Strategic Timing of AntiRetroviral Treatment (START)

Sponsored by:
The University of Minnesota
Minneapolis, Minnesota, USA

In collaboration with four International Coordinating Centers (ICCs) of the INSIGHT Network:

Copenhagen HIV Programme (CHIP), Rigshospitalet, University of Copenhagen, Denmark
Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL) -- London, United Kingdom
The Kirby Institute for Infection and Immunity in Society, University of New South Wales -- Sydney, Australia
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The START protocol is being managed and conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) with primary support by the U.S. National Institutes of Health through grants from the Division of AIDS, NIAID, and other NIH institutes to the University of Minnesota.

The University of Minnesota will serve as the sponsor for the study and will subcontract with four ICCs that will be responsible for implementation of Good Clinical Practice (GCP) and for oversight of the conduct of the trial at clinical research sites. The University of Minnesota is a constitutional entity under the laws of the State of Minnesota and assumes liability only to the extent provided under the Minnesota Tort Claims Act, Minnesota Statutes, Section 3.736.

The legal representative for the START trial in Europe is the Copenhagen HIV Programme (CHIP).

J. D. Nt
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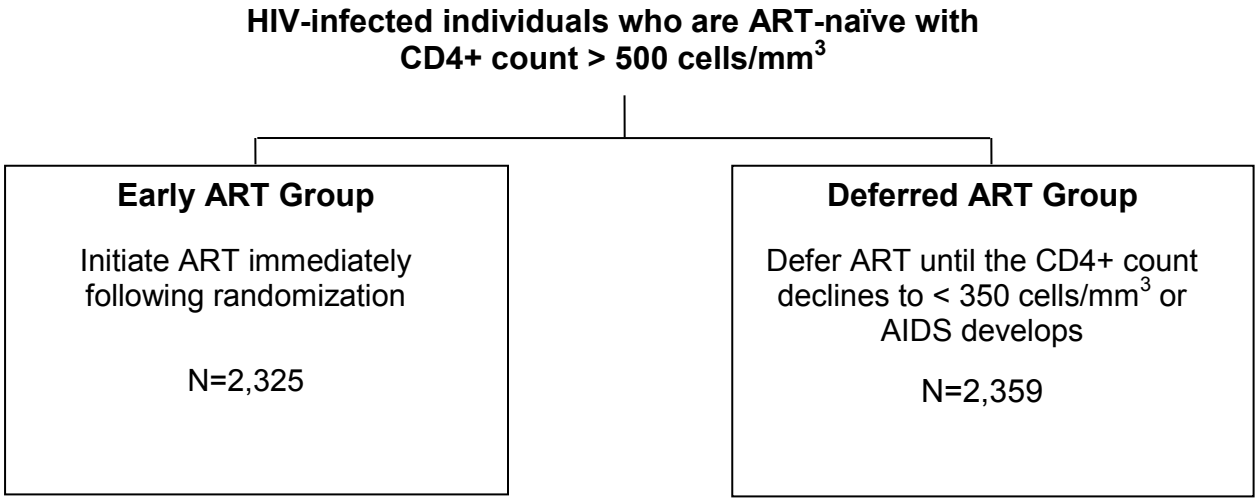
TABLE OF CONTENTS

1 Synopsis

The START trial 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) or deferred ART 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 this question 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 offered ART.

Even though the findings from START unequivocally indicate that immediate ART has substantial benefits on major clinical outcomes compared to deferred ART, longer follow-up, as recommended by the DSMB, is warranted for several scientific and practical reasons.

The general aim of long-term follow-up, formulated as two hypotheses stated below, is to determine whether the risk of major morbidity and mortality associated with deferral of ART is eliminated once ART is initiated or whether it persists due to the lower CD4+ cell count at ART initiation.

This version of the protocol describes the rationale and the plan for continued follow-up of START participants through 2021. The major difference between this version of the protocol and Version 3.0 is that the data collection plan after 2017 has been greatly simplified, and beginning in 2018, as originally planned, antiretroviral treatment will be provided through local sources and not through a Central Drug Repository (CDR).

Rationale for Extended Follow-up

Follow-up through 2021 will provide 6 years of additional follow-up (9.5 years total from randomization) from January 2016 by which time 81% of participants in the deferred arm had initiated ART; by the end of 2016 93% of participants in the deferred ART group had initiated ART. This is a large increase from the 48% of deferred arm participants taking ART in May 2015.

Extended follow-up is important for several reasons:

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

- The START cohort is unique in many respects: 1) it is 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 have now started ART, 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, may 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 so far may be 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 will be more precisely estimated.

- The extended follow-up coupled with the experimental design of START allows 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, we have formulated two scientific hypotheses that will be addressed through follow-up of the study participants through 2021. These hypotheses take advantage of the initial randomization and experimental design of START. Importantly, no other study has the capability of addressing these questions.

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 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.

Primary Endpoint of START

The primary composite endpoint of START is the development of a serious AIDS event ("AIDS*"), a serious non-AIDS event ("non-AIDS"), or death from any cause.

This endpoint will remain the primary focus of the extended follow-up planned.

Serious AIDS events (or AIDS*) include most traditional opportunistic conditions but exclude non-fatal esophageal candidiasis and chronic *Herpes simplex* (see Appendix A for a complete list of conditions). 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.

In this protocol, the term "AIDS" (without an asterisk) denotes all opportunistic conditions, including non-fatal esophageal candidiasis and chronic *Herpes simplex* (see Appendix A).

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).

START Participants

Participants enrolled in START were in reasonably good health, and in the clinician's opinion, able to adhere to the protocol (i.e., be willing to accept and adhere to the data collection schedule and assigned treatment strategy).

Participants had to meet the following inclusion and exclusion criteria to be randomized:

Inclusion Criteria

- Signed informed consent

- HIV infection documented by a plasma HIV RNA viral load, rapid HIV test or any licensed[1] 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
- 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)

All HIV-positive participants in START are eligible to continue in extended follow-up.

Data Collection Plan for Extended Follow-up

In January 2016, the START protocol was amended as Version 3.0. Version 3.0 described plans to continue follow-up with existing funding through December 2017 and to seek funding for longer follow-up through December 2021. Study visits are required twice each year in Version 3.0. ART was being provided through a CDR until the end

[1] The term "licensed" refers to an FDA-approved kit or, for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country. Confirmation of the initial test result must use a test method that is different than the one used for the initial assessment.

of 2017 at which time, as originally planned, sites were required to transition all participants to a local ART supply.

This version of the protocol (Version 4.0) describes plans for a much simplified follow-up data collection plan beginning in 2018. In person study visits will no longer be required. Data collection will occur once each year and focus on major clinical events. In addition, after 2017, the START trial no longer includes substudies. ART is no longer provided through the study and the protocol does not specify ART regimens to be used. Since follow-up data are collected retrospectively on an annual basis, serious and unexpected adverse reactions attributed to ART will no longer be collected in real time and reported to regulatory authorities by the sponsor. Investigators will be reminded of their obligation to report to regulators per their countries' requirements for reporting post-marketing adverse events considered related to ART. The occurrence of specific adverse outcomes (see below) will be collected on at least an annual basis as part of the trial data.

The major clinical outcomes to be collected have been assessed since the beginning of the trial using similar methods, allowing the two treatment strategies to be compared for the outcomes below for three calendar periods: 1) from randomization to December 31, 2015; 2) from January 1, 2016 to December 31, 2021; and 3) cumulatively from randomization through December 2021.

Primary Endpoint
Time to AIDS*, non-AIDS, or death from any cause (first event) (see Appendix A)

Major Secondary Endpoints
- AIDS* or death from AIDS
- Non-AIDS or death not attributable to AIDS
- CVD (myocardial infarction, stroke, coronary revascularization) or death due to CVD
- Cancer (AIDS and non-AIDS malignancy, excluding basal and squamous cell skin cancers)
- All-cause mortality
- Tuberculosis
- Serious bacterial infections

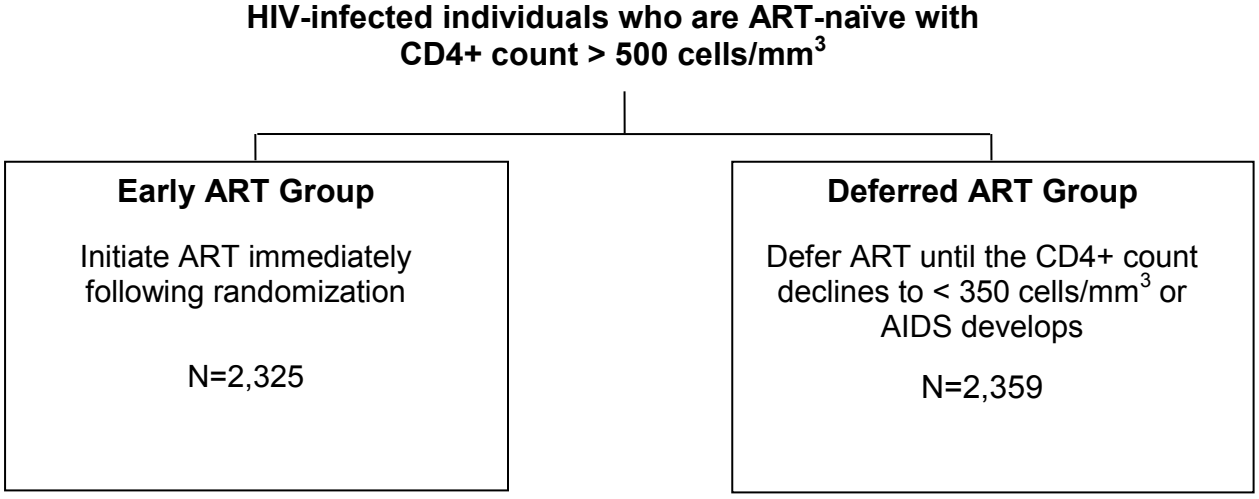
Other Secondary Outcomes

- ESRD (initiation of dialysis, renal transplantation)
- Decompensated liver disease
- Non-AIDS malignancy, including basal and squamous cell skin cancers
- AIDS
- Unscheduled hospitalizations

2 Background and Rationale

The START trial 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) or deferred ART group.[1] 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 this question 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.

