FLAMINGO: how much rosier can antiretroviral therapy get?

In the SPRING-2 trial, dolutegravir showed non-inferiority to raltegravir, another integrase inhibitor, in antiretroviral-naive adults with HIV-1 infection. In the SINGLE trial, dolutegravir showed superiority over a non-nucleoside reverse transcriptase inhibitor, efavirenz. The next obvious step of the dolutegravir targeted strategy was to compare dolutegravir with a boosted protease inhibitor such as darunavir plus ritonavir. The comparison between dolutegravir and a boosted protease inhibitor is particularly interesting because boosted protease inhibitors are very potent and, by contrast with raltegravir and efavirenz, extremely resilient to HIV resistance development even when used as monotherapy.

In The Lancet, Bonaventura Clotet and colleagues present the FLAMINGO study, in which 484 antiretroviral-naive HIV-infected patients were randomly assigned to receive two nucleos(t)ide reverse transcriptase inhibitors (tenofovir-emtricitabine or abacavir-lamivudine) plus either dolutegravir (50 mg) or the boosted protease inhibitor darunavir (800 mg) plus ritonavir (100 mg). After 48 weeks of follow-up, more than 80% of patients in each group achieved virological suppression (217 [90%] patients receiving dolutegravir and 200 [83%] patients receiving darunavir plus ritonavir had HIV-1 RNA of less than 50 copies per mL, adjusted difference 7·1% [95% CI 0·9–13·2]), and no patient developed drug resistance. It is difficult to imagine a better outcome for a clinical trial in a disease that just two decades ago did not have an effective treatment.

In a prespecified secondary analysis, dolutegravir also showed superiority to darunavir plus ritonavir. The data suggest that superiority was driven both by better tolerability (nine [3%] patients in the dolutegravir group and 20 [9%] patients in the darunavir plus ritonavir group discontinued for non-virological reasons) and better efficacy (virological success in 217 [90%] patients in the dolutegravir group vs 200 [83%] patients in the darunavir plus ritonavir group), especially in the 25% of patients who started with viral loads greater than 100 000 copies per mL. But is dolutegravir really superior to darunavir plus ritonavir? This is a difficult question to answer for various reasons.

First, FLAMINGO is an open-label clinical trial with two pills a day taken by patients in the dolutegravir group versus four pills a day taken by those in the comparator group (darunavir plus ritonavir). The open-label design might have led to patients, disappointed with their treatment assignment, choosing not to continue. In fact, six patients withdrew in the darunavir plus ritonavir group very early on compared with the one patient who withdrew in the dolutegravir group.

Second, results cannot be automatically extrapolated to all antiretroviral-naive patients because most patients recruited were young white men whose median CD4 cell count was almost 400 cells per μL. This cell count was within the threshold for starting therapy for most guidelines but above the mean CD4 cell count at HIV diagnosis in patients in high-income countries (336 cells per μL).

Third, integrase inhibitors tend to reduce viral load very rapidly, often reaching undetectability in less than 8 weeks, whereas protease inhibitors tend to cause a more gradual decrease. This effect could lead to patients starting with a very high viral load in the darunavir plus ritonavir group still having a detectable but falling viral load, even after 48 weeks. They might have reached a very low viraemia of 50–200 copies per mL but not virological suppression at that time, even though viral load might have subsequently become undetectable. The detailed viral load results of 48-week outcomes in patients with very high viral loads at initiation (>100 000 copies per mL and >500 000 copies per mL), and the 96-week study data are analyses important in understanding the outcomes.

