Bictegravir and dolutegravir: head to head at 96 weeks

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In *The Lancet HIV*, David Wohl and colleagues[1] present 96 week data on bictegravir in a fixed-dose combination with emtricitabine and tenofovir alafenamide versus fixed-dose dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1, while Hans-Jürgen Stellbrink and co-workers[2] report 96 week data on co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for the same indication, both from randomised, double-blind, placebo-controlled, multicentre, phase 3 non-inferiority trials. The study by Wohl and colleagues[1] describes a comparison of two different, three-drug, co-formulated single-tablet regimens. By contrast, the study by Stellbrink and co-workers[2] compares bictegravir directly with dolutegravir, given that the same emtricitabine plus tenofovir alafenamide backbone is used in both groups. Both studies had participants who were young (median ages were 31–34 years), included a small proportion of participants with advanced HIV (10–14% had CD4 counts <200 cells per µL) and included proportionately few women (11% across both studies).

Wohl and colleagues[1] cite the well known practical advantages of the bictegravir, emtricitabine, and tenofovir alafenamide combination over dolutegravir, abacavir, and lamivudine—namely that HLA-B*5701 testing is not needed and that the drugs can be used in patients co-infected with hepatitis B. 629 participants were enrolled, randomly assigned to a treatment group, and received at least one dose of their assigned treatment. 48-week data were published previously,[3] and in this 96-week extension, non-inferiority of the bictegravir regimen was shown, virological failure was rare, and no one developed treatment-emergent resistance to any study drug.

Study drug-related adverse events were reported for 28% of participants in the bictegravir group and 40% in the dolutegravir group, but these were primarily mild or moderate, and most occurred before week 48. The main driver of this difference was drug-related nausea. Nausea was reported by 11% of participants given bictegravir and 24% given dolutegravir and was attributed to the study drug in 6% and 17% (p<0·0001). A higher prevalence of nausea was reported in those receiving dolutegravir, abacavir, and lamivudine than in those receiving bictegravir, emtricitabine, and tenofovir alafenamide throughout the 96-week study period. Diarrhoea (15% vs 16%) and headache (13% *vs* 16%) occurred in similar proportions in both groups. Overall, few discontinuations were due to intolerance or adverse events in either group. No participant discontinued bictegravir, emtricitabine, and tenofovir alafenamide compared with five (2%) who discontinued dolutegravir, abacavir, and lamivudine.

Much has been made of the unfavourable effect of tenofovir alafenamide on lipid concentrations when compared with its predecessor, tenofovir disproxil fumarate.[1,4] In the study by Wohl and colleagues,[1] increases from baseline in total cholesterol (p=0·002), LDL cholesterol (p<0·0001), and total cholesterol-to-HDL ratio (p=0·003) were greater in the bictegravir, emtricitabine, and tenofovir alafenamide group than in the dolutegravir, abacavir, and lamivudine group. Despite these difference, the use of lipid-lowering therapy was low in both groups, suggesting that over 2 years, in a young cohort, the clinical effect of these differences of about 10 mg/dL (1·67 mmol/L) between the groups was minimal. Longer-term follow-up with clinical outcomes, in older people in particular, will be essential to review cohorts treated with these regimens.

Another debated topic is that of possible excess weight gain in people receiving an integrase inhibitor as part of their antiretroviral regimen.[5] Increases in weight after treatment initiation did occur in both groups in the study by Wohl and colleagues,[1] although it is perhaps unsurprising that weight gain occurs in people living with HIV who are initiating treatment for the first time. The median weight gain was 3·6 kg (IQR 0·0–8·5) in the bictegravir, emtricitabine, and tenofovir alafenamide group and 2·4 kg (–0·4 to 5·8) for those in the dolutegravir, abacavir, and lamivudine group. Clearly, more long-term data are needed and studies switching patients from other stable regimens, rather than those who are treatment naive, might give a clearer indication whether there is a true adverse effect of these drugs on weight.