Two months following the recommendation by the DSMB, the primary results of START were published.[2] Key findings from the primary report of START are summarized below:

- Over an average follow-up of 3 years, immediate use of ART provided significant benefit over deferred ART for the primary endpoint of START (HR=0.43; 95% CI: 0.30-0.62); p<0.001) and each of its major components, serious AIDS (p<0.001) and serious non-AIDS events (p=0.04).

- The magnitude of benefit of immediate ART as compared to deferred ART was greater for serious AIDS events (HR=0.28; 95% CI: 0.15-0.50) than for serious non-AIDS events (HR=0.61; 95% CI: 0.38-0.97).

- While the overall rate of serious non-AIDS events was lower in the immediate compared to the deferred arm, the relative difference varied by type of event. The HR for non-AIDS cancer was 0.50 (95% CI: 0.22-1.11; p=0.09). For cardiovascular disease, for which a similar number of participants (26) experienced an event as for non-AIDS cancer (27 participants) the HR was 0.84 (95% CI: 0.39-1.81).

- All-cause mortality rates favored the immediate ART group but the confidence interval was wide due to the small number of deaths (HR=0.58; 95% CI: 0.28-1.17; p=0.13).

- Symptomatic grade 4 events (potentially life-threatening events) and unscheduled hospitalization for reasons other than AIDS progression occurred at similar rates in the two treatment groups (HR= 1.01; 95% CI: 0.73-1.39; p=0.97 and HR=0.91, 95% CI: 0.77-1.08; p=0.28, respectively). The HR for a composite measure of clinical benefit that included the primary endpoint, grade 4 events, and unscheduled hospitalization, favored immediate ART and was 0.82; 95% CI: 0.71-0.96; p=0.01).

- During the follow-up period, the average CD4+ count was 194 cells/mm^3 higher (95% CI: 185-203) in the immediate ART group compared to the deferred ART group.

- In both treatment groups, once ART was initiated, a high percentage of participants (over 90%) achieved and maintained virologic suppression (viral load 200 copies/mL or less).

- In the deferred arm, 68 of 96 primary events (71%) occurred before ART was initiated. Fifty-seven of the 96 events in the deferred arm occurred at CD4+ counts > 500 cells/mm^3; 23 of the primary events occurred at counts > 650 cells/mm^3.

Concurrent with the findings of START, findings from a trial of early ART that included participants with a median age of 35 years from the Ivory Coast (TEMPRANO) showed that immediate ART led to lower rates of severe illness after an average follow-up of 2.3 years as compared to deferral of ART according to World Health Organization (WHO) criteria, which varied over follow-up, among those with CD4+ counts of at least 500 cells/mm^3 at study entry.[3] These findings reinforced findings from START that early ART has benefits in populations across the world including Africa where the prevalence of HIV is highest. Like START, follow-up in TEMPRANO was relatively short considering that ART treatment is life-long.

After START was initiated and prior to the interim findings of START becoming available, a large randomized clinical trial showed conclusively that lowering viral replication in the HIV-infected person substantially reduces heterosexual transmission.[4] Another recent study supports reduced transmission in both hetero- and homosexual relationships having condomless sex.[5]

Taken together, the findings from these studies provide strong evidence for both an individual benefit to the person with HIV over a 2 to 3 year period and a public health benefit to early use of ART. As a consequence of these studies guidelines across the world have changed.[6,7,8]

Following the DSMB's recommendation in May 2015, participants in the deferred arm who had not started treatment were offered ART. At the time of the DSMB recommendation in May 2015, 48% had initiated ART. By the beginning of 2016, ART had been started for 81% of participants in the deferred ART group; by the end of 2016 93% of participants in the deferred ART group had initiated ART. Participants in the deferred ART group initiated ART a median (25^{th}, 75^{th} percentile) of 2.5 (1.6, 3.4) years after participants in the immediate ART group. Ninety-five percent of participants in the deferred ART group who started ART are currently virologically suppressed.

The median CD4+ count at ART initiation for deferred arm participants by the end of 2016 was 468 cell/mm^3. This CD4+ count is approximately 180 cells/mm^3 lower than the median count at initiation in the immediate ART group. In addition, the most recent follow-up CD4+ counts for immediate and deferred arm participants are 882 and 711 cells/mm^3, a difference of 172 cells/mm^3 which is very similar to the difference in CD4+ counts at ART initiation for the two treatment groups.

Recently, a panel of inflammatory, coagulation, and vascular injury biomarkers were measured at baseline and 8 months after randomization.[9] Immediate ART reduced the level of these biomarkers compared to deferred ART, and D-dimer and interleukin-6 (IL-6) increased in the deferred ART group.

These data on inititation of ART in the deferred ART group, HIV RNA supppression after initiating ART, and CD4+ cell count and biomarker differences provide a strong foundation for testing the HIV RNA and Nadir CD4+ hypotheses.

In January 2016, the START protocol was amended as Version 3.0. Version 3.0 described plans to continue follow-up with existing funding through December 2017 and to seek funding for longer follow-up through December 2021. Those plans have not changed; however, this version of the protocol describes plans for greatly simplified data collection beginning in 2018. Currently participants who consented to Version 3.0 are being seen twice each year. ART is being provided through a Central Drug Repository (CDR) until the end of 2017. By that time, all participants will have transitioned to local sources of ART.

Continued follow-up of START participants for morbidity and mortality is important because many individuals who become HIV positive will not initiate ART until their CD4+ cell count declines to less than 500 cells/mm^3 because of delayed diagnosis or unavailability of ART. Many individuals living with HIV are not aware of it. The WHO estimates this percentage to be 40% worldwide;[10] estimates for the U.S. and Europe are 13% and 15%, respectively.[11,12] Further, late diagnoses are common in resource-rich and –poor settings.[13,14,15,16,17,18] A demonstration in a randomized trial of persistent poor prognosis with deferred ART will create a further impetus for individuals to seek HIV testing and treatment, and for health systems to more comprehensively ensure access to these services.

Additionally, data from the extended follow-up of START participants will provide important insights into the pathophysiology of the impact of prior levels of HIV-induced immunodeficiency on risk of morbidity and mortality once HIV is controlled.

It is critical to determine whether the risk of major morbidity and mortality associated with delayed initiation is completely eliminated once ART is initiated and HIV RNA levels are suppressed or whether it persists due to the delay in initiating ART. No prior randomized trial has addressed this question. START is the only trial that will ever settle this question.

Observational studies have attempted to address this question. A cohort analysis published around the time of the START results found that mortality differences among different ART initiation strategies for participants with a CD4+ count > 350 cells/mm^3 were small and decreased over time;[19] importantly, as they note, their estimates relied on the assumption of no unmeasured confounding. Another recent report based on a cohort study found that after surviving for 5 years of ART, the mortality of those who started ART with low baseline count converged to those with high baseline counts.[20] Other observational studies suggest residual excess risk of non-AIDS morbidity associated with lower nadir CD4+ counts, but their design makes them unable to demonstrate whether the associations are causal.[21,22,23]

In addition, the long-term follow-up will provide more information on rates of specific non-AIDS conditions and all-cause mortality in this unique cohort of individuals most of whom will be treated with ART that provides long-term virologic suppression.

In summary, this streamlined version of the protocol (Version 4.0) with a more focused, cost-effective data collection plan and with locally sourced ART, allowing for the elimination of sponsor-reported serious and unexpected adverse reactions attributed to ART will enable START to address an important scientific question at substantially reduced cost. Sites will report serious and unexpected events to national and international regulatory authorities according to local post-marketing reporting requirements.

