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Dolutegravir monotherapy as a simplified strategy in virologically suppressed HIV-1-infected patients

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Sir,

I have read with interest the articles by Rokx *et al.*¹ and Gubavu *et al.*² describing the efficacy of a simplified dolutegravir regimen as a maintenance strategy in virologically suppressed HIV-1-infected patients. However, there is insufficient evidence regarding whether simplification to dolutegravir monotherapy in virologically suppressed HIV-1-infected patients is effective and safe. Thus, the clinical evidence was evaluated and a meta-analysis of observational studies was performed to assess the efficacy and safety of switching to dolutegravir monotherapy (50 mg once daily) in patients with long-term virological suppression. Studies were considered eligible if they provided data with respect to efficacy and safety of dolutegravir monotherapy in virologically suppressed HIV-1-infected adult patients. Systematic searches of PubMed and conference proceedings were conducted with the following keywords: 'dolutegravir', 'monotherapy', 'dolutegravir-based monotherapy' and 'HIV'. The primary outcome was the proportion of patients maintaining HIV-1 RNA levels <50 copies/mL. In addition, the proportion of subjects that developed treatment failure was calculated. Secondary outcomes included the proportion of subjects developing treatment adverse events and primary dolutegravir resistance mutations. Treatment failure was defined as discontinuation, switching of the regimen or virological failure (i.e. two consecutive viral loads >50 copies/mL). Outcomes were assessed over a 24 week period, with the exception of two studies that were assessed at 32 and 48 weeks. Meta-analysis of observational studies in epidemiology was performed. The proportion rate and 95% CIs were estimated using random-effects models and heterogeneity was assessed using the I^2 statistic.³ Comprehensive Meta-Analysis, version 3.0, was used for the analyses.

Four studies met the inclusion criteria and included a total of 87 patients,^{1,2,4,5} with the median age ranging from 48 to 63 years. Forty-eight patients (55%) were males, with the median time since HIV diagnosis ranging from 11 to 20 years. The HIV viral load was undetectable from 5.9 to 8 years. Antiretroviral strategies used at baseline in the 87 patients before switching to dolutegravir monotherapy were triple ART (47%), dual ART (22%) and mono ART (31%). Twenty-three patients (26.4%) had prior integrase inhibitor (INI) use. The reasons for switching included comorbidities

($n=37$), drug–drug interactions ($n=28$), ART-related adverse effects ($n=29$) and archived resistance compromising ART efficacy ($n=16$).

The proportion of patients maintaining virological suppression after switching to dolutegravir monotherapy was 91.9% (95% CI 82.4–96.5; $Z=5.34$; $I^2=12.5\%$) (Table 1). Furthermore, the proportion of treatment failures was 8.1% (95% CI 3.5–17.6; $Z=5.34$; $I^2=12.5\%$). No patient experienced serious adverse effects or discontinued dolutegravir monotherapy. Four out of five patients that had virological failure had prior INI exposure, but without viral failure at baseline. Four developed major INI resistance-associated mutations that compromised dolutegravir activity (i.e. 118R, 138K, 148R, 74I and 155H).

Evidence from observational studies suggests that heavily treatment-experienced and virologically suppressed HIV-infected patients have a higher chance to maintain viral suppression when switching to dolutegravir monotherapy.

Several properties make dolutegravir attractive for use as a simplified regimen. Dolutegravir has a high genetic barrier comparable to a boosted PI. Those that failed on an initial dolutegravir-based regimen did not develop dolutegravir-associated mutations, in contrast to other agents of the same class (i.e. elvitegravir and raltegravir).⁶ Further, dolutegravir has been shown to have superior antiviral potency compared with efavirenz, darunavir and raltegravir, especially in patients with a higher viral load (i.e. HIV viral load >100 000 copies/mL).⁶ Even in treatment-experienced patients, irrespective of previous INI failure, dolutegravir was superior to raltegravir in achieving virological suppression.⁷ Lastly, registration studies of dolutegravir showed an excellent safety profile, with severe reactions (grade III or IV) in 1%.⁶ Moreover, a large amount of the drug is not metabolized by the cytochrome P450 metabolic pathway, averting potential drug–drug interactions commonly seen with other antiretroviral agents.

I believe that switching to dolutegravir monotherapy in specific HIV-infected patients is beneficial.

Table 1. Meta-analysis results showing the proportions of patients maintaining virological suppression (HIV RNA <50 copies/mL) with dolutegravir monotherapy in observational studies

	Virological suppression		Weight (%)	Proportion rate, Mantel–Haenszel, random (95% CI)
	events	total		
Rokx <i>et al.</i> ¹	4	5	16.38	80 (30.9, 97.3)
Gubavu <i>et al.</i> ²	21	21	10.04	97.7 (72.3, 99.9)
Rojas <i>et al.</i> ⁴	32	33	19.82	97 (81.4, 99.6)
Katlama <i>et al.</i> ⁵	25	28	53.75	89.3 (71.6, 96.5)
Total (95% CI)		87	100	91.9 (82.4, 96.5)
Total events	82			
Test for overall effect	$Z=5.34$ ($P=0.001$)			
Heterogeneity	$I^2=12.5\%$			

Weights are calculated by random-effects models.

Monotherapy potentially avoids the adverse reactions that could arise if an NRTI backbone was coadministered. This fact is important as HIV patients are ageing and considerably exposed to polypharmacy and other comorbidities. Although there is no cost-effective analysis showing the superiority of monotherapy compared with triple dolutegravir-based therapy, I suggest that monotherapy would considerably cut drug costs. Finally, monotherapy would potentially increase patient adherence and avoid treatment fatigue in the long-term, considering the ease of administration of this regimen (i.e. 50 mg once daily).

It is alarming that patients who experienced virological failure after dolutegravir monotherapy developed major dolutegravir-associated mutations. Rigorous patient selection before switching is mandatory, as previous characteristics have been associated with virological failure in PI monotherapy trials.⁸ Recognizing that four out of five viral failures had a prior history of INI use and developed dolutegravir-associated mutations, it is prudent to avoid simplification in subjects who have had prior INI-containing regimens.

I understand that the current results are preliminary and additional evidence is needed before making a formal recommendation of this simplification strategy. In this context, there are two planned non-inferiority clinical trials in the Netherlands and Spain, evaluating the safety, tolerability and efficacy of dolutegravir-based simplification strategies in HIV-infected patients with prolonged virological suppression.^{9,10}

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Transparency declarations

None to declare.

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