Supplementary Appendix

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

Supplement to: INSIGHT Strategic Timing of AntiRetroviral Treatment (START) Study Group. Long-Term Benefits from Early Antiretroviral Therapy Initiation in HIV Infection. NEJM Evid. DOI: 10.1056/EVIDoa2200302.

Supplementary Appendix

Supplement to:

Long-term Benefits from Early Antiretroviral Therapy Initiation in HIV Infection

INSIGHT **S**trategic **T**iming of **A**nti**R**etroviral **T**reatment (START) Study Group Study Group

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Category	Description
Disease, problem, or condition under investigation	HIV infection; long-term impact of earlier versus delayed ART initiation.
Special considerations related to:	
Sex and gender	HIV impacts all genders, with global variation.
Age	In 2021, there were 38.4 million PLWH; 36 million were adults.[1] Median age in START was 36 years; 11% with age 18-25 and 23% age ≥ 45.
Race or ethnic group	HIV impacts all race/ethnicity groups.
Geography	HIV infection is a global epidemic.
Other considerations	In 2021, key populations with high risk of infection (e.g., MSM, sex workers, etc.) accounted for 94% of new HIV infections outside sub-Saharan Africa, and 51% of new infections in Sub-Saharan Africa.[1] 55% of the START population were MSM.[1] In sub-Saharan Africa, 63% of new HIV infections were among women/girls. [1]Among the 1000 participants enrolled in START from Africa, 70% were female.
Overall representativeness of this trial	START enrolled participants in 35 countries across 5 continents with relevant applicability to today's global HIV population. The participants enrolled within each country were representative of their HIV population. In 2021, 85% of PLWH were aware of their status, and 75% were accessing ART. [1] With a high proportion of PLWH still not on ART, data from long-term follow-up of START is relevant.

ART=antiretroviral therapy; MSM=men who have sex with men; PLWH=people living with HIV

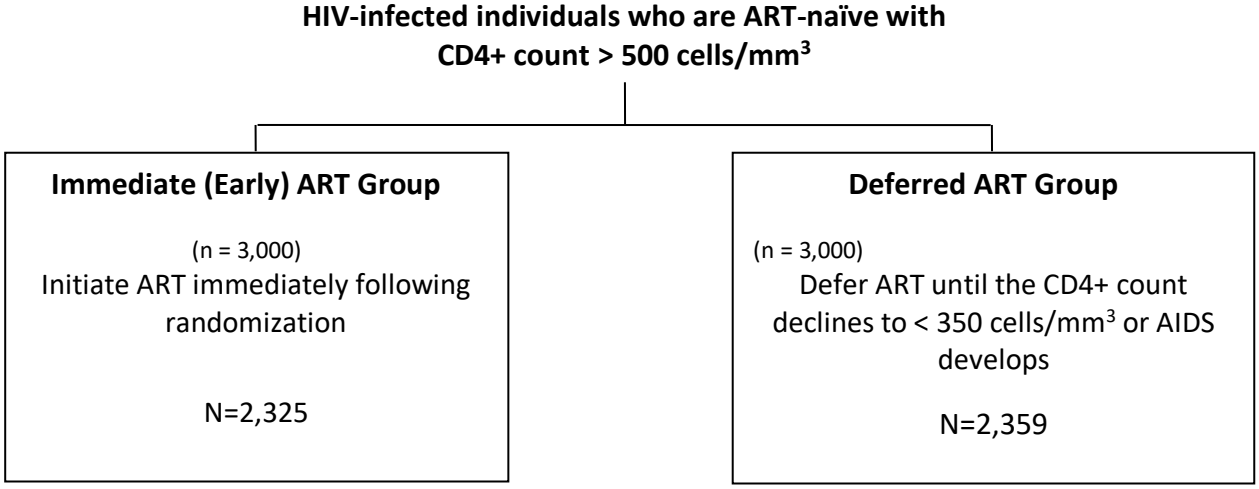
[1] United Nation Joint Programme on HIV/AIDS (UNAIDS), Fact Sheet 2022; available at: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf [accessed 4 December 2022]

Section 3: Study Design

The START trial, as previously reported, was designed to address the following question: In HIV-1 (subsequently referred to as HIV) infected asymptomatic participants with a CD4+ count greater than 500 cells/mm^3, is immediate use of antiretroviral therapy (ART) superior to deferral of ART until the CD4+ count declines to 350 cells/mm^3 or AIDS develops in terms of morbidity and mortality? In this international randomized trial, participants were randomized in a 1:1 allocation ratio to the immediate (early) ART following randomization or deferred ART group within strata defined by clinical site. Treatment assignments were obtained using a web-based application. Due to the nature of the study, investigators and study participants were not blinded to their treatment assignment. Endpoints were reviewed by an endpoint review committee (ERC) blinded to treatment group.

The design is illustrated in the schematic below with the sample sizes in each group that were achieved.

START Design Schematic: Original Design



On May 15, 2015 the independent Data and Safety Monitoring Board (DSMB) for START determined that the question stated above had been addressed. Immediate use of ART provided significant benefit over deferred ART for the primary composite endpoint of START and its two major components, serious AIDS and serious non-AIDS events over an average follow-up of 3 years. The DSMB recommended offering ART to participants in the deferred arm who had not yet started ART. They also recommended continued follow-up of study participants.

START investigators and study participants were informed of these recommendations on May 27, 2015 and per the DSMB's recommendation, participants in the deferred arm who had not started treatment were advised to start ART if they had not already done so.

Even though the findings from START unequivocally indicated that immediate ART had substantial benefits on major clinical outcomes compared to deferred ART, longer

follow-up, as recommended by the DSMB, was warranted for several scientific and practical reasons. These reasons and two hypotheses concerning the long-term follow-up results which were formulated are stated in the protocol (version 4.0) and summarized below.

The novel data in this report is the follow-up through 2021; it provides 6 years of additional follow-up (9.5 years total from randomization) from January 2016.

Extended follow-up is important for several reasons:

- To determine whether the harm resulting from deferral of ART could be eliminated for the primary and key secondary endpoints, overall and for key subgroups.

- The unique nature of the START cohort warranted long-term study: 1) it was demographically and geographically diverse; 2) participants had a median CD4+ count of 651 cells/mm^3 at baseline; approximately 25% had counts > 800 cells/mm^3; 3) approximately one-third of participants had a viral load < 5000 copies/mL at entry; and 4) the median time since diagnosis of HIV was one year.

- Although most participants in the deferred arm had started ART by 2017 when version 4.0 of the START protocol was written, the randomized allocation to immediate or deferred ART treatment led to a median difference in CD4+ cell counts of 180 cells/mm^3 at the time of ART initiation at the end of 2016, substantial differences in exposure to ART (a median of 2.5 years between ART initiation in the immediate and deferred groups), and consequently to large differences in viral load, CD4+ count, and markers of inflammation, coagulation, and vascular injury. These differences, as well as differences in other factors, could impact treatment differences in clinical outcomes even after ART is initiated for participants in the deferred ART group.

- Treatment for HIV is life-long and the median age of the cohort at study entry was 36 years. The average three years of follow-up accrued was considered insufficient to understand the full benefits of ART. It is important to more fully understand those benefits in order to inform calculations of cost-effectiveness of approaches for diagnosing people as rapidly as possible after infection.

- For key clinical outcomes such as cardiovascular disease, cancer and all-cause mortality, the number of participants with events were small, and with long-term follow-up the effects of immediate ART compared to deferred ART on these outcomes would be more precisely estimated.

- The extended follow-up coupled with the experimental design of START allowed new scientific questions which are clinically relevant to HIV positive participants and the people who are providing their care to be addressed in this unique cohort.

Based on the initial findings of START, two hypotheses were formulated for the follow-up of the study participants through 2021. These hypotheses take advantage of the initial randomization and experimental design of START.

The information below is taken from section 3.2.1 of version 4.0 of the protocol.

Hypothesis 1 (HIV RNA Hypothesis): As a consequence of nearly all deferred arm participants initiating ART by the end of 2015 and the resulting similar HIV RNA levels after 2015 for the two treatment groups, the primary event rate in the two treatment groups will be similar between 2016 and 2021; the cumulative event rates in the two arms at the end of 2021 will remain significantly different from one another, reflecting the difference in accrued events when the study was unblinded, but the treatment difference will be substantially smaller than at the time of DSMB's recommendation in May 2015.

In terms of the treatment hazard ratio (HR), we hypothesize the true HR will be 1.0 and the estimated HR for the time period between 2016 and 2021 will not differ significantly from 1.0; the average HR for the entire follow-up period from randomization through 2021, will be significantly less than 1.0 but much closer to 1.0 than the HR of 0.43 reported following the DSMB recommendation.

In other words, participants who were randomized to deferring ART until the CD4+ count decreased to 350 cells/mm^3 have an increased risk of the primary endpoint during the deferral period, and this risk is nearly completely eliminated once ART is initiated.

Hypothesis 2 (Nadir CD4+ Hypothesis): As a consequence of deferred arm participants initiating ART, on average, 2.5 years after the immediate ART group, the primary event rate for the deferred ART group will remain substantially higher than in the immediate ART group between 2016 and 2021; as a consequence, the cumulative event rates in the two arms at the end of 2021 will also remain substantially different from one another with only a modest movement of the overall average HR towards 1.0 from 0.43.

In other words, participants who were randomized to deferring ART to 350 cells/mm^3 have an increased risk of the primary endpoint during the deferral period that persists, albeit at lower levels, for 6 years after initiating ART. This increased risk resulting from deferred ART persists because of a number of factors including, the lower CD4+ cell count at which ART was initiated, lower CD4+ count levels during extended follow-up, increased exposure during the deferral period to activated inflammatory and coagulation pathways, and a reduced ability to normalize markers of inflammation, coagulation and vascular injury after ART is initiated. If data are consistent with this hypothesis, we will estimate the rate with which the HR moves toward 1.0 over the 6 years, if at all.

The inclusion and exclusion criteria used to enroll participants in START are shown below.

Inclusion Criteria

- Signed informed consent
- HIV infection documented by a plasma HIV RNA viral load, rapid HIV test or any licensed ELISA test; and confirmed by another test using a different method including but not limited to a rapid HIV test, Western Blot, HIV culture, HIV antigen, or HIV pro-viral DNA at any time prior to study entry.
- Age ≥ 18 years (≥ 35 years after 4,000 participants were enrolled in July 2013)

- Karnofsky performance score ≥ 80 (an indication that the participant can perform normal activities)
- Perceived life expectancy of at least 6 months
- For women of child-bearing potential, willingness to use contraceptives as described in the product information of the ART drugs they are prescribed
- Two CD4+ cell counts > 500 cells/mm^3 at least 2 weeks apart within 60 days before randomization

Exclusion Criteria

- Any previous use of ART or IL-2 treatment
- Diagnosis of any clinical AIDS event before randomization (including esophageal candidiasis and chronic *Herpes simplex* infection)
- Presence of HIV progression such as oral thrush, unexplained weight loss, or unexplained fever at randomization
- Cardiovascular event (myocardial infarction, angioplasty, coronary-artery bypass grafting, stroke) within 6 months before randomization
- Non-AIDS-defining cancer, excluding basal and squamous cell skin cancer, within 6 months before randomization
- Dialysis within 6 months before randomization
- Diagnosis of decompensated liver disease before randomization
- Current imprisonment, or compulsory detention (involuntary incarceration) for treatment of a psychiatric or physical illness
- Current pregnancy or breastfeeding (a negative serum or urine pregnancy test is required within 14 days before randomization for women of child-bearing potential)

The primary and secondary endpoint of START are defined below.

Primary Outcome

The primary composite endpoint of START is the development of a serious AIDS event (also referred to as “AIDS*” in the protocol and statistical analysis plan), a serious non-AIDS event (“non-AIDS”), or death from any cause.

This endpoint remained the primary focus of the extended follow-up through 2021 which was carried out.

Serious AIDS events (or AIDS*) include most traditional opportunistic conditions but exclude non-fatal esophageal candidiasis and chronic *Herpes simplex*. Non-fatal esophageal candidiasis and chronic *Herpes simplex* are not counted in the primary endpoint of serious AIDS events because they are more common than most other opportunistic events at higher CD4+ counts and usually do not cause significant limitations for people in whom they occur.

Esophageal candidiasis and chronic *Herpes simplex* infection were only counted as part of the serious AIDS (AIDS*) if they were the cause of death.

