Supplementary Appendix

Contents

The START study

START is an international, open-label, randomized trial funded by the National Institute of Allergy and Infectious Disease, National Institutes of Health. It was designed to assess whether immediate antiretroviral therapy (ART) at CD4+ counts >500 cells/mm^3 is superior to the deferral of ART until the CD4+ declines to 350 cells/mm^3 or other conditions requiring ART among HIV-positive adults.[1] The primary endpoint of START was a composite outcome with two major components: 1) serious AIDS-defining illnesses or death from AIDS; and 2) serious non-AIDS conditions (cardiovascular disease, end-stage renal and liver diseases, and non-AIDS-defining cancers) or non-AIDS-related death. Each reported START primary endpoint was reviewed by an Endpoint Review Committee (ERC) to determine if the event met pre-specified diagnostic criteria. [2,3]

In addition to these events, grade 4 events defined as potentially life-threatening symptomatic events not attributable to AIDS and unscheduled hospitalizations were collected and coded using the *Medical Dictionary for Regulatory Activities*, version 18.0.[4] START required the use of a drug combination for the first ART regimen prescribed in each treatment group that was based on guidelines of the Department of Health and Human Services (DHHS). The list of approved regimens was updated regularly during the course of the trial based on updates to the DHHS guidelines.

Enrollment into START took place between April 2009 and December 2013. Participants were enrolled across 215 sites located in 35 different countries. In May 2015, on the basis of an interim analysis, the independent data and safety monitoring board (DSMB) for START determined that the study question had been answered and recommended that participants in the deferred ART group be offered ART and that follow-up continue. The data were immediately unblinded, a report was prepared for publication,[5] and plans were made to follow participants through 2016.

Version 1.0 of the START protocol, dated December 2008 was used until October 2010 when an amended Version 2.0 was prepared. This version updated background data and described the movement from a pilot phase to a full-scale study. Under both Versions 1.0 and 2.0, follow-up was expected to be completed by the end of 2016. Another amendment (Version 3.0) was issued in February 2016. In this version, the follow-up data collection schedule was changed to twice yearly from every 4 months and extended participant follow-up through 2017. Version 4.0 of the protocol was issued in 2017 and extended follow-up through 2021. All four versions of the START protocol included sample informed consents as an appendix to the study protocol that were prepared by the study sponsor (University of Minnesota). The sponsor did not require re-consent for Version 2.0 but did require re-consent for Version 3.0 and Version 4.0. In some cases, local ethics committees required re-consent for Version 2.0. Typically, sites would submit the sample informed consent that was included with the protocol with minimal modification to their institutional review board (IRB) or ethics committee (EC). In some cases the IRB/EC required changes and a revised consent with a different version number was prepared by the site. All IRB/EC approved consents were to be submitted to the sponsor for review prior to use. All sites were required to document the consent process in each participant's chart, have the signature page of each signed consent on file, and provide a copy of the consent to the participant.

Since follow-up of START participants in ongoing, the total number of reported START clinical events remains blinded to the monitoring substudy.

Data in START are collected on structured case report forms (CRFs) and faxed to a statistical center at the University of Minnesota where the central database is maintained. START clinical sites are overseen by one of the four INSIGHT coordinating centers located in Copenhagen, London, Sydney and Washington DC.[6,7] The START trial is overseen by a study team, who work closely with the coordinating centers and the statistical center on the conduct and management of the trial.

Description of central, local, and on-site monitoring

Central monitoring

Central monitoring was performed by the statistical center utilizing data in the central database on a continuous basis. This monitoring included regular review of:

- Missing data (e.g., missed visits or individual data items);
- Timeliness of data submission and query resolution;
- Data queries;
- Discrepancies between specimens stored at the central repository and specimens collected by site as reported on CRFs for each study visit;
- Losses to follow-up and withdrawals of consent; and
- Findings on daily computer edit checks (largely deterministic) that flagged inadmissible values for single items and combinations of items on case report forms.

Reports summarizing these data were provided to all sites via the INSIGHT website and were updated regularly (daily, weekly, or monthly). In addition to the regular updates of central monitoring findings on the website, summary data were also shared with site investigators at least twice a year at investigator meetings and at regional meeting conducted by the coordinating centers. START sites and an INSIGHT committee composed of staff from the statistical center and coordinating centers also reviewed data summarizing each site's performance every 6 months and provided quantitative feedback to clinical sites on study performance. These reviews focused on participant retention, data quality, timeliness and completeness of START endpoint documentation, and adherence to local monitoring requirements.

In addition, trained nurses at the statistical center reviewed grade 4 events and unscheduled hospitalizations for possible primary START clinical events and asked sites to submit the appropriate documentation if a possible START primary endpoint was identified.

