Delayed HIV Treatment Raises Risk of Complications and Death Years Later

Inflammation before initiation of antiretroviral therapy can have long-term consequences, including AIDS, cardiovascular disease and death.

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People with HIV who delayed initiation of antiretroviral treatment continue to be at higher risk for an AIDS diagnosis, serious non-AIDS conditions or death several years later, and this appears to be associated with higher levels of inflammation, according to study results presented at the Conference on Retroviruses and Opportunistic Infections (CROI 2024) in Denver.

These findings emphasize the need to diagnose HIV early to facilitate early treatment, Kanal Singh, MD, of the National Institute of Allergy and Infectious Diseases, and colleagues with the INSIGHT START Study Group concluded.

At a time when HIV medications were harder to use and caused more severe side effects, the best time to start antiretroviral therapy (ART) was controversial. START—the Strategic Timing of Antiretroviral Treatment trial—compared the effects of immediate versus deferred ART, aiming to determine the optimal balance between risks and benefits. The trial enrolled more than 4,600 previously untreated adults in 35 countries who entered the study with a CD4 T-cell count above 500. They were randomly assigned to either start treatment immediately or delay therapy until their CD4 count fell below 350 or they developed symptoms of AIDS.

The trial was halted ahead of schedule in 2015 when an interim analysis provided definitive evidence that initiating treatment early, before immune function substantially declines, leads to better outcomes. As described in the New England Journal of Medicine, immediate treatment was associated with a 57% lower risk for a combined endpoint of AIDS-related events (opportunistic infections and AIDS-defining cancers), serious non-AIDS events (cardiovascular disease, advanced kidney or liver disease and non-AIDS cancers) or death. Based on these and other findings, treatment guidelines now recommend ART initiation as soon as possible after an HIV diagnosis.

When these results were revealed, the randomized portion of the START trial was stopped, the study was unblinded and all participations were advised to start treatment, but follow-up continued to assess long-term outcomes. In 2022, researchers reported that delayed antiretroviral therapy was associated with an excess risk of AIDS and serious non-AIDS conditions that persisted for years after treatment initiation.

Singh's team sought to determine whether prolonged inflammation could help explain why people who delay treatment still have an increased risk for complications and death even after starting therapy. From the earliest stages of infection, HIV integrates into human cells and establishes a long-lasting reservoir that antiretrovirals can't reach. Another START analysis previously showed that people who started treatment early had a substantially smaller viral reservoir. While antiretrovirals can keep HIV replication under control, this persistent virus can still cause chronic immune activation and inflammation that contributes to a wide range of health problems. And the longer viral replication continues without treatment, the harder this may be to reverse.

In a START sub-study, biomarkers of inflammation and blood coagulation, including interleukin 6 (IL-6) and D-dimer, were measured at baseline, at eight months into the study and annually thereafter. Biomarker levels from study entry through 2015 were compared for the immediate and delayed treatment groups. Compared with the immediate treatment group, the delayed treatment group had significantly higher levels of IL-6 and D-dimer over this period. Levels remained higher in the delayed treatment group after study unblinding, though the difference diminished.

The new analysis, which included data from 2,114 START participants, looked at the association between biomarker levels during that period and the subsequent occurrence of AIDS, serious non-AIDS events or death during 2016-2021. By January 2016, 87% of participants in the delayed treatment arm had started treatment, with a median of 2.5 years until ART initiation, and 79% had achieved viral suppression. As expected, almost everyone (99%) assigned to the immediate treatment group had started ART, and 94% had viral suppression.

Overall, 126 cases of AIDS, serious non-AIDS events or death were recorded between 2016 and 2021. Comparing the immediate and delayed treatment groups, the former had about a 30% lower risk out these outcomes, but this did not reach the threshold for statistical significance during this period ($p=0.07$).

The researchers then compared outcomes among participants with the highest quartile of IL-6 and D-dimer levels versus those with the lower three quartiles combined. Interestingly, they found that people who had the highest IL-6 and D-dimer levels through 2015 in both the immediate and delayed treatment groups had about double the risk of complications and death during 2016-2021.

"Compared to immediate ART initiation, ART deferral resulted in higher levels of systemic inflammation during follow-up in START," the researchers concluded. "Our findings emphasize the need to diagnose HIV earlier, which can facilitate earlier initiation of ART, and thus shorten the duration of viremia that may contribute to future inflammation-associated adverse clinical events."

As a limitation, they noted that the modest total number of events over six years limited their ability to assess the effects of inflammation prior to treatment on events that take longer to manifest, such as cardiovascular disease and cancer.

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