AIDS* conditions are listed below:

- Aspergillosis (invasive)
- Bartonellosis
- Candidiasis of the bronchi, trachea, or lungs
- Invasive cervical cancer
- Chagas disease (American trypanosomiasis) of the central nervous system (CNS)
- Cytomegalovirus virus (CMV) disease (radiculomyelitis, meningoencephalitis, or other disease)
- CMV retinitis
- Extrapulmonary or disseminated coccidioidomycosis
- Cryptosporidiosis with diarrhea > 1 month
- Cryptococcosis, meningitis or extrapulmonary
- HIV-related encephalopathy, including AIDS Dementia Complex
- Disseminated *Herpes zoster*
- Extrapulmonary or disseminated histoplasmosis
- Isosporiasis with diarrhea > 1 month
- Kaposi's sarcoma, mucocutaneous or visceral
- Leishmaniasis (visceral)
- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma, all cell types
- Primary lymphoma of the brain
- Tuberculosis, pulmonary and/or extrapulmonary
- Microsporidiosis with diarrhea > 1 month
- *Mycobacterium avium* complex (MAC), disseminated
- Other nontuberculous species or unidentified species of *Mycobacterium*, disseminated
- Nocardiosis
- Penicilliosis, disseminated
- Extrapulmonary *Pneumocystis jiroveci*
- *Pneumocystis jiroveci* pneumonia
- Recurrent bacterial pneumonia (2 episodes within 12 months)
- Progressive multifocal leukoencephalopathy (PML)
- *Rhodococcus equi* disease
- Recurrent *Salmonella* septicemia (2 episodes within 12 months)
- Toxoplasmosis of the brain
- Wasting syndrome due to HIV

The term "AIDS" (without an asterisk) denotes all opportunistic conditions, <u>including non-fatal</u> esophageal candidiasis and chronic *Herpes simplex*.

The following serious non-AIDS conditions are the components of the primary composite endpoint referred to as serious non-AIDS events, or "non-AIDS":

- Cardiovascular disease (CVD) (myocardial infarction, stroke, coronary revascularization);

- End-stage renal disease (ESRD) (initiation of dialysis, renal transplantation);
- Decompensated liver disease; and
- Non-AIDS-defining cancers (excluding basal and squamous cell skin cancers).
- Deaths from causes other than AIDS

Together the AIDS* and non-AIDS components of the primary endpoint include all deaths.

Secondary Outcomes

The secondary outcomes include the major components of the primary outcome and other major outcomes.

- Serious AIDS (AIDS*)
- Serious non-AIDS
- Fatal or non-fatal non-AIDS conditions (excluding non-AIDS mortality other than deaths due to CVD, ESRD, decompensated liver disease, and non-AIDS-defining cancers
- Death from any cause
- Tuberculosis
- AIDS cancer
- Non-AIDS defining cancer (excluding basal and squamous cell skin cancers)
- Cancer (AIDS and non-AIDS)
- CVD (myocardial infarction, stroke, coronary revascularization)

Section 4. Versions of the Protocol and Statistical Analysis Plan

Version 1.0 of the START protocol was issued on December 9, 2008. Version 1.0 described the planned pilot phase to assess feasibility and the planned definitive phase to be implemented when feasibility was established.

Version 2.0 of the protocol was issued on October 25, 2010 following the successful completion of the pilot phase under version 1.0 of the START protocol. New sites joined the study for the definitive phase and version 2.0 updated the background section with new information, including updated treatment guidelines. Other changes were minor.

In both version 1.0 and 2.0 of the START protocol, total sample size was planned to be 4,000 participants; and a target of 370 primary endpoints was specified. This estimate was based on a 2-sided level of significance 0.05 and power=0.90. Ninety percent power was specified, in part, to ensure that there would be adequate power to address the components of the composite endpoint, non-AIDS and fatal AIDS or non-fatal AIDS*.

The follow-up schedule for data collection was defined to be the same in both treatment groups. Data collection visits in both versions occurred at 1 and 4 months after randomization, and every 4 months thereafter.

A letter of amendment was issued in February 2013 following a sample size re-estimation. The planned enrollment was increased from 4000 to 4600 participants and

the event target to maintain 90% power was reduced to 213 primary events instead of 370. These changes were recommended because the CD4+ cell count at baseline was higher than initially projected and the pooled (both treatment groups combined) event rate was lower. It was also recommended that the final 600 participants enrolled all be at least 35 years of age in order to ensure the event target could be achieved after all participants had been followed for a minimum of 3 years.

All participants enrolled in START were enrolled under either version 1.0 or 2.0 of the protocol.

Version 3.0 of the START protocol was issued on February 1, 2016. Study objectives were revised and expanded to reflect that all participants were being offered antiretroviral therapy. The composite primary endpoint, however, remained the same. The data collection schedule was revised to include only two (rather than three) study visits per year: an annual visit and a 6-month visit. Data collection was also reduced and plasma for storage was no longer collected at non-annual visits.

Version 4.0 was issued on August 28, 2017. The major changes with this version were:

- To reduce data collection to one time per year. Also, it was planned that most data would be collected by abstraction from existing medical records of participants' regular care.
- Data collection was further reduced: No laboratory data was collected other than CD4+ counts and HIV viral load measurements. All available CD4+ and HIV RNA measurements in the medical record since the last assessment were to be recorded on an eCRF. Concomitant medications and diagnoses other than those comprising the primary endpoint were no longer be collected. Plasma and urine for storage were no longer collected.
- Beginning in 2020, available results for SARS-CoV-2 testing were also recorded.
- Participants were transitioned from donated antiretroviral drugs from the Central Drug Repository (CDR) after 31 December 2017 to locally supplied drugs.

Version 0.4 of the Statistical Analysis Plan (SAP) was used for the report of the primary results of START in 2015. That SAP was written on December 12, 2014. Version 2.0 of the SAP was finalized on May 3, 2017, and an addendum to the SAP was finalized on July 25, 2022. Both version 2.0 and the addendum follow version 4.0 of the protocol in which the long-term follow-up of all study participants through 2021 is described. The purpose of the addendum was to describe final changes to the analysis plan, including the following:

- The closeout process implemented for the last year of follow-up in 2021. Since the annual data collection for many participants was carried out before the end of the year, in 2021 the data collection was expanded to the completion of an eCRF in the first half of 2022 that verified primary endpoint and vital status as of December 31, 2021.
- The two analysis cohorts to be used for analyses for the follow-up period from 2016 to 2021.
- An analysis to supplement the intention to treat analyses that was restricted to participants enrolled by 162 of the 218 sites with the best follow-up through 2021.

Version 4.0 of the protocol and version 2.0 of the SAP and the addendum are included in the supplemental materials.

Section 5. Power Considerations and Analysis Considerations

For both the HIV RNA and the Nadir CD4+ hypotheses, it was assumed when version 4.0 of the protocol was written in August 2017 that 90% of the surviving 4,684 HIV+ participants randomized would be under follow-up on 1 January 2018. It was also assumed that very few participants would experience both AIDS* and serious non-AIDS events, and that the lost-to-follow-up percent would be 1% per year after 2017.

Considering these assumptions, we estimated 406 primary events would occur by December 31, 2021 under the Nadir CD4+ hypothesis; 242 primary events are expected to occur between 2016 and 2021. Under the HIV RNA hypothesis, 177 primary events are expected to occur between 2016 and 2021 and 341 events are predicted between randomization and the end of 2021. Based on the assumptions above, the predicted HRs and 95% confidence intervals (CIs) for the two hypotheses are given below.

Hypothesis	**HR (randomization through 31 December 2015)**	**HR (2016-2021; 6 years)**	**HR (randomization through 2021; 9.5 years)**
# 1 (HIV RNA)	0.47 (95% CI: 0.34-0.65)	1.00 (95% CI: 0.74-1.36)	0.70 (95% CI: 0.56-0.87)
# 2 (Nadir CD4+)		0.57 (95% CI:0.43-0.74)	0.53 (95% CI: 0.43-0.65)

With 242 events, power is 0.98 during the calendar period January 2016 through December 2021 to detect a HR (Imm/Def) of 0.60; power is 0.79 to detect a HR of 0.70, a difference that is more conservative than the projected HR of 0.57 under the Nadir CD4+ hypothesis.

The primary comparisons between the two randomized treatment groups will be made over 3 time periods (from randomization through 2015, from 2016 through 2021, and from randomization through 2021) using time-to-first-event statistical methods. The comparisons for the time periods from randomization was by intention-to-treat. For treatment comparisons in the time period from 2016-2021, participants who died or withdrew consent prior to 2016 did not contribute follow-up time to the 2016-2021 comparison; thus, that comparison is by “modified” intention-to-treat.

Two analysis cohorts are used for the time period from 2016-2021.

1. Participants alive and who did not withdraw consent prior to 2016; and
2. Participants who did not experience a primary event or withdraw consent prior to 2016.

Both analysis cohorts defined for 2016-2021 are relevant to the two hypotheses stated in the protocol. The HIV RNA Hypothesis and Nadir CD4+ Hypothesis, aim to

determine whether (and if so, the extent to which) the excess risk of the START primary endpoint resulting from the deferral of ART is eliminated when ART is initiated and HIV RNA level is suppressed.

The 1st analysis cohort informs whether the excess risk of deferral during 2016-2021 is modified when participants who experienced a primary endpoint prior to 2016 are considered in the risk set. The results using this analysis cohort consider the possibility that primary endpoints that developed before 2016 contribute to the long-term risk of ART deferral. The 2nd analysis cohort during 2016-2021 considers only the 1st event participants experienced and is therefore similar to how the follow-up data prior to 2016 were summarized.

Event rates (per 100 person years) will be calculated as the number of participants with events/total person years at risk*100. Differences between groups in event rates will be tested using Cox proportional hazard regression models (stratified by six geographic regions if event numbers permit: 1) Africa, 2) Asia, 3) Europe and Israel, 4) North America, 5) South America and Mexico, and 6) Australia). Additionally, cumulative proportions of participants with events will be estimated with Kaplan-Meier curves, and groups will be compared using log-rank tests.

The primary objective aimed at determining whether the benefit of immediate versus deferred ART was maintained, increased or reduced following the initiation of ART in the deferred group, and the HIV RNA hypothesis and nadir CD4+ hypothesis are addressed using a single Cox model that includes data from randomization for all participants, an indicator variable for treatment group, a time-updated indicator variable for calendar time (0 for the time from randomization to 31 December 2015, 1 thereafter), and their interaction. The significance of the interaction term assesses the extent to which the hazard ratios for periods 1) and 2) differ. For the Cox regression analyses using the 1st analysis cohort, the risk set at the beginning of 2016 was expanded to include participants who experienced a non-fatal primary endpoint prior to 2016 (pre-2016) and analyses consider the time to first event beginning January 1, 2016 (post-1Jan2016).

For continuous variables (e.g., CD4+ cell count), treatment differences at fixed time points (visits or calendar time) will be estimated with 2-sided 95% confidence intervals using linear regression models adjusted for baseline and other covariates (e.g., geographic region) as appropriate. Average treatment differences through follow-up will be estimated with 2-sided 95% confidence intervals by fitting linear mixed models with random effects for intercept and fixed effects for treatment assignment and, as appropriate, other adjustment covariates, such as baseline level and geographic region.

Differences between groups in binary outcome variables (e.g., HIV RNA level ≤ 200 copies/mL) will be tested using chi-squared tests, or logistic regression models for adjusted analyses (presented with 2-sided 95% confidence intervals). Treatment differences for average changes from baseline through follow-up will be estimated with 95% confidence intervals using generalized estimating equations (GEE); the treatment difference will be modelled as the interaction effect between the treatment group indicator and an indicator variable for follow-up.

Section 6: Missing Data

Prior to unblinding the treatment differences through 2021, two groups of sites were defined according to the pooled follow-up experience of the two treatment groups. For these analyses the groups were formed from 218 sites that collected data in START, including some sites that never enrolled, but followed transfer participants (see the addendum to the analysis plan for more details):

- 162 sites with < 25% of participants with unknown vital status on December 31, 2021. These sites followed 3,581 participants and the percentage with known vital status was 89%.
- 56 sites with ≥ 25% of participants with unknown vital status on December 31, 2021. These sites followed 1,103 participants and the percentage with known vital status was 58%.