Local monitoring

Twice yearly, clinical site staff associated with START were to carry out specific quality assurance activities and report findings to the statistical center. This monitoring included review of:

- Regulatory files, including informed consent documents for each version of the START protocol
- Study specimen storage and labeling (if specimens were stored and/or processed on-site)
- Study drug management and accountability (if the site utilized the START central drug repository)
- Verify the source documents for eligibility criteria, informed consent, changes in ART, follow-up visits, and reportable START clinical events for a sample of participants

Sites completed standardized CRFs to record their local monitoring findings. The type of standardized forms provided for each local monitoring reporting period changed throughout the course of the study. For part of the study, sites were provided with paper CRFs to report their findings. These paper CRFs included specific "yes/no" questions and these answers, and any corrective actions were entered into the central databases. In 2013, the local monitoring reporting system piloted an electronic data capture system select sites. The electronic CRFs still included specific "yes/no" questions, but also required the site to provide a description of the finding along with any corrective actions taken, all of which were available in the central databases. During this pilot period, both paper and electronic CRFs were being used. In 2014, all sites switched to the electronic CRFs to report the local monitoring findings. Therefore, the central databases have detailed descriptions on the findings for only part of the substudy.

Example of a paper CRF used for local monitoring:

A. Participant Records and Documentation		No	Yes	NA
1. Informed Consent	a. Applies to all participants: Is the most recently signed IRB/IEC-approved main study consent on file?	0☐	1☐	
	b. Did the participant sign and date (in ink) the appropriate IRB/IEC-approved version of the main study consent prior to any study-specific procedures being done (i.e., required by the study and not done as part of the participant's usual care, for example, urine collection for storage) and prior to randomization? *(This item only needs to be reviewed once per PID)*	0☐	1☐	2☐ Previously reviewed
	c. Are the signatures and dates on the initial main study informed consents made by the participant? *(This item only needs to be reviewed once per PID)*	0☐	1☐	2☐ Previously reviewed
	d. For participants required to sign a new IRB/IEC-approved main study consent since the last review and who have attended a study visit, was the new consent signed prior to any study visit or study-specific procedures done (i.e., required by the study and not done as part of the participant's usual care, for example , urine collection for storage)?	0☐	1☐	2☐
	e. For main study informed consents signed since the last CQMP review, were all signatures and dates made by the participant?	0☐	1☐	2☐

During each local monitoring reporting period, the coordinating centers were provided a listing of findings, and a description (when available) and corrective actions taken. The coordinating centers had access to copies of each completed local monitoring CRF (scanned copies of the paper CRFs and access to the electronic forms), and were responsible for reviewing each finding and following up with the site to ensure the finding was properly resolved.

On-site monitoring

On-site monitoring of START was performed annually by a coordinating center-designated monitor, who were either coordinating center staff or staff located in the country of the sites being monitored. Of the 99 sites in the on-site monitoring group, 67 sites were monitored by coordinating center staff and 32 sites were monitored by staff located in-country. Every on-site monitor was required to have appropriate scientific and clinical knowledge to monitor clinical research studies, including:

- Bachelor's/University degree or equivalent in nursing, pharmacy, biology, or other biomedical sciences
- Experience in monitoring clinical trials, implementing HIV/AIDS studies, working with community and/or hospital or laboratory staff, training clinical staff, or performing quality assurance audits

- Familiarity with the START protocol and amendments, informed consent forms, and source documentation requirements

An individual new to on-site monitoring was to be mentored by an experienced monitor until it was determined they were ready to function independently. The monitoring assignments for external on-site monitors were similar to tasks performed by the local monitors. Each on-site monitoring visit included the review of:

- Regulatory files, including informed consent documents for each version of the START protocol
- Study specimen storage and labeling (if specimens were stored and/or processed on-site)
- Study drug management and accountability (if the site utilized the START central drug repository)
- Verify the source documents for eligibility criteria, informed consent, changes in ART, and reportable START clinical events for a sample of participants

Prior to each monitoring visit, the on-site monitor was provided a standardized report to complete and submit. This report included general "yes/no" questions (e.g., was an informed consent violation found?). For all issues identified, the monitor was asked to describe the situation and list any corrective actions needed at the site. All on-site monitoring reports were reviewed by a coordinating center before being submitted to the statistical center. The "yes/no" data fields were entered into the central databases, and then the full report (including all free text) was reviewed by designated staff at the statistical center. Eventually, the descriptions of the informed consent violations found by on-site monitors were entered into a database for central review at the statistical center.

For both local monitoring and on-site monitoring, the list of participants for source document verification was prepared by the statistical center. Participant charts were prioritized for review if any of the following had occurred since the previous review: (1) START clinical event reported; (2) participant became newly

lost to follow-up or withdrew from the study; (3) participant transferred from one site to another; (4) participant was previously identified as lost to follow-up and was still lost. This prioritization was to ensure adequate event documentation was being pursued, translated, and reported, and to verify appropriate steps were being taken to locate participants lost to follow-up and to obtain data from participants who moved away. The remainder of the participant list prepared for on-site monitors was then sorted by length of time since the previous review, with the longest period since last review given priority.

