Tough requirements for new antiretroviral drugs

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Medical and social attention to HIV infection has declined globally and is increasingly focused on developing regions, where the epidemic is still largely uncontrolled. In North America and western Europe, AIDS is rarely in newspaper headlines or mentioned in television news. The success of antiretroviral therapy largely explains this change in the perception of HIV/AIDS, which was once a life-threatening disease but is now, more many, viewed as a chronic illness. Indeed, individuals on treatment currently benefit from life expectancies close to those of people who are HIV negative.

With the advent of safer and more effective antiretroviral agents, indications for treatment have expanded from advanced immunodeficiency, and now anyone with HIV should receive treatment as soon as possible. Furthermore, antiretrovirals are now recommended for people at risk of HIV as pre-exposure prophylaxis.[1] Long-acting formulations of antiretrovirals that will allow weekly or monthly prescriptions are on the horizon.[2,3] Clearly, there is a sense of victory and relief after major gaps in HIV/AIDS therapy have been filled. In this scenario, is there still any room for developing a new antiretroviral agent?

In the *Lancet HIV*, Dirk Schürmann and colleagues[4] report the results of a phase 1b trial with islatravir (also known as MK-8591; previously known as EFdA), a first-in-class nucleoside reverse transcriptase translocation inhibitor.

Briefly, 30 antiretroviral-naive adults with HIV infection received one of five distinct single oral doses of the drug at one clinic in Berlin, Germany.[4] The study was done between 2015 and 2017. Roughly a third of patients had drug-related adverse effects, but none of these effects were serious. The lowest dose, 0·5 mg, of islatravir suppressed plasma HIV RNA by more than 1 $\log_{10}$ copies per mL at 1 week. Given the safety, potency, and long intracellular half-life of the triphosphorylated active form of the drug (78 h), the authors propose further clinical development of islatravir.

Enthusiasm unabated, we think it worth considering the convenience of developing such a drug. We identified at least four important caveats. The first refers to safety. The phase 1b study ended in 2017, and no serious adverse events were reported during the short follow-up of a single oral dose. Longer exposure to the drug and longer follow-up would be needed to explore safety issues adequately. Given that islatravir is an adenosine analogue, like didanosine, worrisome metabolic effects in the middle or long term should be excluded, including lipoatrophy, lactic acidosis, neuropathies,[5] and non-cirrhotic portal hypertension.[6]

Second, the claim for a unique distinct mechanism of action for islatravir needs to show clinical meaning, especially regarding an absence of cross-resistance with already marketed nucleoside or nucleotide reverse transcriptase inhibitors. Although in-vitro experiments have highlighted a high barrier to resistance for islatravir, with a characteristic Met184Ile/Val substitution that only results in a five times loss of drug potency, only studies testing a prolonged exposure to the drug as monotherapy will show whether the addition of more mutations could significantly impair islatravir inhibitory activity. Notably, several reverse transcriptase mutations, including Lys65Arg, Leu74Val, and Gln151Met, render viruses hypersusceptible to islatravir.[7] In this regard, islatravir could be a preferred option in patients with these drug-resistant viruses.

Third, women should be part of trials to avoid controversies such as occurred after the recent US Food and Drug Administration approval of emtricitabine plus tenofovir alafenamide for HIV prevention in at-risk uninfected adults "excluding those who have receptive vaginal sex".

The drug has not been authorised for most sexually active women because of paucity of data,[8] acknowledging that differences in drug concentrations between rectal and vaginal mucosa could affect its efficacy on HIV prevention. In addition, given that most people who now need HIV therapy are living in developing countries, where the proportion of women of childbearing age is higher than in high-income countries, studies of teratogenicity of islatravir should be prioritised.

Finally, in sub-Saharan Africa, where more than 75% of people with HIV are living, HIV-2 is present alone or as coinfection with HIV-1. Therefore, for the achievement of the UNAIDS 90-90-90 goal, 1 therapeutic effort must include HIV-2,[9] because problems arising from mismanaging patients with HIV-2 could hamper the expected success.[10] Therfore, the in-vivo activity of islatravir against HIV-2 isolates must be determined.

In summary, islatravir is a promising new antiretroviral oral drug that preliminarily depicts a good safety profile, high potency, and long half-life. Because most currently approved HIV drugs are already given as single pills once a day, the challenges of lifelong drug compliance are already well addressed by existing medications.

What would be the added value of islatravir? Among others, we identified four areas of interest: improved middle-term and long-term safety, high resistance barrier, high efficacy in women and children, and HIV-2 activity. We believe that positioning the drug advantageously in these niches would push its clinical development.

We declare no competing interests.

Carmen de Mendoza, Vicente Soriano
cmendoza@idiphim.org

Department of Internal Medicine, Puerta de Hierro Research Institute, Majadahonda, Spain (CdM); and UNIR Health Sciences School & Medical Center, Madrid, Spain (VS)

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