We indicated in our analysis plan that in addition to the analysis including all sites, we would carry out an analysis restricted to the 162 sites with the best follow-up. Randomization was carried out within site and we assumed that if the findings for the 162 best sites were similar to the findings for all 218 sites, the higher level of censoring resulting from the inclusion of the 56 sites was not introducing significant bias. The analysis for the 162 sites is shown in Table S5 of this supplement and the analysis for all sites is shown in Figure 3 of the main paper.

We also defined a subgroup analysis by site follow-up success that would be carried out for the primary endpoint for the follow-up period between 2016 and 2021 and for the period from randomization through 2021. These analyses are shown in Figure 5 of the main paper and Figure S10 of this supplement.

Section 7: Results

For each supplemental figure and table, a brief description is given in this section 3. These tables and figures are also referenced in the main paper by number.

Figure S1. START Consort diagram showing follow-up completeness for the primary endpoint and mortality.

The number of participants randomized to immediate and deferred antiretroviral treatment and the number of these participants alive, who had not withdrawn consent, and were still under follow-up at the end of 2015 is shown in Figure S1 along with completeness of their follow-up through 2021.

As noted in Methods, 2 analysis cohorts are considered for the post-1Jan2016 cohort.

1. Participants alive and who did not withdraw consent prior to 2016; and
2. Participants who did not experience a primary event or withdraw consent prior to 2016.

The 1st cohort includes 2210 immediate and 2226 deferred group participants. The exclusion of 115 randomized participants in the immediate group and the 113 randomized participants in the deferred group are for deaths (19 and 28), withdrawal of consent (58 and 57), and also for 86 participants (38 immediate and 48 deferred) for whom the last known vital status date was before 1 January 2016. While efforts to find these participants continued through 2021, their last known alive date was not able to be updated so they provided no additional information during the post-1Jan2016 period.

The 2nd cohort excludes an additional 114 participants (33 participants in the immediate and 81 in the deferred group) who experienced a non-fatal primary endpoint prior to 2016.

At the end of the extended follow-up period on 31 December 2021, the primary endpoint status could not be confirmed for 16.6% of participants in the immediate group and 18.4% in the deferred group. These percentages were 17.1% and 19.3% for participants for whom vital status could not be confirmed on 31 December 2021.

These percentages were also determined using 28 February 2021 as the date for assessing vital status (i.e., 10-months before the end of follow-up to allow for the possibility that some participants could not be contacted during the closeout process to verify vital status on 31 December 2021. The percentage of immediate and deferred ART participants for whom vital status could not be confirmed on 28 February 2021 was 14.1% and 15.2%, respectively.

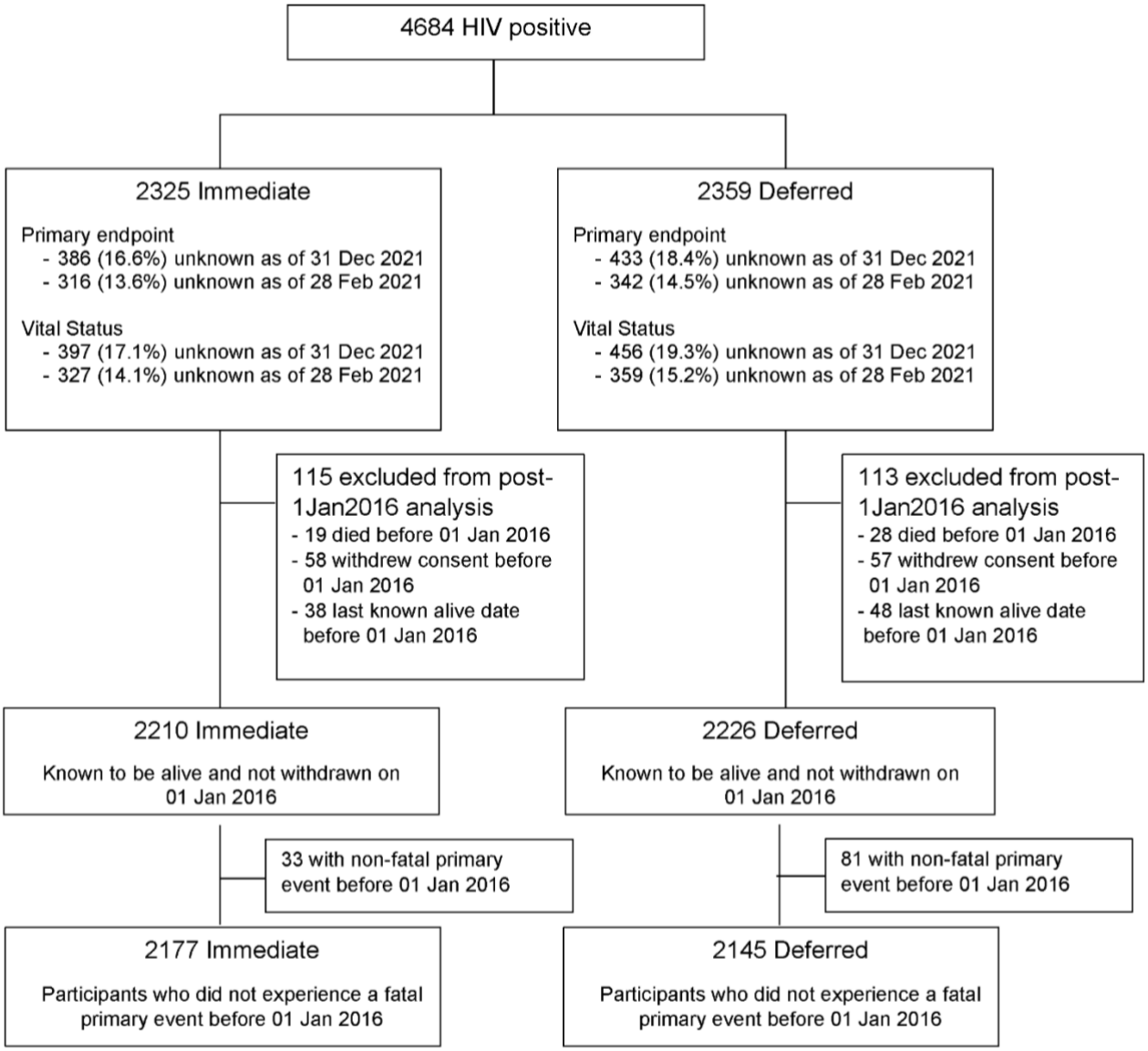

4684 HIV positive
2325 Immediate
Primary endpoint
- 386 (16.6%) unknown as of 31 Dec 2021
- 316 (13.6%) unknown as of 28 Feb 2021
Vital Status
- 397 (17.1%) unknown as of 31 Dec 2021
- 327 (14.1%) unknown as of 28 Feb 2021
2359 Deferred
Primary endpoint
- 433 (18.4%) unknown as of 31 Dec 2021
- 342 (14.5%) unknown as of 28 Feb 2021
Vital Status
- 456 (19.3%) unknown as of 31 Dec 2021
- 359 (15.2%) unknown as of 28 Feb 2021
115 excluded from post-1Jan2016 analysis
- 19 died before 01 Jan 2016
- 58 withdrew consent before 01 Jan 2016
- 38 last known alive date before 01 Jan 2016
113 excluded from post-1Jan2016 analysis
- 28 died before 01 Jan 2016
- 57 withdrew consent before 01 Jan 2016
- 48 last known alive date before 01 Jan 2016
2210 Immediate
Known to be alive and not withdrawn on 01 Jan 2016
2226 Deferred
Known to be alive and not withdrawn on 01 Jan 2016
33 with non-fatal primary event before 01 Jan 2016
81 with non-fatal primary event before 01 Jan 2016
2177 Immediate
Participants who did not experience a fatal primary event before 01 Jan 2016
2145 Deferred
Participants who did not experience a fatal primary event before 01 Jan 2016

Figure S2. Distribution of the CD4 cell count at time of treatment initiation by treatment group during the pre-2016 period

In the pre-2016 period (randomization through 31Dec2015), the median CD4+ cell count at the time when antiretroviral treatment was initiated was 188 cells higher for the immediate (red) compared to the deferred (blue) group. The median CD4+ counts at treatment initiation for the immediate and deferred group were 648 cells/mm^3 and 460 cells/mm^3, respectively.

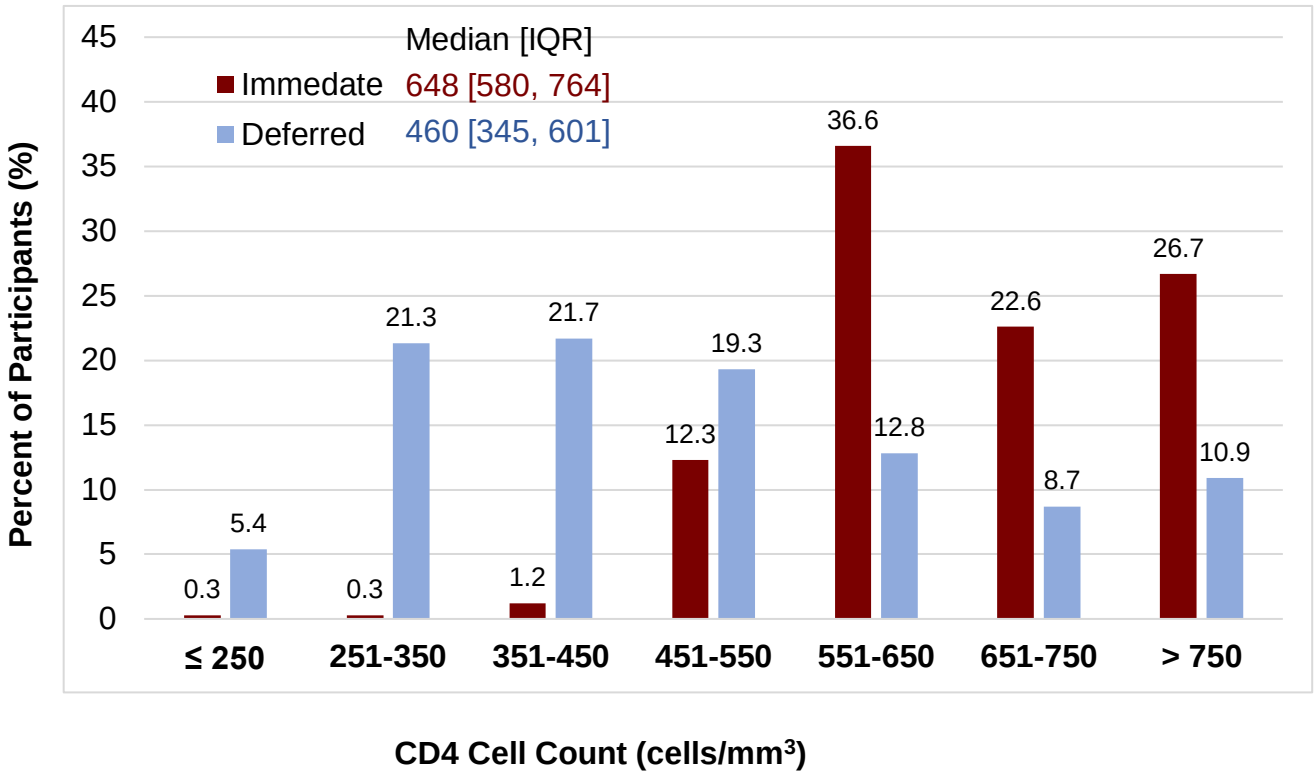


Figure S3. Summary of the percentage of participants on antiretroviral therapy and percentage with HIV RNA level ≤200 copies/mL by month of follow-up starting from randomization through 2021.

