From the START, antiretrovirals for all

The International AIDS Society Meeting in Vancouver 2015 was the setting for the presentation of the START (Strategic Timing of Antiretroviral Treatment) trial results. START was designed to assess the effect of initiation of antiretroviral therapy in early asymptomatic HIV infection [1].

Study design

4,685 HIV-positive patients with CD4 cell counts greater than 500 cells/mm³ were randomly assigned to start immediate antiretroviral therapy or to defer until their CD4 count declined to 350 cells/mm³ or they developed acquired immunodeficiency syndrome (AIDS) or another condition for which antiretroviral treatment was indicated. The primary endpoints were AIDS-defining illness, death from AIDS and serious non-AIDS events, non-AIDS cancers, cardiovascular, end stage renal and decompensated liver disease.

Demographics

There were 25 participating sites worldwide in different healthcare settings. Most acquisition was sexual: MSM 55.2%, heterosexual 38%, blood products/unknown 5.2% and injection drug use 1.4%. On average patients had a known diagnosis of a year, the median CD4 count was 651 cells/mm³ and the median viral load was 12,759 copies/mL. The commonest antiretroviral combination used in both groups was tenofovir, emtricitabine and efavirenz.

Results

Interim reviews were conducted annually. In May 2015, the Data and Safety Monitoring Board advised that the primary study question had been answered and recommended immediate dissemination of results and to offer antiretroviral therapy to all participants in the deferred group, whilst continuing follow-up. At this point the mean follow-up was 3 years.

The primary endpoint took place in 42 (1.8%) of the immediate-initiation group compared with 96 (4.1%) of the deferred group; hazard ratio of 0.43 (95% confidence interval 0.30-0.62, p<0.001).

The most frequent endpoints that occurred were cardiovascular disease, non-AIDS-defining cancer and tuberculosis. The benefit of immediate initiation was consistent irrespective of age, gender, race, location, CD4 cell count and viral load at trial entry.

Surprisingly, most primary events took place at higher CD4 cell counts; 88% of primary events in the immediate-initiation arm and 59% in the deferred arm occurred at a CD4 count above 500 cells/mm³. After one year of treatment, viral suppression was achieved in 98% of the immediate and 97% of the deferred group. The estimated difference between the groups' mean CD4 cell count was 194 cells/mm³ during follow-up.

Serious AIDS events

46% serious AIDS events were observed versus the 23% predicted. There was a relative risk reduction of 72% of serious AIDS events with immediate initiation compared with deferral; estimated hazard ratio was 0.28 (95% CI, 0.15–0.50, p< 0.001). The most commonly observed serious AIDS events were tuberculosis, Kaposi's sarcoma and malignant lymphoma. A majority of the tuberculosis cases were seen in African patients. Strikingly, most serious AIDS events took place at higher CD4 cell counts. Separation of the Kaplan–Meier curves for the two groups transpired at 4 to 6 months. Grade 4 toxicities and unexpected hospitalisations were alike in the two groups. The only

significant difference was that the risk of bacterial infection was 62% lower in the immediateinitiation compared with the deferred group (hazard ratio of 0.38, 95% CI 0.20–0.70, p=0.002).

Serious non-AIDS events

The estimated hazard ratio for comparing the immediate with the deferred group was 0.61 (95% CI 0.38-0.97, p=0.04). The Kaplan-Meier curve did not split as quickly. Fewer events happened than predicted; 54% versus 77% anticipated. They were predominantly non-AIDS cancers and cardiovascular disease, most occurred in patients from Australia, Europe, Israel and the United States. Higher-income countries have longer life expectancies and thus may be more likely to have higher rates of these conditions. Consistent benefit was observed in the immediate initiation group.

Deaths

The estimated hazard ratio for death of any cause was 0.58 (95% Cl 0.28–1.17, p=0.13). The Kaplan–Meier curves separated only after 2 years of follow-up.

