Development of the R263K Mutation to Dolutegravir in an HIV-1 Subtype D Virus Harboring 3 Class-Drug Resistance

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Dolutegravir (DTG), a second-generation integrase strand-transfer inhibitor (INSTI), is equivalent or superior to current non-nucleotide reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and first-generation INSTI-based antiretroviral regimens (ARVs). It has the potential to make big improvements in HIV globally and within patients. This is perhaps the most "precious" HIV drug available. The integrase mutation R263K has been observed in tissue culture experiments and in patients treated with dolutegravir monotherapy in clinical trials. Globally, adherence and monitoring may be less than optimal and therefore DTG resistance more common. This is particularly important in low–middle-income countries, where patients may remain on failing regimens for longer periods of time and accumulate drug resistance. Data on this mutation in non–subtype B infections do not exist. We describe the first report of the R263K integrase mutation in a dolutegravir-exposed subtype D–infected individual with vertically acquired HIV. We have used deep sequencing of longitudinal samples to highlight the change in resistance over time while on a failing regimen. The case highlights that poorly adherent patients should not be offered dolutegravir even as part of a combination regimen and that protease inhibitors should be used preferentially.

Keywords. adolescents; ARVs; dolutegravir; HIV; resistance.

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CASE REPORT

A 22-year-old East African woman with vertically acquired HIV had been diagnosed shortly after birth. Her baseline viral load (VL) was 375,000 copies/mL, her CD4 was 150 cells/mm³, and she had subtype D infection. At diagnosis, zidovudine monotherapy was commenced. Didanosine was added...
2 years later, and she was switched to stavudine, lamivudine, and nelfinavir at 3 years of age. The VL dropped to 700 copies/mL; however, it rebounded to 6000 copies/mL at that time, a first resistance test showed M184V and D30N mutations. The patient then received zalcitabine, abacavir, and amprenavir. Subsequently, she maintained poor virological control despite changing antiretrovirals three times, with NNRTIs introduced during these changes (Table 1). Poor adherence continued until 11 years of age, when virological suppression was achieved with maraviroc, etravirine, and twice-daily darunavir/ritonavir. Subsequently, she disengaged from care, with inconsistent attendance over a period of 8 years. On re-engagement in care, her VL was 1610 copies/mL, and her CD4 was 104 cells/mm³.

At that time, resistance testing showed NRTI (M184V, T69D, T215V, T215Y, D67N, K219Q), NNRTI (Y181C, Y188L, H221Y) and PI (L10I, D30N, K20T, L33F, K43T, N88D) resistance, with PI resistance to nelfinavir. Integrase polymorphisms (17N, 256E, 112V, 201I, 234I) were detected. Maraviroc, etravirine, and darunavir/ritonavir (twice daily) were restarted. This regimen was simplified to darunavir/ritonavir and maraviroc, and subsequently to darunavir/ritonavir monotherapy once virological suppression was achieved. Six months later, the VL rebounded to 8600 copies/mL, and DTG 50 mg once a day was added. Poor engagement continued for 18 months; at this later time, inte grase resistance testing showed the R263K mutation conferring low-level resistance to DTG and raltegravir, with intermediate resistance to elvitegravir. R263K was confirmed by next-generation sequencing (NGS) using an analysis percentage minority variant threshold of >20%. To avoid accumulation of integrase resistance mutations with ongoing poor adherence, she was switched to tenofovir, darunavir/ritonavir. Follow-up NGS sequencing 3 months after the first resistance test showed the R263K mutation at <5% in a sample with a VL of 61 000 copies/mL.

Reasons for poor adherence and disengagement over time included drug adverse reactions and pill burden, a lack of family support, and lack of finances to attend outpatient appointments. The patient reported low mood, which reduced her motivation to take ARVs and engage in care. Despite multiple strategies to facilitate adherence, this patient declined psychological and mental health support.

**DISCUSSION**

The World Health Organization has recommended that countries consider a change from efavirenz-based regimens to dolutegravir-based regimens where pretreatment drug resistance to NNRTI has exceeded 15% [16, 17]. If DTG scale-up is to occur, drug resistance to DTG in different HIV subtypes needs to be monitored. Although at present significant DTG resistance in sub-Saharan populations is very rare [18], it has been documented recently in a heavily experienced patient who had previously failed raltegravir. We report occurrence of the R263K integrase mutation 18 months into treatment with DTG in the context of vertically acquired subtype D infection. This mutation is known to reduce viral fitness, and its loss was associated with an increase in viral load [19]. Further surveillance for dolutegravir resistance is warranted globally.

| Table 1. Summary of Antiretroviral History |

| Age, y | Antiretrovirals | VL on Starting ARVs | VL After Starting ARVs | Resistance Test on Regimen |
|--------|----------------|---------------------|------------------------|---------------------------|
| 0      | AZT            | 375 000             | -                      |                           |
| 2      | AZT, DDI      | -                   | 375 000                |                           |
| 3      | D4T, 3TC, NFV | -                   | 700                    | M184V, D30N               |
| 4      | DDC, ABC, AMP | 6000                | -                      |                           |
| 6      | D4T, DDI, NVP | -                   | 31 000                 |                           |
| 8      | DDI, EFV, NVP | 17 000              | 25 000                 |                           |
| 10     | TIP, TDF, FTC | 34 000              | <50                    |                           |
| 18     | MVC, ETV, DRV/RIT | 1610          | 1610                   | M184V, T69D, T215V, D67N, K219Q, Y181C, Y188L, H221Y, L10I, D30N, K20T, L33F, K43T, N88D |
|        | MVC, DRV/RIT  | -                   | <50                    |                           |
|        | DRV/RIT       | <50                 |                        |                           |
|        | DRV/RIT, DTG (ODI) | 8600              | 8600                   | R263K INT 60.8%, L32F PR 99.7%, N88D PR 99.7%, D30N PR 99.9%, K43T PR 99.8%, D67N PR 99.7%, T215S PR 99.7%, K219Q PR 99.7%, T69D PR 99.7%, Y181C PR 99.7%, Y188L PR 99.7%, H221Y PR 99.7%, L10I PR 99.7% |
| 20     | DRV/RIT, TDF  | 99 000              | 99 000                 | R263K INT 20.7%, K20T PR 99.7%, L32F PR 99.7%, N88D PR 99.9%, D30N PR 99.8%, K43T PR 99.7%, D67N PR 99.7%, T215S PR 99.7%, K219Q PR 99.7%, T69D PR 99.7%, Y181C PR 99.7%, Y188L PR 99.7%, H221Y PR 99.7% |

% refers to abundance by ultradepth sequencing for the last 2 time points.

Abbreviations: 3TC, lamivudine; ABC, abacavir; AMP, amprenavir; AZT, zidovudine; D4T, stavudine; DDC, zalcitabine; DDI, didanosine; DRV/RIT, darunavir/ritonavir; EFV, efavirenz; ETV, etravirine; FTC, emtricitabine; INT, integrase; MVC, maraviroc; NFV, nelfinavir; NGS, next-generation sequencing; NVP, nevirapine; OD, once a day; PI, protease inhibitor; RT, reverse transcriptase; TDF, tenofovir; TIP, tipranavir.
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