Long term benefits from early antiretroviral therapy initiation in HIV infection

INSIGHT Strategic Timing of AntiRetroviral Treatment (**START**) Study Group*

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ABSTRACT (250 words)

Background: For people with HIV and CD4+ count >500 cells/mm^3, early initiation of antiretroviral therapy reduces serious AIDS and serious non-AIDS (SNA) risk compared to deferral of treatment until CD4+ <350 cells/mm^3. Whether excess risk of AIDS and SNA persists once ART is initiated for those who defer treatment is uncertain.

Methods: The START trial, as previously reported, randomized 4684 ART-naïve HIV+ adults with CD4+ >500 cells/mm^3 to immediate treatment initiation following randomization (n=2325) or deferred treatment (n= 2359). In 2015, a 57% lower risk of the primary endpoint (AIDS, SNA or death) for the immediate group was reported, and the deferred group was offered ART; this article reports the follow up that continued to 31Dec2021. Cox models were used to compare hazard ratios (HRs) for the primary endpoint from randomization through 31Dec2015 with 1Jan2016 through 31Dec2021.

Results: As reported previously, through 31Dec2015, median CD4+ count was 648 and 460 cells/mm^3 in immediate and deferred groups at treatment initiation; the percentage of follow-up time spent on ART was 95% and 36% for the immediate and deferred groups; the time-averaged CD4+ difference was 199 cells/mm^3. Post-1Jan2016, the percentage of follow-up time on treatment was 97.2% and 94.1% for the immediate and deferred groups; the CD4+ count difference was 155 cells/mm^3. Post-1Jan2016, 89 immediate and 113 deferred group participants experienced a primary endpoint; HR=0.79 (95% CI, 0.60 to 1.04; p=0.09) versus 0.47 (95% CI, 0.34 to 0.65, p<0.001) before 2016 (p=0.02 for HR difference).

Conclusions: Among adults with CD4+ count >500, excess risk of AIDS and SNA associated with delaying treatment initiation was diminished after antiretroviral treatment initiation, but persistent excess risk remained.

INTRODUCTION

In 2015, a recommendation to initiate antiretroviral therapy in people as soon as possible after HIV diagnosis, regardless of CD4+ count became globally accepted.[1,2] This followed the reporting of interim findings of the Strategic Timing of AntiRetroviral Treatment (START)[3,4] and TEMPRANO studies in 2015.[5] The planning of START began following the interim report of the Strategies for Management of Antiretroviral Therapy (SMART) in 2006 .[6] SMART established that interrupting antiretroviral therapy (ART) increased the risk of both AIDS and serious non-AIDS outcomes. The results of SMART in 2006 provided the necessary impetus to initiate a study of whether to begin lifelong ART in people living with HIV who had a CD4 count of above 500 cells/mm^3, a question about which there was substantial uncertainty.[7]

START was designed to determine whether immediate initiation of ART following randomization by adults with HIV and CD4+ count greater than 500 cells/mm^3 reduced major morbidity and mortality, compared to deferral of ART until the CD4+ count declined to <350 cells/mm^3 or AIDS developed.[8] After an average of 3 years of follow-up, the risk of the primary composite endpoint of serious AIDS or serious non-AIDS was reduced by 57% among those randomized to immediate initiation of ART compared to those randomized to deferred ART initiation.[4]

Globally, delays in diagnosis of HIV and initiation of ART remains an important public health challenge.[9-11] Experimental evidence that quantifies the long-term excess risk from delayed diagnosis and delayed treatment initiation is lacking.

After the interim findings from the START trial were reported, participants in the deferred group were advised to initiate ART, if they had not already done so, and both treatment

groups were followed until the end of 2021. The primary objective of the 6-year extended follow-up reported herein was to determine whether excess risk due to deferring ART was maintained, increased, or reduced. The randomized design of START was ideally suited to inform this question.