3 Methodology

3.1 Study Design

This version of the START protocol continues follow-up of the HIV-positive participants in START, using a reduced data collection schedule to optimize resources and thus allow for a longer follow-up period. START is a multicenter, international, randomized trial that compares initiation of ART at a CD4+ cell count > 500 cells/mm^3 (early ART) versus initiation of ART at a CD4+ cell count of < 350 cells/mm^3 (deferred ART) for a composite outcome of AIDS*, non-AIDS, and death from any cause (see Appendix A).[2] From April 2009 through December 2013, eligible participants were randomized in a 1:1 ratio to either the early ART group or the deferred ART group. Randomization was stratified by clinical site. A total of 4,684 HIV-positive participants were randomized (one randomized participant included in the primary result paper was later determined to be HIV-negative). Participants in the early ART arm commenced ART immediately following randomization. Participants in the deferred ART group, the control arm, were to commence treatment when the CD4+ declines to < 350 cells/mm^3 or if an AIDS-defining diagnosis occurs.

3.2 Extended Follow-up Objectives

3.2.1 Primary Objective and Hypotheses

With extended follow-up of participants in START, the primary objective is to determine whether the benefit of early ART as compared to deferred ART in delaying the occurrence of a composite outcome consisting of AIDS*, non-AIDS, or death from any cause is maintained, increased or reduced.

Two scientific hypotheses, both of which take advantage of the randomized design of START and the extended follow-up through 2021, have been formulated to address the primary objective. These hypotheses are:

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 follow-up in 2021 will remain significantly different from one another, 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 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; therefore, the cumulative event rates in the two arms at the end of follow-up in 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 persists resulting from deferred ART, is due to a number of factors including, the lower CD4+ cell count at which ART was initiated, lower CD4+ count levels during 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.

3.2.2 **Secondary Objectives**

As secondary objectives, we will evaluate these two hypotheses for major components of the START primary endpoint and other major outcomes between 2016 and 2021 and using all of follow-up through 2021. The two hypotheses will also be evaluated for baseline-defined subgroups.

a. To compare early ART to deferred ART for the following components of the primary composite outcome:
   - AIDS* or death from AIDS
   - Non-AIDS or death not attributable to AIDS
   - CVD (myocardial infarction, stroke, coronary revascularization) or death due to CVD
   - Cancer (AIDS and non-AIDS malignancy, excluding basal and squamous cell skin cancers)
   - All-cause mortality
   - Tuberculosis
   - Serious bacterial infections

b. To compare early ART to deferred ART for the following other clinical outcomes:
   - ESRD (initiation of dialysis, renal transplantation)
   - Decompensated liver disease
   - Non-AIDS malignancy, including basal and squamous cell skin cancers

- AIDS
- Unscheduled hospitalizations

c. To compare early ART with deferred ART for the primary composite outcome and other major clinical outcomes in subgroups defined by the following characteristics measured at baseline:
   - Age
   - Gender
   - Race/ethnicity
   - Presence and levels of risk factors, including risk scores which are based on several risk factors, for serious non-AIDS and AIDS conditions in addition to age, gender and race/ethnicity (e.g., smoking, estimated GFR (eGFR), hepatitis co-infection, diabetes mellitus, estimated CVD risk, lipids, blood pressure, presence of resting ECG abnormalities)
   - Baseline CD4+ cell count
   - Baseline CD8+ cell count
   - Baseline HIV RNA level
   - Baseline IL-6 level
   - Baseline D-dimer level
   - Duration of HIV infection, including those recently infected and those who are slow/non-progressors.
   - Viral characteristics, including subtype, and evidence of transmitted drug resistance
   - Host genetic traits
   - Geographic region
   - High versus low/moderate income countries
   - Calendar date of enrollment

3.2.3 **Other Objectives**

a. To compare the early and deferred ART groups for:
   - ART use over follow-up
   - HIV RNA levels over follow-up
   - CD4+ and CD8+ cell counts over follow-up

b. To compare the early and deferred ART groups for maintained virologic suppression following the initiation of ART during follow-up according to:
   - Presence of ART drug resistance at baseline
   - Geographic setting with and without access to routine resistance testing
   - Viral characteristics, including subtype

c. Among participants in both treatment groups, to study predictors, including genomic correlates, of the primary endpoint and its components

d. To study the effects of time-updated HIV RNA, CD4+ and CD8+ cell count levels on risk of the primary endpoint and its components, and the extent to which changes in

these laboratory markers explain treatment differences in major clinical outcomes during the three calendar periods for which the immediate and deferred ART groups will be compared to address the HIV RNA and Nadir CD4+ hypotheses. The three calendar periods are: 1) from randomization to December 31, 2015; 2) from January 1, 2016 to December 31, 2021; and 3) cumulatively from randomization through 2021.

3.3 Primary Study Endpoint

The primary composite endpoint, defined in Appendix A, remains the same as it has been throughout START and includes the following three major components:

- AIDS* or death from AIDS

  Opportunistic events consistent with the 1993 CDC expanded surveillance definition plus additional events associated with immunosuppression in the patient population targeted for enrollment. Esophageal candidiasis and chronic *Herpes simplex* infection will be counted as primary endpoints only if they result in death.

- Non-AIDS
  - CVD: myocardial infarction, stroke, coronary revascularization
  - ESRD: initiation of dialysis, renal transplantation
  - Decompensated liver disease
  - Non-AIDS-defining cancers, excluding basal and squamous cell skin cancers. Basal and squamous cell skin cancer will be counted as a primary endpoint only if they result in death.

- Death not attributable to AIDS, including death of unknown cause

The primary outcome of START and each of the major components of the primary outcome will be evaluated as the time to the first occurrence of one of the above events. Other major endpoints are referred to in the Study Objectives (section 3.2).

3.4 Statistical Considerations

In this section, assumptions underlying the predicted HRs and 95% CIs cited for the 6 year period from January 2016 to December 2021 and cumulatively from randomization through 2021 for the HIV RNA and Nadir CD4+ count hypotheses are given.

Assumptions Underlying HIV RNA Hypothesis

- In the immediate ART group, the rate of AIDS* does not change over time. Rates of serious non-AIDS and all-cause mortality increase due to aging by 7.5% per year after December 31, 2016.
- In the deferred ART group, as a consequence of the great majority of participants initiating ART, event rates for AIDS*, serious non-AIDS and all-cause mortality will be the same as rates in the immediate ART group between 2016 and 2021.

Assumptions Underlying Nadir CD4+ Count Hypothesis

- In the immediate ART group, the rate of AIDS* does not change over time. Rates of serious non-AIDS and all-cause mortality increase due to aging by 7.5% per year after December 31, 2016.
- In the deferred ART group, the event rate for the primary endpoint between 2016 and 2021 will be 75% higher than rate in the immediate ART group as a consequence of their lower nadir CD4+ count and continued CD4+ cell count difference between treatment groups, e.g., the CD4+ count difference between treatment groups at the latest follow-up visit is currently 172 cells/mm^3.

For both hypotheses, it is assumed that 90% of participants of the 4,684 HIV+ participants will be under follow-up on 1 January 2018. It is also assumed that very few participants will experience both AIDS* and serious non-AIDS events, and that the lost-to-follow-up percent will be 1% per year after 2017.

Considering these assumptions, we estimate 406 primary events will occur by 31 December 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 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.

3.5 Participant Selection

Participants enrolled in START were in reasonably good health, and in the clinician's opinion, able to adhere to the protocol (i.e., were willing to accept and adhere to the data collection schedule and the assigned treatment strategy).[2,24] The inclusion and exclusion criteria used at study entry are given in the synopsis for reference.
All HIV-positive participants in START who sign a consent for Version 3.0 (or Version 4.0 if required by the local ethics committee) are eligible to continue in extended follow-up with the exception of those who are involuntarily incarcerated. Incarcerated participants may be re-consented to Version 4.0 upon release.

3.6 Study Plan

Through May 26, 2015, the management of participants was guided by their assigned treatment strategy (see below). On May 27, 2015 investigators and participants were informed that on May 15, 2015 the independent DSMB determined that the primary question of START had been addressed. The DSMB recommended offering ART to participants in the deferred arm who had not yet started ART and continuing follow-up of all study participants.

3.6.1 **Treatment Strategies**

For reference, this section describes the two treatment strategies in START through May 26, 2015. Beginning on May 27, 2015, all participants in the deferred arm were offered ART.

Before a participant was randomized, a potent combination ART regimen was pre-specified by the study clinician. The initial regimen used was to be from a list of regimens based on DHHS guidelines. This list of regimens was regularly updated following changes in those guidelines.

After randomization, participants in the two groups were to use potent combination ART as follows:

a. Participants assigned to the **early** ART group were to start the prespecified ART regimen as soon as possible.

b. Participants assigned to the **deferred** ART group were to defer ART until one of the following conditions occurs:
   - CD4+ cell count declines to < 350 cells/mm^3 and is confirmed by a repeat CD4+ measurement within 4 weeks, or
   - AIDS develops, or
   - Conditions specified by local guidelines occur that indicate initiation of potent combination ART, e.g., symptoms indicative of HIV progression such as oral thrush, unexplained weight loss, or unexplained fever.

The intent of the deferral strategy used in START was to initiate ART as soon as possible after the CD4+ count dropped below 350 cells/mm^3. The CD4+ count was monitored closely as it approached 350 cells/mm^3.

