

POSTER PRESENTATION

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Toxic intracellular anabolite levels of tenofovir and didanosine causing a steep CD4-cell decline

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Introduction

HIV-protease inhibitors may increase tenofovir plasma AUC by 22-37%. Whether this affects tenofovir-diphosphate (TFV-DP) intracellular levels, especially in the presence of didanosine, which is also eliminated through active tubular secretion, is unclear.

Case report

A 52-year-old HIV-1 positive Caucasian male started zidovudine (AZT), lamivudine, nelfinavir in 1999 at a CD4-cell count of 210/ μ L. In July 2007 treatment was switched because of viral blips to atazanavir, ritonavir, tenofovir, emtricitabine and didanosine (250 mg). Within one year his CD4-cell count declined from 1140 to 140/ μ L despite complete virological suppression [1]. Renal clearance (Cockcroft-Gault) decreased from 86 to 74 mL/min and renal phosphate threshold to 0.24 mmol/L (n=0.8-1.35), indicative of proximal tubular dysfunction. There was 8 kg weight loss, his serum glucose and lactate were elevated.

In addition, following the ART-switch a thrombocytosis (1355×10^9 /L) was noticed. After exclusion of other causes, essential thrombocythemia was diagnosed and hydroxyurea started. Thrombocytes were elevated before initiation of ART (427×10^9 /L) and before therapy switch (659×10^9 /L), suggesting AZT-related bone marrow suppression may have prevented a further increase in platelet count in the preceding years.

Suspecting NRTI-related mitochondrial and tubular dysfunction, we measured intracellular ddA-TP (didanosine) and TFV-DP (tenofovir) in PBMCs [2]. TFV-DP was 10xULN ($1350 \text{ fmol}/10^6$ cells) and ddA-TP 21xULN ($105 \text{ fmol}/10^6$ cells). Hydroxyurea may have increased ddA-TP levels, but was used for only 2 weeks. ART was

changed to AZT, lamivudine, atazanavir, ritonavir, raltegravir. Two weeks later TFV-DP was still $250 \text{ fmol}/10^6$ cells, demonstrating an intracellular $t_{1/2}$ of approximately 140 hrs and ddA-TP $57.4 \text{ fmol}/10^6$ cells, $t_{1/2}$ 385 hrs, but didanosine and tenofovir plasma levels were undetectable. After switch his CD4-cell count increased again from 140 to $340/\mu$ L and his platelet count decreased to 725×10^9 /L following re-initiation of AZT.

Conclusions

Elevated TFV-DP and ddA-TP led to tubular dysfunction and mitochondrial toxicity. Inhibition of purine-nucleoside-phosphorylase by TFV-DP and DNA-polymerase- γ by ddA-TP may have caused the steep CD4-cell decline. We believe interactions between tenofovir, didanosine and atazanavir/ritonavir were responsible for this toxicity.

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