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EDITORIAL

Why START? Reflections that led to the conduct of this large long-term strategic HIV trial

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

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Introduction

This monograph describes a cohort of 4685 HIV-positive persons, most of whom were recently infected, who volunteered to dedicate several years to being participants in a research study that addresses the question of when antiretroviral therapy (ART) should be initiated. Should it be started early after HIV infection occurs, or should it be deferred until the infection has started to impair immune function but before the risk of AIDS increases?

There has been consensus based on robust data for many years that ART should be initiated following the development of AIDS. Also, within the past 6 to 7 years, data from randomized trials [1–3] and observational studies [4–7] emerged that supported the initiation of ART when the CD4 cell count declined to < 350 cells/μL among asymptomatic individuals. It has been hotly debated whether the clinical benefits of initiating ART at a CD4 cell count > 500 cells/μL, compared with deferring ART until the CD4 cell count decreases to 350 cells/μL, as is being tested in the Strategic Timing of AntiRetroviral Treatment (START) study, outweigh the risks [8–10]. The debate is lively because the data available are not optimal. The fact that 4685 persons from 215 clinics in 35 countries volunteered to be randomized in START reflects the considerable uncertainty that many individuals with HIV infection and investigators around the world have about the answer to the question being addressed by START.

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How START got started

In early 2006, the Strategies for Management of AntiRetroviral Therapy (SMART) study [11] was prematurely stopped because the interim data established that use of ART intermittently rather than continuously led to an excess risk of not only AIDS-related events, but also what are now known collectively as serious non-AIDS-related events (major cardiovascular, renal or liver disease or non-AIDS-related cancers) [12,13]. The mortality rate, which was primarily attributed to end-organ disease and cancer and not AIDS, was also greater among participants randomized to receive ART intermittently compared with those assigned to continuous ART [11]. This was a surprising and unexpected finding. Before data from SMART were available, many experts were of the opinion that intermittent ART was safe [14]. Opinions were based on data from observational studies, uncontrolled studies of ART cessation, and small, short-term randomized trials. The definitive evidence provided by SMART trumped these opinions, and treatment guidelines were quickly modified.

The key unanswered question in the aftermath of SMART was whether initiation of ART early in the course of HIV infection – when the risk of AIDS is low to negligible and morbidity and mortality are almost entirely driven by serious non-AIDs-related events – would provide clinical benefits that outweighed the risks. For this to be the case, early ART would probably have to result in a reduced risk of serious non-AIDS-related events as well as AIDS [13].

By the summer of 2006, a few months following the early termination of SMART, the International Network for

Strategic Initiatives in Global HIV Trials (INSIGHT) study group prioritized "when to start ART" as the next key question for which they would mount an international trial. At that time, there was still a paucity of information as to whether the initiation of ART at a CD4 cell count > 250 cells/μL had a favourable risk/benefit profile compared with deferral to a CD4 cell count < 200 cells/μL. Thus, considerable time was spent discussing the target population and deferral strategies of the trial for proposal to the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH). There was even consideration of the possibility of carrying out two trials because of the uncertainty around the benefit of the strategy of deferral until the CD4 count is < 350 cells/μL, rather than deferral until a lower count, to be used in the control group. By September 2007, the current design of START had been approved, and NIAID agreed to fund a pilot study with 900 participants. If the pilot study demonstrated that enrolment was feasible, the definitive trial with 4000 participants would be funded.

It was also realized that a trial design where half the study participants were randomly allocated to remain untreated for several years would present a unique opportunity to assess the impact of early ART on various end-organ disorders. Thus, following the decision to support START by NIAID, the INSIGHT group sought funding from other governments and from other NIH institutes for the substudies that are described in this monograph. INSIGHT also began working with NIAID on clinical trial agreements with pharmaceutical companies for the donation of ART.

Shortly before START was to begin, an administrative challenge arose. INSIGHT was informed by NIAID in July 2008 that they had been advised by their general council that they could not sponsor a trial including subjects from European Union member states because of the requirements of the sponsor to indemnify or provide insurance for research-related injury [15]. After several months of negotiation, the University of Minnesota agreed to be the sponsor in November 2008. Version 1.0 of the protocol was released in December 2008, and plans for implementing the trial in 2009 were initiated. Enrolment began in April 2009, the pilot study was judged to be successful in 2010, and, as described in the paper on enrolment in this monograph, the last participant enrolled entered START on 23 December 2013.

There have been a number of other challenges during the enrolment phase of START. About the time enrolment in START was finally able to begin, the first [4] of several observational studies [5–7] aimed at determining at what CD4 cell count ART should be initiated was published. The authors argued that initiating ART at counts > 500 cells/μL resulted in a survival benefit [4]. Later, other observational studies were published that came to different conclusions [5,7]. It remains unclear which of these diverging findings are correct and whether indeed the claim made that observational studies can provide reliable answers [10] to a question like the one posed by START is correct. START will assist in clarifying this controversy.