After discussion with their clinicians, participants in the deferred ART group who developed any of the conditions noted above were to start an ART regimen selected from the same list of regimens based on DHHS guidelines that regimens for the immediate ART group used.

Women assigned to the **deferred** ART group who become pregnant before the CD4+ cell count declines to < 350 cells/mm^3 were to be prescribed ART using a regimen in keeping with local treatment guidelines.

3.6.2 **Concomitant Medications**

There are no restrictions on concomitant medications for participants in either group.

3.6.3 **Baseline Screening**

For reference, below we describe the data collected prior to randomization. These data will be used to address many of the stated objectives of long-term follow-up.

All consenting participants had the following information and measurements collected within 60 days before randomization unless otherwise noted. All measurements were done locally unless otherwise noted.

- Demographics, including education
- Documentation of HIV infection
- CD4+ cell count and CD4%: two measurements at least 2 weeks apart, with the earliest within 60 days before randomization
- Karnofsky score
- For women of child-bearing potential, a pregnancy test (serum or urine) done in the clinic must be documented to be negative within 14 days before randomization
- Targeted health history including date of first diagnosis of HIV infection, likely mode of HIV infection, history of non-AIDS events, pregnancy status, and history of fractures
- Brief clinical evaluation including weight, height, sitting blood pressure, pulse, and smoking status
- Nadir CD4+ cell count and CD4% and maximum HIV RNA level available in the medical record from any time in the past
- Up to three most recent (before the above baseline measurements) CD4+ cell counts, CD4%s, and HIV RNA measurements available in the medical record
- Findings from previous genotypic or other form of HIV resistance testing (such as virtual phenotype and/or phenotypic resistance testing), if performed and available Selected concomitant medications
- Quality of life assessment
- Use of alcohol and recreational drugs
- HIV transmission risk behavior assessment
- Health-care utilization
- HIV RNA measurement
- Additional laboratory assessments (participants should be asked to abstain from food, except water, for at least 8 hours prior to providing blood for glucose and lipid measurements):
    - Complete blood count (CBC): hemoglobin, hematocrit, white blood cell count (WBC) with differential and platelets
    - CD8+ T-cell count and CD8%
    - Renal function: serum creatinine to estimate GFR[25]
    - Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin and albumin
    - Glucose

  - Lipids: total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides
  - Dipstick urinalysis for measurement of protein
- Documentation of hepatitis B and C status: hepatitis B surface antigen, core antibody and surface antibody; hepatitis C antibody and, if available, genotype and viral load. Documented positive tests at any time in the past or documented negative tests in the 6 months before randomization may be used.
- In a subset of participants, a resting ECG (at sites with a study-provided ECG machine and a certified technician)
- ART regimen to be prescribed for the participant if randomized to the early group and whether the regimen would be obtained locally or through the INSIGHT CDR
- For consenting participants, stored plasma (sufficient for eight 1-mL transport tubes) for future HIV-related research (e.g., HIV resistance testing, CVD biomarkers)
- For consenting participants, stored urine (sufficient for six 1-mL transport tubes) for future HIV-related research

In participants who were to be prescribed abacavir, HLA-B*5701 screening test results for abacavir hypersensitivity had to be available before prescription.

In addition to the aforementioned data, the following laboratory measurements, which will also be used to address objectives of long-term follow-up have been made on stored baseline specimens:

- IL-6, D-dimer, high sensitivity C-reactive protein (hsCRP), IL-27, serum amyloid A (SAA), soluble intercellular adhesion molecule-1 (sICAM-1), and soluble vascular cell adhesion molecule-1 (sVCAM-1) were measured in all randomized participants who consented to the storage of blood for future research.
- In a subsample of participants who reported recent infection and/or recent an HIV diagnosis, a Limiting Antigen-Avidity assay and a Johns Hopkins avidity modified Genetic Systems (GS) HIV-1/HIV-2 PLUS O enzyme immunoassay (EIA) were measured to identify participants with early HIV infection.[26,27]
- In 2,549 START participants who consented to store DNA, a genome wide association study (GWAS) has been performed to investigate genetic determinants of immune function, ART toxicities, elevated biomarker levels, and AIDS and serious non-AIDS events.
- Among 3,785 participants who consented to store specimens for future research with a baseline HIV RNA level > 1,000 copies/mL, next generation sequencing for HIV resistance was performed.

3.6.4 **Participant Follow-up**

The planned follow-up is through December 2021. The extent of data collection and methods for data collection varied between Versions 1.0/2.0, Version 3.0 and Version 4.0. In Versions 1.0 and 2.0, participants were seen at routine follow-up visits which occurred at 1 and 4 months after randomization, and every 4 months thereafter. Beginning with Version 3.0, data collection visits occurred at 6 month intervals. The table below summarizes follow-up data collection under Versions 1.0 and 2.0, Version 3.0 and Version 4.0 of the START protocol.

Data/Samples Collected	Versions 1.0 and 2.0	Version 3.0	Version 4.0
Primary endpoint and components	X	X	X
Basal and squamous cell skin cancers	X	X	X
Esophageal candidiasis and chronic *Herpes Simplex* infection	X	X	X
Bacterial pneumonia	X	X	X
Grade 4 events that do not lead to hospitalization	X	X	
Unscheduled hospitalizations	X	X	X
CD4+ and CD8+ counts	X	X	X
HIV RNA level	X	X	X
ART	X	X	X
Self-administered questionnaires: quality of life, health care utilization, alcohol and recreational drugs, HIV transmission risk behavior	X		
Serious adverse events for regulatory authorities	X	X	
Complete blood count (other than CD4+ count), chemistries, lipids, urine dipstick	X	X	
Other targeted medical diagnoses,	X	X	

including fractures			
Concomitant treatments	X	X	
Weight, blood pressure and smoking status	X	X	
Resting ECG (subsample)	X	X (completed in 2016)	
Stored blood and urine	X (every visit)	X (annual visits only)	
Results of locally performed resistance tests	X	X	
Pregnancy outcomes	X	X	
Substudies: arterial elasticity, pulmonary, bone density, neurocognitive, site monitoring, informed consent, liver fibrosis, HIV-1 reservoir	X	X (all substudies were completed in 2016 except for liver fibrosis which will continue through December 2017)	

In Version 4.0, follow-up data collection will occur once each year. The following information will be collected:

- ART regimen currently prescribed
- CD4+ cell counts and CD8+ cell counts measured since the last assessment, if available.
- HIV RNA levels determined since the last assessment, if available.
- Event documentation for serious AIDS, serious non-AIDS and deaths which constitute the START primary endpoint.
- Event documentation for the following secondary outcomes:
  - Non-AIDS malignancy, including basal and squamous cell skin cancers
  - All AIDS events, including esophageal candidiasis and chronic *Herpes Simplex*
  - Bacterial pneumonia
- Unscheduled hospitalizations, including an assessment of the severity of the condition that led to the hospitalization.

For most participants these data will already exist as a consequence of routine care. At some sites in order to collect these data, participants will be seen for a study visit. Whether the data exist already or are collected as part of a study visit, electronic case reports forms (eCRFs) will used to record the data at each site.

The INSIGHT Endpoint Review Committee (ERC) has established objective criteria for each event comprising the primary endpoint and for major secondary endpoints; these criteria are also found in the *START Protocol Instructions Manual.* The ERC is responsible for reviewing each reported primary event to determine the level of diagnostic certainty. Events which are judged as confirmed or probable will be included in the primary analysis.

3.6.5 **Participant Relocation to a New Site**

If a participant relocates to an area without a START site where the participant could be transferred, data collection of items that are considered to be part of routine care (e.g., HIV RNA level, CD4+ cell count, clinical events) will continue if the participant gives permission. The *START Protocol Instructions Manual* provides guidance on how to collect data for participants who relocate and/or transfer to another START clinical site.

3.6.6 **Stored Samples and Future Research**

After 2017, no blood or urine specimens will be obtained for storage. Specimens collected through December 2017 will be stored at a central specimen repository for use in HIV-related research concerning the effects of HIV and ART on AIDS and non-AIDS conditions. Proposed research utilizing these specimens will be reviewed and approved by the INSIGHT Scientific Steering Committee. Results of research tests on individual specimens will not be given to participants or their clinicians, but aggregate research results will be made available.

4 Clinical Management Issues

4.1 Antiretroviral Treatment

Based on the results of START, all participants should be offered ART with a goal of continually suppressing HIV RNA levels. Local guidelines which stipulate that once ART is started the goal should be viral suppression should be followed for clinical management.

4.2 HIV Transmission Counseling

All participants should receive counseling regarding prevent*ion of HIV transmission to others as* indicated.

4.3 Study Withdrawal

Participants may withdraw from the study at any time at their request and resume participation at any time upon re-consent. A participant may be withdrawn if:

- S/he relocates and data can no longer be collected.
- S/he is imprisoned, or involuntarily incarcerated for medical reasons. In this case, no data will be collected during the imprisonment or involuntary incarceration. However, once released from imprisonment or involuntary incarceration, an individual may resume participation upon re-consent.

