

START STUDY AND THE MANAGEMENT OF HIV



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The Strategic Timing of Antiretroviral Treatment (START) study, a multinational, randomised trial conducted by the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT), aimed to determine risks and benefits of the immediate initiation of antiretroviral therapy (ART) in asymptomatic HIV-positive patients who had a CD4+ count of greater than 500 cells/ μ L as compared with those who were deferred treatment until their CD4+ count was 350 cells/ μ L or below.¹

While the study (which began in 2009 and opened widely in March 2011) was meant to conclude at the end of 2016, it was terminated in May 2015 after an interim review found that, among other things, the “risk of developing serious illness or death was reduced by 53% among those in the early treatment group, compared to those in the deferred group.”²

The study was the second randomised trial to demonstrate the benefit of early ART, with previous research from the French TEMPRANO study finding similar results in a cohort of 2 056 HIV-positive patients in Abidjan, Ivory Coast.³

The START study effectively ended the decades-long debate as to whether the benefits outweighed the potential consequences of early ART, with Anthony Fauci of the National Institute of Allergies and Infectious Diseases declaring the evidence “clear-cut... with global implications for HIV treatment,” while START Co-Chair Jens Lundgren proclaimed the study, “an important milestone in HIV research.”²

The investigators further concluded that the findings were consistent irrespective of geographic location, or whether patients were from low-, middle-, or high-income countries. SA, Nigeria and Uganda were among the 35 countries participating in the trial.

FROM SMART TO DEBATING START

The START study was essentially an extension of the earlier Strategies for Management of Antiretroviral Therapy (SMART) study, the latter of which was terminated early when it was concluded

that intermittent ART, when compared to continuous ART, was associated a far higher risk of both AIDS-related and serious non-AIDS-related events.⁴

Beyond these definitive results, the SMART study also offered one unexpected finding: In addition to higher rates of mortality in patients on intermittent ART, deaths in this group were attributed predominately to non-AIDS-related cancers and end-organ disease, and not to AIDS itself.⁵

This led many researchers to question whether the initiation of ART in early infection, when the risk of AIDS is low, might provide clinical benefit by way of a reduced incidence of non-AIDS-related morbidities and death.

It was a hypothesis that many found controversial. At the time of the SMART study's termination in 2006, there was still little evidence that starting ART at CD4 counts above 250 cells/ μ L had any benefit over deferring ART until the CD4 count fell below 200 cells/ μ L. The WHO guidance at the time, in fact, still recommended ART at CD4 counts below 200 cells/ μ L in asymptomatic patients,⁶ a decision largely driven by the high rates of drug-related toxicities, particularly those associated with the widespread use of stavudine (d4T).⁷

By 2008, as efforts were in place to pilot the newly christened START trials, detractors were quick to express their doubts, given the paucity of evidence related to either the risks (e.g., drug resistance, long-term mitochondrial toxicities) or benefits (e.g., survival) of early ART.

Even as WHO guidelines were revised and access to newer-generation drugs was expanded, many urged caution and restraint, citing research

(including a 2010 observational study from the multi-continental CASCADE cohort) which show no survival benefit and no decrease in AIDS incidence in patients provided ART at CD4 counts over 500 cells/ μ L.⁸

It was against this backdrop – and in this context – that the final participant of the START study was enrolled on 23 December 2013.⁹

START STUDY OVERVIEW

The START study was conducted at 215 sites and enrolled 4,685 HIV-infected men and women who had never previously been exposed to ART. The median age of the participants was 36, while 27% were female and 21% were from Africa.

Patients were eligible for inclusion if they had no previous history of AIDS and had two CD4+ counts of at least 500 cells/ μ L six weeks prior to enrolment.

Patients enrolled in the study had acquired HIV primarily through male to male sexual contact (51%), followed by heterosexual sex (38%), contaminated blood products (5%) and injecting drug use (1%). Most had been confirmed HIV-positive for a period of one year.