Fourth, since no patient developed resistance after virological failure in either group, the superiority of dolutegravir does not translate into an advantage with

<table>
<thead>
<tr>
<th>N</th>
<th>Treatment emergent resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRTI</td>
</tr>
<tr>
<td>ABC/3TC-dolutegravir</td>
<td>414</td>
</tr>
<tr>
<td>TDF/FTC (or ABC/3TC)-dolutegravir</td>
<td>411</td>
</tr>
<tr>
<td>TDF/FTC (or ABC/3TC)-dolutegravir</td>
<td>242</td>
</tr>
<tr>
<td>TDF/FTC/efavirenz</td>
<td>419</td>
</tr>
<tr>
<td>TDF/FTC (or ABC/3TC)-raltegravir</td>
<td>411</td>
</tr>
<tr>
<td>TDF/FTC (or ABC/3TC)-dartanavir</td>
<td>242</td>
</tr>
</tbody>
</table>

Data are number of patients. TDF=tenofovir. FTC=emtricitabine. ABC=abacavir. 3TC=lamivudine. NRTI=nucleotide reverse transcriptase inhibitors. NNRTI=non-nucleotide reverse transcriptase inhibitors.

Table 1: Treatment emergent resistance in phase 3 clinical trials of dolutegravir
respect to preserving future treatment options. Finally, a third of the patients in the control group received abacavir plus lamivudine and darunavir plus ritonavir. This combination has not been widely studied before, and data about its efficacy are scarce, especially in patients with high viral loads.

To patients and clinicians these criticisms might seem rhetorical since dolutegravir has been shown to be as effective, if not more, than a comparator regimen that requires a higher pill burden, longer time to achieve viral suppression, more drug-drug interactions, and less favourable lipid changes. The only apparent management issue with dolutegravir is its effect on lowering the estimated, but not true, glomerular filtration rate due to its action on inhibiting organic cation transporter-1 in the tubule and decreasing creatinine secretion. Although this issue is not a true renal toxic effect, and in FLAMINGO no participant developed grade 3–4 increase in creatinine, physicians have to be aware of this phenomenon, especially in patients with underlying renal disease, so that any changes in creatinine can be interpreted correctly. Another note of caution is that long-term follow-up is needed to continue to look out for adverse events.

In FLAMINGO, the development of resistance was zero in both treatment groups. Dolutegravir is the first drug outside the boosted protease inhibitor family not to be associated with development of resistance in clinical trials of antiretroviral-naive patients (table). However, whether this similarity with boosted protease inhibitors means that dolutegravir can be used as monotherapy or dual therapy along with a single nucleoside reverse transcriptase inhibitor or non-nucleoside reverse transcriptase inhibitor is unknown.

The results of FLAMINGO also support the idea that we are entering the integrase inhibitor era in HIV therapeutics. Integrase inhibitors are on the recommended list of drugs for initiation of antiretroviral therapy in most major guidelines, and the US Department of Health and Human Services has now included dolutegravir. It might not be too long before some of the well established non-nucleosides and protease inhibitors are relegated to the alternative list by guideline panels. The dominance of the non-nucleoside efavirenz as a drug of choice in HIV is being questioned because of its common short-term and potentially long-term neuropsychiatric side-effects, including the increase risk of suicidality and the increasing availability of other better-tolerated drugs, which also can be coformulated as a regimen in a single pill.

However, the rosy future of integrase inhibitors could be threatened by generic drugs. Guidelines do not usually take into account cost-effectiveness, and as more drugs come off patent and budgets become restrained, will new drugs be affordable? One strategy might be to start patients on a generic regimen and switch them to an integrase inhibitor if they develop side-effects or intolerance. This might be an economic solution, but a robust discussion is needed regarding the acceptability of such approaches when drugs such as dolutegravir have shown superior trial outcomes over current standards of care.

Anton L Pozniak, Jose R Arribas
HIV Directorate, Chelsea and Westminster Hospital NHS Foundation Trust, London SW10 9NH, UK (ALP); Imperial College London, London, UK (ALP); and HIV Unit, Hospital La Paz, IdiPAZ, Madrid, Spain (JRA)
anton.pozniak@chelseawards.nhs.uk

ALP receives advisory fees, speaker’s fees, or grant support from Viiv, Tibotec, Janssen, Bristol-Myers Squibb, Gilead Sciences, Merck Inc, and Tobira.
JRA receives advisory fees, speaker’s fees, or grant support from Viiv, Tibotec, Janssen, Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Inc, and Tobira.