- The study is discontinued.

All participants should otherwise be followed according to protocol.

4.4 Co-enrollment in Other Studies

Co-enrollment in other studies is permissible.

5 Evaluation

5.1 Data Analysis

The primary analysis will be by intention to treat, comparing the early and deferred groups. Time-to-event methods, including stratified log-rank tests, proportional hazards regression analysis, and Kaplan-Meier cumulative event curves, will be used to summarize the primary endpoint (i.e., time to the first event) and major secondary outcomes.[28] Unless otherwise stated, analyses will be based on a Cox model with a single indicator for treatment group and with strata corresponding to geographic region (North America, South America, Europe, Australasia, and Africa).

Analyses will be carried out for the following three calendar periods: 1) from randomization to December 31, 2015; 2) from January 1, 2016 to December 31, 2021; and 3) cumulatively from randomization through 2021. These analyses will focus on the primary endpoint, serious AIDS events, serious non-AIDS events, all-cause mortality, CVD, non-AIDS cancer, and unscheduled hospitalizations.

To assess whether treatment hazard ratios differ between the follow-up period prior to January 1, 2016 and afterwards, Cox models which include an interaction term with the calendar follow-up period will be used. Similar analyses will use the cutoff of May 27, 2015. Cox models will also be used to assess the homogeneity of hazard ratios over the entire follow-up period, during the period between 2016 and 2021, and during the period before (May 27, 2015) and after investigators and participants were informed of the interim results.

The randomized comparisons planned above will be supplemented with analyses that take into account the timing of ART use (viral suppression) in the deferred ART arm and consider ART use (viral suppression) and latest CD4+ count as time-updated covariates in order to determine the extent to which the treatment HR is explained by those factors.

Subgroup analyses for the primary endpoint and major secondary outcomes will also be performed for the following three calendar time periods: 1) from randomization to December 31, 2015; 2) from January 1, 2016 to December 31, 2021; and 3) cumulatively from randomization through 2021. Subgroup analyses will be aimed at determining whether the treatment effect (immediate versus deferred) differs qualitatively across various baseline-defined subgroups. Subgroup analyses will be performed by age, gender, race/ethnicity, geographic region, including low versus

moderate/high income countries, the presence of risk factors, including risk scores, for serious non-AIDS and AIDS conditions, baseline CD4+ cell count, baseline HIV RNA level, baseline levels of IL-6 and D-dimer, duration of HIV infection at enrollment, viral characteristics, including subtype, and evidence of transmitted drug resistance, and calendar date of enrollment in order to assess the effect of different treatment patterns that may emerge. The consistency of the treatment difference across participating countries will also be assessed. An overall test of heterogeneity will provide evidence of whether the magnitude of the treatment difference varies across baseline subgroups.

HIV RNA levels, CD4+ and CD8+ cell counts will be compared for the early and deferred groups. Likewise, discontinuation of ART in the early and deferred groups will be closely monitored. Kaplan-Meier life-table methods will be used to estimate the cumulative percent of participants in the deferred group who initiate therapy after different periods of follow-up. Follow-up levels of HIV RNA and CD4+ count will be summarized in a number of ways. Follow-up time spent in various categories will be compared. Longitudinal measurements of viral load and CD4+ cell count will be summarized using measured levels (or log transformed) and using repeated binary assessments (e.g., viral load below 50 copies/mL).

Analyses which take into account use of ART by deferred arm participants will also be carried out for comparing the immediate and deferred ART groups for the time period between 2016 and 2021. These analyses will be aimed at estimating the effect of initiating ART on the residual excess risk of the primary endpoint after taking into account the duration of ART after 2016.

5.2 Data Monitoring

The trial will be conducted under the direction of the START study protocol team which includes representatives from the community, the major funder (NIAID), and from different scientific and administrative disciplines.

During the extended follow-up the protocol team and other INSIGHT committees will closely monitor the data for completeness and quality.

There are no planned interim analyses that would lead to earlier reporting of findings related to the two major hypotheses that will be addressed with extended follow-up. However, at least on an annual basis, the protocol leadership will review a report on data quality, the completeness of follow-up, and treatment differences for the primary and major secondary outcomes.

6 Protection of Human Subjects & Other Ethical Considerations

6.1 Local Review of Protocol and Informed Consent

Prior to the initiation of Version 4.0 of the protocol at each clinical research site, the protocol, and the participant Information materials will be submitted to and approved by the site's IRB or IEC. Likewise, any future amendments to the study protocol will be submitted and approved by each site's IRB or IEC.

6.2 Ethical Conduct of the Study

The study will be conducted according to the Declaration of Helsinki in its current version; the requirements of Good Clinical Practice (GCP) as defined in Guidelines, EU Clinical Trials Directive (2001/20/EC and subsequent revisions), and EU GCP Directive (2005/28/EC and subsequent revisions); Human Subject Protection and Data Protection Acts; the US Office for Human Research Protections (OHRP); or with the local law and regulation, whichever affords greater protection of human subjects.

6.3 Informed Consent of Study Participants

All study participants must have signed all applicable approved informed consent forms prior to any study-related procedures. The sponsor does not require an additional informed consent for Version 4.0 of the protocol if the participant consented to Version 3.0. Appendix D provides the Version 3.0 consent for reference, and a sample informed consent for Version 4.0 for those sites that may require it.

6.4 Confidentiality of Study Participants

The confidentiality of all study participants will be protected in accordance with GCP Guidelines and national regulations.

7 Other Important Documents and Policies

7.1 Reference Documents

Study procedures are described in detail in the *START Protocol Instructions Manual.*

7.2 Data Collection and Monitoring

Study data will be collected on electronic case report forms (eCRFs) once each year for each participant. Monitoring may be performed by staff from the INSIGHT International Coordinating Centers or Site Coordinating Centers or by contractors of the primary funder.

At a minimum, all items referenced in the protocol as being relevant to the research study will be recorded in the participant's research record in accordance with standard procedures. In addition, all items specifically required by the protocol will be recorded on eCRFs.

7.3 Publications and Presentations

Publications and presentations related to data obtained from the START study will adhere to the INSIGHT Publications and Presentations Policy on the INSIGHT website (see Appendix B)

APPENDIX A: PRIMARY ENDPOINT DEFINITION

The primary composite endpoint for START is non-fatal serious AIDS events (or "AIDS*"), non-fatal serious non-AIDS (or "non-AIDS") events, and death from any cause. It includes the following components:

- Fatal AIDS or non-fatal AIDS* events
  These include opportunistic events consistent with the 1993 CDC expanded surveillance definition plus additional events associated with immunosuppression in the participant population targeted for enrollment. Esophageal candidiasis and chronic *Herpes simplex* infection will only be counted in the primary endpoint if fatal events.

  AIDS* events include:
  - 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

AIDS events include:

- All conditions defined as AIDS* above
- Esophageal candidiasis
- Chronic *Herpes simplex*

- Non-fatal serious non-AIDS events (“non-AIDS”)
  - Cardiovascular disease (CVD) (myocardial infarction, stroke, coronary revascularization)
  - End-stage renal disease (ESRD) (initiation of dialysis, renal transplantation)
  - Decompensated liver disease
  - Non-AIDS-defining cancers (excluding basal and squamous cell skin cancers)

- Deaths not attributable to AIDS

The INSIGHT Endpoint Review Committee (ERC) has established objective criteria for each event and its level of diagnostic certainty. These criteria are given in the *START Protocol Instructions Manual.* The ERC is responsible for reviewing each reported event to determine the level of diagnostic certainty. Events that are judged as confirmed or probable will be included in the primary analysis.

APPENDIX B: REFERENCES ON INSIGHT WEBSITE

The INSIGHT website (**www.insight-trials.org**) will maintain updated links to the following documents referenced in the START protocol and to other information pertinent to the study:

- The *START Protocol Instructions Manual*

- The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (or "DAIDS AE Grading Table"), as applicable for START

- INSIGHT Publications and Presentations Policy

APPENDIX C: LIST OF ACRONYMS

ACSR	AIDS Cancer Specimen Resource
ADS	Average Deficit Score
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome (see Appendix A)
AIDS*	Modified definition of AIDS (see Appendix A)
ALT	Alanine aminotransferase
ANRS	Agence Nationale de Recherches sur le SIDA et les Hépatites Virales
ART	Antiretroviral Therapy
AST	Aspartate aminotransferase
AWP	Average Wholesale Price
BMBF	Bundesministerium für Bildung und Forschung (German Ministry)
BP	Blood Pressure
cART	Combination Antiretroviral Therapy
CASCADE	Concerted Action on Seroconversion to AIDS and Death in Europe
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention (U.S.)
CDR	INSIGHT Central Drug Repository
CES-D	Center for Epidemiologic Studies Depression Scale
CFR	Code of Federal Regulations (U.S.)
CI	Confidence Interval
CNS	Central Nervous System
CPE	CNS Penetration Score
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CVD	Cardiovascular Disease
D:A:D	Data Collection for Adverse Events of Anti-HIV Drugs
DAIDS	The Division of AIDS, NIAID, NIH (U.S.)
DC	Drug Conservation (Arm in SMART Study)
DHHS	Department of Health and Human Services (U.S.)
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
DVT	Deep Vein Thrombosis
EAE	Expedited Adverse Event
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
EMEA	European Medicines Agency
ERC	Endpoint Review Committee
ESPRIT	Evaluation of Subcutaneous Pro-leukin in a Randomized International Trial
ESRD	End-stage Renal Disease
EU	European Union
FDA	Food and Drug Administration (U.S.)
FIRST	Flexible Initial Antiretrovirus Suppressive Therapies