Upon enrolment, the participants were randomly assigned, with 2 326 patients receiving immediate ART and 2 359 patients deferring treatment as per the then-current recommendations of U.S. Department of Health and Human Services (DHHS)¹⁰ and WHO.¹¹

ART was prescribed as per the DHHS guidelines of 2009, which had recommended either an NNRTI or a boosted PI used in combination with a dual-NRTI in first line-therapy.¹⁰

At the time of initiation, the median

CD4+ count in the immediate arm was 651 cells/ μ L, while the median HIV RNA viral load was 12,759 copies/ μ L. By contrast, the median CD4+ count in the deferred arm was 408 cells/ μ L, while the median HIV RNA viral was 41 525 copies/ μ L.

[Reasons for earlier ART in the deferred group included reduced risk of HIV transmission (10.9%), patient wish (10.2%), elevated viral load (9.3%), rapidly declining CD4 or low CD8% (9.2%), other clinical event/diagnosis (8.2%), or clinician request (6.3%).]

The mean follow-up time was three years, with the majority of patients receiving tenofovir (89% both groups), emtricitabine (89% immediate, 88% deferred), and efavirenz (73% immediate, 51% deferred).

The investigators defined the study's composite primary end point as, “any serious AIDS-related event, which included death from AIDS or any AIDS-defining event” or “any serious non-AIDS-related event, including death from causes other than AIDS.”

OUTCOMES AND INTERPRETATIONS

Irrespective of the baseline viral load or the timing of treatment initiation, the vast majority of patients were able to achieve full viral suppression by 12 months (98% immediate vs 97% deferred).

However, during the follow-up period, patients in the immediate arm had an average CD4+ count 194 cells/ μ L higher than those in the deferred arm. It was in this latter group that the average CD4+ count was seen to decline during the first year following randomisation, eventually stabilising

>> Continued on page 26

<< Continued from page 24

and gradually recovering as more individuals were placed on ART.

This trend was largely mirrored in the distribution of major events in the two arms. Of the 42 primary end points reported in the immediate arm, only four (10%) occurred before the initiation of ART. By contrast, the 71% primary end points in the deferred arm – 69 out of 96 cases – occurred during what might be considered a window of vulnerability prior to ART initiation.

The disparity was further echoed in higher rates of serious AIDS-related events, serious non-AIDS-related events, and deaths by any cause among

patients who deferred ART.

Overall, 42 participants in the immediate group experienced a major event, compared to 96 in the deferred group. This corresponded, respectively, to a 72% relative reduction in serious AIDS-related events (or 0.60 events per 100 person-years) and a 39% relative reduction in serious non-AIDS-related events (or 1.38 events per 100 person-years). The difference yielded a hazard ratio of 0.43, with a 95% confidence interval from 0.30 to 0.62, which was significant at $P < 0.001$.

On a comparative, per-case basis, the most common events included in

the combined primary end point were, as follows:

Type of event	Immediate ART	Deferred ART
Tuberculosis, pulmonary or extrapulmonary	6	19
Kaposi sarcoma	1	11
Lymphoma, Hodgkin's and non-Hodgkin's	3	10
Cardiovascular disease	12	14
Cancer, non-AIDS	9	18

While, on a per-case basis, death from all causes disproportionately affected the deferred group – with 12 deaths in the immediate arm vs 21 in the deferred arm – they were weighted by such events as suicide

(three deaths), accident/violence (three deaths) and substance abuse

(two events). As such, the difference between the two arms was not considered statistically relevant.

The researchers did, however, note clear differences in the distribution of AIDS- and non-AIDS-related events, most of which were unsurprising given their prevalence within affected regions.

Tuberculosis events occurred most frequently in Africa, the continent which carries the burden of worldwide infections (281 per 100,000 cases, compared with a global average of 133).¹² Similarly, cardiovascular disease and non-AIDS-cancers were more common in higher-income countries (the latter of which is today the leading cause of death among people with HIV in the developed world).¹³

Despite differences in outcomes, the benefits of immediate ART were consistent in all geographic regions. The 39% relative reduction in non-AIDS-related events, by example, was driven largely by the reduction of non-AIDS-cancers, while the 76% relative reduction in AIDS-related events were due primarily to lower rates of tuberculosis, Kaposi sarcoma, and malignant melanomas. One of the more notable – and unexpected – findings in the study was the distribution of primary events by CD4+ count. According to the data, 68% of such events occurred in patients whose CD4+ counts were above 500 cells/ μ L. The findings were consistent in both groups, occurring in 88% of the immediate arm events and 59% of the deferred arm events.

