START Newsletter

The Strategic Timing of AntiRetroviral Treatment – An INSIGHT Trial

Number 32 ▪ June 2019

We have now reviewed all aspects of the first round of electronic annual data collection in 2018 of the START trial and developed a strategy for the next 2019 round of data collection.

Rationale for the extended follow-up of the START trial cohort:

START is the only trial that will be able to experimentally determine whether late versus earlier initiation of ART leads to permanent damage, even after ART has been initiated and HIV RNA viral load suppressed. We know from the data captured so far that most participants randomized to defer ART had started ART by early 2016. We also know that those on ART in both arms of the study have, to a very large extent, achieved full and durable virological suppression. But the nadir CD4⁺ cell count is – for obvious reasons – lower (by around 200 cells/μL) in those who were originally randomized to deferral compared to those allocated to immediate start of ART. ***Hence, we will be able to answer the BIG question of whether the longer time spent untreated in the deferred arm, allowing the HIV infection to further progress, will or will not lead to continued higher clinical disease progression rates.*** Only in 2021 will we have sufficiently robust data to address this question. The annual data collection is the core instrument we have to progress towards that ultimate goal.

Two key indicators of how well the data capture process functions are completion of data capture and the proportion of participants providing additional follow-up information. The closer to 100% for each of these indicators, the better it is. Conversely, a high proportion of participants who are lost-to-follow-up (for whatever reason) would be a warning sign. Losses-to-follow-up can introduce bias in the planned comparisons of the immediate and deferred groups.

Losses to follow-up as of 31 December 2018

We define losses to follow-up as participants for whom there has been no update of vital status for at least 12 months or who have withdrawn consent for follow-up. We operationalize this by examining the last known alive date reported by sites for each participant and counting those for whom that date is ≥ 12 months before the cutoff date or those who report withdrawal of consent before the cutoff date of the analysis.

Figure 1 illustrates the percent lost-to-follow-up using this definition at the end of each of the 5 previous years (2014-2018). The percent lost-to-follow-up has increased from 3.9% at the end of 2015 to 13.9% at the end of 2018. This overall percent lost is increasing due to both lack of an update on survival status and to consent withdrawal, primarily the former.

Of particular concern is the large increase in the percent lost-to-follow-up between the end of 2017 and the end of 2018 – 3.6%. This results from a 2.3% increase in the number with no update on vital status for 12 months and a 1.3% increase in consent withdrawals.

This large increase in the percent lost-to-follow-up between 2017 and 2018 prompted us to carefully evaluate our new method of annual data collection implemented in 2018. The 2018 eCRF was required to be completed for all participants who were alive and who had not withdrawn consent as of 01 January 2018 (n=4,401). Two hundred sites have registered for Version 4.0 of the START protocol that requires this annual data collection through 2021.

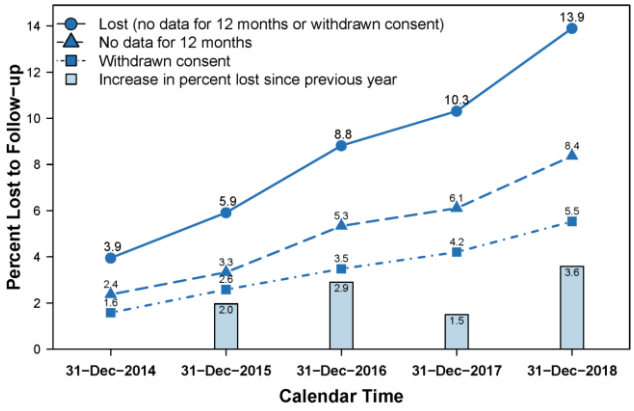

Figure 1. Percent of START cohort lost-to-follow-up by end of each calendar year from 2014-2018.

The key overall findings from 2018 eCRF data collection:

- An eCRF was completed for 4,374 (97%) of the 4,401 participants. This is outstanding.
- No queries were identified for 90% of the submitted eCRFs. This is also outstanding.
- For 365 participants (8% of those with completed eCRFs) there was no update in the last known alive date from what had been entered on the CRFs in 2017 and this resulted in an additional 129 participants meeting our lost-to-follow-up definition. We need to improve this by a substantial amount.
- An additional 49 participants withdrew consent. This is problematic. Please try to obtain consent for partial data collection).

