

## Canary in the Coal Mine? Transmitted Mutations Conferring Resistance to All Integrase Strand Transfer Inhibitors in a Treatment-Naive Patient

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Transmitted drug resistance to the integrase strand transfer inhibitor (INSTI) class of antiretrovirals is very rare. We present a case of a treatment-naive female patient with human immunodeficiency virus harboring resistance to all INSTIs, including bicitegravir and dolutegravir.

**Keywords.** HIV; integrase; transmitted resistance; treatment naive.

Transmitted drug resistance (TDR) to human immunodeficiency virus (HIV) reverse-transcriptase (RT) and protease (PR) inhibitors is well described [1–3]. Prevalence of TDR to at least 1 antiretroviral (ARV) drug in high-income settings is estimated at 10%–17% [4, 5], and it is growing in low- and middle-income countries as well. In Africa, the prevalence of nonnucleoside RT inhibitor (NNRTI) TDR ranges from 8.1% to 15.4% [6].

To avoid initiating ARVs to which a patient may already be resistant, current US guidelines recommend obtaining routine genotyping to detect RT and PR resistance mutations before initiation of treatment and at time of virologic failure [4, 7]. There is no consensus opinion regarding baseline testing for integrase strand transfer inhibitor (INSTI) resistance, however, principally because of low prevalence of INSTI mutations in surveillance data and low estimated cost-effectiveness [7–9]. Indeed, cohort studies in the United States and Europe have shown the prevalence of INSTI TDR to be

0%–0.1% [4, 9]. Only 2 cases of transmitted INSTI resistance have been reported [10, 11], and their analysis focused exclusively on resistance to the first-generation INSTIs, elvitegravir (EVG) and raltegravir (RAL). Transmitted drug resistance mutations impacting second-generation INSTIs dolutegravir (DTG) and bicitegravir (BIC) have not been previously reported in the literature nor in clinical trials [4]. In this study, we describe a case of a treatment-naive, female patient with HIV harboring resistance predicted to all INSTIs, including BIC and DTG.

### CASE REPORT AND RESULTS

In May 2018, a 42-year-old black female was diagnosed with HIV based on a reactive antigen/antibody combination assay obtained during a routine gynecology visit. At diagnosis, she was asymptomatic and reported no significant prior medical history. Between her most recent prior negative HIV test in August 2016 and her reactive result, she reported 1 male sexual partner whom she knew to be HIV infected. She denied any prior history of other sexually transmitted infections, injection drug use, or recent international travel. The patient also denied any prior exposure to ARVs, including for purposes of pre- or postexposure prophylaxis.

At her initial visit in June 2018, specimens were obtained for baseline testing per US guidelines, and she was prescribed bicitegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF). Her initial CD4 and HIV-1 ribonucleic acid (RNA) were 941 cells/mm<sup>3</sup> and 216 copies/mL, respectively. Four weeks after this visit, her baseline (pretreatment) genotypic resistance test (GenoSure Prime; Monogram Biosciences, South San Francisco, CA) revealed polymorphisms in RT (V118V/I) and PR (I62V and A71T) along with 3 major INSTI mutations (E138A, G140S, and Q148H) conferring resistance to all drugs in the INSTI class.

Because of insurance barriers, the patient never filled the prescription for BIC/FTC/TAF and was subsequently initiated on FTC/rilpivirine/TAF given the genotype findings. Sixteen days after starting this regimen, her HIV-1 RNA was <20 copies/mL. At the follow-up visit 16 days after starting FTC/rilpivirine/TAF, a GenoSure Archive (Monogram Biosciences) that analyzes proviral DNA redemonstrated E138A, G140S, and Q148H integrase mutations.

Investigation later revealed that the sexual partner's ARV treatment history included the following: nelfinavir, didanosine, zidovudine (AZT), darunavir, ritonavir, RAL, and DTG, and his virus harbored many HIV resistance mutations (Table 1). In November 2016, the sexual partner's genotype revealed the E138A, G140S, and Q148H mutations.

