Integrase inhibitors go head-to-head

Lancet HIV 2017
Published Online February 14, 2017 http://dx.doi.org/10.1016/S2352-3018(17)30017-6
See Online/Articles http://dx.doi.org/10.1016/S2352-3018(17)30016-4

Bictegravir is a new, once-daily integrase strand transfer inhibitor (INSTI) that does not require boosting; it has shown potency in a phase 1 study[1] with no serious adverse events or development of INSTI resistance. The drug has also shown in-vitro activity against viruses, with resistance to raltegravir, elvitegravir, and dolutegravir.[2] In *The Lancet HIV*, Paul Sax and colleagues[3] present 48 week results from a phase 2 study comparing bictegravir (75 mg) with dolutegravir (50 mg), both combined with tenofovir alafenamide (25 mg) and emtricitabine (200 mg). Bictegravir and dolutegravir were placebo controlled, whereas tenofovir alafenamide and emtricitabine were given open label. Both bictegravir and dolutegravir were well tolerated and efficacious. Although this small phase 2 study was not powered to show non-inferiority, both drugs showed equivalence with regard to the primary endpoint at week 24. 63 (97%) of 65 participants receiving bictegravir and 31 (94%) of 33 receiving dolutegravir had undetectable viral loads (<50 copies per mL).

The INSTI class for treatment of HIV-1 infection has become standard of care in guidelines for first-line therapy.[4-6] INSTIs have potent efficacy, with rapid reduction in viral load, good tolerability, and low potential for drug interactions. Existing INSTIs have limitations. Raltegravir has been, to date, part of a multitablet, twice-daily regimen, and elvitegravir has required boosting with cobicistat, with the potential for other drug interactions. Dolutegravir, the most recent INSTI, was eagerly anticipated given the absence of the need for boosting, once-daily dosing, and its coformulation into a single-tablet regimen with abacavir and lamivudine. As an unboosted, coformulated INSTI, dolutegravir has seemed the obvious first choice, with the ability to combine with tenofovir (as tenofovir disproxil fumarate or tenofovir alafenamide) and emtricitabine in patients for whom abacavir is contraindicated or not tolerated. Although dolutegravir has indeed been highly effective, tolerability issues have occurred in some cases, including insomnia and neuropsychiatric side-effects,[7,8] suggesting that room remains for further options within the INSTI class.

To comment on clinical use from phase 2 studies is difficult, but the data are promising, with the possibility of an unboosted INSTI plus tenofovir alafenamide-containing single-tablet regimen likely to be very popular with clinicians and patients in areas where cost is not a primary concern. Some caveats exist. This study was done solely in the USA and used tenofovir alafenamide, which remains unavailable or unaffordable for many of those living with HIV globally. Some ethnic diversity was present in participants, with 57% of participants being white and 37% being black, but participants were overwhelmingly male (96%). The study recruited only those with CD4 counts of more than 200 cells per µL and stipulated no previous AIDS-defining illness, coinfection with hepatitis B or C, or pregnancy, so data will also be needed in these groups from future studies, including in those with advanced disease and immunosuppression. One of the benefits of tenofovir alafenamide is reduced anxiety around renal functioning and monitoring, yet this study enrolled only those with a baseline estimated glomerular filtration rate of at least 70 mL per min. Data for use of bictegravir in those with impaired renal function would be highly desirable.

Regarding resistance, having no tenofovir-associated or emtricitabine-associated mutations was an entry criterion, but INSTI sequencing was not done. No resistance was seen in the bictegravir group, but one participant in the dolutegravir group did develop a T97A mutation and was discontinued from the study. In terms of safety, although no treatment-related serious adverse events or deaths occurred, one participant switched away from bictegravir after an episode of urticaria. More grade 2–4 rises in aspartate aminotransferase, alanine aminotransferase, and creatine kinase concentrations occurred in the bictegravir group than in the dolutegravir group. Although transient (and not associated with rhabdomyolysis, in the case of the creatine kinase), these elevations might have implications for safety monitoring in clinical practice and need close consideration when phase 3 results are available.

Bictegravir is clearly an exciting drug. From an international perspective, cost pressures might be important as well as being well tolerated and efficacious, unboosted, and coformulated. Many drugs are now available as generics and although patients might prefer single-tablet regimens, the cost benefit is not entirely clear. Some countries are facing pressure

to switch patients away from expensive single-tablet treatments to regimens of generic component drugs. Elvitegravir is not available as a single agent, limiting the ability of clinicians to offer patients choice and to save money if necessary. Efficacy and safety are expected of all new developments in HIV therapeutics and these aspects will hopefully be borne out by bictegravir, but phase 3 studies underway continue to use the backbone of tenofovir alafenamide and emtricitabine (NCT02607956 and NCT02607930). Unless a bictegravir plus tenofovir alafenamide and emtricitabine single-tablet regimen is extremely competitively priced, it could face challenges in times of increased financial caution. Further data are needed to see the efficacy of bictegravir with alternative backbones, with the potential to offer real prescribing choice and flexibility to clinicians and patients globally.

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I have received speaker's and advisory board honoraria, and conference support, from Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp & Dohme, and ViiV.

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