

Case Report

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Stable Virologic Suppression during Raltegravir plus Atazanavir Dual-Therapy Taken Every other Day: A Case Report

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Abstract

Adherence to Highly Active Antiretroviral Therapy can be affected by a number of factors limiting the outcome of the treatment. We report the case of a 39 year-old HIV-HCV co-infected woman in stable virologic suppression and immune recovery during a raltegravir plus unboosted atazanavir dual-therapy taken every other day. Measurement of HIV-1 RNA plasma levels (viral load), CD4+ T-cell counts and the therapeutic drug monitoring through validated high-performance liquid chromatography methods, were performed to assess the effectiveness of this regimen. Our data on raltegravir pharmacokinetics in association with atazanavir show adequate minimum effective concentrations of raltegravir throughout 36 and 48 hours despite the every other day intake of the drug. Further studies are recommended in order to identify the determinants that could enable a reduction in antiretroviral dosing frequency in case of difficult management of HIV-infected patients due to low adherence to therapy. By reporting our medical experience, we focused on the utility of performing therapeutic drug monitoring especially in cases of poor adherence, drug and/or alcohol abuse, co morbidities and co-administration of other drugs.

Keywords: HAART; Raltegravir; Therapeutic drug monitoring; HIV/HCV co-infection; Adherence

Introduction

Adherence to Highly Active Antiretroviral Therapy (HAART) is still a concern in treating HIV-infected patients. Age, lifestyle, job, adverse events, resource-limited settings, alcohol and drug abuse are only some of the factors that could affect patients adherence to therapy [1]. Mannheimer et al. reported that after eight months of therapy only 60% of patients had a 100% adherence [2]. In another study, more than 35% of patients experienced discontinuation or interruption of first HAART within 11 months from therapy starting, mainly because of the persistence of side effects and the complexity of therapeutic schemes [3]. Recently, a study aimed to identify the predictors of self-chosen HAART interruptions in a cohort of 296 HIV-infected people taking HAART was performed. Authors observed that 23% of the patients self-reported suboptimal adherence, 45% reported of having asked their physician to interrupt the current regimen and 25% reported at least one interruption of a minimum of 1 day of any of the drugs included in the regimen [4]. Low adherence may lead to sub-optimal exposure to antiretrovirals (ARVs), selection of resistances to them and, finally, to treatment failure. Although the number of new drugs available is constantly increasing, cross-resistance among drugs of the same class restricts clinical options after a treatment failure. Therefore, maintaining successful virological outcomes even in case of poor treatment adherence appears to be a challenging problem to address [5]. Furthermore, individual characteristics or comorbidities and drug-drug/drug-food interactions could alter the absorption, distribution, metabolism, and elimination of drugs, determining variable plasma concentrations and influencing the outcome of therapy [6]. Therapeutic Drug Monitoring (TDM), could be feasible to optimize the therapy through dosage adjustment tailored to patient specific pharmacokinetic (PK) and pharmacodynamic parameters [7,8].

The present paper describes a case of stable virologic suppression during an unusual antiretroviral regimen, whose effectiveness was assessed by performing HIV-1 RNA viral load, CD4+ T-cell counts and TDM.