METHODS

The International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) (Supplemental Appendix, Section 1) designed and conducted START.

Participants

As described previously, people with HIV who were 18 years or older and had not yet initiated ART, had no history of AIDS and were in general good health, were eligible for the study if they had two CD4+ cell counts greater than 500 cells/mm^3. [4,8] Full eligibility details are in the Supplemental Appendix (Section 3). The study was approved by the ethics committees at participating sites; written informed consent was obtained from all participants.

Study Design

The START study evaluated two strategies for initiating ART: 1) immediate initiation of ART following randomization; and 2) deferral of ART until the CD4+ count declined to <350 cells/mm^3, or when AIDS or other conditions that dictated use of ART (e.g., pregnancy) occurred.

Participants were randomized to the immediate and deferred treatment groups with equal probability.[4,8] ART that was consistent with Department of Health and Human Services

guidelines was donated through 2017 and provided to sites through a central drug repository. The 2.5-year period between 2015, when the START study results were originally reported, and 2017 provided sites the time needed to transition participants in both treatment groups from the centrally provided ART to locally obtained ART; as noted below, the sites were - successful in so doing.

The primary endpoint was a composite outcome that included: 1) Serious AIDS or death from AIDS ("Serious AIDS"): opportunistic events consistent with the 1993 CDC expanded surveillance definition[12] plus Hodgkin's lymphoma. Non-fatal esophageal candidiasis and *Herpes simplex* virus infection were not counted as primary events because of their lesser severity; and 2) Serious non-AIDS.[13] or death not related to AIDS ("Serious non-AIDS"): cardiovascular disease (CVD), end-stage renal disease, liver disease, non-AIDS defining cancer (except basal or squamous cell skin cancer), and death not attributable to AIDS or one of the non-AIDS conditions (Supplemental Appendix, Section 3).

An Endpoint Review Committee (ERC), blinded to treatment group, reviewed all reported Serious AIDS and non-AIDS events and deaths using pre-established criteria. Events considered confirmed or probable by the ERC were counted as endpoints.

Secondary endpoints included Serious AIDS, Serious non-AIDS, and death from any cause (Section 3 of the Supplemental Appendix provides additional details on the primary endpoint and its components).

Follow-up

Participants were seen every 4 months through 2015; during 2016 and 2017, follow-up visits were conducted every 6 months; and for 2018 through 2021, data collection was

carried out annually. For the last year of data collection, sites were asked to confirm the primary and secondary endpoints status of each participant as of 31 December 2021.

The authors vouch for the accuracy and completeness of the analyses and data reported. The primary funding organization participated in the preparation of the protocol and the manuscript.

Statistical Analysis

In version 4.0 of the protocol for long-term follow-up (see Protocol and Section 4.0 of the Supplemental Appendix), two overarching scientific hypotheses were formulated for the period after 2015 : 1) the HIV-RNA hypothesis – the primary endpoint event rate in the immediate and deferred group will be similar between 2016 and 2021, because ART use and HIV RNA levels after 2015 would be similar for the two treatment groups, and 2) the nadir CD4+ count hypothesis - the primary endpoint rate in the deferred group would remain substantially higher than in the immediate group between 2016 and 2021, as a consequence of initiating ART at a lower CD4+ count an estimated 2.5 years after the immediate ART group. (See Supplemental Appendix, Section 3 for the rationale for two hypotheses and Section 5 for power considerations.) No corresponding statistical hypotheses were formulated in terms of predetermined boundaries for the treatment difference in the primary endpoint event rate (hazard ratio for the immediate versus deferred ART group). Therefore, results are not reported as distinguishing between the two hypotheses from the data gathered; the extent to which excess risk due to deferring ART was reduced is described by the HRs and their 95% CI for the periods pre and post 1 Jan 2016 as detailed below.