Two randomized trials addressing the question of when to start ART were also completed during the enrolment phase of START: the Haiti trial [2] and HIV Prevention Trials Network (HPTN) 052 [16]. Both trials were designed and executed with a belief that HIV infection could be left untreated as long as the CD4 cell count remained above 200 cells/μL; a belief that also guided the design of SMART. The results of these trials affirmed that the deferral strategy used in START, as opposed to deferral until a lower CD4 count as was considered in the design stage, was better for the control group. Indeed, global consensus was already reached in 2007, as reflected in the change of all guidelines, that ART should commence once the CD4 cell count has decreased to around 350 cells/μL.

A concerted effort was initiated in 2007–2008 to determine a plausible biological explanation for why the results of SMART turned out the way they did. Interruption of ART was found to lead to activation of inflammation and coagulation pathways [17]. Subsequent extensive research, workshops, and reviews have debated whether the activation of the immune system that results from untreated HIV infection (like any infection) has long-term clinical consequences. The status of this debate remains a resounding "perhaps." Inflammatory biomarkers, such as interleukin-6 [18–22], and coagulation biomarkers, such as D-dimer [19,21,23], are strong prognostic indicators of these clinical outcomes. However, none of the studies to date have been able to address the key question in relation to this, namely, whether use of an intervention (e.g. ART) that dampens activated inflammatory and coagulation processes in the body results in a reduced risk of clinical disease. Concerted efforts are under way in the cardiovascular field to address directly the continued uncertainty of whether a causal link exists between inflammation and cardiovascular disease [24,25]. The START study will contribute to clarifying this question in the field of HIV infection.

The science in START

The science to be derived from the findings of START, once the follow-up data have been unblinded, will address two principal questions. The narrow and focused question is whether initiation of ART at CD4 cell counts > 500 cells/μL (immediate ART) is superior to deferral of ART until the CD4 count declines to 350 cells/μL in terms of reducing morbidity and mortality, which are expected to be largely

attributed to serious non-AIDS-related events. The broader question that the results of START will contribute to answering relates to the public health strategic role ART may serve. ART unquestionably lowers the infectiousness of the person taking the treatment [16]. If START demonstrates clinical benefit from early use of ART, the benefits to the individual HIV-positive person and to public health are aligned. This will not be the case if START fails to demonstrate early benefit.

The design of START

The design of START (Fig. 1) is simple [26]. Participants with a CD4 cell count > 500 cells/μL are randomized to one of two equal-sized groups, where one group initiates ART immediately and the other initiates ART once the CD4 count has decreased to < 350 cells/μL. The primary endpoint is any AIDS-related event (excluding oesophageal candidiasis and chronic *Herpes simplex virus* infection), serious non-AIDS-related event or death from any cause. Originally, a total of 4000 participants were to be enrolled and followed for 3 years after the last participant was randomized. This follow-up period was estimated to be sufficient to accrue 370 primary endpoints. This event target provided 90% power to detect a 27% difference in risk between the two arms of the study [25]. In 2012, these assumptions were modified based on a planned sample size re-estimation. The sample size re-estimation was performed while participants were still being enrolled so that if the sample size had to increase the enrolment period could be extended. The re-estimation resulted in the required number of primary endpoints being lowered to 213 to maintain the 90% power, while the sample size was increased to 4600 and remaining enrolment was restricted to persons older than 35 years. These changes were made because: (1) the baseline CD4 cell count was much greater than originally assumed (median about 650 cells/μL compared with 566 cells/μL as originally assumed) and this led to a greater predicted risk difference between the two treatment groups than originally hypothesized; and (2) the pooled (both treatment groups combined) primary event rate was lower than assumed.

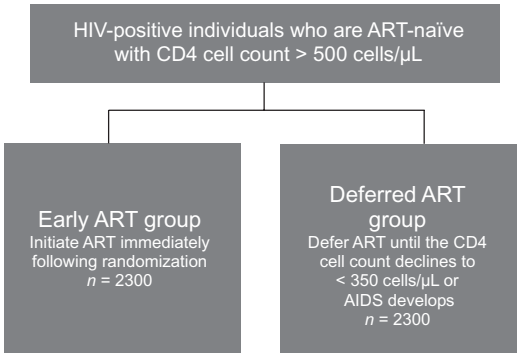

Fig. 1 The design of the Strategic Timing of AntiRetroviral Treatment (START) trial. Antiretroviral therapy (ART)-naïve (i.e. not previously having used ART) HIV-positive persons with normal immune function (i.e. a CD4 cell count > 500 cells/μL) are randomly allocated to start ART immediately or when the CD4 count has further decreased to a level (350 cells/μL) below which the person starts to become at risk of contracting opportunistic diseases (i.e. AIDS) if left untreated; if AIDS develops when the CD4 count is still > 350 cells/μL then ART should also be initiated.