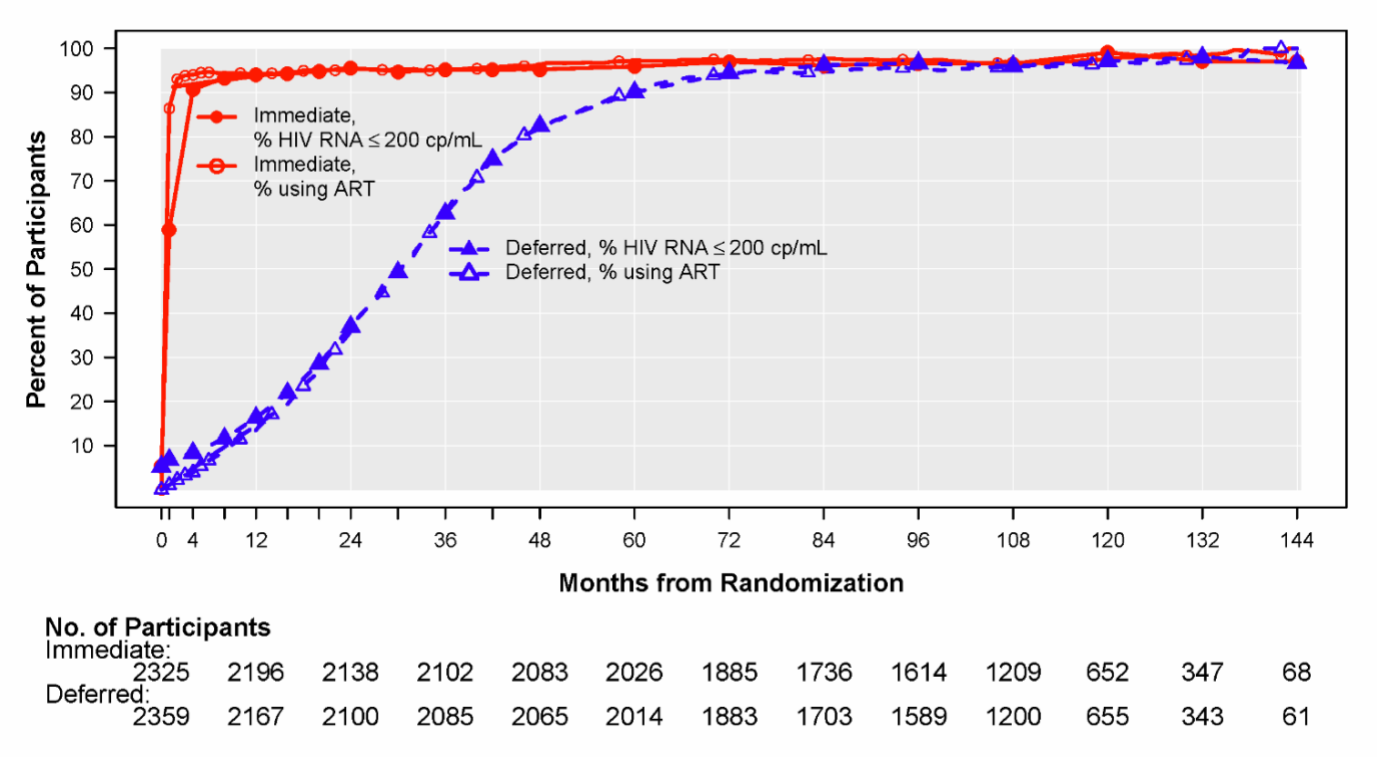


Figure S4. Summary of the average CD4+ cell counts by month of follow-up starting from randomization through 2021.

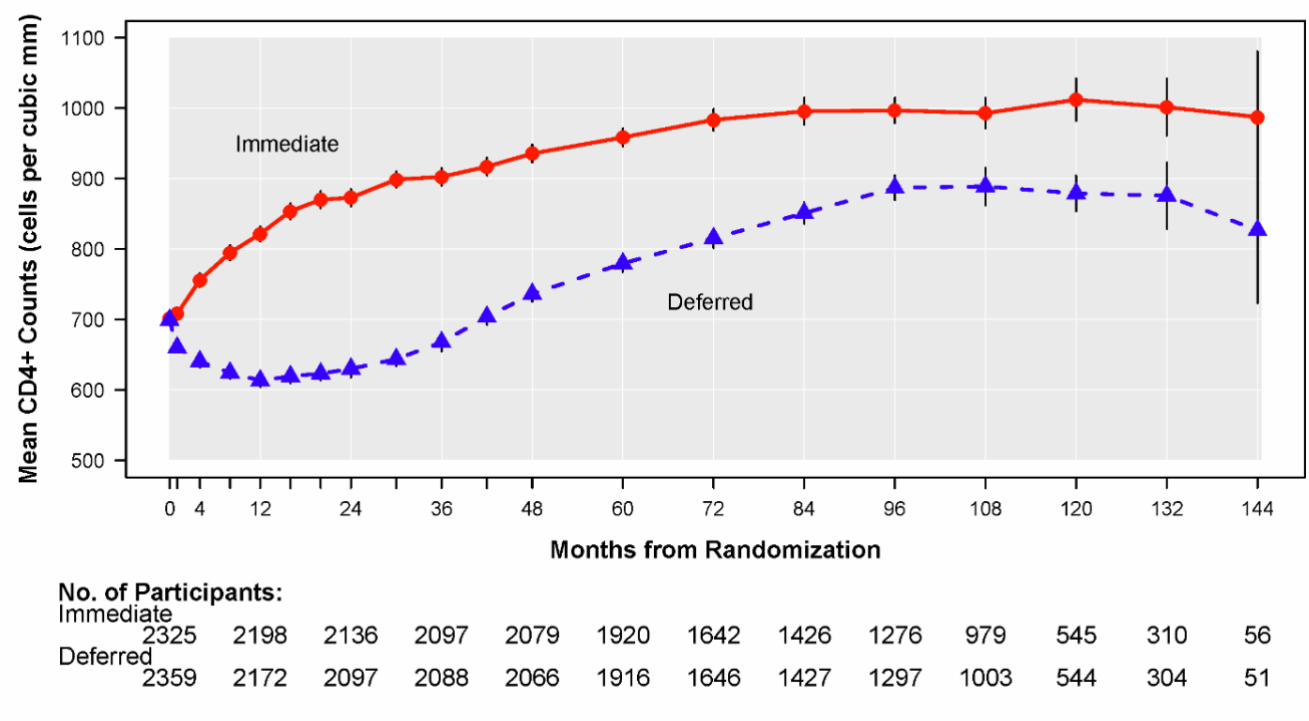
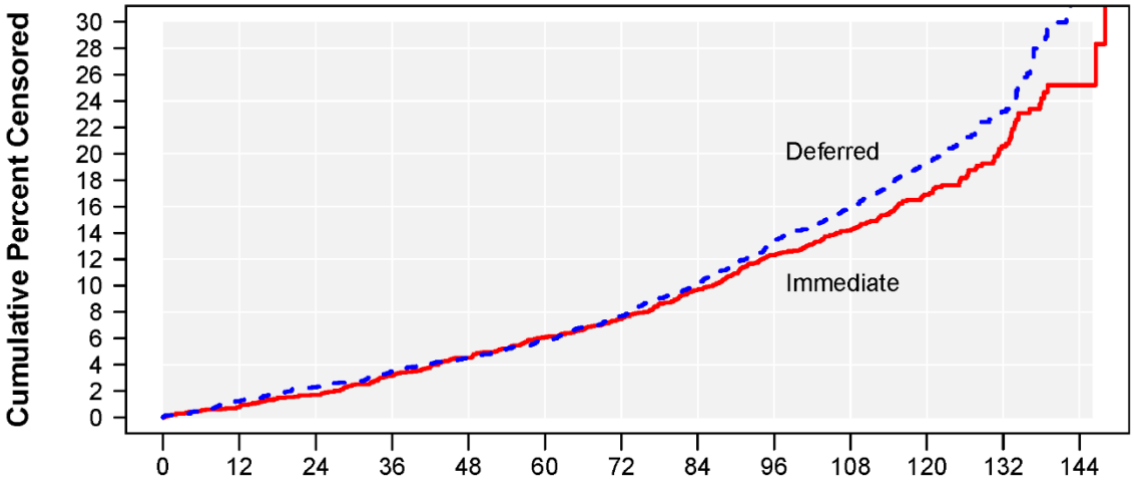


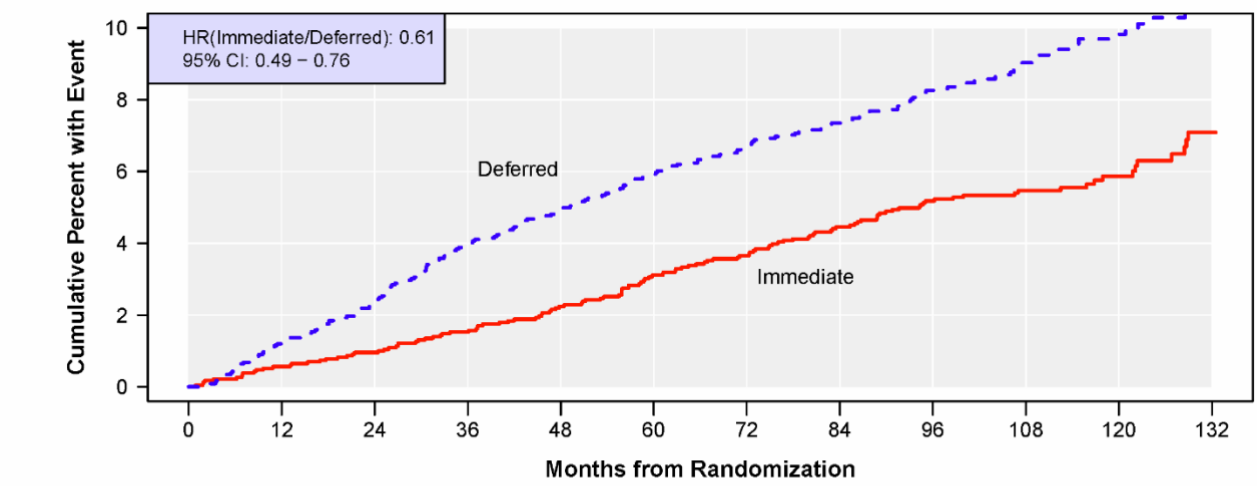
Figure S5. Kaplan-Meier curves for cumulative percentage of participants censored for last known vital status between randomization and 31 December 2021, by treatment group

A Kaplan-Meier curve for cumulative percent censored for when vital status was last known during the full follow-up period is shown in Figure S5. Through much of follow-up the curves for the immediate and deferred ART groups were superimposed. Toward the end of follow-up contact with participants was more difficult due to the COVID-19 pandemic and the deferred group (dashed blue) curve was higher than the curve for the immediate group (solid red).



No. at Risk:													
Immediate:	2325	2302	2274	2238	2199	2157	2120	2058	1986	1426	769	402	44
Deferred:	2359	2322	2292	2250	2219	2182	2133	2065	1981	1425	733	368	30
Pct Censored:													
Immediate:		0.8	1.7	3.2	4.5	6.1	7.5	9.7	12.3	14.2	16.9	20.6	25.2
Deferred:		1.2	2.3	3.5	4.6	5.9	7.7	10.2	13.4	16.0	19.3	23.2	34.8

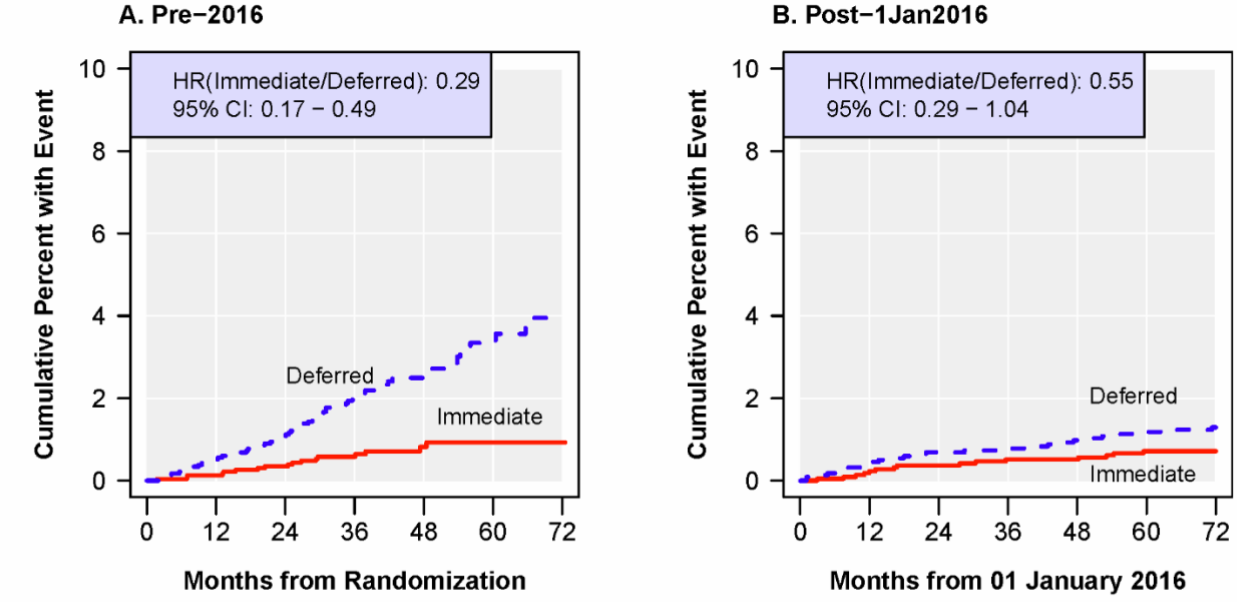
Figure S6. Kaplan-Meier curves of the cumulative percentage with the primary endpoint by treatment group for the period from randomization through 2021.



