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Chapter 3

Multi-nucleoside reverse transcriptase inhibitor resistant HIV type-1 in a patient from Sierra Leone failing stavudine, lamivudine and nevirapine

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ABSTRACT

We report a 33-year-old HIV type-1 (HIV-1)-infected male from Sierra Leone who harboured extensive drug resistance mutations to all nucleoside reverse transcriptase inhibitors (NRTIs) and non-NRTIs, including the multi-NRTI-resistance Q151M complex, K65R, M184I and Y181I, after using standard first-line generic fixed-dose stavudine, lamivudine and nevirapine (Triomune™) for 36 months. In the context of non-B subtypes in resource-limited countries, first-line stavudine-containing regimens have been associated with more extensive and complex mutation patterns, compared with subtype B viruses. Whether the extensive and complex NRTI resistance patterns found among African patients failing first-line antiretroviral therapy is explained by viral genetic diversity or by different patient monitoring strategies remains to be elucidated. Emerging multi-NRTI resistance in sub-Saharan Africa would not only compromise second-line treatment options and the success of antiretroviral rollout, but could also contribute to the spread of drug-resistant variants worldwide.

INTRODUCTION

Expanded access to combination antiretroviral therapy (ART) for HIV type-1 (HIV-1)-infected individuals in sub-Saharan Africa during the past decade [1] has resulted in significant reductions of HIV-1-related morbidity and mortality [2–4]. In resource-limited countries, ART is generally delivered using a public health approach developed by the World Health Organization, which is based on decentralized service delivery, standardized treatment regimens and simplified treatment monitoring [5]. Absence of routine virological monitoring, as is often the reality in poorly resourced settings, might lead to late detection of therapy failure and, consequently, to the continuation of failing regimens after initial virological breakthrough, allowing for accumulation of drug resistance-associated mutations [6]. Moreover, the extensive genetic viral diversity in HIV-1 subtypes and circulating recombinant forms (CRFs) that are present in sub-Saharan Africa have been reported to influence mutational pathways to drug resistance [7], which might have an effect on therapy effectiveness.

CASE PRESENTATION

A 33-year-old HIV-1-infected male from Sierra Leone presented at the outpatient department of the Onze Lieve Vrouwe Gasthuis (OLVG) general hospital (Amsterdam, the Netherlands) with symptoms of nausea, weight loss and painful dark-coloured skin lesions on the foot soles. In Sierra Leone, he had used generic fixed-dose stavudine, lamivudine and nevirapine (Triomune™; Cipla), which is still the most commonly used first-line ART regimen in many sub-Saharan African countries, for 36 months with allegedly good adherence. Recent sputum analysis in Sierra Leone had demonstrated the presence of acid-fast bacilli, suggestive of pulmonary tuberculosis, for which he had used rifampin, isoniazide, pyrazinamide and ethambutol during the past 6 weeks. He presented at the OLVG general hospital during a family visit to the Netherlands and was admitted to the infectious diseases inpatient department for further diagnostic evaluation and treatment. Initial laboratory investigations revealed a low CD4+ T-cell count of 40 cells/μl (pretreatment nadir not documented) and detectable plasma HIV-1 RNA (13,730 copies/ml), indicating treatment failure. Skin biopsy of the foot lesions demonstrated Kaposi's sarcoma. Standard genotypic analysis of the *pol* region was performed using the ViroSeq HIV-1 Genotyping System (Abbott Laboratories, Abbott Park, IL, USA). Detected drug resistance-associated mutations included K65R, V75I, F116Y, Q151M, M184I and Y181I in reverse transcriptase, and multiple resistance-related natural polymorphisms but no major drug resistance-associated mutations in protease. The Y181I mutation confers high-level cross-resistance to all non-nucleoside reverse transcriptase inhibitors (NNRTIs) [8].

HIV-1 variants harbouring Q151M with accompanying mutations V75I and F116Y, known as the multi-nucleoside reverse transcriptase inhibitor (NRTI) resistance Q151M complex, and the K65R resistance mutation, confer extensive cross-resistance to all NRTIs [8]. Phylogenetic analysis using the neighbor-joining method indicated that the sequence belonged to viral clade CRF02_AG. Based on these findings, the antiretroviral regimen was switched to darunavir 600 mg twice daily, ritonavir 100 mg twice daily, raltegravir 400 mg twice daily and enfuvirtide 90 mg twice daily. Because of a subsequent flare of chronic hepatitis B infection (hepatitis B surface antigen-positive, hepatitis B e antigen-negative and HBV DNA 963 IU/ml), possibly related to the withdrawal of lamivudine, tenofovir disoproxil fumarate 245 mg once daily was added to the regimen. *Mycoplasma fortuitum* was cultured in sputum, at which point the tuberculostatic drugs were withdrawn and antibiotic treatment with cotrimoxazole and ofloxacine was initiated. In the course of the following months, the patient showed gradual clinical improvement, with immune restoration, weight gain, regression of Kaposi's sarcoma and complete viral suppression, after which time the ART regimen was simplified.