Time-to-event methods including Kaplan-Meier survival curves and Cox proportional hazards regression models, stratified by geographical region, were used to compare the immediate and deferred randomized treatment groups for three time periods: 1) from randomization through 2015 (pre-2016); 2) from 2016 through 2021 (post-1Jan2016); and 3) from randomization through 2021.

Hazard ratios (HRs) for the immediate versus deferred group for the pre-2016 and post-1Jan2016 periods were estimated using a single Cox model that included data from randomization through 2021 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 interaction term assesses the extent to which the HRs differ for the pre-2016 and post-1Jan2016 periods.

P-values and confidence intervals were not adjusted for multiplicity and results should not be considered clinically directive. Additional analysis details are given in the Supplemental Appendix (Sections 5 and 6). Statistical analyses were done using SAS, version 9.4 (SAS Institute), or R, version 4.0 (R Foundation).

RESULTS

As reported previously, from April 2009 through December 2013, 4,684 participants were randomly assigned to receive immediate (n=2325) or deferred (n=2359) ART (Figure S1). Participants were enrolled at 215 sites in 35 countries. Selected baseline characteristics

are given in Table S1A. The participants enrolled were globally representative of adults with HIV who had not initiated ART (Supplemental Appendix, Section 2).

In the next two sections we summarize treatment comparisons for ART use, HIV RNA level and CD4+ cell count during the pre-2016 and post-1Jan2016 periods. These sections are followed by summaries of primary and secondary endpoint comparisons for this report of extended follow-up.

For the pre-2016 period, analyses are based on all randomized participants (2,325 in the immediate group and 2,359 in the deferred group). At the beginning of the post-1Jan2016 period, 4,436 randomized participants (2,210 in the immediate group and 2,226 in the deferred group) were alive, had not withdrawn consent, and had vital status determined in the post-1Jan2016 period; of these, 4,322 participants (2,177 in the immediate group and 2,145 in the deferred group) had not experienced a primary event (Figure S1).

Pre-2016: Immediate compared with deferred antiretroviral therapy

The median (25^{th}, 75^{th} percentile) follow-up was 3.6 (2.9, 4.8) years during the pre-2016 follow-up period. The distribution of CD4+ cell counts at the time of treatment initiation is shown in Figure S2; as expected, the median CD4+ count in the immediate group was comparable to the baseline count (648 and 651 cells/mm^3, respectively) but lower (460 cells/mm^3) in the deferred group.

Figures 1A and 2A summarize ART use and HIV RNA levels and CD4+ count, respectively, from randomization through the end of 2015. The percentage of follow-up time spent on therapy was 95% for the immediate group and 36% for the deferred group.

Almost all participants on ART achieved HIV RNA level ≤ 200 copies/mL. ART was initiated in the deferred arm a median (IQR) of 2.5 (1.6, 3.5) years after randomization. Large differences in the CD4+ cell counts were observed soon after randomization and the time-averaged difference between treatment groups during this period was 199 cell/mm^3 (95% CI: 190-208) (Figure 2A).

Post-1Jan2016: antiretroviral therapy for all participants

By the end of 2015, for the cohort of 4,436 participants followed from 2016 through 2021 (Figure S1), 99% of the immediate group and 85% of the deferred group had initiated ART (Table S1B). Figures 1B and 2B summarize ART and HIV RNA levels and CD4+ count, respectively, from the beginning of 2016 through 2021. In the deferred group, lower CD4+ count and higher HIV RNA level were strongly associated with initiating therapy by 2016 (Table S2). During the post-1Jan2016 period, the percentage of follow-up time during which participants were receiving ART was 97.2% for the immediate group and 94.1% for the deferred group. As in the pre-2016 period, initiation of ART led to rapid declines in HIV RNA levels to ≤ 200 copies/mL. The time-averaged CD4+ count difference during this period was 155 cell/mm^3 (95% CI: 148-168) (Figure 2B).

