Antiretroviral Therapy Regimens for Newly Diagnosed Patients with HIV

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HIV is a significant global health issue for which there is no cure. However, the availability of antiretroviral therapy (ART) has made it possible to effectively treat and prevent HIV infection, leading to a considerable decrease in associated deaths and illnesses.[1,2] Most HIV treatment and pre-exposure prophylaxis (PrEP) plans involve the use of daily oral combination ART tablets, which are taken by an individual for their lifetime to suppress the virus. While these therapies are highly successful, their effectiveness depends on the individual's adherence to the daily regimen. Consequently, the development of long-acting ART formulations became crucial. In 2021, two formulations received recommendation by the UK National Institute for Health and Care Excellence and were approved by the US Food and Drug Administration: cabotegravir (ViiV Healthcare, London, UK) and rilpivirine (Janssen Pharmaceuticals, Beerse, Belgium).[3]

In this expert interview, Dr Monica Gandhi discusses the first-line ART regimens currently available for treating patients with newly diagnosed HIV and the adherence challenges commonly faced by patients on oral ART. She also highlights the advances in long-acting ART, particularly in patients who are treatment naïve, and the findings from the phase III trials FLAIR (ClinicalTrials.gov identifier: NCT02938520),[4] ATLAS (ClinicalTrials.gov identifier: NCT02951052)[5] and ATLAS-2M (ClinicalTrials.gov identifier: NCT03299049).[6] Finally, she discusses the significance of seroconversion occurring in a patient on long-acting PrEP and how it affects the treatment approach and considerations for initiating ART.

Q. What are the current first-line antiretroviral therapy regimens recommended for patients with newly diagnosed HIV? What clinical trial data supports their use?

In 2023, World Health Organization (WHO), European, UK and US guidelines support integrase inhibitors as first-line therapy worldwide.[7–9] The regimen involves an integrase inhibitor, usually either dolutegravir or bictegravir, combined with two nucleoside reverse transcriptase inhibitors. In early 2013, when dolutegravir first came out, there were five big trials investigating dolutegravir in patients who were treatment experienced and patients who were treatment naïve.[10–14] In the treatment-naïve population, the trials compared dolutegravir with standard nucleoside reverse transcriptase inhibitors-based therapy and protease inhibitor-based therapies and showed dolutegravir to be equal or superior. Moreover, many trials compared bictegravir with the standard of care at the time in patients who were treatment naïve treatment naïve and showed bictegravir to be equally effective.[15–18] Currently, bictegravir and dolutegravir have become the dominant first-line therapies recommended worldwide.

Q. What is rapid antiretroviral therapy initiation, and why is it considered beneficial for patients with newly diagnosed HIV?

Since the early 2010s, data have suggested that there are advantages to starting therapy immediately after a diagnosis.[19] It brings down the viral load quickly, which is beneficial to people

who are newly diagnosed with HIV that have very high viral loads. Being able to tell a patient that you can do something about a new diagnosis right away is very empowering. Studies worldwide have shown both in resource-limited and resource-rich settings that rapid ART initiated as soon as possible after the date of diagnosis is beneficial, as it leads to more durable virologic suppression rates.[20–24] As a result, rapid ART has become the standard of care and is mentioned in treatment guidelines by the WHO and the US Department of Health and Human Services. If possible, as sometimes there are barriers such as patient reluctance, insurance issues and difficulties with adherence, it is ideal to initiate someone on therapy immediately after their diagnosis.

Q. What are the innovative applications of long-acting antiretroviral therapy, in particular in patients who are treatment naïve?

Long-acting ART is somewhat young as only one regimen has been approved: a dual regimen with long-acting cabotegravir and rilpivirine, which was approved by the US Food and Drug Administration in January 2021.[25] This long-acting combination was approved both in patients with HIV who are treatment naïve and those with treatment experience switching from a suppressive regimen. The FLAIR study investigated the use of cabotegravir and rilpivirine in patients who were treatment naïve.[4] They were put on oral therapy first (dolutegravir, abacavir and lamivudine for 20 weeks) and then switched over to long-acting cabotegravir and rilpivirine. In the ATLAS and ATLAS-2M trials, the long-acting injections were administered 1 month and 2 months apart, respectively.[5,6] The investigators looked at patients who were virologically suppressed on whatever regimen they were on. These patients had been suppressed for at least 6 months on an oral regimen and then switched over to long-acting cabotegravir and rilpivirine and remained suppressed. If you look at the design of these registrational clinical trials (FLAIR, ATLAS and ATLAS-2M), they were all conducted in patients who were virologically suppressed on oral ART. Therefore, it is important to note that when these medications were approved, the package insert instructed their use in patients who are suppressed on oral ART.