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**Table 1. Genotype Results for Index Patient (Sexual Partner)**

| Date          | RT Mutations         | PR Mutation                     | IN Mutations            |
|---------------|----------------------|---------------------------------|-------------------------|
| November 2005 | 41L<br>184V          | 71T<br>77I                      | N/A                     |
| April 2006    | None                 | None                            | N/A                     |
| March 2008    | 65R<br>100I<br>103N  | 62V<br>63P<br>71V<br>77I<br>93L | N/A                     |
| February 2010 | 100I<br>103N<br>181I | 62V<br>63P<br>71V<br>77I<br>93L | N/A                     |
| November 2016 | None                 | I62V<br>A71A/I/T/V              | E138A<br>G140S<br>Q148H |

Abbreviations: IN, integrase; N/A, not applicable; PR, protease; RT, reverse transcriptase.

## DISCUSSION

This is the first documented case of transmitted INSTI resistance affecting second-generation INSTIs, DTG, and BIC. Based on available surveillance data suggesting a low prevalence of INSTI resistance mutations and clinical experience, and in the absence of sexual partner data on presentation, our index for suspicion of transmitted INSTI resistance was low. In accordance with current US guidelines and following best practices in rapid ART initiation, the patient was started on an INSTI-based regimen at time of her first clinic encounter [7, 12].

Integrase strand transfer inhibitors have quickly become the mainstay of treatment among ARV-naïve patients given their ability to rapidly suppress HIV-1 viral load, their excellent tolerability, and the seemingly low prevalence of resistance. The second-generation INSTIs (DTG and BIC) rarely select for resistance mutations among ARV-naïve and treatment-experienced patients in clinical trials [13–18]. Previously reported cases of INSTI TDR involved mutations conferring resistance to first-generation INSTIs (EVG and RAL), but the mutations observed would not be expected to significantly reduce susceptibility to DTG or BIC [19].

Currently, the most recent guidelines from the US Department of Health and Human Services and the International Antiviral Society–USA Panel recommend against testing for transmitted INSTI resistance [4, 7]. However, beginning in 2013, providers at Duke University’s Infectious Disease Clinic decided to include INSTI resistance testing as part of baseline laboratory assessments for all ARV-naïve patients living with HIV. This decision was predicated on 2 key factors. First, although we acknowledged the very low prevalence of transmitted INSTI mutations reported in population surveillance data, that prevalence was not zero, and it seemed reasonable to assume that prevalence might rise over time with expanded use of INSTIs [20]. Second, utilization of genotyping for integrase, in addition

to PR and RT, represented a relatively low additional cost for the added information provided. We believe our policy served this patient well.

Three transmitted INSTI resistance mutations were found in this case. E138K/A substitution is a non-polymorphic, accessory mutation elicited by RAL-, EVG-, or DTG-based therapy and usually occurs in tandem with Q148 mutations, as we observed here. G140S/A/C mutations usually co-occur with Q148 in patients receiving RAL and EVG. Q148H/K/R mutations develop in viruses exposed to RAL and EVG, as well as during virologic failure on DTG monotherapy. In combination with E138 and G140 mutations, Q148H/K/R reduce RAL and EVG susceptibility >100-fold, and DTG and BIC susceptibility is reduced up to 10-fold [21]. This case illustrates that 2 of the most common co-occurring INSTI mutations, Q148 and G140, in addition to E138 confers high-grade INSTI resistance and is transmissible.

The clinician treating our patient believed that using an ARV regimen with 3 fully active ARV drugs was the most appropriate management, but it is not fully clear what magnitude of decreased DTG and BIC susceptibility is conferred by E138, G140, and Q148 mutations. Retrospective analysis of baseline resistance status in phase 3 studies of BIC identified 1 participant with pre-existing Q148H and G140S. Although this combination is predicted to confer at least intermediate resistance to BIC [21], the study participant’s HIV RNA was <50 copies/mL at week 4 and she/he maintained viral suppression through week 72 [22].

## CONCLUSIONS

This case serves a reminder that despite the prominent role of INSTIs as first-line ARV agents for the treatment of HIV-1, the prospect of resistance is always lurking. Recognizing that treatment-emergent and TDR mutations are always a possibility is a critical consideration for the management of persons living with HIV.

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