No. at Risk:												
Immediate:	2325	2295	2264	2219	2171	2117	2075	2009	1934	1387	741	382
Deferred:	2359	2301	2253	2189	2142	2090	2035	1965	1877	1329	671	329
Estimated Cumulative Pct with an Event:												
Immediate:		0.6	1.0	1.5	2.2	3.1	3.7	4.5	5.2	5.5	5.9	7.1
Deferred:		1.2	2.3	3.9	4.9	5.9	6.7	7.3	8.3	9.0	9.8	10.7

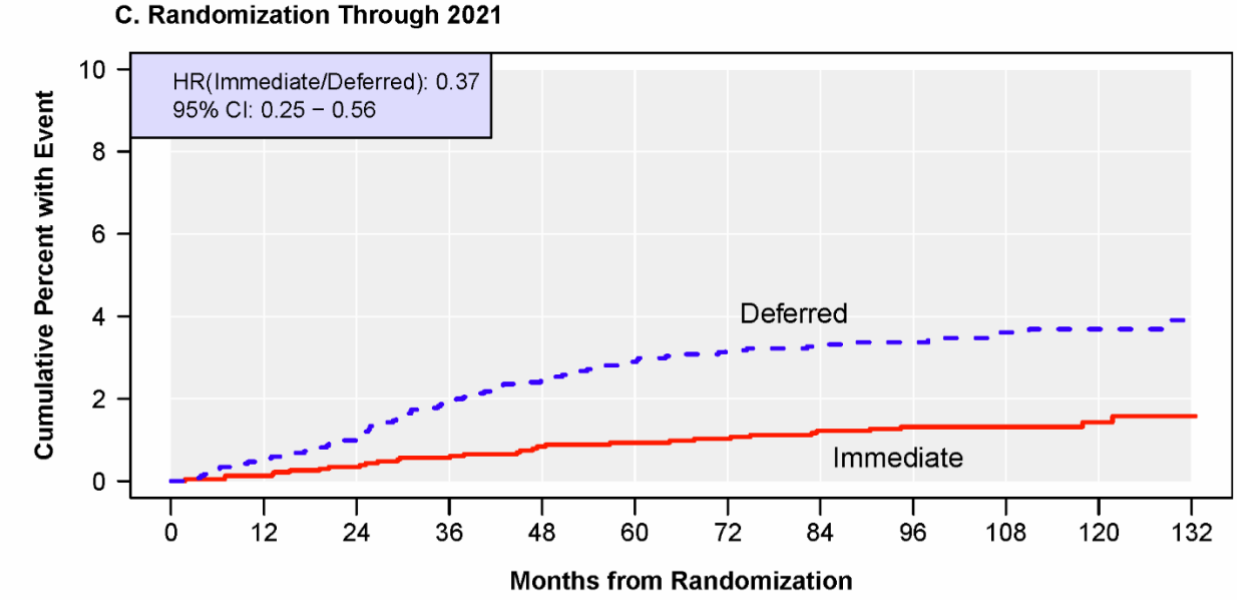
Figure S7. Kaplan-Meier curves for AIDS* by treatment group: A. Pre-2016 period, B. Post-1Jan2016 period, and C. randomization through 2021.

The cumulative percentage of participants developing serious AIDS (AIDS*) for the immediate (solid red) and deferred (dashed blue) groups is given for 3 time periods in Figure S7. Figure S7A and S7C show time measured from randomization for all randomized participants (n=4684). Figure S7B plots the percentages for months beginning 1Jan2016 through 31Dec2021 for the cohort of participants alive and who have not withdrawn consent as of 1Jan2016 (n=4436).



No. at Risk:							
Immediate:	2325	2299	2267	1630	889	475	53
Deferred:	2359	2312	2270	1638	880	445	40
Estimated Cumulative Pct with an Event:							
Immediate:		0.1	0.3	0.6	0.8	0.9	0.9
Deferred:		0.5	1.0	2.0	2.6	3.3	4.0

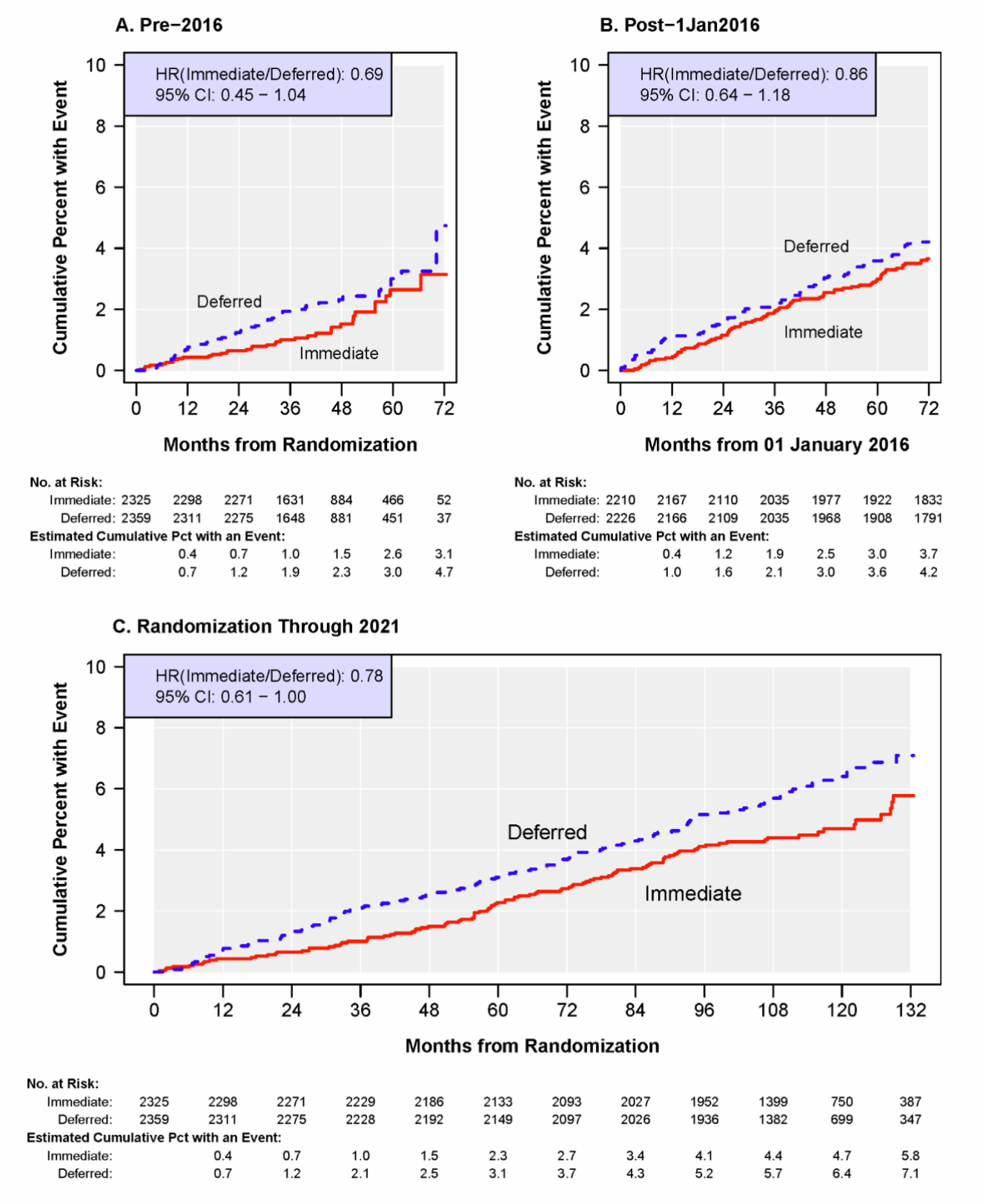
No. at Risk:							
Immediate:	2210	2165	2117	2045	1994	1938	1853
Deferred:	2226	2167	2113	2038	1976	1916	1799
Estimated Cumulative Pct with an Event:							
Immediate:		0.2	0.4	0.5	0.5	0.7	0.7
Deferred:		0.5	0.7	0.8	1.0	1.2	1.3



No. at Risk:												
Immediate:	2325	2299	2267	2228	2184	2141	2102	2040	1967	1414	760	397
Deferred:	2359	2312	2270	2211	2169	2123	2070	2002	1920	1370	705	350
Estimated Cumulative Pct with an Event:												
Immediate:		0.1	0.3	0.6	0.8	0.9	1.0	1.2	1.3	1.3	1.4	1.6
Deferred:		0.5	1.0	1.9	2.5	2.9	3.2	3.3	3.4	3.6	3.7	3.9

Figure S8. Kaplan-Meier curves for serious non-AIDS by treatment group: A. Pre-2016 period, B. Post-1Jan2016 period, and C. randomization through 2021.

The cumulative percentage of participants developing serious non-AIDS for the immediate (solid red) and deferred (dashed blue) groups is given for 3 time periods are given in Figure S8. The 3 time periods and the START participants considered in each graph are the same as Figure S7.



No. at Risk:

Immediate:	2325	2298	2271	1631	884	466	52
Deferred:	2359	2311	2275	1648	881	451	37

Estimated Cumulative Pct with an Event:

Immediate:	0.4	0.7	1.0	1.5	2.6	3.1
Deferred:	0.7	1.2	1.9	2.3	3.0	4.7

No. at Risk:

Immediate:	2210	2167	2110	2035	1977	1922	1833
Deferred:	2226	2166	2109	2035	1968	1908	1791

Estimated Cumulative Pct with an Event:

Immediate:	0.4	1.2	1.9	2.5	3.0	3.7
Deferred:	1.0	1.6	2.1	3.0	3.6	4.2

No. at Risk:

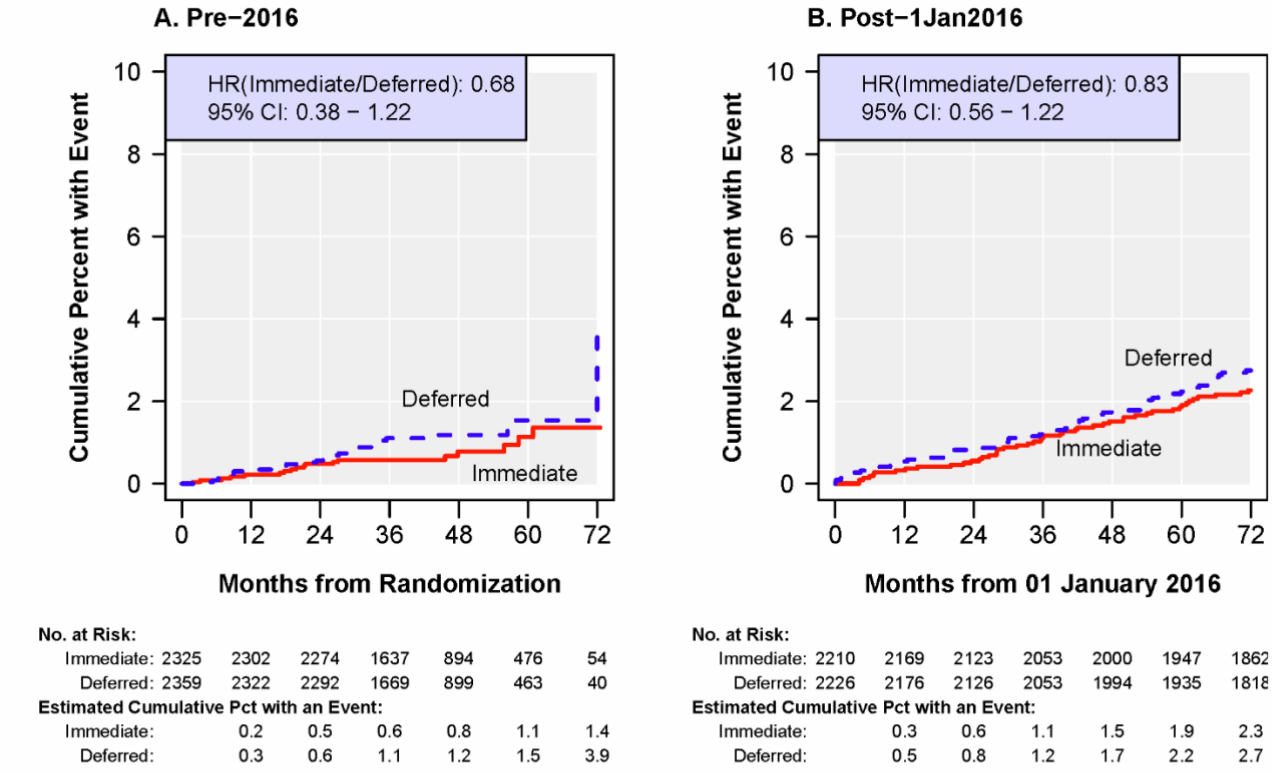
Immediate:	2325	2298	2271	2229	2186	2133	2093	2027	1952	1399	750	387
Deferred:	2359	2311	2275	2228	2192	2149	2097	2026	1936	1382	699	347