Defining eligibility violations

START had 7 inclusion criteria and 9 exclusion criteria. The monitoring substudy team focused on 3 eligibility violations that could have the largest impact on participant safety or the results of the START primary results (failing to have 2 CD4+ cell counts > 500 cells/mm^3 within 60 days before randomization, prior ART or interleukin-2 [IL-2] use, or female participant who was pregnant at randomization). During the course of the substudy, 3 HIV-negative participants were identified. The monitoring substudy team felt that this eligibility violation needed to be included in the primary monitoring outcome due the potential impact on participant safety.

Defining late START clinical events

A 6 month time period from primary and serious clinical event occurrence was used for defining potentially missed START primary and serious events because regularly scheduled START visits were to occur every 4±2 months under versions 1.0 and 2.0 of the START protocol. Sites were expected to have contact with participants at least once every 6 months. Also, by specifying a time-frame that was associated with the unreported event, it provided some allowance of time for the site investigator to assemble the required documentation for each event. All clinical events considered possible START primary endpoints were to be submitted for review by the ERC. With the approach used, if a START clinical event that occurred 3 months beforehand was found by an on-site monitor before it was reported by the site investigator, it would not be counted as a primary monitoring outcome. Similarly, if a site investigator regained contact with a lost participant and identified a START primary or serious clinical event that occurred greater than 6 months beforehand, it would be counted as a primary monitoring outcome for the monitoring substudy.

Table S1: Eligibility violations

	On-site		No on-site	
	Found by site staff, No. pts	**Found by on-site monitor No. pts**	**Found by site staff, No. pts**	**Found by on-site monitor No. pts**
Any eligibility violation	5	7	1	0
Eligibility violation				
- HIV-negative	2	1	0	0
- Did not have 2 consecutive CD4+ cell counts >500 within 60 days prior to randomization	1	0	1	0
- Prior use of antiretroviral therapy or IL-2	2	6	0	0
- Pregnant	0	0	0	0

Table S2: Subgroup analysis for Monitoring Substudy primary outcome

	On-site		No on-site				Int.
Subgroup	**Pts**	**Events[a] (%)**	**Pts**	**Events[a] (%)**	**OR (95% CI)[b]**	**p-value[b]**	**p-value[c]**
Prior experience[d]							0.04
Yes	1233	82 (6.7)	1690	71 (4.2)	1.4 (0.8, 2.4)	0.26	
No	874	52 (5.9)	574	14 (2.4)	3.2 (1.6, 6.1)	<0.001	
Prior on-site monitoring visit[e]							0.33
Yes	948	59 (6.2)	1322	50 (3.8)	1.3 (0.6, 2.7)	0.48	
No	1159	75 (6.5)	942	35 (3.7)	2.0 (1.1, 3.7)	0.02	
ICC							0.45
Copenhagen	299	14 (4.7)	278	9 (3.2)	1.5 (0.6, 3.7)	0.37	
London	528	40 (7.6)	487	12 (2.5)	5.9 (2.4, 14.3)	<0.001	
Sydney	446	26 (5.8)	455	19 (4.2)	1.3 (0.5, 3.7)	0.62	
Washington	834	54 (6.5)	1044	45 (4.3)	1.1 (0.6, 2.3)	0.72	
Geographic region							0.36
Africa	498	22 (4.4)	504	12 (2.4)	1.9 (0.9, 4.3)	0.11	
Asia	148	6 (4.1)	209	1 (0.5)	5.4 (3.0, 9.9)	<0.001	
Australia	42	2 (4.8)	67	7 (10.4)	0.4 (0.1, 2.9)	0.39	
Europe+Israel	610	47 (7.7)	617	15 (2.4)	3.8 (1.9, 7.5)	<0.001	
North America	275	28 (10.2)	227	29 (12.8)	0.9 (0.4, 1.9)	0.77	
South America	534	29 (5.4)	640	21 (3.3)	1.8 (0.7, 4.5)	0.22	
Estimated enrollment							0.85
< 15	181	11 (6.1)	120	4 (3.3)	2.8 (0.3, 23.1)	0.33	
15-30	845	64 (7.6)	825	40 (4.8)	1.7 (1.0, 3.2)	0.14	
> 30	1081	59 (5.5)	1319	41 (3.1)	1.6 (0.7, 3.3)	0.25	
Actual enrollment							0.95
< 15	406	36 (8.9)	351	22 (6.3)	1.7 (0.8, 3.9)	0.17	
15-30	439	32 (7.3)	551	21 (3.8)	2.0 (0.8, 5.2)	0.14	
> 30	1262	66 (5.2)	1362	42 (3.1)	1.6 (0.8, 2.9)	0.17	
START Treatment Group							0.35
Immediate ART	1049	52 (5.0)	1122	28 (2.5)	1.8 (1.0, 3.3)	0.04	
Deferred ART	1058	82 (7.8)	1142	57 (5.0)	1.6 (1.0, 2.7)	0.06	

[a] Number of participants with event
[b] Logistic regression hierarchical model with fixed effects comparing the on-site group to the no on-site group
[c] Interaction p-value from model with indicators for monitoring group, subgroup, and the interaction between subgroup and monitoring group
[d] Prior experience with the INSIGHT SMART or ESPRIT study
[e] Received on-site monitoring visit before the START monitoring substudy opened

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