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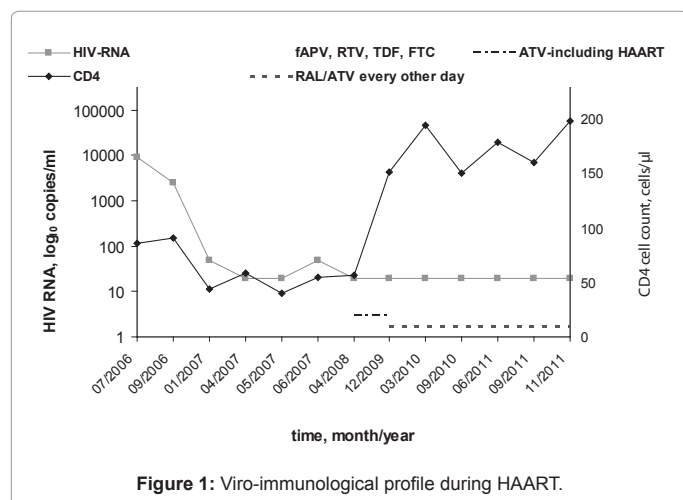
We report the case of a 39 year- old HIV-HCV co-infected Caucasian woman in stable virologic suppression during a raltegravir (RAL) plus unboosted atazanavir (ATV) dual-therapy taken every other day. Her medical history was significant for abuse of alcohol, inhaling cocaine, HCV-related cirrhosis (CHILD-Pugh score: 8, Class B), polycystic ovarian disease, obesity and depression. HIV infection (CDC stage B3) was diagnosed in 1998, and in 2006, a boosted fosamprenavir plus emtricitabine/tenofovir-including HAART was initiated. From the very beginning the patient showed poor adherence to therapy due to intolerance to anti retrovirals (ARVs). After several therapeutic switches, RAL 400 mg BID plus ATV 300 mg QD dual-therapy was proposed. According to recent studies, RAL plus un boosted ATV dual-therapy showed a favourable safety and tolerability profile [9,10]. The patient referred general well-being after self-reduction of the therapy to every other day. As illustrated in Figure 1, the patient's HIV-1 RNA reached undetectable within one year of initiating FPV/RTV/FTC/TDF and despite erratic adherence. However, the CD4+ T-cell count remained below 100 cells/ μ l despite the virologic suppression. Upon the addition of ATV, CD4+ T-cell count significantly increased and remained above 150 cells/ μ l (>22%) after starting RAL/ATV dual-therapy. HIV-1 RNA remained undetectable on the RAL/ATV regimen. In addition to the measurement of HIV-1 RNA viral load and CD4+ T-cell counts, TDM was used to confirm that patient achieved detectable and sufficient levels of both RAL and ATV to maintain virologic suppression and

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	Concentration, ng/mL				
	C _{min}	C _{max}	C _{12h}	C _{24h}	C _{36h}
ATV	98	1594	853	176	104
RAL	<20	3696	1081 ^a 1148 ^b	Not done	768

ATV: atazanavir; RAL: raltegravir; C_{min}: drug concentration after a 48 hour wash-out period; C_{max}: drug concentration 2 hours after intake; C_{12h}, C_{24h}, C_{36h}: 12, 24 and 36 hours postdose trough concentration; ^a at 20:00, ^b at 08:00.

Table 1: Concentrations of ATV and RAL during multiple blood sampling throughout a 36 hour period.

immunologic recovery despite a less than ideal dosing regimen. Hence, we performed multiple bloods sampling throughout a 36-hour post-dosing period. RAL/ATV plasma concentrations were determined by validated high-performance liquid chromatography methods [11]. Primary PK parameters were: minimum plasma concentration after a 48 hour wash-out period from HAART (C_{min}); maximum plasma concentrations after two hours from ARVs administration (C_{max}); 12, 24 and 36 hours post-dose trough concentration (C_{trough}) for ATV; 12 and 36 hours post-dose C_{trough} for RAL (Table 1). No other drugs except for ARVs and opiate replacement therapy with 2 mg buprenorphine daily were administered. ATV C₃₆ was slightly under the minimum recommended level (>150 ng/mL), while RAL C₃₆ was still detectable and far above the median C_{trough} obtained from clinical trials and international guidelines (Figure 2) [12-14].