Estimated Cumulative Pct with an Event:

Immediate:	0.4	0.7	1.0	1.5	2.3	2.7	3.4	4.1	4.4	4.7	5.8
Deferred:	0.7	1.2	2.1	2.5	3.1	3.7	4.3	5.2	5.7	6.4	7.1

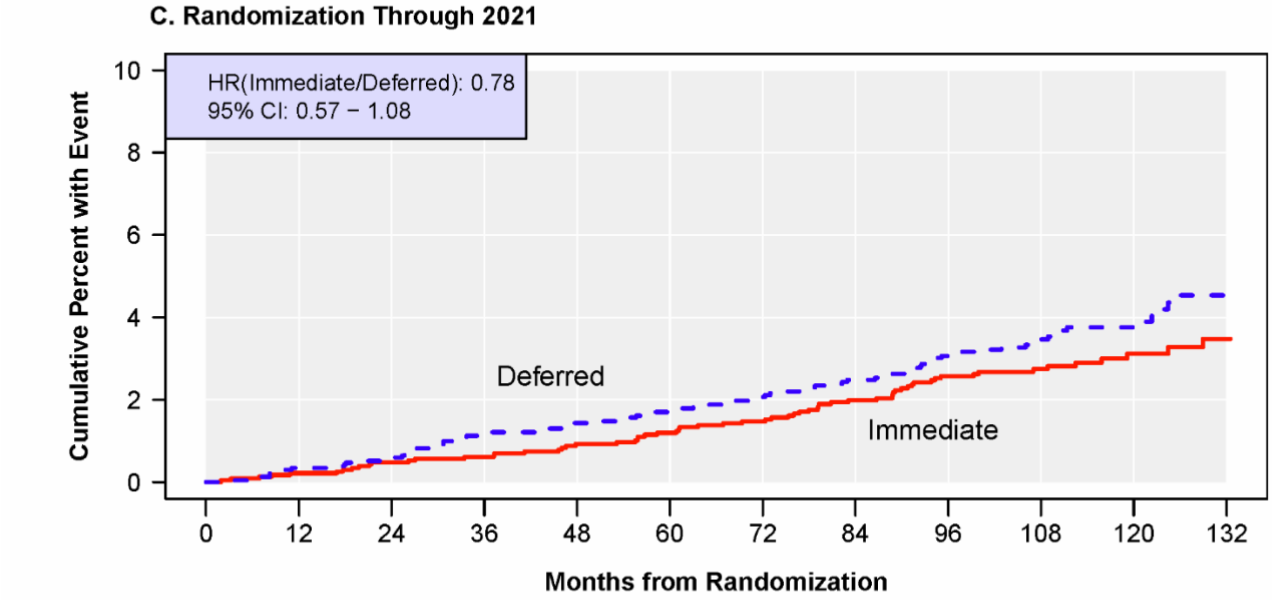
Figure S9. Kaplan-Meier curves for all-cause mortality by treatment group: A. Pre-2016 period, B. Post-1Jan2016 period, and C. randomization through 2021.

The cumulative percentage of participants dying from any cause for the immediate (solid red) and deferred (dashed blue) groups is given for 3 time periods are given in Figure S9. The 3 time periods and the START participants considered in each graph are the same as Figure S7.



No. at Risk:							
Immediate:	2325	2302	2274	1637	894	476	54
Deferred:	2359	2322	2292	1669	899	463	40
Estimated Cumulative Pct with an Event:							
Immediate:		0.2	0.5	0.6	0.8	1.1	1.4
Deferred:		0.3	0.6	1.1	1.2	1.5	3.9

No. at Risk:							
Immediate:	2210	2169	2123	2053	2000	1947	1862
Deferred:	2226	2176	2126	2053	1994	1935	1818
Estimated Cumulative Pct with an Event:							
Immediate:		0.3	0.6	1.1	1.5	1.9	2.3
Deferred:		0.5	0.8	1.2	1.7	2.2	2.7



No. at Risk:												
Immediate:	2325	2302	2274	2238	2199	2157	2120	2058	1986	1426	769	402
Deferred:	2359	2322	2292	2250	2219	2182	2133	2065	1981	1425	733	368
Estimated Cumulative Pct with an Event:												
Immediate:		0.2	0.5	0.6	0.9	1.2	1.5	2.0	2.6	2.7	3.1	3.5
Deferred:		0.3	0.6	1.2	1.4	1.7	2.1	2.5	3.1	3.5	3.8	4.5

Figure S10. Forest plot. Subgroup analyses for the primary endpoint for the period from randomization through 2021.

Pre-specified subgroups for the primary endpoint from randomization through 31Dec2021 are shown. All HRs are <1.0 favoring the immediate group. For reference, the HR for the primary endpoint for all participants for the full follow-up period, randomization through 2021, was 0.61 (95%CI: 0.49-0.76) (see Figure S6).

With one exception, the subgroups are defined used data collected prior to randomization. The one exception is a pre-specified subgroup defined by the follow-up completeness for sites during post-1Jan2016 period. Among the 218 START sites that collected data (see addendum to Statistical Analysis Plan),162 sites (74% of total) had at least 75% of participants with vital status known on December 31, 2021; for 18 of the 24 sites that closed, at least 75% of participants had a last known alive date within 90 days of the most recent withdrawal. These 18 sites are included among the 162 sites.

The remaining 56 sites (26% of total) had 25% or more of participants with unknown vital status on December 31, 2021; these 56 sites included 6 sites that closed that did not meet the criteria of having 75% or more participants with last known alive date within 90 days of the most recent withdrawal at the site. This subgroup analysis was carried out to assess the possible impact of missing data on the primary analysis. Findings for the two subgroups for the primary endpoint are similar: HRs are 0.59 and 0.65 for those with at least 75% of participants with vital status known at the end of the trial and for those with < 75%, respectively.

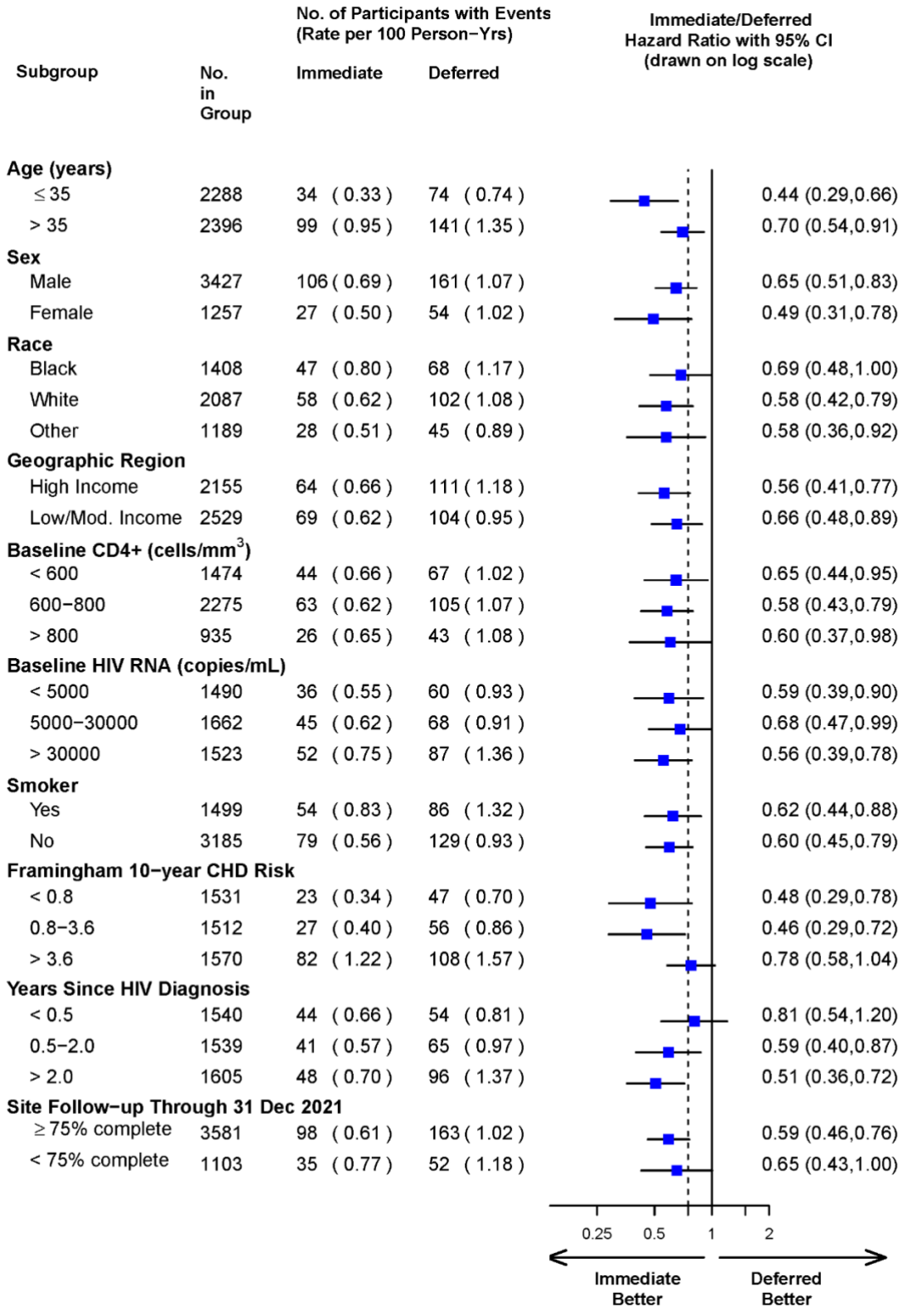

No. of Participants with Events (Rate per 100 Person−Yrs)
Immediate/Deferred Hazard Ratio with 95% CI (drawn on log scale)
Subgroup
No. in Group
Immediate
Deferred
Age (years)
≤ 35 2288 34 (0.33) 74 (0.74) 0.44 (0.29,0.66)
> 35 2396 99 (0.95) 141 (1.35) 0.70 (0.54,0.91)
Sex
Male 3427 106 (0.69) 161 (1.07) 0.65 (0.51,0.83)
Female 1257 27 (0.50) 54 (1.02) 0.49 (0.31,0.78)
Race
Black 1408 47 (0.80) 68 (1.17) 0.69 (0.48,1.00)
White 2087 58 (0.62) 102 (1.08) 0.58 (0.42,0.79)
Other 1189 28 (0.51) 45 (0.89) 0.58 (0.36,0.92)
Geographic Region
High Income 2155 64 (0.66) 111 (1.18) 0.56 (0.41,0.77)
Low/Mod. Income 2529 69 (0.62) 104 (0.95) 0.66 (0.48,0.89)
Baseline CD4+ (cells/mm3)
< 600 1474 44 (0.66) 67 (1.02) 0.65 (0.44,0.95)
600−800 2275 63 (0.62) 105 (1.07) 0.58 (0.43,0.79)
> 800 935 26 (0.65) 43 (1.08) 0.60 (0.37,0.98)
Baseline HIV RNA (copies/mL)
< 5000 1490 36 (0.55) 60 (0.93) 0.59 (0.39,0.90)
5000−30000 1662 45 (0.62) 68 (0.91) 0.68 (0.47,0.99)
> 30000 1523 52 (0.75) 87 (1.36) 0.56 (0.39,0.78)
Smoker
Yes 1499 54 (0.83) 86 (1.32) 0.62 (0.44,0.88)
No 3185 79 (0.56) 129 (0.93) 0.60 (0.45,0.79)
Framingham 10−year CHD Risk
< 0.8 1531 23 (0.34) 47 (0.70) 0.48 (0.29,0.78)
0.8−3.6 1512 27 (0.40) 56 (0.86) 0.46 (0.29,0.72)
> 3.6 1570 82 (1.22) 108 (1.57) 0.78 (0.58,1.04)
Years Since HIV Diagnosis
< 0.5 1540 44 (0.66) 54 (0.81) 0.81 (0.54,1.20)
0.5−2.0 1539 41 (0.57) 65 (0.97) 0.59 (0.40,0.87)
> 2.0 1605 48 (0.70) 96 (1.37) 0.51 (0.36,0.72)
Site Follow−up Through 31 Dec 2021
≥ 75% complete 3581 98 (0.61) 163 (1.02) 0.59 (0.46,0.76)
< 75% complete 1103 35 (0.77) 52 (1.18) 0.65 (0.43,1.00)
0.25
0.5
1
2
Immediate Better
Deferred Better

Table S1. Baseline characteristics, A. Selected baseline characteristics for the full cohort, and B. Characteristics by treatment group at the end of 2015 for those with follow-up in the post-1Jan2016 period.