Cancer

The estimated hazard ratio for cancer (including AIDS and non-AIDS cancers) comparing immediate initiation with deferral was 0.36 (95% CI, 0.19–0.66; p=0.001); a relative risk reduction of 64%. The separation on survival curves became apparent from 1 year. Many of the cancers observed were related to pro-oncogenic viruses and occurred more frequently in the deferred arm.

START Trial recommendations and conclusions

- Starting antiretroviral treatment in all HIV-positive patients regardless of their CD4 cell count.
- HIV-induced immunodeficiency occurs early in HIV.
- CD4 cell counts are not a reliable reflection of immunodeficiency; a better biomarker is needed.
- More than antiretrovirals are needed to manage patients with HIV.

The limitations

The study participants were a young cohort with a mean age of 36 years. The follow-up was short (only 3 years), and patients were on different treatments for varying time periods. By stopping the deferral strategy prematurely, there is a reduced statistical power when measuring benefit. On average, participants had been diagnosed for just 1 year. Around 5% of the study subjects had a viral load below 200 copies/mL. Relatively few primary events transpired, less than predicted. 95% of those in the deferred group did not experience any events. 99% of both groups were alive at the early conclusion. Follow-up is challenging as 50% of the deferred group had started treatment by the trial termination, few treatment-naive patients remain. The gap between the groups' survival curves had looked like it was continuing to increase.

The absolute difference in the risk of a serious event was small at 0.60 per 100 person-year followup compared with 1.38 per 100 person-year follow-up; therefore few additional events per personyear of follow-up were seen in the deferred cohort. In low-risk patients with a high CD4 cell count who chose monitoring only, the data can provide reassurance that the short-term risk is low. Substudy analysis to identify the patients who would benefit most from early initiation was absent from the trial; this could have helped prioritise treatment in resource-limited settings.

The numbers needed to treat were not calculated. These are vital to influence policy and budgets, when attempting to adopt recommendations in times of economic downturn. The number of

primary endpoints in the immediate treatment arm could be said to be actually lower; 4 of the 42 endpoints occurred before treatment started. There was disappointment at the unexpected and mostly negative sub-study outcomes. The authors commented that no adjustments were made for type I error for the number of subgroups examined and so the statistical power was restricted.

The sub-studies hypothesised that early treatment would be advantageous by reducing inflammation. The restraints frequently cited were short follow-up and the young cohort population.

Cardiac sub-study

There were 332 participants. The median 10-year risk of coronary heart disease was calculated at 1.9% in both groups. Small artery elasticity is predictive in coronary heart disease, stroke and renal function decline and was measured with sensors tracing blood pressure waveforms throughout the diastolic component of the cardiac cycle at baseline, 24 and 36 months. An increase in elasticity implies an improvement. Immediate treatment with antiretrovirals did not significantly improve small or large arterial elasticity. The lack of difference persisted despite sensitivity analysis.

Pulmonary sub-study

It has been proposed that HIV is detrimental to pulmonary health. Lung function decreases naturally with aging. Researchers hypothesised that immediate treatment would slow lung functional decline. Baseline and annual spirometry assessed function longitudinally over 2 years. Of the 1,026 recruited: 28% were tobacco smokers, 10% ex-smokers and 61% never smokers. Recreational drug use and household smoke were not accounted for. There was no statistically significant difference in the rate of decline of respiratory function between the two groups.

Bone mineral density (BMD) sub-study

The primary hypothesis was that the immediately treated group would have more BMD loss. A secondary aim was to assess hip and spine BMD among untreated HIV subjects compared with those treated. There were 424 participants, mostly from south of the equator, median age 32–33 and 27% were women. A statistically significant greater loss of bone mineral density was seen in the immediate-initiation group, with lower z scores (matched for age, gender and race). There was a significantly greater loss of BMD at both hip and spine in those randomised to immediate treatment compared with deferred subjects; the estimated mean difference of BMD at the hip was -1.6% and at the spine -1.6%. The loss of BMD continued beyond 1 year. Of those on treatment: 82% were on tenofovir and 62% were on a combination of tenofovir, emtricitabine and efavirenz.

