In *The Lancet HIV*, David Wohl and colleagues1 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-workers2 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 colleagues1 describes a comparison of two different, three-drug, co-formulated single-tablet regimens. By contrast, the study by Stellbrink and co-workers2 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 colleagues1 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,1 and in this 96-week extension, non-inferiority of the bictegravir regimen was shown, virological failure 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 disoproxil 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 differences, 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 previously6 and the results at least one dose of their assigned treatment. 48-week data were reported previously6 and the results at week 96 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 dolutegravir18 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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