriptase inhibitors (ABC=abacavir; 3TC=lamivudine; TDF=tenofovir; FTC=emtricitabine; ZDV=zidovudine); non-nucleoside reverse transcriptase inhibitors (EFV=efavirenz; RPV=rilpivirine), protease inhibitors (ATV=atazanavir; /r=ritonavir boosted; DRV=darunavir; FPV=fosamprenavir; LPV=lopinavir), and integrase inhibitors (RAL=raltegravir; EVG/c=elvitegravir boosted with cobicistat). Not per protocol (NPP) drug combinations are shown in aggregate (see Section 3 of this Supplementary Appendix for protocol-allowed combinations).

Table S3. Composition of the Primary Endpoint, and the Incidence (Number of Participants) by Type of Event.

Type of Event	Composition of the Primary Endpoint[1]		Number of Participants with Event	
	Imm. ART	Def. ART	Imm. ART	Def. ART
Serious AIDS[2]				
Bacterial pneumonia	0	1	0	1
Tuberculosis, pulmonary	6	16	6	17
Tuberculosis, extrapulmonary	0	3	0	3
Cytomegalovirus	1	0	1	0
Herpes zoster, disseminated	0	3	0	3
Cryoptococcosis, extrapulmonary	1	0	1	0
Pneumonia, Pneumocystis jirovecii	1	5	1	5
Cervical carcinoma	1	0	1	0
Kaposi's sarcoma	1	11	1	11
Lymphoma, Hodgkin's	1	1	1	1
Lymphoma, non-Hodgkin's	2	9	2	9
AIDS-death	0	1	1	4
Subtotal, any Serious AIDS	14	50	14	50
Serious non-AIDS				
Cardiovascular disease	12	14	12	14
Acute myocardial infarction	6	5	6	5
Coronary revascularization	4	5	8	5
Stroke	1	4	1	4
Death due to cardiovascular causes	3	1	3	1
Cancer, non-AIDS	9	18	9	18
Anal cancer	1	2	1	2
Lung cancer	2	2	2	2
Prostate cancer	2	3	2	3
Other non-AIDS cancer [3]	4	11	4	11
Death due to cancer	0	0	1	1
Liver or renal disease	1	2	1	2
End-stage renal disease, non-fatal	1	0	1	0
Death due to liver or renal disease	0	2	0	2

Type of Event	Composition of the Primary Endpoint[1]		Number of Participants with Event	
	Imm. ART	Def. ART	Imm. ART	Def. ART
Death, other than above	6	12	7	13
Accident or violence	4	3	4	3
Diabetes	0	1	0	1
Infection	0	1	0	1
Suicide	0	2	0	3
Substance abuse	0	2	0	2
Unknown cause	2	3	3	3
Subtotal, any Serious non-AIDS	28	46	29	47
Total	42	96	42	96

[1] Each participant is counted only for the event type that occurred first. Counts across types of cardiovascular disease do not add up to 12 and 14 for the immediate and deferred ART groups, respectively, because one participant in each group experienced acute myocardial infarction and revascularization on the same day, and one participant in the immediate ART group experienced a stroke and died on the same day. Four out of 42 (10%) primary events in the immediate group occurred before initiation of ART compared to 68 out of 96 (71%) in the deferred group. In the immediate ART group, the latest HIV-RNA level prior to their primary event was less than 200 copies/mL for 32 of 42 participants (76%), compared with 19 of 96 (20%) in the deferred ART arm.

[2] Esophageal candidiasis and herpes simplex were not part of the Serious AIDS primary endpoint. Esophageal candidiasis was experienced by 1 participant in the immediate ART group and 7 in the deferred ART group. Herpes simplex, bronchitis, pneumonitis, esophagitis, or other visceral disease was experienced by 2 participants, both in the immediate ART group, whereas none had mucocutaneous ulcerations lasting for more than 1 month.

[3] Immediate ART group: squamous cell carcinoma, plasma cell myeloma, bladder cancer, fibrosarcoma. Deferred ART group: gastric adenocarcinoma, breast cancer, ureteric cancer, malignant melanoma, myeloid leukemia, thyroid cancer, testicular cancer (2), leiomyosarcoma, liver cancer, squamous cell carcinoma of head and neck.