In Wohl and colleagues' subgroup analyses,[1] older age seemed to favour bictegravir, emtricitabine, and tenofovir alafenamide, with all of 40 participants aged 50 years or older achieving undetectable viral

loads (<50 copies per mL) at week 96 compared with 35 (85%) of 41 in the dolutegravir, abacavir, and lamivudine group (p value could not be calculated). Perhaps surprisingly, dolutegravir, abacavir, and lamivudine was favoured in those with worse cumulative adherence (established by pill count showing adherence of <95%): in the dolutegravir, abacavir, and lamivudine group, 103 (86%) of 120 of those meeting the low adherence criteria achieved undetectability compared with 71 (74%) of 96 in the bictegravir, emtricitabine, and tenofovir alafenamide group (p=0·029).

In the study by Stellbrink and co-workers,[2] 645 participants were randomly assigned and received at least one dose of their assigned treatment. 48-week data were reported previously[6] and the results at 96 weeks remain reassuring. Non-inferiority was shown, viral rebound was rare, no treatment-emergent resistance occurred in either group and, in fact, no participants met criteria for resistance testing between weeks 48 and 96. At week 96, study drug-related adverse events were reported in both groups (20% in the bictegravir group *vs* 28% in the dolutegravir group). These differences were greatest for gastrointestinal and neuropsychiatric and sleep-related symptoms. No participants discontinued the bictegravir regimen because of an adverse event between weeks 48 and 96; by contrast, three discontinued the dolutegravir regimen in this period.

Both bictegravir and dolutegravir clearly have important roles in managing HIV-1 infection, and these studies support the use of both, with slightly less favourable results for dolutegravir than bictegravir when paired with abacavir and lamivudine because of tolerability, but a less clear picture when emtricitabine and tenofovir alafenamide is used. Cost, of course, will be important in some settings, but it is also important to consider that although long-term data are available for dolutegravir, abacavir, lamivudine, and emtricitabine, both bictegravir and tenofovir alafenamide are quite new. Neither long-term clinical experience nor long-term cohort data are available to assess possible signals that might not be evident in short randomised studies. For example, are the concerns about weight gain and lipid concentrations justified? Furthermore, increasing data are available on the efficacy and tolerability of oral two-drug regimens based on dolutegravir[7,8] and injectable two-drug regimens based on cabotegravir.[9–11] Some unanswered questions remain about these regimens and the long-term implications and safety of two-drug regimens is unclear. Nonetheless, a paradigm shift has arrived. Bictegravir might be important, but future studies will need to closely scrutinise how two-drug regimens fare against three-drug regimens, even those containing novel drugs.

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1 Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2019; published online May 5. http://dx.doi.org/10.1016/S2352-3018(19)30077-3.

2 Stellbrink H-J, Arribas JR, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2019; published online May 5. http://dx.doi.org/10.1016/S2352-3018(19)30080-3.

3 Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet* 2017; **390:** 2063–72.

4 Wang H, Lu X, Yang X, Xu N. The efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy: meta-analysis. *Medicine* 2016; **95:** e5146.

5 Hill A, Waters L, Pozniak A. Are new antiretroviral treatments increasing the risks of clinical obesity? *J Virus Eradication* 2019; **5:** e45–47.

6 Sax PE, Pozniak A, Montes ML, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet* 2017; **390:** 2073–82.

7 Llibre JM, Hung CC, Brinson CC, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. *Lancet* 2018; **391:** 839–49.

8 Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet* 2019; **393:** 143–55.

9 Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet* 2017; **390:** 1499–510.

10 Orkin C, Arasteh K, Hernandez-Mora MG, et al. Long-acting cabotegravir + rilpivirine for HIV maintenance: FLAIR week 48 results. Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA; March 4–7, 2019. 140LB (abstr).

11 Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir + rilpivirine as maintenance therapy: ATLAS week 48 results. Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA; March 4–7, 2019. 139 (abstr).