EDITORIAL

Monthly Injectable Antiretroviral Therapy — Version 1.0 of a New Treatment Approach

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Combination antiretroviral therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection is one of the most important advances in medicine in the past quarter century. The availability of several single-tablet multidrug treatment regimens that effectively control the replication of HIV type 1 (HIV-1) has dramatically improved the prognosis of people living with HIV who are able to adhere to daily oral therapy.

Now two pivotal international, phase 3, randomized trials — Antiretroviral Therapy as Long Acting Suppression (ATLAS) and First Long-Acting Injectable Regimen (FLAIR), the results of which are reported in the *Journal*[1,2] — show 48-week outcomes among people living with HIV who received ART as monthly injections of long-acting suspensions of the integrase strand-transfer inhibitor cabotegravir and the nonnucleoside reverse-transcriptase inhibitor rilpivirine. In both trials, participants who had undetectable plasma HIV-1 RNA received intramuscular injections of both drugs every 4 weeks. The main findings were that the monthly injectable treatment was noninferior to continued daily oral treatment and that participants in both trials clearly preferred monthly injections over daily oral therapy. When approved by regulators, this major advance in treating HIV infection will provide a new option for a select group of patients who currently have viral suppression while taking ART and represents the first step toward making less-frequent dosing of ART a reality. For many, freedom from the need for daily oral therapy is a major advance, even at the cost of having to receive monthly injections. That said, the overall effect that this new treatment approach has on the HIV epidemic will depend on our ability to address a few associated questions and challenges.

Currently, most people living with HIV who are in care are seen in a clinic for monitoring every 6 months. Requiring monthly visits for injections will be challenging for busy HIV clinics. Can we learn from other disciplines that have years of experience with long-acting injectable treatment options to ensure equitable access to this promising approach? Experience in psychiatry with the use of long-acting injectable antipsychotic agents for the treatment of schizophrenia has highlighted the important role that provider attitudes and clinic operations play in the use of this method of treatment.[3]

Longer intervals between doses will improve feasibility for scale-up of this treatment, and data to support this approach are expected soon in the ATLAS-2M trial, which is evaluating a dosing schedule of every 8 weeks for combined injectable cabotegravir and rilpivirine.[4] Differentiated models of care, wherein injections could be provided outside the conventional clinic setting, deserve evaluation. Mechanisms to provide oral bridging therapy for people who are late for injections, as was provided in the ATLAS and FLAIR trials, will also need to be developed. In addition, close monitoring of the early clinical experience will be vital for an understanding of the "forgiveness" of this regimen when dosing is delayed, ensuring that virologic failure with resistance remains a rare event. We need to build a platform for the delivery of long-acting inject-

able treatment and evaluate how well it works, with input and feedback from people living with HIV and from providers.

In ATLAS and FLAIR, the incidence of injection-site reactions was high (81% and 86%, respectively), yet few participants stopped receiving injections for this reason during the first 48 weeks. Clearly, the benefits of not taking a daily oral pill outweighed this inconvenience for participants in the first year of treatment, but will this trade-off become less acceptable over time? The development of long-acting treatment options that can be delivered less frequently than once a month remains a priority until we have a cure. We also need to be prepared for people to choose injectable treatment during periods of their lives when daily therapy is less appealing and to anticipate that patients may switch between oral and injectable treatment. We need to understand the pharmacologic implications of these changes in order to support patients' preferences over time.

Although it was reassuring to see a low incidence of virologic failure in each trial, the high incidence of resistance among those who had treatment failure, in particular those with HIV-1 subtype A1 in FLAIR, deserves further investigation, as noted by the authors. Plans to carefully monitor resistance as this treatment is rolled out will be needed, especially if virologic failure occurs as a result of delays in receipt of regular injections.

To date, trials of cabotegravir and rilpivirine have focused on nonpregnant adults in whom viral suppression was first achieved while they were taking conventional ART, which was followed by a period of oral therapy and therapy with injectable agents. Long-acting injectable treatment has the potential to be a major advance in the treatment of HIV infection during pregnancy and in the postpartum period, when adherence challenges undermine virologic suppression, as well as for children and adolescents, including those in low-resource settings. However, to date, studies involving these populations are lacking. The ongoing AIDS Clinical Trials Group LATITUDE (Long-Acting Therapy to Improve Treatment Success in Daily Life) trial (ClinicalTrials.gov number, NCT03635788) is addressing the use of conditional cash transfers as an incentive for adherence, to facilitate virologic suppression before a transition to injectable treatment among those with a documented history of nonadherence. We need creative approaches that will allow us to deploy injectable treatment in the absence of virologic suppression in order to have the greatest effect on ending the HIV epidemic. Additional therapeutic agents in development that have long half-lives and alternative delivery systems may help us address these concerns. These approaches will require collaboration between industry partners, as was demonstrated during the development of injectable cabotegravir and rilpivirine.

The ATLAS and FLAIR trials are important milestones in the development of HIV therapeutics and represent major steps into the era of long-acting ART. Version 1.0 of long-acting ART holds promise for the millions of people living with HIV if we make addressing the challenges involved a priority.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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3. Potkin S, Bera R, Zubek D, Lau G. Patient and prescriber perspectives on long-acting injectable (LAI) antipsychotics and analysis of in-office discussion regarding LAI treatment for schizophrenia. BMC Psychiatry 2013;13:261.
4. ViiV Healthcare reports positive phase III study results of investigational, long-acting, injectable HIV-treatment regimen administered every two months. August 22, 2019 (https://viivhealthcare.com/en-gb/media/press-releases/2019/august/viiv-healthcare-reports-positive-phase-iii-study-results-of-inve/).

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