Figures S3 and S4 provide similar summaries for ART/HIV RNA and CD4+ count over the full follow-up period from randomization through 2021 for all 4,684 randomized participants. At the end of follow-up for all randomized participants, primary endpoint status and vital status on 31 December 2021 was verified for 82.5% and 81.8%, respectively (Figures S1 and S5).

Primary endpoint

The rate of the composite primary endpoint declined in the deferred group from 1.29 per 100 person years during the pre-2016 period to 0.93 per 100 person years during the post-1Jan2016 periods; rates for these two time periods for the immediate group were 0.61 and 0.73 per 100 person years. The HR (immediate/deferred) increased from 0.47 (95% CI: 0.34-0.65) in pre-2016 to 0.79 (95% CI: 0.60-1.04) in the post-1Jan2016 period (p=0.02 for difference) (Figures 3, 4A, and 4B); the increase in the HR denotes a decrease in the treatment difference between the immediate and deferred groups post-1Jan2016 compared with the pre-2016 time period. The increase in the HR, expressed as the ratio between the HRs for the post-1Jan2016 and the pre-2016 period, was 1.67 (95% CI: 1.09-2.96); a ratio > 1.0 indicates a higher HR (and smaller treatment difference) in the post-1Jan2016 period compared to the pre-2016 period. HRs increased from 0.65 (95% CI: 0.41-1.01) in 2016-2017 to 0.88 (95% CI: 0.54-1.42) in 2018-2019, and 0.91 (95% CI: 0.54-1.56) in 2020-2021; p=0.04 for the test of proportional hazards (Table S3).

For the above analyses, participants who developed the primary endpoint before 2016 and survived were included in the post-1Jan2016 cohort and followed for a new event. When participants who experienced the primary event pre-2016 are excluded in the post-1Jan2016 period, i.e., a time to first event analysis, results are similar (Table S4).

During the median (IQR) 9.3 (8.5, 10.4) years (average 9.0 years) of follow-up from randomization through the end of follow-up in 2021, the HR for the primary endpoint was 0.61 (95% CI, 0.49 - 0.76) (Figure S6).

The impact of missing data on the primary endpoint results was assessed using data from 162 sites with the most complete follow-up; this accounted for 3,581 out of 4,684 enrolled

participants. HRs were similar to those for all participants (Table S5). Findings were also consistent with the inclusion of additional endpoints reported to the endpoint review committee but on adjudication were not considered to fulfill the definition of the primary endpoint (Table S6).

Components of the primary endpoint

HRs for the pre-2016 and post-1Jan2016 periods, and for randomization through 2021 for serious AIDS and serious non-AIDS, and for all-cause mortality are summarized in Figure 3; Kaplan-Meier curves for the three time periods are given in Figures S7, S8, and S9. The difference in HRs between the post-1Jan2016 and pre-2016 periods expressed as the ratio between the two HRs was 1.91 (95% CI: 0.83-4.29) for serious AIDS, 1.26 (95% CI: 0.75, 2.11) for serious non-AIDS and, 1.21 (95%CI: 0.60, 2.44) for death (Figure 3).

Causes of death are summarized in Table S7. Cause of death could not be ascertained for 33 of the 104 deaths (32%) (16 in the immediate group and 17 in the deferred group) during the post-1Jan2016 period. Among participants for whom the cause was determined, non-AIDS cancer was the most common cause of death (8 immediate and 11 deferred); this was followed by suicide (4 immediate and 7 deferred).

Tuberculosis and AIDS-defining cancers were the most common AIDS events (Tables S8A and S8B). The rate of tuberculosis in the deferred group declined from 0.30 per 100 person years pre-2016 to 0.08 per 100 person years in the post-1Jan2016 period and treatment HRs for the pre-2016 and post-1Jan2016 periods were 0.31 (95% CI: 0.14-0.68) and 0.89 (95% CI: 0.36-2.20), respectively. AIDS-defining cancer rates were 0.07 per 100 person years for the immediate group and 0.28 per 100 person years for the deferred group in the pre-2016 period and 0.04 for the immediate group and 0.11 for the deferred

group in the post-1Jan2016 period. The corresponding HRs (immediate/deferred) for the pre-2016 and post-1Jan2016 periods were: 0.24 (95% CI: 0.10-0.59) and 0.38 (95% CI: 0.14-1.07), respectively (Table S10).

