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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/μL. 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/μL despite complete virological suppression [1]. Renal clearance (Cockgroft-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 (1355x10^9/L) was noticed. After exclusion of other causes, essential thrombocythemia was diagnosed and hydroxyurea started. Thrombocytes were elevated before initiation of ART (427x10^9/L) and before therapy switch (659x10^9/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 fmol/10^6 cells) and ddA-TP 21xULN (105 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 fmol/10^6 cells, demonstrating an intracellular t½ of approximately 140 hrs and ddA-TP 57.4 fmol/10^6cells, t½ 385 hrs, but didanosine and tenofovir plasma levels were undetectable. After switch his CD4-cell count increased again from 140 to 340/μL and his platelet count decreased to 725x10^9/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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References

1. Negredo E, Molto J, Burger D, Viciana P, Ribera E, Clotet B, *et al*: **Unexpected CD4 cell count decline in patients receiving didanosine and tenofovir-based regimens despite undetectable viral load.** *AIDS* 2004, **18**:459-463.
2. Pruvost A, Negredo E, Benech H, Theodoro F, Puig J, Grau E, *et al*: **Measurement of intracellular didanosine and tenofovir phosphorylated metabolites and possible interaction of the two drugs in human immunodeficiency virus-infected patients.** *Antimicrob Agents Chemother* 2005, **49**:1907-1914.

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