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Integrase resistance emergence with dolutegravir/lamivudine with prior HIV-1 suppression

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Background:

There are no reports of virological failure with emergence of integrase or reverse transcriptase resistance mutations in treatment-experienced individuals starting co-formulated dolutegravir/lamivudine with suppressed HIV-1 viraemia. This switch strategy has been studied in two large Phase III randomized trials (TANGO and SALSA) including 615 participants with follow-up of 1 and 3 years and many real-life series, with widespread use and no resistance selection reported to date.

Methods:

We report the first case of integrase resistance emergence in an individual who switched to co-formulated DTG/3TC started after a history of prolonged viral suppression.

Results:

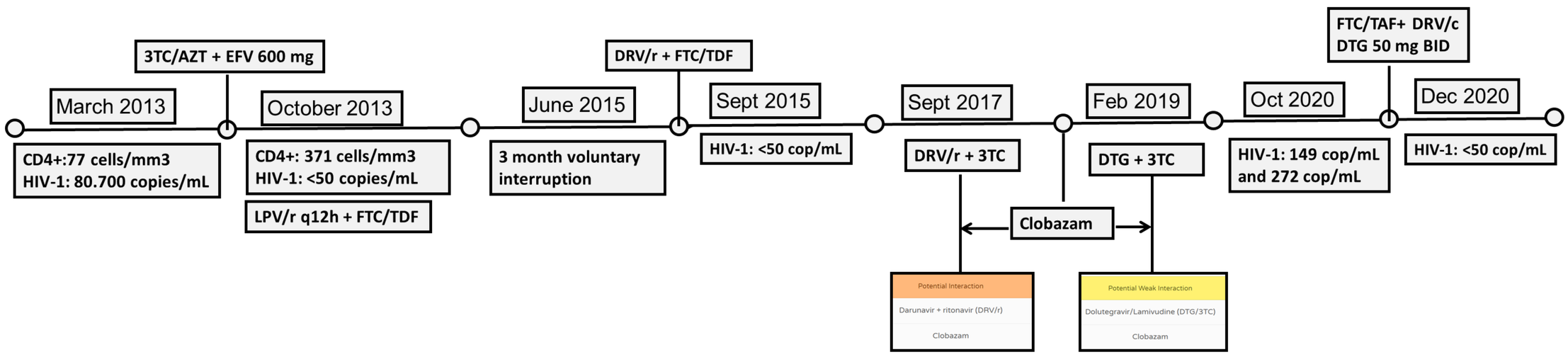
A 57-year-old man was diagnosed with advanced HIV-1 infection and multifocal leukoencephalopathy in 2013. Baseline laboratory results revealed an absolute CD4+ count of 77 cells/mm^3 and an HIV-1 RNA viral load (VL) of 80 700 copies/mL. ART with co-formulated lamivudine/zidovudine and efavirenz 600 mg was started without baseline HIV-1 genotyping. Seven months after ART initiation his CD4+ count increased to 371 cells/mm^3 and the HIV-1 VL was <50 copies/mL and remained so thereafter. The ART was subsequently switched to lopinavir/ritonavir q12h+emtricitabine/tenofovir disoproxil fumarate q24h. In 2015, after a 3 month voluntary interruption of ART, therapy was resumed with darunavir/ritonavir 800/100 mg+emtricitabine/tenofovir disoproxil fumarate, achieving re-suppression of the VL to <50 copies/mL, with sustained posterior control of viral replication. In March 2017 his ART was simplified to co-formulated once-daily darunavir/cobicistat+lamivudine, with equivalent efficacy and a better safety profile than the previous regimens.

In February 2019 the patient started anticonvulsant therapy with clobazam because of epilepsy. Therefore, his ART was switched to a co-formulated combination of the integrase inhibitor dolutegravir and lamivudine to avoid the pharmacokinetic interaction between PIs and clobazam, a drug primarily metabolized through CYP3A4 (major) and CYP2B6 and CYP2C19 (minor).

He had never been exposed to an integrase inhibitor and had maintained suppressed HIV-1 viraemia below 50 copies/mL for 4 years.

In October 2020, two consecutive monitoring HIV-1 VL tests revealed detectable HIV-1 levels (149 and 272 copies/mL, respectively). ART was immediately adjusted to co-formulated once-daily darunavir/cobicistat/emtricitabine/tenofovir alafenamide + twice-daily dolutegravir 50 mg and an HIV-1 genotypic resistance test was performed. Three months after this ART change, HIV-1 RNA was not detected (<50 copies/mL) and remained undetectable thereafter.

