physicians in the LB setting, with concordant results of good science on one side and opinions based on questionable interpretation of medical science on the other.

**Note**

**Potential conflicts of interest.** Both authors report no potential conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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**Clinical Infectious Diseases** 2019;68(11):1975–6 © The Author(s) 2018. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com. DOI: 10.1093/cid/ciy1013

**Resistance Testing for Integrate Strand Transfer Inhibitors in Naive, Human Immunodeficiency Virus–infected Individuals**

To the Editor—We read very closely the 20 July issue of *Clinical Infectious Diseases*, which contained the updated Recommendations of the International Antiviral Society’s United States Panel for testing of human immunodeficiency virus (HIV) drug resistance. Recommendations were provided for patients whose antiretroviral therapy (ART) has failed and for the HIV-naive population [1]. For the latter group, the recommendations are in line with the latest guidelines for the treatment and prevention of HIV infection [2].

The recommendation is to test only for resistance to nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors, and to reserve testing for integrase strand transfer inhibitor (InSTI) resistance to cases of suspected exposure to InSTI-resistant strains (when there is detection of resistance to other drug families). The authors considered that, although there is interest in the testing of InSTI baseline resistance, it is not currently cost effective. The guidelines recognize, however, that this recommendation may change as more resistance emerges with the widespread use of InSTI (first-line regimens are InSTI-based) [1].

The main reasoning for avoiding baseline testing of InSTI resistance is the infrequent transmission of signature mutations (such as Y143R/C, N155H, or Q148K/R/H) [3], and we agree with the statement that there is generally no need to monitor it prior to treatment initiation. However, InSTI polymorphisms that can reduce InSTI activity are not infrequent. There have been reports in Europe of a 14% prevalence of such substitutions, on the basis of samples collected in naive patients between 2006 and 2007 (before the introduction of InSTI in clinical practice) [4]. In our institution, prevalence was also 14% in naive patients with acute/recent HIV infections (<6 months post-infection) diagnosed in 2015 and 2016. The most frequently found was the E157Q substitution, with all patients being infected with subtype B strains, the most common in Europe. The substitution, therefore, seems unrelated to specific recombinant forms or subtypes [5]. In other European countries, such as Austria or the United Kingdom, reported rates of these polymorphisms and substitutions are lower, although still significant, at around 6% [6, 7].

Antiretroviral-naive patients carrying viruses with polymorphisms such as E157Q have been reported as presenting virological failure with raltegravir- [8] and elvitegravir/cobicistat-based [9] regimens. Indeed, Charpentier et al [9] reported virological failures in 2 out of 8 (25%) antiretroviral-naive patients starting elvitegravir/cobicistat-based ART. Consequently, the French ANRS (National Agency for AIDS Research) algorithm considers strains carrying E157Q as resistant to raltegravir and elvitegravir/cobicistat (http://www.hiv-frenchresistance.org/).

In light of this, we think testing the baseline InSTI genotype might be considered in specific epidemiological settings where such polymorphisms are reportedly frequent in given populations, regions, or HIV-risk groups, particularly if raltegravir or elvitegravir/cobicistat are the InSTI used. This is the practice at our institution, and raltegravir- and elvitegra- vir/cobicistat-based regimens are avoided when these polymorphisms are present, at least in patients with primary HIV infections, who frequently have high viral loads at ART initiation. Regimens with bictegravir or dolutegravir would not be affected by such polymorphisms, and should thus be chosen in settings without InSTI resistance testing, where these substitutions are known to be frequent.

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integrate strand transfer inhibitor (InSTI) activity are not infrequently detected in human immunodeficiency virus type 1 (HIV-1)–infected drug-naïve individuals, particularly those with subtype B infection [2–4]. They point out that E157Q at baseline has been associated with raltegravir- and elvitegravir/cobicistat-based regimens in some cases [5, 6] and, thus, that baseline InSTI resistance testing might be considered if treatments with raltegravir or elvitegravir/cobicistat are planned. We await evidence that these polymorphisms increase the risk of failure with InSTI-based regimens, especially with the newer recommended regimens that contain dolutegravir or bictegravir [7, 8].

The reason we have not recommended routinely performing baseline InSTI-associated resistance testing is that, to date, there have been only very limited reports of transmitted major InSTI resistance, and the large phase 3 trials with raltegravir and elvitegravir/cobicistat failures were not associated with polymorphisms potentially associated with InSTI resistance mutations [9–12]. Therefore, these tests are not yet cost effective. In addition, current recommendations for initial antiretroviral therapy include those InSTIs with a higher resistance barrier (dolutegravir or bictegravir) [8, 13, 14]. For these drugs, integrate polymorphisms have not yet been shown to result in any impact on treatment responses.

As we have stated in our recommendations, surveillance for the emergence of transmitted InSTI resistance in all geographic regions is important because we do not know the future consequences of expanded use of InSTIs in resource-rich and low- and middle-income countries. With the introduction of next-generation sequencing for routine genotypic testing instead of Sanger sequencing, the costs may decrease in the future to allow general recommendations for routine baseline resistance testing covering a larger portion of the HIV genome.

Note

Potential conflicts of interest. All authors: No reported conflicts of interest.


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Clinical Infectious Diseases®

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Reply to Ambrosioni et al

To the Editor—We read with interest the letter by Ambrosioni, Mosquera, and Miro [1]. They raise the issue that polymorphisms, for example, E157Q and T97A, that can potentially reduce

References


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