What did we learn from the bictegravir switch studies?

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In *The Lancet HIV*, Eric S Daar and colleagues[1] and Jean-Michel Molina and colleagues[2] report the results of two large randomised controlled, phase 3 trials of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens or dolutegravir-based regimens in virologically suppressed adults with HIV-1. What new information did we learn from these studies?

The efficacy of bictegravir, emtricitabine, and tenofovir alafenamide was previously shown in two large trials[3,4] in previously untreated adults with HIV-1 infection who had HIV-1 RNA of 500 copies per mL or higher (median HIV-1 RNA was 4·4 $\log_{10}$ copies per mL). Establishing non-inferior efficacy among individuals who are already virologically suppressed (HIV-1 RNA <50 copies per mL) does not add to our understanding of the potency or efficacy of bictegravir, emtricitabine, and tenofovir alafenamide. Switch studies have the potential to enhance knowledge only if the new regimen is expected to have additional benefits to participants (table).

In Daar and colleagues' switch study,[1] participants receiving a regimen consisting of two nucleoside or nucleotide reverse transcriptase inhibitors and a boosted protease inhibitor (either darunavir or atazanavir) maintained the same degree of virological suppression up to 48 weeks after switching to bictegravir, emtricitabine, and tenofovir alafenamide. These results are expected based on findings from previous studies in treatment-naive individuals.[3,4] Although people switching from a previously well tolerated protease inhibitor-based regimen might have headache or other drug-related adverse events (not an uncommon occurrence when switching regimens), they might benefit from fewer drug interactions and lower pill burden, and avoid the well established long-term metabolic complications of boosted protease inhibitors.[5]

Molina and colleagues[2] found that participants who were virologically suppressed on one single-tablet regimen (dolutegravir, abacavir, and lamivudine as a single-tablet regimen in 95% of study participants, with the remaining 5% of participants receiving two or three tablets at baseline) could switch to another single-tablet regimen (bictegravir, emtricitabine, and tenofovir alafenamide) and maintain virological suppression without any other demonstrable benefits. Arguably, discontinuation of abacavir might reduce the risk of cardiovascular events,[6] but this association has not been definitively proven, and it was certainly controversial at the time of enrolment to the switch study in 2015–16.[7] Furthermore, the first evidence of an association with cardiovascular events was reported in 2008,[8,9] which was 9 years after abacavir had been approved in Europe and the USA. Given the limited experience with bictegravir and tenofovir alafenamide, it is unknown whether these drugs will be associated with cardiovascular events, or with other unexpected toxic effects, when more experience is accumulated in a larger population

	Two NRTIs plus boosted protease inhibitor		Dolutegravir, abacavir, and lamivudine		
	Theoretical	Evidence from switch study[1]	Theoretical	Evidence from study in treatment-naive individuals[3]	Evidence from switch study[2]
Efficacy	Unknown	Non-inferior	Unknown	Non-inferior	Non-inferior
Adherence	Reduced pill burden (might improve adherence)	NA	Equal pill burden but reduced pill size (might improve adherence)	NA	NA
Drug interactions	Reduced	NA	Unknown (incompletely characterised)	NA	NA
Toxicity	Reduced metabolic toxic effects	Reduced concentration of triglycerides and ratio of total cholesterol to HDL cholesterol at week 48	Reduced nausea, neuropsychiatric events, sleep disturbances, and cardiovascular events	Nausea reduced (10% vs 23%; p<0·0001), but no difference in neuropsychiatric events or sleep disturbances; not powered to assess cardiovascular events	Nausea reduced (0% vs 2%; p=0·030), but no difference in neuropsychiatric events or sleep disturbances; not powered to assess cardiovascular events

NRTI=nucleotide or nucleotide reverse transcriptase inhibitor. NA=not assessed.

Table: **Advantages of bictegravir, emtricitabine, and tenofovir alafenamide over other regimens**

of patients. Have the study participants just traded one tenuous risk for another unknown risk?

Regarding the potential benefit of switching off dolutegravir to avoid neuropsychiatric adverse events, Molina and colleagues' study was not powered to show a meaningful benefit of switching to bictegravir, emtricitabine, and tenofovir alafenamide because participants were not preselected for neuropsychiatric symptoms.[10] Sleep disorders and other neuropsychiatric symptoms might be class effects of integrase strand transfer inhibitors;[11] indeed, studies[3,4] in treatment-naive individuals found no difference between bictegravir and dolutegravir in the occurrence of neuropsychiatric events. Furthermore, as Molina and colleagues state, "adverse effects on the CNS…have been reported more frequently with dolutegravir in clinical practice and cohort studies than in published results of clinical trials",[2] which is not unexpected given that populations in clinical trials are highly selected. How do we know whether or not a similar experience will occur with bictegravir once it is widely available for use outside of clinical trials? A switch study with restrictive entry criteria will not answer this question.

So what did we learn from these switch studies in terms of potential benefits of bictegravir, emtricitabine, and tenofovir alafenamide? The results of the protease-inhibitor switch study[1] suggested an improvement in lipid parameters, at least among participants taking abacavir at baseline. Other potential benefits of switching to a simpler regimen with fewer drug interactions are reasonably tangible. By contrast, in the dolutegravir switch study,[2] no benefits to participants would have been expected from making the switch from one successful, well tolerated single-tablet regimen to another, and indeed none were shown. The theoretical benefits of decreasing cardiovascular risk are controversial and not possible to establish within 48 weeks.

The ethics of antiretroviral switch studies with virological primary endpoints have been discussed in detail elsewhere.[10] Once regimen potency has been established in studies in treatment-naive individuals, a well designed switch study (ie, one that excludes individuals with previous treatment failure or resistance to any components of the study regimen) will ensure virological non-inferiority. Future antiretroviral switch studies should, therefore, be designed and powered to show that the regimen under investigation can provide clinically meaningful benefits. If the potential benefit is improvement in a side-effect or toxicity profile, presence of that toxic effect should be an entry criterion and assessed regularly throughout the study; if the side-effect is subjective, the study should be done double blind. If the potential benefit is reduction in pill burden or regimen simplification, adherence should be systematically measured in both study groups and quality-of-life assessments should be included in the study design and reported in the paper. Finally, in view of the substantial costs associated with expanding access to lifelong antiretroviral treatment to all HIV-infected people worldwide, cost-effectiveness analyses should be included in all switch studies.

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