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MILESTONE 21

STARTing treatment immediately

In August 2015, the INSIGHT START study group published the results of the START trial investigating the timing of initiation of antiretroviral therapy (ART) in patients with asymptomatic HIV infection. The trial results showed that immediately initiating ART in adults who were positive for HIV and had CD4$^+$ T cell counts of >500 cells/mm^3 was more beneficial than deferring treatment until their CD4$^+$ T cell counts dropped to ≤350 cells/mm^3.

For years, when to start ART had been a topic of debate, and initially patients at a high risk of developing AIDS (those with low CD4$^+$ T cell counts of ≤200 cells/mm^3) were prioritized for treatment. However, evidence emerged of the benefits of initiating treatment early. In 2009, the results of a cohort study suggested that initiation of ART before CD4$^+$ T cell counts fell below 351 cells/mm^3 or 500 cells/mm^3 improved survival. Interim analysis of HPTN 052 study data in 2011 showed that starting ART in patients with CD4$^+$ T cell counts between 350 and 550 cells/mm^3 before symptoms manifested or CD4$^+$ T cell counts were ≤250 cells/mm^3 reduced the rate of HIV transmission and clinical events.

The case of the 'Mississippi baby' also provided some evidence for the benefit of early ART initiation. This baby was given ART 30 hours after being born to an HIV-positive woman and tested positive for HIV herself. Treatment was continued until she was 18 months old, and she had undetectable levels of HIV between the ages of 29 days and 3 years, 10 months. Although HIV became detectable after treatment was stopped, these observations suggested that starting ART early is beneficial in controlling HIV. As new data such as these became available, the cutoff for starting ART progressively increased, eventually reaching ≤500 CD4$^+$ T cells/mm^3.

In this context, the START study aimed to assess the benefits and risks of immediately initiating or deferring ART. This study was conducted at 215 centers in 35 countries, included 4,685 patients with CD4$^+$ T cell counts of >500 cells/mm^3 and the mean follow-up duration was three years. Patients in the immediate-treatment arm received ART straight away, whereas those in the deferred-treatment arm were not given ART until their CD4$^+$ T cell counts decreased to ≤350 cells/mm^3. Overall, 41 events (including death, AIDS and serious non-AIDS events) occurred in the immediate-treatment group compared with 86 events in the deferred-treatment group—a 57% reduction. Furthermore, no increase in the rate of adverse events was observed in the immediate-treatment group.

The original completion date for the START study was 2018. However, after the interim analysis in May 2015, the data and safety monitoring board decided that the study question had been answered and recommended that all patients in the deferred-treatment arm be offered ART.

The results of the START study contributed to the World Health Organization (WHO) issuing a recommendation to treat all patients as soon as possible after diagnosis (the treat-all policy, also known as test and treat) in September 2015. The results are also cited as supporting evidence in the WHO's consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, which were published in 2016. These guidelines contain the new recommendation that "ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4$^+$ cell count."

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Starting ART early can preserve intestinal lymphoid structures and dendritic cell maturation pathways in the gut. Early initiation of treatment can also help to maintain HIV-1-reactive memory B cells in the gut and follicular T helper cells. Furthermore, early ART reduces the size of the HIV reservoir in the long term compared with deferring treatment.

In 2017, analysis of self-assessed quality-of-life (QOL) outcomes from patients involved in the START study showed that immediate ART resulted in better outcomes than deferred ART after a mean follow-up duration of three years. QOL outcomes were improved for those receiving immediate treatment regardless of demographic or clinical subgroup. Later the same year, the WHO published analysis of the adoption and implementation status of the treat-all policy. As of November 2017, adoption rates were promising, with 70% of low- to middle-income countries and 89% of countries in the Fast-Track strategy for ending AIDS signing up to the treat-all policy. These adoption rates support the 90–90–90 targets for ending the AIDS epidemic by 2030.

Louise Stone,
Nature Reviews Urology

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