Clinical case, evolution of HIV-VL and TCD+ 4 cells ount



A plasma HIV-1 genotypic deep sequencing test (Vela System) performed at viral rebound revealed the emergence of **R263K (79.6%)** and **S230N (99.4%)** mutations in the integrase region, which confer intermediate resistance to dolutegravir (score= 30 Stanford HIVDB 9.0). Unfortunately, the reverse transcriptase and protease regions could not be amplified due to low VLs. Six months after the viral rebound (March 2021), we attempted proviral DNA genotyping from PBMCs using next-generation sequencing, which was unsuccessful due to the low HIV-1 DNA levels. A second attempt of PBMC DNA deep sequencing of the reverse transcriptase and integrase regions performed in October 2021 (Deep-Check HIV assay genotyping, ABL) revealed mutations in both the reverse transcriptase and integrase regions [**M184I (14.29%)** and **M230I (6.25%)**, conferring high-level resistance to lamivudine and low-level or intermediate resistance to all NNRTIs, and **G163R (9.77%)** and **S230N (98.8%)**, conferring lowlevel resistance to elvitegravir and raltegravir, respectively]. **R263K** was only found at extremely low levels (0.07%).

Discussion:

The efficacy and safety of co-formulated dolutegravir/lamivudine in switch were confirmed in two Phase III randomized clinical trials with 615 patients exposed to dolutegravir/lamivudine (TANGO and SALSA studies), with no cases of confirmed virological withdrawal or resistance emergence mutations reported at weeks 144 and 48, respectively. There are two cases reported of resistance selection with dolutegravir/lamivudine in treatment-naive individuals in clinical trials, with **M184V** (reverse transcriptase) and **R263R/K** (integrase) mutations selected in both of them. They received dolutegravir and lamivudine separately, poor treatment adherence was reported in both and selective nonadherence of one of the compounds was pointed out as the presumable cause of treatment failure and resistance selection. Our patient took his ART as a DOT in a nursing home and he received coformulated dolutegravir/lamivudine; therefore, it is unlikely that treatment non-adherence or selective non-adherence had a role in this case. He had been taking the anticonvulsant benzodiazepine **clobazam** for 16 months, which is extensively metabolized to N-desmethylclobazam by CYP3A4 and, to a lesser extent, CYP2B6 and CYP2C19. At clinically meaningful concentrations in vitro, neither clobazam nor N-desmethylclobazam have been found to significantly induce or inhibit CYP1A2, CYP2B6, CYP2C8, CYP2D6 or CYP3A4. At significantly greater concentrations than standard clinical dosing, clobazam demonstrated the potential to induce **uridine diphosphate glucuronosyltransferase (UGT) 1A1** and N-desmethylclobazam demonstrated inhibition of CYP2C9, UGT1A6 and CYP2B4. The current interpretation of the drug interaction between clobazam and dolutegravir in the University of Liverpool website is a potential weak interaction (yellow light). As such, additional actions, monitoring or a dosage adjustment are unlikely to be required. The reading is that co-administration has not been studied (very low level of evidence) and clobazam as a weak inducer of UGT1A1 could potentially decrease dolutegravir exposure, although to a limited extent. No interactions are expected with lamivudine. Likewise, the summary of product information of dolutegravir shows no reference to any potential drug interaction with clobazam or contraindication against its co-administration. This case urges a complete investigation of the potential drug– drug interaction between clobazam and dolutegravir. When our patient started co-formulated dolutegravir/lamivudine, he did not have any other comorbidity and was not taking comedications that could decrease dolutegravir/lamivudine absorption.

The key integrase mutation selected at virological failure, **R263K**, is a well-known non-polymorphic mutation that confers intermediate resistance to dolutegravir, the patient was never exposed to an integrase inhibitor, which makes it unlikely that this mutation was present previously. In subsequent proviral **DNA genotyping**, we identified the presence of **M184I** and **M230I**. However, both minority **M184I** and M230I mutations are significantly associated with APOBEC3G/F host restriction factor activity. **M184I** is a transition to **M184V**, which makes it very unlikely that this mutation would be detected for this long period of time following any unnoticed prior virological failure.

This case demonstrates that integrase resistance selection can emerge in individuals treated with co-formulated dolutegravir/lamivudine with no known risk factors for resistance selection. The data available on this case do not allow us to confirm the role of a potential drug–drug interaction between dolutegravir and clobazam as the cause of virological failure. However, our findings raise awareness of the need to carefully consider and monitor drug–drug interactions, even when regarded as having a low potential, in subjects treated with dolutegravir/lamivudine despite the absence of risk factors for resistance selection.

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