DISCUSSION

This HIV-1-infected patient from Sierra Leone presented with extensive resistance to all NRTIs after using only a single ART regimen for 3 years. In HIV-1 subtype B viruses, the selection of drug-resistant variants during treatment with stavudine-containing regimens is rather limited. Stavudine usually selects for thymidine analogue mutations (TAMs). Accumulation of ≥2 TAMs is associated with broad NRTI cross-resistance [9, 10]. TAM selection might be reduced or delayed by combination treatments with lamivudine or emtricitabine selecting for the M184V mutation [11]. Q151M usually requires a relatively lengthy period of time to emerge under therapy and has been observed in <5% of HIV-1-infected European patients on long-term NRTI-based ART [12]. K65R and TAMs represent antagonistic pathways of NRTI resistance [13], and K65R is found at low rates among viruses from subtype-B-infected individuals in genotypic databases [14].

In the context of non-B subtypes in resource-limited countries, however, first-line stavudine-containing regimens have been associated with more extensive, less predictable and more complex mutation patterns. Several recent studies in subtype-C-infected patients who experienced treatment failure have reported considerable rates of NRTI mutations including K65R [15–19] and Q151M [16, 18]. Notably, a recent study reported the presence of extensive NRTI resistance in a subtype-C-infected Malawian cohort after clinical or immunological failure on fixed-dose stavudine, lamivudine and nevirapine, with 56% TAMs, 23% K70E or K65R, 19% Q151M and 16% Q151M associated with either

K65R or K70E [16]. It was recently suggested that the presence of two subtype-C-specific nucleotide polymorphisms at positions 64 and 65 in reverse transcriptase could favour the selection of K65R [20]. In patients infected with CRF02_AG who fail stavudine-containing regimens, the multi-NRTI resistance Q151M complex has been anecdotally reported [21], and has been associated with K65R [15]. Additional studies are warranted to establish whether certain NRTI resistance mutations (particularly K65R and/or Q151M) are preferentially selected in the various non-B subtypes.

Currently, there is no robust evidence that the possible added survival benefit of routine viral load monitoring in resource-limited settings is cost-effective. A recent review demonstrated, however, that genotypic resistance to lamivudine, NRTIs (TAMs), and NNRTIs appeared substantially higher in less frequently virologically monitored patients who experienced treatment failure, compared with frequently monitored patients [6]; therefore, the potential long-term impact of inadequately guided treatment changes on resistance, subsequent treatment outcomes and the spread of resistance among the wider population should receive more attention.

Given that ART is a lifelong intervention and that roll-out programmes in sub-Saharan African countries mature, increasing numbers of patients are expected to fail their first-line regimens, requiring switch to second-line regimens [22]. Current standard second-line regimens, if available, combine a ritonavir-boosted protease inhibitor (bPI) with two previously unused and/or recycled NRTIs [5]. Once multi-NRTI resistance has occurred, standard second-line regimens will primarily offer the benefit of the bPI, with limited or no additional effect of the NRTI backbone. Data available to date suggest that mono-bPI therapy might be clinically successful, but the selection of resistance to bPIs in PI-naive individuals has been reported after such therapy [23–25].

In conclusion, further research is warranted to elucidate whether the extensive and complex NRTI resistance patterns found among African patients failing first-line ART is explained by viral genetic diversity or different patient monitoring strategies. Emerging multi-NRTI-resistance in sub-Saharan Africa would not only compromise second-line treatment options and the success of antiretroviral rollout, but could also contribute to the spread of drug-resistant variants worldwide. Strategies should be directed at minimizing accumulation of drug resistance by developing cost-effective laboratory monitoring strategies, phasing out the use of stavudine, and enhancing access to simple and robust second-line options with non-overlapping drug resistance profiles.

Contributors

RLH, MSA and JPHF were involved in the clinical management of the patient and conceived the idea for this report. NKTB performed the genotypic resistance test. RLH wrote the first draft of the manuscript. AMJW and JPHF revised it critically for important intellectual content. All authors contributed to subsequent drafts and reviewed and approved the final manuscript.

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