GCP	Good Clinical Practice
GEE	General Estimating Equations
GFR	Glomerular Filtration Rate
GID	Generated Identification Number
HAART	Highly Active Antiretroviral Therapy
HBM	Human Biological Material
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus Type 1
HIVAN	HIV-Associated Nephropathy
HLA	Human Leukocyte Antigen
HR	Hazard Ratio
HVLT-R	Hopkins Verbal Learning Test
ICC	International Coordinating Center (INSIGHT)
IEC	Institutional Ethics Committee
IL-2	Interleukin-2
INSIGHT	International Network for Strategic Initiatives in Global HIV Trials
IRB	Institutional Review Board
LDL	Low Density Lipoprotein
MACS	Multicenter AIDS Cohort Study
mL	Milliliter
mm	Millimeter
NCI	National Cancer Institute, NIH (U.S.)
NFL	Neurofilament Protein
NIAID	National Institute of Allergy and Infectious Diseases, NIH (U.S.)
NIH	National Institutes of Health (U.S.)
NIMH	National Institute of Mental Health, NIH (U.S.)
NINDS	National Institute of Neurological Disease and Stroke, NIH (U.S.)
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
Non-AIDS	Serious Non-AIDS Conditions (see Appendix A)
NRTI	Nucleoside/Nucleotide Reverse Transcriptase Inhibitor
OHRP	Office for Human Research Protections (U.S.)
PHI	Primary HIV Infection
PHS	Public Health Service (U.S.)
PI	Protease Inhibitor
PID	Participant Identification Number
PIM	Protocol Instructions Manual
QNPZ	Quantitative Neurocognitive Performance Z Score
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Standard Deviation
SDMC	Statistical and Data Management Center (INSIGHT)
SF-12	Medical Outcomes Study Short-Form-12 Item Survey
SMART	Strategies for Management of Antiretroviral Therapy
START	Strategic Timing of Antiretroviral Treatment

SUSAR	Suspected Unexpected Serious Adverse Reactions
TACC	Tri-Service AIDS Commission, Department of Defense (U.S.)
U.K. CHIC	United Kingdom Collaborative HIV Cohort Study
U.S.	United States of America
VS	Viral Suppression (Arm in SMART Study)
WAIS-III	Wechsler Adult Intelligence Scale-III
WBC	White Blood Cell Count
WHO	World Health Organization

Appendix D: Informed Consent Forms

This appendix includes the sample informed consents for Version 3.0 and 4.0 of the START protocol.

All START participants were asked to re-consent to Version 3.0, because at that time we were asking for participant consent to be followed until 2021, several more years than originally planned. Participants who did not wish to continue follow-up under Version 3.0, with its reduced data collection schedule, withdrew from START. Although sites must obtain appropriate IRB/EC approvals and registration with INSIGHT for Version 4.0 of START, the study sponsor is not requiring participants to re-consent in order to continue follow-up under Version 4.0. The duration of follow-up under Version 4.0 is the same as that to which participants consented for Version 3.0. Data collection requirements have again been reduced, so we are not asking anything more from participants than what they have already consented to provide. These changes can be communicated to participants in any way the site considers appropriate for its population, including verbal communication (documented in the participant's record) at the participant's next clinic visit. A sample participant information sheet will be provided should sites wish to use it.

As participants may move their care to another START site during follow-up or participants who have been lost to follow up and have yet to consent to version 3.0 may return to clinic, a sample informed consent document for Version 4.0 of the protocol is also included in this appendix. In addition, in some countries, individual sites' IRBs/ECs may elect to require that participants re-consent to continue follow-up under Version 4.0. In such cases, if participants decline re-consent they will be withdrawn from START.

START STUDY SAMPLE CONSENT FOR EXTENDED FOLLOW-UP (Version 3.0)

University of Minnesota: SPONSOR
NIAID: PRIMARY FUNDER

Protocol Title:
Strategic Timing of AntiRetroviral Treatment
(START)

A Multicenter Study of the
International Network for Strategic Initiatives in Global HIV Trials
(INSIGHT)

Short Title of the Study: START

CONSENT FOR PARTICIPATING IN AN NIH-FUNDED RESEARCH TRIAL

SITE LEADER: _____ PHONE: _____

ALL SITE INSTRUCTION THAT IS INCLUDED IN A TEXT BOX SHOULD BE REMOVED FROM THE SITE'S INFORMED CONSENT FOR SUBJECTS

OHRP Requirements to be read by the sites:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBS ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB, AND NOTED IN THE IRB MINUTES. JUSTIFICATION AND IRB APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER.. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB MAY OTHERWISE ADDITIONALLY REQUIRE.

INTRODUCTION

You are being asked to continue to participate in the START study through 2017, and possibly through 2021 if funding is available. This extended follow-up will provide important additional information on the long-term benefits and risk of taking HIV medicines.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives you information about the planned long-term follow-up of participants in the START study that will be discussed with you. Once you understand

the reasons for extended follow-up, and if you agree to take part, you will be asked to sign this consent form. You will be given a copy to keep.

Before you learn about the extended follow-up, it is important that you know the following:

- Your participation is entirely voluntary;
- You may decide not to take part or to withdraw from the planned follow-up at any time without losing the benefits of your routine medical care.

START is being funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), U.S. National Institutes of Health (NIH), through a grant to the University of Minnesota, which is the lead institution in the INSIGHT group. The University of Minnesota is the sponsor of this study. This study is also being conducted with additional funding from Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS, France); Australian National Health and Medical Research Council (NHMRC); Danish National Research Foundation; Medical Research Council (MRC, United Kingdom); National Heart, Lung, and Blood Institute (NHLBI); National Institute of Mental Health (NIMH); National Institute of Neurological Disorders and Stroke (NINDS); and Division of Clinical Research (NIAID). Additional support is being provided by AbbVie Laboratories, Inc.; Bristol-Myers Squibb; Gilead Sciences, Inc.; GlaxoSmithKline, Inc.; Merck & Co., Inc, and Janssen Pharmaceuticals, Inc.

WHY IS FOLLOW-UP CONTINUING THROUGH 2021?

On May 15, 2015 the independent Data and Safety Monitoring Board (DSMB) for START determined that the primary study question had been answered. Beginning HIV medicines right away (the Early arm) was better than waiting to start HIV medicines (the Deferred arm) for the primary endpoint of START and its two major outcomes, serious AIDS illnesses and other non-AIDS serious medical illnesses. The DSMB recommended offering HIV medicines to participants in the Deferred arm who had not yet started HIV medicines. The DSMB also recommended continued follow-up of study participants.

START investigators and study participants were told about these recommendations, and participants in the deferred arm who had not started treatment were offered HIV medicines.

This consent describes the plan for continued follow-up of START participants through 2021. Currently, the START study has enough funding for follow-up through 2017. If the request for more funding to continue follow-up through 2021 is not successful, the follow-up and data collection described in this consent will end in 2017.

The primary reason for continuing follow-up is to find out the differences in serious illnesses between the Early and Deferred HIV medicines groups. Your continuing participation in START is very important to our ability to learn about these long-term effects, even if you are now taking HIV medicines.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?
All HIV-positive participants randomized to START are being invited to be in the extended follow-up.

HOW LONG WILL YOU BE IN THE STUDY?
You will be in this study at least until the end of 2017. We are asking you to consent to be followed through the end of 2021, because we plan to seek funding for follow-up through 2021.

HOW WILL THE STUDY WORK?
If you consent, we plan to see you at clinic visits for data collection twice each year (about every 6 months), instead of three times a year as before. We will follow your regular HIV care and collect a little additional information from you, but not as much as in the past.

At these visits, your study doctor or nurse will ask questions about your health and your HIV infection and will give you a short medical examination. You will have about 5-10 mL (about 1-2 tablespoons) of blood drawn. This blood will be used to measure the amount of HIV in your blood, CD4+ cell count, and CD8+ cell count (another type of blood cell that is affected by HIV).

Once each year, you will also have an extra 40-55 mL (3-4 tablespoons) of blood drawn to test how your kidneys and liver are working and to look at the amount of sugar and types of fats (called lipids) in your blood. You will be asked to not eat anything for at least 8 hours before these tests for sugar and lipids, and to not drink anything except water during that time. You will give a urine sample which will also be tested to see how your kidneys are working.

These results will be shared with you when they are available. You will be asked what medicines you are taking.

Site instruction:
If your site will not be collecting study-specific ECGs please remove the text in italics in the next paragraph. If your site will be doing ECGs, please change the text to not be in italics.