Sixty-nine of 200 sites (35%) registered for Version 4.0 of START had an increase in the number of participants who are lost-to-follow-up; 15 of 35 (43%) countries had an increase (Figure 2).

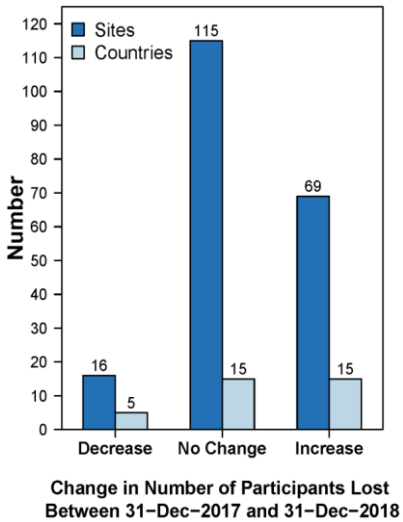

Figure 2. Distribution of sites and countries based on the net change in number of participants lost between end of December 2017 and end of December 2018. Limited to the 200 sites participating in START V4.0.

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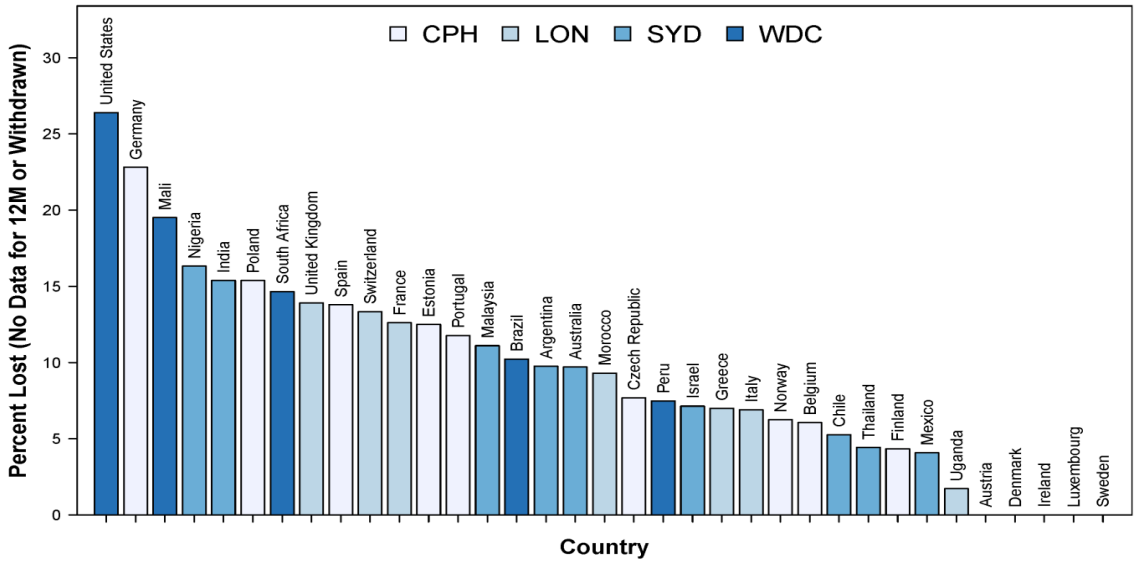

Figure 3: Country level distribution of the percent of participants lost to follow-up as of 31-Dec-2018. Ranked by highest percentage to lowest. Limited to the 200 sites participating in START V4.0.

The percent of participants lost-to-follow-up ranges from 0% to 26% among the 35 countries participating in START (Figure 3); for 10 countries, the percent lost to follow-up is < 5.9% (i.e. the lost % at the end of 2015 (Figure 1)). This is outstanding.

At the site level, for 74 sites the percent lost-to-follow-up was < 5.9%. These sites are shown in the table below according to how many participants they are following. There are many sites (small, medium and large) who have done outstanding job following their participants (congratulations!).

Focus points for the 2019 annual data collection:

➢ ***The 2019 annual data collection will begin earlier for all sites***

Sites will be able to enter new data as of **1 July 2019 through 31 December 2019**; an eCRF can be submitted at *any time* during this window. You should not postpone data entry to a later date in the window - in order to capture the most up-to-date information - for participants who are scheduled for clinic later in 2019. This information will be captured during the 2020 data window. Sites will have more time for query resolution through until 14 February 2020.