It is not an entirely unusual finding given that large observational studies in both the developed and developing world have shown similar trends in ART-naïve patients, with a significant number of AIDS-related events occurring at CD4+ counts between 500 and 750 cells/ μ L.^{14,15} This suggests that HIV-infected persons – even those virologically suppressed on ART – are not fully immune reconstituted in terms of an AIDS-related risk until their CD4+ count increases to more than 750 cells/ μ L.

IMPLICATIONS AND CHALLENGES

As a result of the publication of the START data, officials at WHO issued a 'treat all' recommendation on 30 September 2015, increasing the number HIV-positive people eligible for immediate ART from 28 million to 37 million.¹⁶

It is estimated that by providing universal ART on diagnosis, as well as offering HIV pre-exposure prophylaxis (PrEP) to individuals at substantial risk of infection, 21 million AIDS-related deaths and 28 million new infections could be averted by 2030.¹⁷

In line with WHO recommendations, the Southern African HIV Clinicians Society (SAHIVCS) released its revised adult ART guidelines endorsing the 'initiation of life long ART for all patients diagnosed with HIV infection. The CD4 count and clinical stage of the patient should no longer be a consideration in the decision to start ART.¹⁸ The SAHIVCS panel further contextualised their recommendations by highlighting some of the structural and functional barriers to universal ART implementation,

including 'financial cost, adequate planning of drug supply and health services capacity,' as well as the sustained funding of ART programmes in the resource-limited settings.¹⁸

According to the United Nations Joint Programme on HIV/AIDS (UNAIDS), an estimated \$31.9 billion will be needed for the AIDS response by 2020, roughly \$10bn more than has been committed by domestic sources, donor governments and multilateral organisations in 2015.¹⁹ SA currently funds the majority of its AIDS programmes, having contributed 88% of the \$1.6bn spent in 2010.²⁰

Yet, despite gains in ART delivery, it is estimated that SA would need up to \$3.1bn each in order to meet the needs of its 1.6 million citizens living with HIV.²⁰ That would require far more than

the 0.4% of the GDP currently allotted to national AIDS programmes. Some estimates suggest that as much as 1.2% of GDP would be needed in order to expand treatment beyond the 33% currently receiving ART in SA.^{20,21}

Beyond the issues of cost and funding, drug stoppages have become an increasing problem in SA, with one in three public clinics reporting shortages of HIV and tuberculosis drugs, 32% of which last more than a month.²²

More concerning, perhaps, is the late linkage of patients to HIV care and treatment in SA. According to a 2014 meta-analysis from Harvard Medical School, CD4+ counts at the time of diagnosis had increased steadily from 2002 to 2012, a testament to the country's AIDS awareness strategy.

However, CD4+ counts at the time of ART initiation averaged a mere 123 cells/μL for the entire decade. Of the sub-Saharan countries included in the study, only Ethiopia performed worse.²³

While it is clear that START will have a profound impact on global and national HIV strategies, spurring ongoing debate as to their scalability and sustainability, it may be at the patient level where the biggest challenges lie. Until we can redress the fundamental barriers to presentation, linkage to care, retention and adherence, policy and funding alone will likely do little to optimise the population-level benefits of ART. **MC**

References available on request.