At your annual visit in 2016, you will also have an electrocardiogram (ECG), a routine test that allows the doctor to look at the rhythm of your heart. This involves lying on a table and having 10 small electrodes stuck to your skin for at least 5 minutes while the test is done. This procedure does not usually hurt. You will not have any more ECGs done in the study after 2016.

Throughout the long-term follow-up of the study

It is very important to let your study doctor or nurse know right away if you are sick or injured or in the hospital. This is important for your safety, and also for the study to learn more about illnesses that happen to people with HIV who are treated early (or defer treatment) for their HIV infection. Your study doctor or nurse will ask you for permission to get medical records from your other doctors or from the hospital (if you were in the hospital). You will be asked to give permission for other doctors or hospitals to share this information with the study team.

You should tell your study nurse or doctor before you take any other medicines or dietary supplements or enroll in other clinical trials. This is important because some medicines should not be taken together. Your study doctor or nurse will help figure out what medicines and supplements are safe for you to take.

Your doctor may decide to see you more often than required for the study based on your needs.

Site Instruction:
Please remove the Stored specimens section that follows if your IRB requires a separate consent for stored specimens

Stored specimens for future research
If you have agreed to have blood and urine specimens stored, you will be asked to give a 15-30 ml sample of blood (about 1-2 tablespoons) and a urine sample once each year. These samples will be stored in a safe and secure laboratory in the United States for use in future research related to HIV infection, its complications, and the immune system.

We will also collect a 10-mL sample of blood (about 2 teaspoons) if you change HIV medicines because of the amount of HIV virus in your blood or because resistance mutations have been detected. You will be asked for this sample before you start taking your new HIV medicines. This blood will be used sometime in the future to confirm whether your HIV virus had stopped responding to the HIV medicines you were taking.

You and your doctor will not receive any results from tests done on these stored samples. No tests of your genes (DNA) will be done on these samples. These samples will not have any information on them that can identify you by name. There is no time limit on how long your samples will be stored. You can still be in the START study even if you do not want to have samples stored.

HOW WILL YOU GET HIV MEDICINES?
If you are already taking HIV medicines provided by the study, you will continue to receive them. Likewise, if you begin to take HIV medicines, you may receive them from the study. The study will be able to give you HIV medicines through 2017. It is possible you will be able to get some or all HIV medicines from the study after 2017, but we do not know that yet. Your study doctor or nurse will let you know at least 6 months ahead

of time if the study will not be able to give you some or all HIV medicines anymore. They will help you arrange to get HIV medicines no longer provided by the study through your insurance or some other program.

WHAT IF YOU MOVE?
If you move or transfer your medical care to another doctor, the study staff would like to continue to collect information about your health. If you give permission, your study doctor or nurse will contact your new doctor and ask him or her to provide information about your health. The types of information your new doctor will be asked for are routine things, such as results of laboratory tests (for example, CD4+ cell count and viral load), what medicines you are taking, and whether you have been sick. When you move, you will be asked by the study staff to give permission for your new doctor to share this information with the study team. Your new doctor may also ask you to give permission.

WHAT ARE THE RISKS AND/OR DISCOMFORTS OF THIS STUDY?
This section describes risks or discomforts that you may have. There may be other risks to you (or to your baby, if you are a woman and become pregnant while taking HIV medicines) that we have no way of knowing about right now. If other risks or benefits are found during the study, your study doctor or nurse will let you know about them right away.

Possible risks of taking HIV medicines
The long-term risks of using HIV medicines are not clear, and as with all medicines, side effects can happen. However, your risks are no greater than taking these medications and not being followed in START.

It is also possible for the HIV virus to develop resistance to any anti-HIV drug. Longer follow-up in START will help us know if beginning to treat HIV earlier or later will lead to resistance to more HIV medicines over time.

It is possible that someone could inadvertently find out that you are infected with HIV if you are taking HIV medicines and someone in your household or at work notices you taking them.

Risks of drug-drug interactions (where one medicine affects how another works)
For your safety, you must tell your doctor or nurse about all medicines, including prescription, over-the-counter (non-prescription), herbal or alternative medicines, and dietary supplements you are taking. This is because there may be serious side effects when other medicines are taken with HIV medicines. Also, please let your nurse or doctor know before you enroll in any other studies while on this study.

Risk of transmitting HIV
Using HIV medicines such that your viral load is undetectable has been shown to substantially lower your ability to transmit HIV to other people, but this does not work 100% of the time. You should continue to use precautions to make sure you do not

infect someone else. Your study doctor or nurse will tell you about how to protect yourself and other people.

Risks of blood drawing
The risks of having blood taken include pain, bleeding, bruising, lightheadedness, anxiousness, and in rare cases fainting or infection or a blood clot where the needle enters the body. You may feel some anxiety while waiting for your test results to be available. You will have blood tests like those in this study done as part of your usual care, even if you decide not to be in this study.

WHAT ARE THE BENEFITS OF THIS STUDY?
By being in START you have already helped in improving the treatment of many people with HIV now and in the future. What we learn from your continued follow-up will tell us more about benefits and risks of therapy. If you stay in START, there could also be some direct benefit to you. For example, by being in a research study you may find out about treatments, services, or other things that could help you live with your HIV infection sooner than you would if you were not in a research study.

It is also possible that you may receive no benefit from being in this study. What we learn from this study may help us to improve the treatment of other people who are infected with HIV.

WHAT IF THERE ARE NEW FINDINGS?
You will be told about any new information learned during the study that might cause you to change your mind about staying in the study.

WHAT IF YOU DON'T WANT TO BE IN THE STUDY ANY LONGER?
If you consent to long-term follow-up in the START study, you may decide to stop participating at any time. Withdrawing from this study will not affect the benefits of your regular medical care. However, if you are receiving HIV medicines from the study, you will not continue to be given HIV medicines from the study after you withdraw. Your doctor or nurse will help you find another way to get HIV medicines.

CAN YOUR STUDY PARTICIPATION BE STOPPED WITHOUT YOUR CONSENT?
You may be taken off the entire study without your consent if:

- Your study doctor decides that continuing in the study would harm you;
- The study is cancelled by the sponsor (the University of Minnesota), the National Institute of Allergy and Infectious Diseases (NIAID), regulatory authorities in your country, or your site's Institutional Review Board (IRB)/Ethics Committee(EC);
- You are in jail or prison; or
- Other administrative reasons, including a lack of funding for START study follow-up past 2017.

WHAT ARE THE COSTS TO YOU?
<Site should insert specific information about what HIV medicines will be provided for free, if any>. You, your insurance company, or some other third-party payer must pay

for all other medicines, including HIV medicines not listed above and medicines needed to prevent or treat other illnesses. We will provide all clinical and professional services, lab work, and other tests that are part of this study and not part of your regular care at no cost to you. As stated above, the study may at some point no longer be able to give you some or all of your HIV medicines. At that time, your study doctor or nurse will help you get your HIV medicines from another source.

HOW IS YOUR PRIVACY PROTECTED?

Researchers will take every reasonable step to keep your health information private and to prevent misuse of this information. You will not be identified by name or any other way in any publication about this study. You will be identified only by a number code, and personal information from your records will not be released without your written permission. We will collect dates of your study visits and of hospitalizations and certain illnesses so that we can answer the study questions as accurately as possible. We will use a 3-letter code given to you at the beginning of START as a check on the number code assigned to you to make sure all of your information stays together.

[The following paragraph must be included at U.S. sites only]

In addition to these efforts to keep your information private, the START study and its substudies are covered by a Certificate of Confidentiality from the U.S. Department of Health and Human Services. This certificate means that researchers cannot be forced to give information collected as part of this study to people who are not involved with the study, such as the court system. However, this certificate has limited protection rights. You should know that it does not stop the doctor in charge of this study from taking appropriate steps to prevent serious harm to yourself or others.

[The following paragraph must be included at international sites only]

We will try to keep your personal information private, but we cannot guarantee complete confidentiality. Your personal information may be released if required by law. Any publication of this study will not use your name or identify you personally.

Your medical and research records may be seen by the *[insert the name of the site]* ethics committee (institutional review board, IRB), the U.S. National Institutes of Health (NIH), the U.S. Office for Human Research Protections (OHRP), and the research staff and monitors, and their designees. The research staff at *[insert the name of the site]* is required to make sure that people not involved with this study cannot see your research and medical records while collecting personal information about you. They will keep your files in a locked cabinet in a safe place and will handle your personal information very carefully. This will also help to protect your privacy.

Site Instruction:
If the information in the next paragraph is not correct for your country/site, please revise the information to inform the subject of the following: 1. what treatment will be provided to the subject; 2. who will pay for the treatment; 3. if there is any plan for compensation for research-related injury issues, such as lost wages, etc.

WHAT IF YOU ARE INJURED?

If you are injured because of being in this study, *[insert the name of the clinic]* will give you immediate necessary treatment for your injuries. The cost for this treatment will be charged to you or your insurance company. You will then be told where you may receive additional treatment for injuries. There is no program for monetary compensation. This means that if you are hurt by being in the study, there is no money set aside to pay for treatment of injuries or other costs. You do not give up any of your legal rights by signing this form.