The baseline characteristics in Table S1A have been previously published and provided here to facilitate the review of this paper.

Characteristics of participants at the end of 2015 for the cohort with follow-up in the post-1Jan2016 period, are summarized in Table S1B. At the last follow-up visit attended prior to 1 January 2016, 99% of participants in the immediate group and 85% in the deferred group were prescribed antiretroviral treatment; and the latest CD4+ count differed for the immediate and deferred group by 226 cells/mm^3.

Table S1A. Selected baseline characteristics.

Characteristic	Median [IQR] or No. (%)
No. randomized	4684
Age, years	36 [29, 44]
Female	1257 (27.3%)
Geographic region	
Africa	999 (21.3%)
Asia	356 (7.6%)
Australia	109 (2.3%)
Europe+Israel	1539 (32.9%)
USA	507 (10.8%)
South America + Mexico	1174 (25.1%)
CD4 cell count (cells/mm^3)	651 [584, 765]
HIV RNA (copies/mL)	12761 [3025, 43482]

Table S1B. Selected characteristics by treatment group at the end of 2015 (before 01Jan2016) for those with follow-up in the post-01Jan2016 period.

Characteristic	Immediate ART Median [IQR], Mean (SD), or No. (%)	Deferred ART Median [IQR], Mean (SD), or No. (%)	Total
No. alive and not withdrawn	**2210**	**2226**	**4436**
Follow-up accrued, years	3.6 [2.9, 4.8]	3.6 [2.9, 4.7]	3.6 [2.9, 4.8]
Latest CD4 (cells/mm^3)	870 [706, 1080]	644 [510, 822]	761 [585, 965]
Latest HV RNA ≤ 200 cp/mL	2063 (93.4%)	1618 (72.7%)	3681 (83.0%)
Initiated ART	2186 (98.9%)	1887 (84.8%)	4073 (91.8%)
Latest CD4 before ART initiation, (cells/mm^3)	694 (181)	496 (209)	602 (219)
Duration of ART use, years	3.5 [2.7, 4.6]	0.6 [0.3, 2.4]	2.6 [0.6, 3.8]
% of Follow-up time on ART	94.5%	35.5%	64.9%

Table S2. Baseline factors associated with starting antiretroviral therapy in the deferred group by 2016, univariate and multivariate analyses.

Baseline predictors of initiating treatment by 2016 are summarized in univariate and multivariable analyses using logistic regression that was stratified by 6 geographic regions: 1) Africa, 2) Asia, 3) Europe and Israel, 4) North America, 5) South America and Mexico, and 6) Australia). Age, gender, smoking status, years since being diagnosed with HIV were not associated with initiating treatment. The strongest associations with initiating ART by 2016 were lower CD4+ count and higher HIV RNA level.

	Univariate		**Multivariate**	
Baseline Covariate	**HR**	**95% CI**	**HR**	**95% CI**
Age (< 35 vs ≥ 35)	0.94	[0.86, 1.03]	0.96	[0.86, 1.08]
Male Gender	1.08	[0.96, 1.21]	0.89	[0.79, 1.01]
Black Race vs White	0.82	[0.70, 0.97]	0.83	[0.70, 0.8]
Other Race vs White	0.83	[0.72, 0.95]	0.80	[0.70, 0.93]
CD4 Count (per 100 cells)	0.91	[0.88, 0.94]	0.93	[0.90, 0.96]
Log10 HIV RNA	1.16	[1.13, 1.19]	1.15	[1.12, 1.18]
Smoker	0.98	[0.89, 1.08]	0.96	[0.86, 1.06]
Framingham Risk Score (5 points)	1.08	[1.03, 1.13]	1.07	[1.01, 1.14]
Years Since HIV Diagnosis	0.98	[0.97, 1.00]	0.99	[0.97, 1.00]
Site Follow-up completeness through 2021 (≥ 75 vs < 75%)	1.20	[1.06, 1.35]	1.18	[1.05, 1.34]
Number of participants	**2359**			
Number of events	**1924**			
Analysis using cox-regression stratified by region				
Program Name = TableS3_predstartart Run date = 13SEP2022 File Creation Date = 27JUL2022				

Table S3. Hazard ratios (HRs) for 2-year calendar periods, beginning in 2016 (post-1Jan2016).

Hazard ratios (immediate/deferred) for the primary endpoint increased from 0.65 in 2016-2017 to 0.91 in 2020-2021. Reflecting this increase, an expanded Cox model that included an interaction between the treatment indicator and log-transformed time measured in days indicated that the proportional hazards assumption was not met.

			Immediate		Deferred		
Event and Time Period	**No. Pts**	**Mean PY**	**N[a]**	**Rate[a]**	**N[a]**	**Rate[a]**	**HR[95% CI][b] Imm/Def**
Primary (AIDS, SNA, death)							
2016-2017	4436	1.95	32	0.74	50	1.15	0.65 [0.41, 1.01]
2018-2019	4200	1.93	31	0.76	35	0.86	0.88 [0.54, 1.42]
2020-2021	3926	1.94	26	0.68	28	0.74	0.91 [0.54, 1.56]

[a] N=number of participants with event; rate per 100 pt-years, based on time to first event (confirmed, probable).
[b] HR, time to first event. Cox proportional hazards model with treatment indicator and stratified by region.

Table S4. Comparison of treatment HRs between the pre-2016 and post-1Jan2016 periods in analyses where the post-1Jan2016 period excluded participants who previously experienced the event.

When HRs for the post-1Jan2016 excluded not only deaths and withdrawals as in the 1st cohort considered but also participants who experienced the same type of event during the pre-2016 period (2nd cohort), the results were similar.

Time Period	No. in Group	No. of Participants with Events (Rate per 100 Person−Yrs) Immediate	Deferred	Immediate/Deferred Hazard Ratio with 95% CI (drawn on log scale)
Primary (AIDS, SNA, Death)				
Pre−2016	4684	53 (0.61)	112 (1.29)	0.47 (0.34, 0.65)
Post−1Jan2016	4322	80 (0.66)	103 (0.88)	0.76 (0.56, 1.01)
Randomization−2021	4684	133 (0.64)	215 (1.06)	0.61 (0.49, 0.76)
AIDS or AIDS Death				
Pre−2016	4684	17 (0.20)	59 (0.67)	0.29 (0.17, 0.49)
Post−1Jan2016	4367	14 (0.11)	24 (0.20)	0.57 (0.29, 1.10)
Randomization−2021	4684	31 (0.15)	83 (0.40)	0.37 (0.25, 0.56)
SNA or non−AIDS Death				
Pre−2016	4684	37 (0.43)	54 (0.62)	0.69 (0.45, 1.05)
Post−1Jan2016	4391	70 (0.58)	83 (0.69)	0.84 (0.61, 1.15)
Randomization−2021	4684	107 (0.51)	137 (0.66)	0.78 (0.61, 1.00)
Death				
Pre−2016	4684	19 (0.22)	28 (0.32)	0.68 (0.38, 1.22)
Post−1Jan2016	4436	47 (0.38)	57 (0.46)	0.83 (0.56, 1.22)
Randomization−2021	4684	66 (0.31)	85 (0.40)	0.78 (0.57, 1.08)

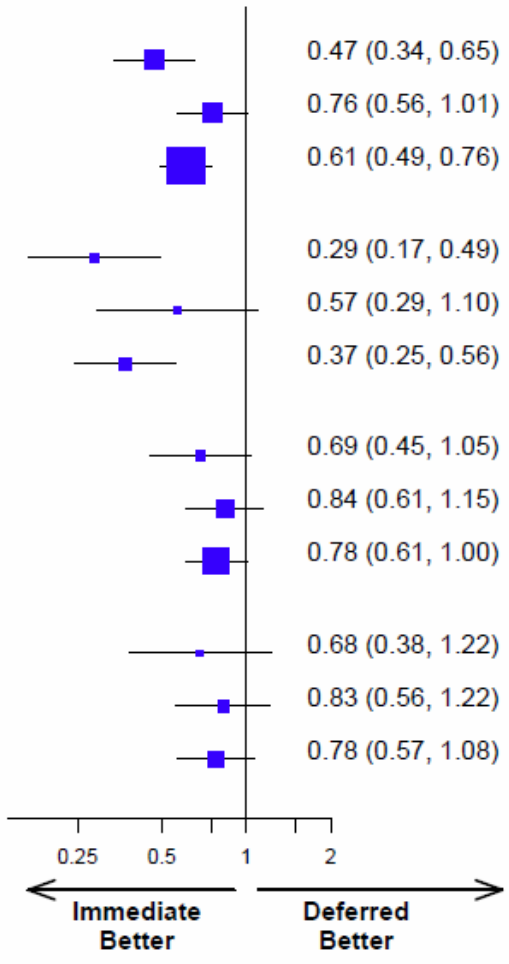


Table S5. HRs for the primary endpoint, pre-2016 and post- 1Jan2016, for sites with at least 75% of participants with known vital status on 31 December 2021.

Pre-2016 and post-1Jan2016 HRs for the primary endpoint were similar to HRs using all participants (see Figure 3) when the analysis was restricted to the 162 sites with the best follow-up.

			Immediate		Deferred		
Event and Time Period	**No. Pts**	**Mean PY**	**N[a]**	**Rate[a]**	**N[a]**	**Rate[a]**	**HR[95% CI][b] Imm/Def**
Primary (AIDS, SNA, death)							
< 2016	3581	3.70	37	0.56	83	1.25	0.44 [0.30, 0.65]
2016 through 2021	3440	5.62	66	0.68	87	0.90	0.76 [0.55, 1.04]

[a] N=number of participants with event; rate per 100 pt-years, based on time to first event (confirmed, probable).
[b] HR, time to first event. Cox proportional hazards model with treatment indicator and stratified by region.

Table S6. HRs for an expansion of the primary endpoint by time period to include events not considered confirmed or probable by the ERC.

When HRs for the primary endpoint for the pre-2016 and post-1Jan2016 period were estimated using all events reported and not only events considered confirmed or probable by the ERC, the results were similar to those that only used confirmed or probable events. For this analysis, the number of participants with a primary event pre-2016 increased from 165 to 205; during the post-1Jan2016 period, the number increased from 202 to 222.

			Immediate		Deferred		
Event and Time Period	**No. Pts**	**Mean PY**	**N[a]**	**Rate[a]**	**N[a]**	**Rate[a]**	**HR[95% CI][b] Imm/Def**
Primary (AIDS, SNA, death)							
< 2016	4684	3.68	62	0.72	143	1.67	0.43 [0.32, 0.58]
2016 through 2021	4436	5.47	99	0.81	123	1.02	0.80 [0.62, 1.04]

[a] N=number of participants with event; rate per 100 pt-years, based on time to first event (confirmed, probable).
[b] HR, time to first event. Cox proportional hazards model with treatment indicator and stratified by region.

Table S7. Summary of causes of death during the pre-2016, post-1Jan2016, and from randomization through 2021 by treatment group.