At Ward 86, we have been looking at the use of long-acting ART in patients with viraemia who are not suppressed. We are looking into this as an investigational indication because long-acting therapy can be used to circumvent some of the barriers to taking oral ART. We have released data from our demonstration project,[26,27] we have released an abstract for CROI 2023,[28] and I talked about it at ACTHIV. We have also recently published an article in the *Annals of Internal Medicine* showing the possible utility of using long-acting cabotegravir and rilpivirine in patients who are virologically non-suppressed and have adherence difficulties.[27] Moreover, we have quite a bit of data on long-acting cabotegravir and rilpivirine in patients who are naïve and suppressed.

Q. What are the common adherence challenges faced by patients on oral antiretroviral therapy? What have real-world studies found in terms of treatment effectiveness?

There are so many common barriers to adherence. In 2022, a large study looking at virologic suppression rates across 31 countries was published in *The Lancet HIV* in a systematic review.[29] The study demonstrated that there is approximately a 65% virologic suppression rate after 3 years of starting oral ART worldwide. Therefore, with a 65% virologic suppression rate, we have not yet reached the 95-95-95 targets set by The Joint United Nations Programme on HIV/AIDS.[30] Therefore, we need adherence interventions. The barriers to adherence really depend on factors such as population or country. There is a range of barriers, such as forgetting to take medication, stockouts, transportation difficulty, childcare, other subsistence needs such as housing and food insecurity, stigma, substance use, and mental health concerns. Barriers are many and vary worldwide; however, we have a very consistent, inadequate suppression rate. We want to be in a different place. This brings up the question: What are the ways to circumvent some of the barriers to adherence? Certainly, one pill once a day has been looked at and thought about for a long time, and now almost all regimens are one pill once a day. However, a one-pill-once-a-day regimen does not circumvent the stigma of taking a pill. Therefore, we and other groups are very fascinated by the potential use of long-acting ART for circumventing many common barriers. It can circumvent stigma; you can get your injection in a clinic and then not have to get it for the next 2 months. It can circumvent forgetting to take a pill every day. It can really help with some of the issues of housing and food insecurity and not having a safe place for medications. There are a lot of reasons why long-acting ART could be an important solution for helping us toimprove adherence and tackle barriers and challenges to adherence in patients with HIV.

Q. What is the significance of seroconversion in a patient on long-acting pre-exposure prophylaxis? How does it affect the treatment approach and considerations for initiating antiretroviral therapy?

Increasingly, we are trying to encourage PrEP use among those who are at risk for HIV. There are two types of PrEP: oral PrEP and long-acting PrEP. Oral PrEP can be tenofovir disoproxil fumarate (TDF)/emtricitabine, tenofovir alafenamide (TAF)/emtricitabine (TAF/FTC), or inttermitent TDF/FTC, depending on the patient population. If an individual had a breakthrough infection and seroconversion on a tenofovir-based regimen, there is a risk that they could have an M184V mutation or other resistance mutations. However, our first-line therapy, integrase inhibitor-based therapy, can usually be given even if the individual has an M184V mutation. At the moment, the guidelines express concern about using long-acting cabotegravir as PrEP. This is due to the fact that if an individual has a seroconversion on long-acting cabotegravir, which is given every 2 months in men and women for prophylaxis of HIV, there could be a breakthrough infection with a mutation against an integrase inhibitor. Although cabotegravir is a very effective form of PrEP and is more effective than oral therapy in both men and women, there is a very low but real risk of a breakthrough infection with integrase inhibitor mutations. If a breakthrough infection occurs while on long-acting cabotegravir, the guidelines recommend using darunavir-based ART until the genotype comes back and it is known whether the individual has an integrase inhibitor mutation. Those are the recommendations on treatment guidelines that make most sense.

Q. Based on the current guidelines, what factors should be considered when choosing the initial antiretroviral therapy regimen for a patient who experienced seroconversion on long-acting pre-exposure prophylaxis?

Integrase inhibitors are the first-line regimens worldwide. The WHO has now recommended tenofovir, lamivudine and dolutegravir as a first-line and often even second-line therapy. As we roll out cabotegravir-based PrEP, we have to remember that, if there is a breakthrough with cabotegravir-based PrEP, we may need to use darunavir-based therapy while waiting for the results of a resistance test. ❑

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