WHAT IF YOU HAVE PROBLEMS OR QUESTIONS?

If you ever have questions about this study or in case of research-related injuries, you should contact *[insert the name of the study doctor at your site]* at *[insert the telephone number]*. If you have questions about research subject's rights you can call *[insert the name and title of the appropriate country- or site-specific person]* at *[insert the telephone number]*.

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN EXTENDED FOLLOW-UP OF THE START STUDY

If you have read the informed consent (or if you have had it explained to you) and understand the information, and you voluntarily agree to continue in START, please sign your name below.

_____
Participant's name
(typed or printed)

_____ _____
Participant's signature Date

OR

_____
Participant's legal guardian or representative name
(typed or printed)

_____ _____
Legal guardian/representative's signature Date

_____
Witness's name
(typed or printed)

_____ _____
Witness's signature Date

NOTE: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the participant. A copy should be placed in the participant's medical record.

A witness to the participant's signature is strongly encouraged.

Site Instruction:
If your IRB/EC requires a separate consent document for specimen storage, do not use this signature page. Instead, use the START STUDY SPECIMEN STORAGE (PLASMA AND URINE) SAMPLE CONSENT (Appendix A-2).

SIGNATURE PAGE FOR CONSENT TO STORE BLOOD AND URINE SPECIMENS

If you have read the information about stored specimens for future research in the informed consent (or if you have had it explained to you) and understand the information, please mark your choice in one of the boxes below and sign or initial as asked.

You can still participate in extended follow-up of the START study even if you do not want to have samples stored.

Please mark your choice:

☐ YES. I agree to have blood and urine samples collected and stored and used for future research. *Please sign below.*

☐ NO. Do not collect and store samples. *Please put your initials and today's date here →*

_____ *Do **NOT** sign below.*

_____
Participant's name (typed or printed)

_____ _____
Participant's signature Date

OR

_____
Participant's legal guardian or representative name (typed or printed)

_____ _____
Legal guardian/representative's signature Date

NOTE: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the participant. A copy should be placed in the participant's medical record.

START STUDY SAMPLE CONSENT FOR EXTENDED FOLLOW-UP

(Version 4.0)

University of Minnesota: SPONSOR
NIAID: PRIMARY FUNDER

Protocol Title:
Strategic Timing of Anti-Retroviral Treatment
(START)

A Multicenter Study of the
International Network for Strategic Initiatives in Global HIV Trials
(INSIGHT)

Short Title of the Study: START

CONSENT FOR PARTICIPATION IN AN NIH-FUNDED RESEARCH TRIAL

SITE LEADER: _____ PHONE: _____

ALL SITE INSTRUCTION THAT IS INCLUDED IN A TEXT BOX SHOULD BE REMOVED FROM THE SITE'S INFORMED CONSENT FOR SUBJECTS

OHRP Requirements to be read by the sites:

PLEASE NOTE THAT THIS SAMPLE LANGUAGE DOES NOT PREEMPT OR REPLACE LOCAL IRB REVIEW AND APPROVAL. INVESTIGATORS ARE REQUIRED TO PROVIDE THE LOCAL IRB WITH A COPY OF THIS SAMPLE LANGUAGE ALONG WITH THE LANGUAGE INTENDED FOR LOCAL USE. LOCAL IRBS ARE REQUIRED TO WEIGH THE UNIQUE RISKS, CONSTRAINTS, AND POPULATION CONSIDERATIONS AS A CONDITION OF ANY APPROVAL. ANY DELETION OR SUBSTANTIVE CHANGE OF INFORMATION CONCERNING RISKS OR ALTERNATIVE TREATMENT MUST BE JUSTIFIED BY THE INVESTIGATOR, APPROVED BY THE LOCAL IRB, AND NOTED IN THE IRB MINUTES. JUSTIFICATION AND IRB APPROVAL OF SUCH CHANGES MUST BE FORWARDED TO THE INTERNATIONAL COORDINATING CENTER. SPONSOR-APPROVED CHANGES IN THE PROTOCOL MUST BE APPROVED BY THE LOCAL IRB BEFORE USE UNLESS INTENDED FOR THE ELIMINATION OF APPARENT IMMEDIATE HAZARD. NEW INFORMATION SHALL BE SHARED WITH EXISTING SUBJECTS AT NEXT ENCOUNTER, WITH ALL NEW SUBJECTS PRIOR TO INVOLVEMENT, OR AS THE LOCAL IRB MAY OTHERWISE ADDITIONALLY REQUIRE.

Because you are a part of the START Study, we invite you to continue to be followed in START through 2021. We hope this follow-up will give helpful additional information about the long-term effects of HIV medicines.

It is up to you whether or not you want to continue. Please ask questions and take as much time as you need to decide.

All of the people already in the START study are being asked to continue follow-up.

WHAT WILL HAPPEN DURING THE EXTENDED FOLLOW-UP IN START?
Starting on 01 January 2018, regular study visits are no longer required for START. Once a year the staff at your study site will collect information about any HIV medicines you are taking, any illnesses or hospitalizations you have had, and the results of CD4, CD8, and HIV viral load tests that you have had. If you are seen at the site for your HIV care, the study staff will review your medical records to collect this information. They may call you if they have questions.

If you do not receive your regular heath care at the site, the research staff will contact you to see how you are doing and may ask you to come in for a study visit. If you get your regular HIV care at a different clinic, the site staff will ask for your written permission to get the records from this clinic to review.

WHAT ARE THE RISKS OF START?
There are no risks associated with continuing your follow-up in START. Your medical care and treatment will be decided by you and your regular doctor. There are no specific study requirements to be followed. All HIV medicines have some side effects. There may also be long-term risks that we do not know about now. This is true for anyone taking HIV medicines, whether or not you are in the START study. Even if you are taking HIV medicines, you may still be able to give HIV to someone else. Your doctor or nurse will tell you about how to protect yourself and other people.

We will tell you if we learn about new risks or any other information that might be important to you.

WHAT ARE THE BENEFITS OF CONTINUING IN START?
Taking HIV medicines can help people with HIV infection. However, we do not know all of the effects that taking them for a long time might have on your general health. By continuing to follow people like you in the START study we will learn more about these effects.

WHAT CHOICES DO YOU HAVE OTHER THAN CONTINUING IN START?
<u>You do not have to continue in START if you do not want to. If you agree to continue, you can stop at any time.</u> If you choose not to continue or to stop, it will not affect your regular medical care.

CAN YOUR PARTICIPATION IN START BE STOPPED EVEN IF YOU DON'T AGREE?
The study doctor can take you out of START if you go to prison, or if the study is stopped by the study funder, sponsor, review committees (IRB/REC) or government authorities, or for other administrative reasons.

WHO WILL BE ABLE TO SEE YOUR MEDICAL INFORMATION?
We will protect the privacy of your medical information as much as legally possible, and release your records only with your written permission. We will label your study records with a code number and three letters, and you will not be identified in any publications about this research. However, your records may be seen by:

- People in the US government agencies that fund or oversee this research, for example, the U.S. National Institutes of Health (NIH).
- Study monitors who make sure the study is being conducted correctly.
- Independent groups (IRBs or ethics committees) that make sure the study is ethically acceptable.

[Include the following paragraph at US sites only]
We have a Certificate of Confidentiality from the US Government. This means that law enforcement officers, the courts, and others cannot force us to give them information about you. However, this does not prevent the study team from taking appropriate steps to prevent serious harm to you or to others.

WHAT IF YOU ARE INJURED AS PART OF THE STUDY?
We will provide treatment right away if you are hurt because of the research. The costs may be charged to you or your insurance company. We will give you information about where you can get additional treatment. You do not give up any of your legal rights by signing this form.

Site Instruction:
If the information is not correct for your country/site, please revise the information to inform the subject of the following: 1. what treatment will be provided to the subject; 2. who will pay for the treatment; 3. if there is any plan for compensation for research-related injury issues, such as lost wages, etc.

WHO CAN YOU TALK TO ABOUT THIS STUDY?
Please contact (*site PI and contact information*) if you have any questions or concerns about this research study or contact *(name and contact info)* if you have concerns about your rights as a research participant or you are injured as part of this study.

SIGNATURE PAGE FOR CONSENT TO PARTICIPATE IN START EXTENDED FOLLOW-UP

If you have read the informed consent (or if you have had it explained to you) and understand the information, and you voluntarily agree to continue in this study, please sign your name below.

_____
Participant's name
(typed or printed)

_____ _____
Participant's signature Date

OR

_____
Participant's legal guardian or representative name
(typed or printed)

_____ _____
Legal guardian/representative's signature Date

_____
Witness's name
(typed or printed)

_____ _____
Witness's signature Date

NOTE: This consent form with the original signatures MUST be kept on file by the principal investigator. A copy must be given to the participant. A copy should be placed in the participant's medical record.

A witness to the participant's signature is strongly encouraged.

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