The number of primary events in the two treatment groups remains blinded except to an independent Data and Safety Monitoring Board (DSMB). These data will remain blinded until either: (1) the DSMB determines that an answer to the question posed by START has been clearly shown or that it is unlikely to obtain a reliable answer; or (2) a total of 213 primary events have accumulated. At the time of writing this monograph, it remains the projection that the latter scenario will occur at the end of 2016, 3 years after enrolment of the last trial participant as stipulated in the protocol. The findings disclosed at the time will then guide decisions on possible future research directions, including the relevance of continued follow-up and use of ART in the deferred arm of the trial.

Serious non-AIDS-related events

Most primary endpoints are projected to be serious non-AIDS-related events as opposed to AIDS-defining events. In addition to the data from the main trial, data collected in the substudies will examine these serious non-AIDS-related outcomes and others in more detail. These outcomes include kidney impairment as determined by the decline in estimated glomerular filtration rate (eGFR) and the development of proteinuria, neurological dysfunction, chronic obstructive lung disease, reduced arterial elasticity, major cardiovascular risk factors, including ischaemic electrocardiogram (ECG) abnormalities, reduced bone mineral density (BMD), and liver fibrosis. The monograph describes and discusses the details of the design and methodology of each of these planned investigations. Together with the major clinical findings of START, these other outcomes will be instrumental in better defining the benefits and risks of early use of ART.

START central repository of specimens

For consenting participants, specimens are collected at baseline and at each follow-up visit for future research. A central repository of biological samples of blood, plasma, urine and host DNA as well as a separate repository of tissue samples from participants who develop cancer during the

study are being maintained. Specimens in the sample repository from the SMART study and other INSIGHT studies have been used to generate a large number of research investigations, and we project that this will also be true for START specimens. INSIGHT invites the larger research community to exploit the wealth of research possibilities once the results of START are available.

Overview of the baseline monograph

An extensive set of data was collected to characterize START participants prior to randomization. This monograph includes 15 papers: a community perspective on the START trial [27]; a description of the challenges and keys to success of the enrolment effort by 215 sites in 35 countries [28]; a description of the informed consent process in START, including the design of a nested cluster-randomized study comparing a "standard" with a "concise" consent [29]; and 12 other papers either describing baseline characteristics of all 4685 HIV-positive participants or describing the participants in the substudies of START. Below we highlight some characteristics of this unique cohort of individuals who were ART naïve and had CD4 cell counts > 500 cells/μL at study entry.

- The median age of the cohort was 36 years and 27% were women. The median CD4 cell count was 651 cells/μL and the median HIV RNA was 12 754 HIV-1 RNA copies/mL [30].
- For 2.4% of participants the HIV RNA level was 50 copies/mL or lower [31].
- Approximately 19% of participants had two or more cardiovascular risk factors; 32% of participants reported smoking [32].
- Chronic kidney disease, defined as eGFR < 60 mL/min/1.73 m^2 or dipstick proteinuria 1 + or greater, was present in 6.2% of participants [33].
- Approximately 17% of participants reported condomless sex with a serodiscordant partner in the 2 months prior to randomization [34].
- There was substantial geographical diversity in carrying out routine screening for transmitted ART-resistant virus, with screening much more likely to occur in resource-rich areas of the world [35].
- Quality of life was mostly favourable; the average of the visual analogue scale of overall current health was 80.9 out of 100 [36].
- Changes in neurocognitive test performance will be compared for the immediate and deferred ART groups in 608 participants. At entry about 20% of participants had at least mild neurocognitive impairment [37].
- Changes in arterial elasticity will be compared for the immediate and deferred ART groups in 331 participants. At entry, impaired (i.e. lower) small and large artery elasticity was associated with increased age, female gender and increased systolic and diastolic blood pressure. Small arterial elasticity was also impaired among those with prior cardiovascular disease, whereas it was higher for those on lipid-lowering therapy [38].
- Changes in pulmonary function will be compared for the immediate and deferred ART groups in 1026 participants. At entry, the prevalence of chronic obstructive pulmonary disease (defined as forced expiratory volume in 1 s divided by forced vital capacity less than the lower limit of normal) was 6.8% [39].
- Changes in liver fibrosis as measured by transient elastography (FibroScan®; Echosens, Paris, France) will be compared for the immediate and deferred groups in 221 participants. At entry, the median FibroScan® score was 4.9 kPa and 7.8% had evidence of significant liver fibrosis [40].
- Changes in BMD as measured by dual-energy X-ray absorptiometry will be compared for the immediate and deferred ART groups in 424 participants. At entry, about 2% had osteoporosis and 35% had a low BMD [41].

Concluding remarks

The goal of this monograph is to provide a detailed description of a unique cohort of individuals – HIV-positive adults who are ART naïve and have CD4 cell counts > 500 cells/μL. Because of the support we have received to carry out this study and the time commitments of so many study participants, much of the data presented here are unprecedented. As in any clinical trial, it is important to understand the target population to whom the findings apply. In that regard, this monograph will be very informative and will surely be used as a reference once follow-up information becomes unblinded and those results are communicated.

The START study is registered at clinicaltrials.gov (NCT00867048).

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