Baseline-transmitted V106V/I/M non-nucleoside reverse transcriptase inhibitor resistance in HIV-1 subtype B infection

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SUMMARY

We report a case in which an antiretroviral therapy (ART)-naïve patient diagnosed with HIV-1 subtype B presented with baseline genotype and phenotype resistance tests, confirming a V106V/I/M nucleoside resistance mutation. The V106V/I/M mutation represents a mixture of virus strains conferring resistance to the non-nucleoside reverse transcriptase inhibitor antiretrovirals efavirenz and nevirapine. V106M mutation is not often observed as a primary resistance mutation in patients infected with HIV-1 subtype B. The patient responded well to an ART regimen consisting of tenofovir–emtricitabine and raltegravir, achieving and maintaining an undetectable HIV RNA.

BACKGROUND

Transmitted, or primary, drug resistance in HIV is well documented: the estimated prevalence is 6–16% in the USA and Europe.¹ Transmission of drug-resistant HIV can limit first-line treatment options for newly infected individuals and can substantially decrease the effectiveness of subsequent antiretroviral therapy (ART).^{2–5} US Department of Health and Human Services and International Antiviral Society-USA HIV treatment guidelines recommend genotypic testing in antiretroviral-naïve patients to detect the presence of transmitted drug resistance and to inform selection of treatment strategies.^{1 6}

Resistance mutations result from specific amino acid substitutions in the viral genome that cause changes in protein sequence, structure and function. Mutations are named after the wild-type amino acid, the position in the sequence of the gene of interest and the substituted amino acid. The V106M mutation refers to the amino acid at sequence position 106 of the reverse transcriptase gene when wild-type valine is substituted by methionine. In addition, a mixture of virus strains may occur, where each strain carries a different mutation at a single position. The V106V/I/M mutation mixture denotes strains with either wild-type valine or isoleucine or methionine at amino acid position 106 of the reverse transcriptase gene. Mutations imparting viral resistance are specified by the consensus mutation figures of the International Antiviral Society-USA.⁷ Here, we present an uncommon case of a newly diagnosed, treatment-naïve, HIV-1 subtype B-infected patient presenting with V106V/I/M baseline-transmitted resistance.

CASE PRESENTATION

A 31-year-old Latino man who has sex with men entered into care at our primary care HIV clinic following a 3-day hospital admission where he was newly diagnosed with HIV infection. The patient presented to the hospital with dysphagia, diarrhoea, shortness of breath and weight loss of 50 pounds over 1 year. Given his clinical presentation and sexual risk factor, an HIV test was performed and the patient was diagnosed with HIV/AIDS while admitted. At the time of diagnosis, the patient's CD4 count by flow cytometry was 10 cells/mm³ and his HIV RNA by real-time PCR was 57 000 copies/ml. The patient was born in Cuba and immigrated to the USA at 7 years of age. The patient did not know when he was infected with HIV, stating his last sexual encounter occurred 1 year prior. Following hospital discharge, at the time of presentation to our clinic, the patient denied prior use of antiretroviral medications.

INVESTIGATIONS

A baseline combination genotype and phenotype resistance test conducted in the hospital at the time of HIV/AIDS diagnosis discerned a V106V/I/M mutation mixture, resistant to efavirenz and nevirapine, and determined that the patient was infected with HIV-1 subtype B (lower limit 10% minority mixtures, PhenoSense GT, Monogram Biosciences, South San Francisco, California, USA). A second genotype resistance test was performed at our clinic prior to the initiation of ART and confirmed a V106V/I/M mutation mixture of the reverse transcriptase gene (lower limit 20% minority mixtures, ViroSeq HIV-1 Genotyping System, ARUP, Salt Lake City, Utah, USA). Sound sample handling with accurate results is assumed for both assays based on proper collection technique by trained phlebotomists and the patient's HIV RNA cut-off high enough to amplify for result reporting.