The most common serious non-AIDS events were cancer and CVD (Tables S9A and S9B). For non-AIDS cancer, HRs for the pre-2016 and post-1Jan2016 periods were 0.45 (95% CI: 0.21-0.99) and 0.85 (95% CI: 0.48-1.50), respectively (Table S10). Findings for all cancers (AIDS and SNA) are also summarized in Table S10. For CVD, HRs for the pre-2016 and post-1Jan2016 periods were 1.07 (95% CI: 0.53-2.17) and 0.87 (95% CI: 0.48-1.59).

Kaplan-Meier curves from randomization through 2021 are shown in Figures S7, S8, and S9. HRs for serious AIDS, serious non-AIDS and all-cause mortality through 2021 were 0.37 (95% CI: 0.25-0.56), 0.78 (95% CI: 0.61-1.00), and 0.78 (95% CI: 0.57-1.08).

Primary endpoint according to subgroups

Outcomes of subgroups based on characteristics at baseline and follow-up experience for the primary endpoint over the post-1Jan2016 follow-up period are summarized in Figure 5 for the post-1Jan2016 period and in Figure S7 for the full follow-up period. In the post-1Jan2016 period, the HR(immediate/deferred) among those older than 35 years (median age at entry) was 1.04 compared to 0.42 for those 35 years or younger. The absolute excess risk from deferring ART expressed as the difference in rates between the immediate and deferred groups was -0.45 per 100 person years (95% CI: -0.71, -0.18) among younger participants compared to +0.04 (95% CI: -0.33, 0.41) among older participants. When age was considered as a continuous variable, the HR (immediate/deferred) increased by 47% (95% CI: 14%-88%) per 10 years older age.

Apart from age, there was no evidence for heterogeneity in HRs for the subgroups including sex, self-declared race, and geographical region for the primary endpoint in the post-1Jan2016 or follow-up period from randomization through 2021. Of note, the HRs for sites categorized by their completeness of follow-up, were quite similar.

DISCUSSION

In 2015, we reported from this large, international, randomized study involving previously untreated adults with HIV and a CD4+ count of more than 500 cells/mm^3, that immediate initiation of ART following randomization was superior to deferral of therapy until the CD4+ count declined to <350 cells/mm^3 or AIDS developed. During 6 years of additional follow-up after recommending initiation of antiretroviral therapy in all participants, we report on the diminished, yet persistent, excess risk of serious clinical disease and lower immune recovery from deferring therapy once therapy was initiated in this group of participants.

Although the excess risk of developing AIDS, non-AIDS, or death was substantially reduced in the deferred group after 2015, there remained 1.27-fold (1/0.79) excess risk from 2016 through 2021 of this composite endpoint among those allocated initially to deferring ART compared to those initiating therapy immediately after randomization (albeit that the 95% CI just included zero excess risk). When comparing this to a 2.13-fold (1/0.47) excess risk during follow-up period before 2016, the decline in excess risk was statistically significant (P=0.02). Of note, the reduction in risk, as reflected by the difference in HRs between the two time periods, may vary by the type of disease and this is the subject of further study.