Neurocognitive test performance sub-study

Primary central nervous system inflammation and neuronal injury is seen in a significant proportion of acute primary HIV infection. The hypothesis was that antiretrovirals would improve neurocognitive performance. Of the 608 recruits, 80% had higher training and 31.8% met depression criteria at baseline. Both groups demonstrated test improvement in the first 12 months, likely due to practice effect. No difference was seen in improved neurocognitive performance between the groups. Deterioration was always less likely in a young population with high or stable CD4 cell counts with short follow-up; less than half of the subjects reached 48 months before unblinding.

Liver fibrosis progression sub-study

This sub-study commenced last. It aimed to determine the impact of early treatment on the rates of change of liver fibrosis in HIV, hypothesising that early antiretrovirals would confer hepatic

protection. There were 230 subjects and the rate of hepatitis co-infection was less than expected; 4% rather than 10%. In the cohort there was not much alcohol and drug use, so not a group traditionally at high risk of liver impairment. Median fibroscan readings in the immediate arm were 4.8 kPa and in the deferred arm 5.1 kPa. The limited time for which patients were monitored was too short a period in which to witness liver fibrosis progression. Factors associated with higher kPa at baseline were a higher viral load in the untreated group and a higher alanine transaminsase (ALT) level.

The global response

The study results met with a generally congratulatory reception at the IAS conference. For many countries who already recommend antiretrovirals for all HIV-positive patients, such as Thailand, Brazil and France, the START study provided evidence for their national practice. In October 2014, Thailand changed their guidelines to offer treatment to all to respond to high rates of HIV in MSM, and Brazil has offered treatment to all for 2 years. It was widely accepted that the START results will help support and implement such guidelines.

The advantages

The high level of acceptability of early treatment, adherence and viral suppression observed in the trial was encouraging to health professionals. These findings also support the potential public health benefits of early HIV treatment, with the advantage extending beyond individual patients to communities by reducing sexual transmission of HIV. French panel members contemplated benefit for negative partners of positive patients. IAS President-Elect, Professor Bekker from South Africa, heralded the opportunity adopting the recommendations would provide to improve retention in care, by engaging patients from diagnosis. This would avoid the historical issue of asymptomatic patients that 'disappear when they are told of their diagnosis, but they do not need treatment'. In countries without a universal treatment guideline, the data will make many health professionals more inclined to recommend antiretrovirals or to convince those patients unsure of starting.

The challenges

There was much discussion that cost-effectiveness demonstrations would be vital in helping improve the healthcare delivery and convince national policy-makers. There was concern about the drastic improvements that would be needed in many health systems to deliver HIV treatment to all; an additional 22 million people [3]. For resource-poorer healthcare settings, the data help lobby policymakers to strengthen infrastructure and improve medical services. However, the recommendations place an even heavier burden on a fragile system where HIV diagnosis is still a major obstacle.

In Uganda, where currently 700,000 patients are on treatment out of the 2 million people living with HIV, there will be major difficulty in increasing the target. It will be a lengthy process and the international community needs to provide support to achieve change. Focus is needed on tuberculosis, much of which was seen in Africa in the study. Considerable antiretroviral provision in poorer resource settings is external and access remains hugely problematic. Anecdotally, one consultant physician from South Africa pointed out that 40% of those patients she starts on antiretrovirals are lost to follow-up by 1 year, highlighting the issue of mobile populations.

Other challenges to early treatment in HIV include the potential long-term toxicity of the drugs, maintaining adherence as patients will be on therapy for longer, and the potential increase in resistance as patients formerly not deemed to be ready to start treatment are commenced.