Hepatitis B serologies were also performed at the clinic, as is standard of care.¹ Results revealed negative hepatitis B surface antigen, negative hepatitis B core antibody and a quantitative hepatitis B surface antibody less than 1.0 ml Units/ml. The patient was found to be uninfected with hepatitis B and susceptible, requiring vaccination.

TREATMENT

Initiation of ART was withheld during the 3-day hospital course because the turn-around-time for resistance assays typically ranges from 1 to 4 weeks, depending on the assay used. Therefore, ART initiation for newly diagnosed individuals is frequently

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reserved for the outpatient setting for short-course hospital admissions. At the time of presentation to our clinic, resistance test results were available and the patient was promptly initiated on an ART regimen consisting of tenofovir–emtricitabine 300–200 mg orally once daily and raltegravir 400 mg orally twice daily. An ART regimen containing a first-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz or nevirapine, was avoided owing to the patient's transmitted resistance to this drug class. The patient also completed a series of three hepatitis B vaccinations.

OUTCOME AND FOLLOW-UP

Administration of tenofovir–emtricitabine and raltegravir led to a rapid decline in HIV viral load to undetectable (below 48 copies/ml) after 4 weeks. The patient continues to maintain an undetectable HIV RNA (below 20 copies/ml) and, at 10 months of therapy, his CD4 count is 242 cells/mm³.

DISCUSSION

Resistance mutations in HIV, including primary resistance mutations, are common and can negatively affect response to ART. Identified primary resistance mutations, along with patient-specific factors, guide initial ART selection and thus improve patient response to therapy. The frequency of transmitted resistance mutations can vary by HIV subtype.

HIV-1 Group M is the predominant HIV-1 group worldwide, and is divided into subtypes, denoted with letters and sub-subtypes denoted with numerals. HIV-1 subtypes (A, B, C, D, E, F, H, J and K), also called clades, are genetically related HIV-1 strains. Subtype B is most common in the Americas, Western Europe and Australia whereas subtype C is concentrated in Eastern and Southern Africa, and India.^{8–9} The spectrum of mutations at some drug-resistance positions differs among subtypes. For example, the reverse transcriptase mutation V106M, which rarely occurs in subtype B isolates after NNRTI exposure, is one of the most common mutations responsible for NNRTI resistance in subtype C isolates.^{2–8–10}

Most cases of primary resistance affect NNRTIs or nucleoside reverse transcriptase inhibitors.^{5–11} The V106M mutation, which confers resistance to the NNRTIs nevirapine and efavirenz, is most often seen in patients with non-subtype B strains after previous exposure to efavirenz. Primary resistance with the V106M mutation is rare in patients with HIV-1 subtype B infection.^{2–3}

We report a case of a patient infected with HIV-1 and baseline transmitted resistance to first-generation NNRTIs. The case is unique in that the atypical resistance-associated mutation V106M conferred resistance at baseline in this patient infected with subtype B virus. The V106M mutation was confirmed on two different resistance tests collected at separate times. ART was withheld at the time of diagnosis in the hospital owing to lag time in receiving genotypic and phenotypic results of

resistance assays. The importance of baseline resistance testing to guide initial ART selection is emphasised.

To maximise the effectiveness of ART, resistance mutation testing with genotype is recommended at baseline regardless of whether treatment will be initiated immediately. Although obtaining resistance test results may take several weeks, the identification of primary mutations, including rare mutations, can prevent selection of contraindicated medications as part of initial therapy. Appropriate resistance profiling can decrease the incidence of initial, as well as subsequent, treatment failure.

Learning points

- ▶ Transmission of drug-resistant HIV strains is common.
- ▶ Baseline HIV genotype resistance testing is essential in USA and European populations to inform selection of initial antiretroviral therapy.
- ▶ Rare primary resistance mutations may confer uncommon resistance patterns.

Competing interests None.

Patient consent Obtained.

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