Case report

Effect of tenofovir subtraction on HIV plasma viraemia, CD4+ T-cell count and resistance in a patient with baseline K65R and M184V mutations

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In vitro, the reverse transcriptase mutation K65R can simultaneously reduce drug susceptibility, replicative capacity and restrict HIV-1 replication. Here, we assessed the effect of tenofovir discontinuation for a patient receiving antiretroviral therapy whose HIV-1 had a dominant K65R/M184V genotype. Although limited by the single-case nature, the data support a hypothesis that there is no HIV viral RNA or CD4+ T-cell count benefit of taking tenofovir for experienced patients with genotypic evidence of K65R/M184V.

Single point-mutations in reverse transcriptase (RT) such as K65R and M184V can simultaneously reduce HIV susceptibility to nucleoside reverse transcriptase inhibitors (NRTIs) and restrict viral replication in vitro [1–6]. These mutations reduce replicative capacity of HIV-1 in vitro, but have opposing phenotypic effects on resistance to tenofovir [7], leading to debate on the clinical utility of tenofovir against HIV with these mutations. We examined the effect of discontinuing tenofovir in a patient with a K65R/M184V genotype.

The patient, a 31 year old HIV-1-infected, homosexual male, was diagnosed in 1998 (hepatitis C negative) and had received zidovudine/lamivudine/nelfinavir, stavudine/lamivudine/efavirenz, didanosine/lamivudine/nevirapine and abacavir/tenofovir/ stavudine/lamivudine during which his CD4+ T-cell count fluctuated between 251–695 cells/mm³ and his HIV RNA was between 3.7–4.8 log₁₀ copies/ml. The mutations K65R, M184V and K103N were detected after dual NRTI therapy initiation and remained constant in two subsequent annual genotypes. The patient requested a therapy interruption, but elected to discontinue tenofovir for a 24-week period. He provided written informed consent (concomitant with institutional review board approval).

Monthly monitoring of laboratory values and viral evolution was performed. The patient’s CD4+ T-cell count was 317 cells/mm³ at tenofovir discontinuation/baseline and 408 cells/mm³ after 24 weeks and ranged between 216–408 cells/mm³ (Figure 1). The patient’s HIV RNA was 4.76 log₁₀ copies/ml at baseline and 4.75 log₁₀ copies/ml at week 24 with little interim variation. Population genotyping and phenotypic analyses (performed by Monogram BioSciences, San Francisco, CA, USA) indicated that K65R, M184V and a K103K/N mixture were maintained through to week 24 and were associated with decreased susceptibility to abacavir, tenofovir, lamivudine and emtricitabine along with increased susceptibility to zidovudine.

HIV samples from screening (4 weeks prior to baseline) through 24 weeks were examined using high-throughput clonal analysis by 454 Life Sciences (Branford, CT, USA). Between 32,796 and 309,433 clones/samples were analyzed (median 34,264) in a PCR-amplified region encoding (RT) amino acids 56–80. K65R was observed in the majority of clones and the percentages of K65R and D67N remained fairly constant throughout tenofovir discontinuation (92.4% and 1.1% at baseline, and 88.53% and 0.9% at week 24, respectively; Figure 1). S68G, previously reported as selected in patients rebounding on tenofovir or other NRTI-containing therapy along with K65R, was detected with a 91% baseline prevalence (90.2% at week 24) [8,9]. L74V was detected in 4.9% of screening clones, but only detected in one sample after tenofovir discontinuation (week 8 [0.03%]). Replicative capacity varied from 37%–117% with no obvious correlation to HIV RNA or genotype.
In summary, the tenofovir component of this antiviral-experienced patient’s regimen was not providing any virological or CD4+ T-cell count advantage over lamivudine monotherapy. Notably, reduced susceptibility to tenofovir persisted through the 24-week period despite the withdrawal of tenofovir from the regimen. No changes in other RT regions (for example, M184V) were detected over the observation period, but the ability to evaluate genotypic changes outside of RT amino acids 56–80 was limited to population sequencing. Although limited by the single-case nature, these results support a hypothesis that there is no additional HIV RNA or CD4+ T-cell count benefit of taking tenofovir for experienced patients with genotypic evidence of K65R/S68G/M184V.

Disclosure statement

RH submitted this study as a research proposal that received research funding from GlaxoSmithKline. ERL, ER, KO and LLR were employed by GlaxoSmithKline at the time of the analysis.

References