There were 47 deaths in the pre-2016 period and 104 deaths during the post-1Jan2016 period. Causes of death are summarized for these two periods and cumulatively (all 151 deaths) for both periods (randomization through 2021) by treatment group. The most common causes of death were non-AIDS malignancy, accidents/other violent deaths, and suicide; 23% of deaths had an unknown cause and 5% were found dead and the cause was not determined. Four deaths (3 immediate and 1 deferred) were attributed to SARS-CoV-2 infection.

	Pre-2016		**Post-1Jan2016**		**Rand. through 2021**	
	Imm.	**Def.**	**Imm.**	**Def.**	**Imm.**	**Def.**
Classification, Adapted CoDe System	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
AIDS, ongoing active disease	1 (5.3)	4 (14.3)	1 (2.1)	3 (5.3)	2 (3.0)	7 (8.2)
Infection, other	0 (0.0)	1 (3.6)	2 (4.3)	1 (1.8)	2 (3.0)	2 (2.4)
Infection, SARS-CoV-2	0 (0.0)	0 (0.0)	3 (6.4)	1 (1.8)	3 (4.5)	1 (1.2)
Chronic viral hepatitis	0 (0.0)	1 (3.6)	1 (2.1)	0 (0.0)	1 (1.5)	1 (1.2)
Non-AIDS malignancy, excl. hepatitis B/C related	2 (10.5)	3 (10.7)	8 (17.0)	11 (19.3)	10 (15.2)	14 (16.5)
Diabetes mellitus	0 (0.0)	1 (3.6)	1 (2.1)	1 (1.8)	1 (1.5)	2 (2.4)
MI or other ischemic heart disease	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.5)	0 (0.0)
Stroke	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)	2 (2.4)
Lung embolism	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.5)	0 (0.0)
Chronic obstructive lung disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	1 (1.2)
Liver failure, excl. hepatitis B/C related	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)	2 (2.4)
Renal failure	0 (0.0)	1 (3.6)	1 (2.1)	0 (0.0)	1 (1.5)	1 (1.2)
Accident/other violent death, excl. suicide	5 (26.3)	4 (14.3)	3 (6.4)	4 (7.0)	8 (12.1)	8 (9.4)
Suicide	1 (5.3)	4 (14.3)	4 (8.5)	7 (12.3)	5 (7.6)	11 (12.9)
Substance abuse	0 (0.0)	2 (7.1)	2 (4.3)	3 (5.3)	2 (3.0)	5 (5.9)
Heart or vascular, other causes	3 (15.8)	2 (7.1)	2 (4.3)	0 (0.0)	5 (7.6)	2 (2.4)
Respiratory disease, other causes	1 (5.3)	0 (0.0)	1 (2.1)	0 (0.0)	2 (3.0)	0 (0.0)
Urogenital disease, other causes	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	1 (1.2)
Obstetric complications	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	1 (1.2)
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	1 (1.2)
Unknown	4 (21.1)	3 (10.7)	13 (27.7)	14 (24.6)	17 (25.8)	17 (20.0)
Sudden	2 (10.5)	0 (0.0)	0 (0.0)	1 (1.8)	2 (3.0)	1 (1.2)
Found dead	0 (0.0)	2 (7.1)	3 (6.4)	3 (5.3)	3 (4.5)	5 (5.9)
Total Deaths	***19***	***28***	***47***	***57***	***66***	***85***

Table S8. Number of participants who developed specific AIDS events by time period and treatment group: A. Pre-2016 and B. Post-1Jan2016

During the pre-2016 period (randomization through 2015), the most common serious AIDS (AIDS*) events were tuberculosis and cancer (Kaposi's sarcoma and lymphoma). These events were also the most common events post-1Jan2016.

Non-fatal esophageal candidiasis and *Herpes simplex* events are also summarized in Table S8. These events were not considered serious AIDS events.

Table S8A. Number of participants who developed specific AIDS* events by treatment group, pre-2016.

	Immediate		Deferred	
Event	**N[a]**	**Rate[a]**	**N[a]**	**Rate[a]**
AIDS*				
Bacterial pneumonia	0	0.00	2	0.02
Tuberculosis, pulmonary or extrapulmonary	8	0.09	26	0.30
Cytomegalovirus, meningoencephalitis, radiculomyelitis, retinitis, other	1	0.01	0	0.00
Herpes zoster, disseminated	0	0.00	3	0.03
Cryptococcosis, meningitis or extrapulmonary	1	0.01	0	0.00
Pneumocystis jirovecii pneumonia	1	0.01	5	0.06
Cervical carcinoma, invasive	1	0.01	0	0.00
Kaposi's sarcoma, mucocutaneous or visceral	1	0.01	13	0.15
Lymphoma, primary, of the brain	0	0.00	1	0.01
Lymphoma, Hodgkin's	2	0.02	1	0.01
Lymphoma, non-Hodgkin's, all cell types	2	0.02	10	0.11
AIDS-Death	1	0.01	4	0.05
any of the above	***17***	***0.20***	***59***	***0.67***
Other AIDS				
Candidiasis, esophageal	1	0.01	8	0.09
Herpes simplex	2	0.02	0	0.00
Any AIDS (expanded)	***19***	***0.22***	***66***	***0.76***
No. of pts	***2325***		***2359***	
Mean follow-up time (years)	***3.76***		***3.75***	

* Co-primary endpoint. Excludes non-fatal esophageal candidiasis and chronic herpes simplex.

[a] N=number of pts with event; rate per 100 pt-years, based on time to first event. Includes events that are confirmed, probable per ERC review; fatal or non-fatal.

Table S8B: Number of participants who developed specific AIDS* events by treatment group, post-1Jan2016.

	Immediate		Deferred	
Event	**N[a]**	**Rate[a]**	**N[a]**	**Rate[a]**
AIDS*				
Toxoplasmosis of the brain	0	0.00	2	0.02
Bacterial pneumonia	1	0.01	1	0.01
Mycobacterium avium complex, disseminated	0	0.00	1	0.01
Tuberculosis, pulmonary or extrapulmonary	9	0.07	10	0.08
Cryptococcosis, meningitis or extrapulmonary	0	0.00	1	0.01
Pneumocystis jirovecii pneumonia	1	0.01	1	0.01
Cervical carcinoma, invasive	0	0.00	1	0.01
Kaposi's sarcoma, mucocutaneous or visceral	1	0.01	4	0.03
Lymphoma, primary, of the brain	0	0.00	1	0.01
Lymphoma, Hodgkin's	2	0.02	1	0.01
Lymphoma, non-Hodgkin's, all cell types	2	0.02	6	0.05
AIDS-Death	1	0.01	3	0.02
any of the above	***15***	***0.12***	***27***	***0.22***
Other AIDS				
Candidiasis, esophageal	1	0.01	1	0.01
Herpes simplex	0	0.00	1	0.01
Any AIDS (expanded)	***15***	***0.12***	***29***	***0.24***
No. of pts	***2210***		***2226***	
Mean follow-up time (years)	***5.59***		***5.54***	

* Co-primary endpoint. Excludes non-fatal esophageal candidiasis and chronic herpes simplex.

[a] N=number of pts with event; rate per 100 pt-years, based on time to first event. Includes events that are confirmed, probable per ERC review; fatal or non-fatal.

Table S9. Number of participants who developed specific serious-non AIDS events by time period and treatment group: A. Pre-2016 and B. Post-1Jan2016

Non-AIDS cancer and cardiovascular disease (CVD) were the most common serious non-AIDS evens in both time periods for the immediate and deferred groups. Non-AIDS cancer rates are summarized in Table S10. During the pre-2016 period, CVD (myocardial infarction, coronary revascularization or stroke) occurred for 16 participants in the immediate ART group and 15 participants in the deferred ART group. Post-1Jan2016, there were 20 participants in the immediate ART group and 23 in the deferred ART group with a CVD event.

Table S9A. Number of participants who developed specific serious non-AIDS (SNA) events by treatment group, pre-2016.

	Immediate		Deferred	
Event	**N[a]**	**Rate[a]**	**N[a]**	**Rate[a]**
Serious non-AIDS (SNA)[c] or non-AIDS death				
Acute myocardial infarction	8	0.09	5	0.06
Coronary revascularization	10	0.11	5	0.06
Stroke	1	0.01	4	0.05
Non-AIDS death, CVD	5	0.06	2	0.02
any CVD (fatal/non-fatal)	*16*	*0.18*	*15*	*0.17*
End-stage renal disease	1	0.01	1	0.01
Non-AIDS death, renal	0	0.00	1	0.01
any renal (fatal/non-fatal)	*1*	*0.01*	*2*	*0.02*
Decompensated liver disease	0	0.00	0	0.00
Non-AIDS death, liver	0	0.00	1	0.01
any liver (fatal/non-fatal)	*0*	*0.00*	*1*	*0.01*
Cancer, non-AIDS	9	0.10	20	0.23
Non-AIDS death, cancer	2	0.02	3	0.03
any cancer (fatal/non-fatal)	*9*	*0.10*	*20*	*0.23*
Non-AIDS death, other	11	0.13	17	0.19
any of the above	***37***	***0.43***	***54***	***0.62***
No. of pts	***2325***		***2359***	
Mean follow-up time (years)	***3.76***		***3.75***	

[a] N=number of pts with event; rate per 100 pt-years, based on time to first event.

[c] Includes events that are confirmed or probable per ERC review; fatal or non-fatal.

Table S9B. Number of participants who developed specific serious non-AIDS (SNA) events by treatment group, post-1Jan2016.

	Immediate		Deferred	
Event	**N[a]**	**Rate[a]**	**N[a]**	**Rate[a]**
Serious non-AIDS (SNA) or non-AIDS death				
Acute myocardial infarction	10	0.08	8	0.07
Coronary revascularization	11	0.09	11	0.09
Stroke	5	0.04	9	0.07
Non-AIDS death, CVD	3	0.02	3	0.02
any CVD (fatal/non-fatal)	*20*	*0.16*	*23*	*0.19*
End-stage renal disease	3	0.02	3	0.02
Non-AIDS death, renal	1	0.01	0	0.00
any renal (fatal/non-fatal)	*3*	*0.02*	*3*	*0.02*
Decompensated liver disease	0	0.00	3	0.02
Non-AIDS death, liver	0	0.00	2	0.02
any liver (fatal/non-fatal)	*0*	*0.00*	*3*	*0.02*
Cancer, non-AIDS	22	0.18	26	0.21
Non-AIDS death, cancer	9	0.07	11	0.09
any cancer (fatal/non-fatal)	*22*	*0.18*	*26*	*0.21*
Non-AIDS death, other	33	0.27	38	0.31
any of the above	***76***	***0.62***	***88***	***0.72***
No. of pts	***2210***		***2226***	
Mean follow-up time (years)	***5.59***		***5.54***	

[a] N=number of pts with event; rate per 100 pt-years, based on time to first event.
Includes events that are confirmed or probable per ERC review; fatal or non-fatal.

Table S10. Number of participants who developed any cancer, serious AIDS cancer, and serious non-AIDS cancer, by follow-up period (pre-2016 and post-2016) and treatment group.

Cancer outcomes (serious AIDS, serious non-AIDS, and total) are summarized for the pre-2016 and post-1Jan2016 periods and the HRs for the two periods for each event are compared.

			Immediate		Deferred		
Event and Time Period	**No. Pts**	**Mean PY**	**N[a]**	**Rate[a]**	**N[a]**	**Rate[a]**	**HR[95% CI][b] Imm/Def**
Cancer (AIDS or non-AIDS) or related death							
< 2016	4684	3.73	15	0.17	45	0.51	0.33 [0.19, 0.60]
2016 through 2021	4436	5.53	26	0.21	37	0.30	0.70 [0.43, 1.16]
Non-AIDS cancer or related death							
< 2016	4684	3.74	9	0.10	20	0.23	0.45 [0.21, 0.99]
2016 through 2021	4436	5.54	22	0.18	26	0.21	0.85 [0.48, 1.50]
AIDS cancer or related death							
< 2016	4684	3.74	6	0.07	25	0.28	0.24 [0.10, 0.59]
2016 through 2021	4436	5.55	5	0.04	13	0.11	0.38 [0.14, 1.07]

[a] N=number of participants with event; rate per 100 pt-years, based on time to first event (confirmed, probable).
[b] HR, time to first event. Cox proportional hazards model with treatment indicator and stratified by region.