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PLEASE SELECT A, B OR C AS THE CORRECT ANSWER

- 1 The START study aimed to determine risks and benefits of the immediate initiation of antiretroviral therapy (ART) in asymptomatic HIV-positive patients who had a CD4+ count of greater than:**

a) 600 cells/μL as compared with those who were deferred treatment until their CD4+ count was 350 cells/μL or below. A B C

b) 500 cells/μL as compared with those who were deferred treatment until their CD4+ count was 350 cells/μL or below. A B C

c) 500 cells/μL as compared with those who were deferred treatment until their CD4+ count was 250 cells/μL or below. A B C
- 2 The study found that:**

a) The risk of developing serious illness or death was reduced by 53% among those in the early treatment group, compared to those in the deferred group. A B C

b) The risk of developing serious illness or death was reduced by 55% among those in the early treatment group, compared to those in the deferred group. A B C

c) The risk of developing serious illness or death was reduced by 60% among those in the early treatment group, compared to those in the deferred group. A B C
- 3 The START study:**

a) Showed that the risks of early ART outweighed the benefits. A B C

b) Showed the benefits outweighed the potential consequences of early ART. A B C

c) Was inconclusive about the benefits vs risk of initiating early ART. A B C
- 4 At the time of the SMART study's termination, there was still little evidence that starting ART at:**

a) CD4 counts above 250 cells/μL had any risk over deferring ART until the CD4 count fell below 200 cells/μL. A B C

b) CD4 counts above 350 cells/μL had any benefit over deferring ART until the CD4 count fell below 200 cells/μL. A B C

c) CD4 counts above 250 cells/μL had any benefit over deferring ART until the CD4 count fell below 200 cells/μL. A B C
- 5 The START study offered an unexpected finding:**

a) In addition to higher rates of mortality in patients on intermittent ART, deaths in this group were attributed predominately to non-AIDS-related cancers and end-organ disease, and not to AIDS itself. A B C

b) In addition to higher rates of morbidity in patients on intermittent ART, deaths in this group were attributed predominately to AIDS itself. A B C

c) In addition to higher rates of morbidity in patients on intermittent ART, deaths in this group were attributed predominately to non-AIDS-related cancers and end-organ disease, and not to AIDS itself. A B C
- 6 Choose the correct option:**

a) Cardiovascular disease and non-AIDS-cancers were more common in low-income countries. A B C

b) Cardiovascular disease and non-AIDS-cancers were more common in higher-income countries. A B C

c) Cardiovascular disease is the leading cause of death among people with HIV in the developed world. A B C
- 7 The START study suggests that:**

a) HIV-infected persons are not fully immune reconstituted in terms of an AIDS-related risk until their CD4+ count increases to more than 500 cells/μL. A B C

b) HIV-infected persons are not fully immune reconstituted in terms of an AIDS-related risk until their CD4+ count increases to more than 600 cells/μL. A B C

c) HIV-infected persons are not fully immune reconstituted in terms of an AIDS-related risk until their CD4+ count increases to more than 750 cells/μL. A B C
- 8 In line with WHO recommendations, the Southern African HIV Clinicians Society (SAHIVCS) released its revised adult ART guidelines endorsing:**

a) ART for all HIV patients, providing their CD4 count is more than 750 cells/μL. A B C

b) The initiation of lifelong ART for all patients diagnosed with HIV infection. A B C

c) The initiation of lifelong ART based on the clinical stage of the patient. A B C
- 9 Barriers to universal ART implementation include:**

a) Cost, adequate planning of drug supply and health services capacity, as well as the sustained funding of ART programmes in the resource-limited settings. A B C

b) Cost, governmental policies and health services capacity, as well as the sustained funding of ART programmes in the resource-limited settings. A B C

c) Adequate planning of drug supply and patient compliance, as well as the sustained funding of ART programmes in the resource-limited settings. A B C
- 10 In SA, it has been found that over a decade:**

a) CD4+ counts at the time of ART initiation averaged 110 cells/μL. A B C

b) CD4+ counts at the time of ART initiation averaged 123 cells/μL. A B C

c) CD4+ counts at the time of ART initiation averaged 130 cells/μL. A B C

This is to state that I have participated in the CPD-approved programme and that these are my own answers.

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INSTRUCTIONS: 1. Go to www.medicalchronicle.co.za 2. Click the tab labelled 'CPD Portal' on the far right tab near the top of the page. 3. Select the relevant questionnaire from the list and complete the form at <http://www.medicalchronicle.co.za/hiv/> 4. If you do not wish to complete this form online, fill in the answers and fax it to: +27 086-534-1922.