➢ ***Various strategies can be considered to capture follow-up information***

The easiest participants for whom to capture data are those still receiving their HIV care at the site. Relevant information can be obtained from the participant's clinical records. However, challenges exist when participants have moved and are now receiving care at another clinic.

Various strategies have successfully been introduced, and are summarized below for you to consider their applicability to your site:

- **For transfers, establish contact with the new clinic site to receive relevant information from their staff.**
- **Ask the participant for contact information to retrieve as much information as possible.**
- **Contact the participant via social media. If not already agreed to by the participants, this can be done proactively subject to approval by your ethics committee.**
- **Acquire access to registries (regional or national cohorts, death registries, etc.) to retrieve data.**
- **Encourage participants to send you copies of their lab tests, even a picture of a lab result is valid information.**
- **Review medical history for visits to other departments in the hospital where the participant is seen.**

➢ ***Launch a campaign to re-establish data capture for participants without information since 2016.***

Around the start time of the 2019 data collection window, we will release a list of PIDs last known to be alive without data in the central trial database during 2017 and 2018. During the data capture window sites able to recover follow-up information from such participants will be acknowledged. Our goal is that for at least 50% of these participants the last-known-alive date will be updated. Sites doing well during the campaign will be acknowledged during the 2020 INSIGHT investigator meeting prior to CROI.

Table 1. Listing of outstanding sites with <5.9% of participants considered lost by end of 2018, grouped by site size.

Site Size				
1-10 participants (n=38)		11-30 participants (n=23)	31-50 participants (n=6)	>50 participants (n=7)
611-016(ARG)	634-102(IRL)	611-002(ARG)	611-003(ARG)	649-014(BRA)
612-006(AUS)	621-101(LUX)	611-012(ARG)	611-302(MEX)	649-016(BRA)
612-007(AUS)	624-013(PRT)	612-002(AUS)	651-004(PER)	611-101(CHL)
612-018(AUS)	626-018(ESP)	612-024(AUS)	651-006(PER)	631-019(FRA)
612-026(AUS)	626-027(ESP)	621-006(BEL)	613-003(THA)	613-001(THA)
612-029(AUS)	625-203(SWE)	625-001(DNK)	634-003(GBR)	634-601(UGA)
625-401(AUT)	625-204(SWE)	625-003(DNK)		634-602(UGA)
625-402(AUT)	636-001(CHE)	625-501(FIN)		
621-007(BEL)	636-004(CHE)	622-016(DEU)		
625-602(CZE)	613-002(THA)	614-004(ISR)		
625-002(DNK)	634-030(GBR)	651-002(PER)		
625-004(DNK)	036-001(USA)	651-003(PER)		
631-001(FRA)	054-001(USA)	626-021(ESP)		
631-003(FRA)	067-001(USA)	613-004(THA)		
631-016(FRA)		613-005(THA)		
631-018(FRA)		634-002(GBR)		
631-020(FRA)		634-004(GBR)		
631-024(FRA)		634-009(GBR)		
631-027(FRA)		634-011(GBR)		
622-031(DEU)		014-001(USA)		
622-032(DEU)		027-001(USA)		
622-352(DEU)		082-001 (USA)		
635-006(GRC)		086-001 (USA)		
635-012(GRC)				

➢ ***Maintain your focus on START***

We appreciate that sites are busy with clinical care and other trials. We want to reach out to all START sites and will be launching several forms of communication. These include:

- **Webinars will be organized in July, August and September 2019 with trial and ICC leadership, at times that are convenient for sites during their regular working hours.**
- **During the 2019 data collection window, we will be centrally releasing monthly updates summarizing progress, as a supplement to the existing communications between sites and their ICC and/or SCC.**
- **START is already generating multiple scientific findings in peer-reviewed journals. You are already receiving monthly updates of new publications. We will also include a lay summary aimed at assisting you in communicating our findings to a broader audience. You can also search the INSIGHT website for publications using this open source link: http://insight.ccbr.umn.edu/index.php?page=&menu=publications&submenu=papers&content=papers_published**

➢ ***Your feedback is welcome***

We continue to encourage sites to maintain direct communication with their ICC and/or SCC with an open, direct and collegial dialogue. Please send us comments. We can only be successful if we continue to work as one team to complete the task of maintaining START trial participants in follow-up until 2021.