In cases of high viral load, as is observed in primary HIV infection, any InSTI has the advantage over other families of antiretrovirals, such as PIs or NNRTIs, of rapidly decreasing viral load, improving symptoms and decreasing transmissibility. However, there are differences in the resistance profile among the three available InSTIs, with raltegravir and elvitegravir presenting a lower genetic barrier to resistance compared with dolutegravir. In addition, regimens containing elvitegravir/cobicistat may increase the risk of serious drug–drug interactions and toxicity of recreational drugs (Chemsex).

Our group has recently published the first year of experience with our cohort regarding the resistance substitutions detected for InSTIs between May 2015 and May 2016 in patients with acute or recent infection, defined as being <6 months. In that paper, although we did not find signature resistance substitutions for this family of drugs, we did frequently find (13.89%) polymorphic and secondary substitutions conferring low-level resistance to first-generation InSTIs (raltegravir and elvitegravir). In our cohort, the polymorphic and accessory substitutions detected were E157Q and Q95K.

Other European groups have found similar results, but this is not consistent among countries, and rates of detection for these substitutions vary. Zoufaly et al. reported that, in Austria, 6% of recently diagnosed individuals had at least potentially low-level resistance to raltegravir or elvitegravir and 1% to dolutegravir. By contrast, in the UK, the rates of these polymorphisms and substitutions are lower; 6 of 101 individuals had minor or accessory mutations in a recent study: one having L74M, two V151I and three E157Q, but only E157Q conferred low-level resistance to raltegravir and elvitegravir. In Switzerland, in a recent paper analysing >1300 sequences of InSTI-naive patients, only 0.1% had a major substitution and 2.9% minor substitutions, more frequently polymorphic and in non-B subtypes. It is also unknown whether these substitutions are more prevalent in patients with primary HIV infection than in chronically infected, naive patients, although no fitness effect has been described.

Although the real risk of virological failure when these substitutions are present in patients with extremely high viral loads (patients with primary HIV infection frequently have millions of copies/mL) is unknown, the preferred practice in our clinic is to initiate dolutegravir plus emtricitabine/tenofovir disoproxil fumarate (which also has some advantages in terms of potential transmitted drug resistance to abacavir/lamivudine as an NRTI backbone) if the resistance test is still pending. We further modify the regimen to one of the single-tablet InSTI-based regimens recommended by the European (EACS) and Spanish (GESIDA) national guidelines, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide or dolutegravir/abacavir/lamivudine, when those low-level resistance substitutions have been excluded.

We consider very useful the data reported by Nozza et al. However, despite there not being any clinical data yet, we want to highlight the potential, theoretical risk of virological failure in places where these InSTI polymorphisms and secondary substitutions have high prevalence.

Transparency declarations
None to declare.

References

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Efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate as treatment for primary or recent HIV infection—authors’ response

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Sir,

We thank Ambrosini et al. for their critical reading of our manuscript. We agree with their observation that the resistance profile among raltegravir, elvitegravir and dolutegravir is different; this is nowadays very well known and in our retrospective study we analyse data collected when elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate was the only available integrase strand-transfer inhibitor (InSTI)-based single-tablet regimen.

However, we would argue that there are still some potential differences, however defined, between our sets of data and those described by our Spanish colleagues. We have reported accessory mutations to InSTIs according to the Stanford University HIV Drug Resistance Database in one patient with primary HIV infection (G163R) and one patient with recent HIV infection (S230N); these data are not in line with those reported by Ambrosioni et al., but rather with our Italian database on patterns of transmitted drug resistance, which supports the choice of an InSTI-based therapy because of the very low prevalence of low-level resistance substitutions and accessory mutations that could be involved in long-term virological failure. Actually, we do not know yet the effect of these accessory mutations on InSTI susceptibility in the setting of naïve patients; we consider that there may be an action of accessory mutations (L74I, T97A, E157Q) according to a recent cross-sectional study among patients treated with second- and third-line antiretroviral regimens.

The most recent European guidelines recommend the use of a boosted PI in a PHI setting; however, they suggest a combination with InSTI in order to induce rapid viral load suppression.

Based on the dolutegravir high genetic barrier data and the possible issue of InSTI mutations in PHI, we agree that there is great clinical interest in having efficacy and safety data on the use of dolutegravir-based regimens in the setting of PHI. We are waiting for the results of studies with adequate sample sizes.

We also agree that the evaluation of InSTI polymorphisms and secondary substitutions may help in refining the prescription of an InSTI regimen.

**Transparency declarations**

None to declare.

**References**