Table S4. Cause of Death

Cause of Death[1]	Immediate ART Group	Deferred ART Group
AIDS, ongoing active disease	1	4
Cardiovascular disease		
Heart or vascular	1	1
Sudden death, cause unknown	2	0
Non-AIDS malignancy, excluding hepatitis B/C related	1	1
Chronic viral hepatitis	0	1
Renal failure	0	1
Infection	0	1
Diabetes mellitus	0	1
Accident/violence	4	3
Suicide	0	3
Substance abuse	0	2
Unknown	3	3
Total number of deaths	12	21

[1]Cause of death was adjudicated by the independent Event Review Committee, and classified according to the CoDe system [4].

Table S5. Line Listing of All Reported Suspected Unexpected Serious Adverse Reactions (SUSAR)[1]

Type of Reaction[2]	Group	Antiretroviral Drugs Used Around the Time of the Reaction[3]	Antiretroviral Drugs Suspected as Cause of the Reaction[3]	Relatedness[1]
Fracture, traumatic complicated of wrist	Immediate	TDF, FTC, EFV	EFV	Possible
Psychosis, overdose cocaine and amphetamine	Immediate	TDF, FTC, DRV/r	TDF, FTC	Possible
Atheroma, ruptured skin	Immediate	TDF, FTC, EFV	TDF, FTC, EFV	Probably not
Suicide attempt (insulin injection)	Immediate	ABC, 3TC, EFV	EFV ABC, 3TC	Possible Probably not
Cholecystolithiasis	Immediate	TDF, FTC, EFV	TDF, FTC, EFV	Probably not
Rectal bleeding	Immediate	TDF, FTC, ETV	TDF, FTC, ETV	Probably not
Hallucinations	Immediate	TDF, FTC, ATV/r	TDF, FTC, ATV/r	Probably not
Transient polyneuropathy of arm	Immediate	TDF, FTC, ATV/r	TDF, FTC, ATV/r	Probably not
Febrile pancytopenia	Immediate	TDF, FTC, EFV	TDF, FTC, EFV	Possible
Acute delerium	Immediate	TDF, FTC, EFV	TDF, FTC, EFV	Possible
Bells palsy	Immediate	TDF, FTC, RPV	TDF, FTC, RPV	Definitively
Eruptive xanthomas	Deferred	TDF, FTC, EFV	TDF, FTC, EFV	Probable
Febrile syndrome	Deferred	TDF, FTC, EFV	TDF, FTC, EFV	Probably not Possible
Ureterolithiasis	Deferred	TDF, FTC, DRV/r	TDF, FTC, RTV DRV	Probably not Possible
Unknown cause of death[4]	Deferred	TDF, FTC, EFV, ABC, 3TC, DRV/r	TDF, FTC, EFV, ABC, 3TC, DRV/r	Probably not Probably not
Anemia, normochromic normocytic	Deferred	TDF, FTC, EFV	TDF, FTC	Probable

[1] These reactions were defined as events that were assessed as related to one or more antiretroviral drug but not expected per the labelling of the drug in question. Relatedness was determined by both, the site investigator and INSIGHT medical officer. Per definition, these reactions were only reported from participants on ART. This table lists all reported SUSARs. Prior to January 12, 2012, events assessed as "probably not related" were considered "related" for SUSAR reporting, along with events assessed as "possibly related" or stronger. After that date, only events assessed as "possibly related" or stronger were reported.

[2] A total of 11 reactions developed during a total of 6607 person-years of follow-up on ART in the immediate group (rate: 0.2 per 100 person-years) and 5 reactions during 1960 person-years in the deferred group (rate: 0.3 per 100 person-years).

[3] Abbreviations for drug names: Nucleos(t)ide reverse transcriptase inhibitors (ABC=abacavir; 3TC=lamivudine; TDF=tenofovir; FTC=emtricitabine); non-nucleoside reverse transcriptase inhibitors (EFV=efavirenz; ETV=etravirine; RPV=rilpivirine), protease inhibitors (ATV=atazanavir; /r=ritonavir boosted; DRV=darunavir).

[4] The participant used EFV/TDF/FTC until 4 days prior to death, at which time the ART regimen was switched to ABC/3TC/DRV/r; ART was discontinued 2 days prior to death.

Supplementary Appendix References

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4. Kowalska JD, Friis-Møller N, Kirk O, et al. The Coding Causes of Death in HIV (CoDe) Project: initial results and evaluation of methodology. Epidemiology 2011;22(4):516-23.