Although they perform the resistance investigations using a different technique and a definition of acute/recent HIV infection that is not exactly the same, their results are quite similar to ours. Remarkably, in terms of the prevalence of detection of polymorphic and accessory substitutions, they found 13.3% of patients with such substitutions, compared with 13.89% in our article.

Moreover, even though they analyse resistance substitutions using population sequencing (with lower sensitivity than the massive sequencing performed in our centre), such an approach would not have modified our results since, in our series, all patients had a mutational load >90% of the viral load. Thus, our prevalence would have been the same using population sequencing. As with our cohort, the patients in the series of Fabrizio et al.1 are mostly MSM, infected with subtype B, and the most frequently detected integrase strand-transfer inhibitor (InSTI) substitution is 157Q.

Several other European studies have noticed different levels of InSTI polymorphic and accessory substitutions in naïve, recently diagnosed individuals. In Austria, 6% of recently diagnosed individuals had at least potentially low-level resistance to raltegravir or elvitegravir and 1% to dolutegravir.2 The rates of these polymorphisms and substitutions are lower in the UK4 and in Switzerland,5 but still present.

In times of extremely effective antiretroviral regimens, even patients with multiple previous virological failures can become undetectable with relatively simple regimens. In this context, we agree with Fabrizio et al.1 that naïve HIV individuals are increasingly being identified as the main source of resistance to antiretrovirals. This has been reported already in important European studies.6

We think that the next step is to identify, in our cohort and in other centres, such as that of Fabrizio et al.,1 whether these patients—who all share the same risk factor for infection, the same strains with the same tropism and the same polymorphic and accessory substitutions—represent clusters of transmission or whether they are unrelated cases. While the prevalence may not change, the epidemiological message does.

Transparency declarations
None to declare.

References

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Comment on: Efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate as treatment for primary or recent HIV infection

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Sir,
We read with great interest the article by Nozza et al.1 recently published in the Journal of Antimicrobial Chemotherapy. In this paper, the authors describe and discuss the efficacy of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate in a reference centre in Milan, Italy, as treatment for primary or recent infection, defining recent infection as being <12 months.

As discussed therein, in this particular setting, patients frequently present with a symptomatic primary infection. This symptomatic disease is a correlate of the extremely high viral load in this period, and ART is usually initiated before the baseline resistance test is available. They also report that, in Italy, the overall transmission of drug resistance to the classic and older families of antiretrovirals (PIs, NRTIs and NNRTIs) is ~8%, which is approximately comparable to our local rates.2

They also report that, in their cohort of 47 patients, 23 having primary HIV infection and 24 having recent HIV infection, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate showed a comparable efficacy between patients with acute and recent infection and a safety profile that was similar to that observed in clinical trials. Only two cases with a minor integrase strand-transfer inhibitor (InSTI) substitution are reported in this paper. They conclude that this combination is a good option in this clinical scenario, both for primary infection and for recent infection.3

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/cobicistat may increase the risk of serious drug–drug interactions and toxicity of recreational drugs (Chemsx).

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 analyzing >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

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

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