What is the role of pre-exposure prophylaxis (PrEP) now? With limited resources, should money be spent on treating all those with established HIV or placing high-risk negative patients on PrEP? There was opinion from one panellist that achieving 90-90-90 (90% of those with HIV are diagnosed, 90% of those diagnosed are on treatment, and 90% of those treated are undetectable) was a primary aim

before focusing on PrEP. If antiretrovirals are available to large numbers of people, who then have undetectable levels of virus, the need for PrEP would decrease anyway. Others disagreed and said PrEP had a front-line role in the HIV epidemic and that PrEP in Africa could be a game changer; sub-Saharan Africa accounts for almost 70% of the global total of new HIV infections [3].

The future

If a public health approach is adopted, a person is tested for HIV and if they are positive they start treatment straightaway. The World Health Organization (WHO) is expected to change their guidelines this December to recommend treating all in time for World AIDS in Durban 2016. There are 36.9 million people living with HIV at the end of 2014, 14.9 million of whom were on treatment [3]. An additional 22 million HIV-positive people will need treatment under the proposed guidance.

This prompted debate about whether the WHO also needed to establish some recommended order for drugs, as there is a need for lifelong therapy now in HIV and several regimens to use. Will integrase inhibitors move up front with a higher profile in HIV treatment? The trial provided further substantiation that certain antiretrovirals decrease bone mineral density; should guidance include avoiding drugs with known bone toxicity in those with recognised osteoporosis? 40 million people cannot feasibly be treated with individualised ARV care.

The risk of opportunistic infection was low in the study and from analysis there did not seem to be a way to predict which patients would experience an event, making it difficult to individualise patient approach. There were many more non-AIDS events than expected; cardiovascular disease and cancer were more frequently observed in higher-income countries and non-Hodgkin's lymphoma had a real impact. This draws the spotlight to rethinking the pathogenesis of HIV. Does HIV create a hole in the immune system, with which for a while patients live without getting sick? If a patient has a risk factor or problem, it gets through the hole, makes them sick and they express clinical disease? The research group openly invited others to access the dataset for further work; the cancer figures were much discussed and many were convinced this was the area that needed prioritising for research.

The results brought scrutiny on the role and reliability of the CD4 cell count as a marker, historically much depended upon. In only five of the 96 events in the deferred group, was the CD4 count less than 350 cells/mm³. It was proposed that viral load monitoring should be standard, that CD4 cell count should be checked at baseline, then not regularly. The subsequent savings could then be used to treat more patients. Alternative biomarkers were deliberated; could IL 6 hold the key?

What does START mean for HIV care in the UK?

Day to day, the data make it easier to persuade patients to start treatment. The UK is renowned for retention in care (95% in 2014 [2]) and treatment coverage (95% in 2014 [2]); will universal treatment decrease these figures as patient selection widens? The draft British HIV Association (BHIVA) antiretroviral guidelines include a recommendation to offer ART to all persons living with HIV who are ready to start treatment, which is not currently included in the NHS commissioning parameters [4]. The UK must not lose focus on diagnosis; a probable 26,100 people in the UK (24% of patients) are unaware that they are HIV positive, a massive risk for onward transmission [2].

In the room as START trial results were presented, the feeling was this trial was going to change HIV management on a global scale. It is vital the health community works together to achieve goals of HIV prevention, testing and access to healthcare, alongside treating and managing all those living with HIV. One week later in clinic with a patient who is considering commencing antiretrovirals and had wanted to discuss this after IAS asked me: 'Are we convinced enough to START?'

Dr S Cavilla, BSUH UK. International AIDS Society Meeting report for BHIVA, Vancouver July 2015.

References

- 1. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. The INSIGHT START Study Group. July 20, 2015, NEJM.
- 2. HIV in the United Kingdom. Public Health England. 2014.
- 3. World Health Organisation July 2015. Factsheet N*360
- 4. HIV matters, member newsletter July 2015. BHIVA