A potential explanation for the enduring excess risk is the fact that the CD4+ count remained clearly lower in the deferred arm participants. Part of the explanation for this could be, that the percentage of follow-up time 2016-2021 not spent on ART was higher in the deferred compared with the immediate group, albeit only slightly, and especially in the first two years post-1Jan2016. This incomplete initial uptake of ART occurred despite a strong recommendation by trial leadership in 2015 to initiate ART for all study participants,

and similar recommendations by treatment guidelines.[1,2] It is possible that at least part of the 27% excess risk in the deferral group post-1Jan2016 was explained by this continued deferral of ART. This hypothesis is consistent with the observed gradual decline of excess risk from 2016 through 2021. However, alternate explanations include effects from slower recovery of immune function or that intrinsic factors linked to deferred therapy may take some time to reverse.

The present findings experimentally inform the long-term effects of deferral of ART initiation over several years after ART was initiated. Numerous observational studies have attempted to address this question but with inconsistent conclusions.[7,14-18] The validity of the findings from these cohort studies relies on unverifiable assumptions including the absence of unmeasured confounders – prognostic factors that are causally related to when ART was initiated and hence to the nadir CD4+ count. In our study, the random allocation of START participants to immediate versus deferred initiation of antiretroviral therapy, provides better protection against the presence of such confounding factors than these observational studies.

The degree to which excess risk remained appeared to differ according to the participant's age. Among younger participants, excess risk persisted overall and post-1Jan2016 whereas this was not seen in older participants. We considered multiple subgroups and had no prior hypothesis of a difference by age so this may well be largely a chance effect, or age may be marker for something else. One other possibility, for which we can only speculate, is that it could reflect the more robust T cell receptor repertoire in the younger group and the inability to reconstitute elements of the repertoire once lost. Uptake of ART did not vary by age group and hence is not a plausible explanation per se.

The strengths of the present findings include randomized comparisons of how immediate versus deferred initiation of antiretroviral therapy affect serious clinical events in a large international cohort of HIV-positive people followed for more than 9 years.

Weaknesses include an inability to provide complete follow-up for the entire cohort. Notably, restricting the analysis to sites with more comprehensive follow-up did not materially affect the key reported findings. An underlying cause could not be established in 32% of the deaths after 2016, therefore the two most common underlying causes after 2016, non-AIDS cancer and suicide, and other causes are likely underestimated. The ability to follow participants in 2020 and 2021 was negatively affected by the SARS-CoV-2 pandemic, whereas COVID-19 was responsible for only a few of the deaths.

Here we further document the extent of the detrimental effects for the individual's health from deferring the initiation of therapy. This is in addition to risks to sexual partners from failure to diagnose HIV and start treatment.[19,20] Hence, our findings underline, and provide quantifiable risk estimates, that can be used as arguments to support the UNAIDS 95:95:95 targets and further intensify efforts to diagnose and place all HIV-positive persons on ART as quickly as possible after the time of infection.[21-24]

In summary, among adult people with HIV, delays in ART initiation result in excess risk of AIDS and serious non-AIDS conditions even among those with CD4+ count >500. This ongoing risk persists after ART is initiated. Overall, the data reinforce the benefit of early diagnosis of HIV and prompt initiation of ART.

Disclosure:

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Figure Legends

Figure 1. A. Summary of percentage of participants on antiretroviral therapy and percentage with HIV RNA level ≤ 200 copies/mL by month of follow-up after randomization in the pre-2016 period; and B. Summary of percentage of participants on antiretroviral therapy and percentage with HIV RNA level ≤ 200 copies/mL by calendar year of follow-up in the post-1Jan2016 period.

Figure 2. A. Summary of average CD4+ counts by month of follow-up after randomization in the pre-2016 period; and B. Summary of average CD4+ count by calendar year of follow-up in the post-1Jan2016 period.

Figure 3. Primary and secondary endpoint event rates (per 100 person years) by treatment group and hazard ratios (HRs), pre-2016 and post-1Jan2016.

Figure 4. Kaplan-Meier plots of the cumulative percentage with the primary endpoint by treatment group, pre-2016, and post-1Jan2016.

Figure 5. Primary endpoint event rate (per 100 person years) and hazard ratios during the post-1Jan2016 period by treatment group according to subgroups.