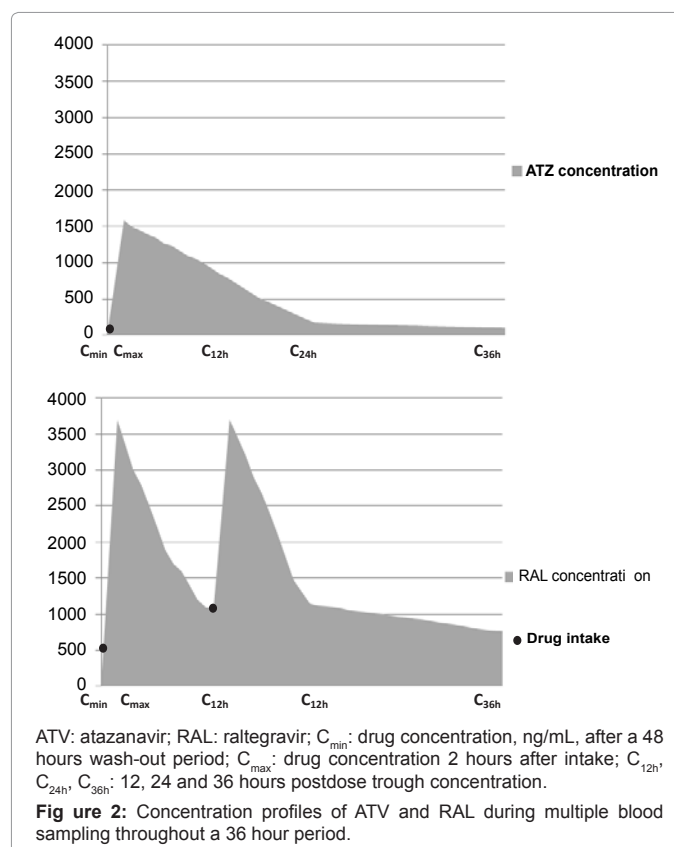
Discussion

RAL metabolism depends on glucuronidation mediated by the uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1) isoenzyme, which is strongly inhibited by ATV. Several studies demonstrated that through this well-known inhibitory effect on UGT1A1, ATV increases the plasma concentration of RAL [15,16]. The increment in RAL area under the curve (AUC) induced by co-administration of unboosted ATV is estimated to be of 72% [12]. Conversely, the effect of RAL on ATV PK is not likely to be clinically meaningful [14]. These data on RAL PK in association with ATV appear to be consistent with our case. In fact, adequate minimum effective concentrations of RAL throughout 36 and 48 hours have been observed, despite every other day intake of the drug. However, these findings contrast with a recent study aimed to compare a standard twice daily RAL 400 mg regimen with a once daily RAL 400 mg plus ATV 400 mg in healthy volunteers [13]. The authors found that the degree of RAL boosting in plasma by ATV was insufficient to ensure that RAL

400 mg once daily would result in concentrations at least similar to those with current standard dosing. Nonetheless, it should be taken into consideration that the study was conducted on healthy volunteers and that no intracellular drug measurement was performed, while *in vitro* studies demonstrated a persistent binding of the drug to its intracellular target, which could enable a decrease in dosing frequency despite low plasma drug concentrations [17].

ATV is a protease inhibitor metabolized by the cytochrome P450 system [18]. A possible effect of substance use and hepatitis virus co-infection on ATV PK has been analyzed in previous studies, finding limited impact of these factors on plasma ATV trough levels [19,20]. However, several co-factors associated with variation in ATV concentrations have been indentified, including concurrent methadone use, cigarette smoking, and substance use status [21]. Our case suggests that, as with other protease inhibitors, careful monitoring of potential drug-drug and drug-disease interactions in clinical practice is necessary. In particular, concurrent hepatitis could modify ATV concentrations by altering the hepatic metabolism of the drug.

Co-administration of buprenorphine with unboosted ATV has been shown to enhance buprenorphine AUC. In addition, this synthetic opioid has been associated with a possible reduction in ATV concentration, which could explain the low ATV C₃₆ detected in our case. Although buprenorphine should not be administered with unboosted ATV, our patient refused all other opioid replacement treatments [12]. Failure to effectively treat opioid dependence is associated with poor treatment outcomes among patients with HIV-HCV co-infection. Trying to stop buprenorphine can increase the risk of relapse and painful withdrawal symptoms [22]. For these reasons we decided not to stop the opioid replacement therapy in this case.



ATV: atazanavir; RAL: raltegravir; C_{min}: drug concentration, ng/mL, after a 48 hours wash-out period; C_{max}: drug concentration 2 hours after intake; C_{12h}, C_{24h}, C_{36h}: 12, 24 and 36 hours postdose trough concentration.

Figure 2: Concentration profiles of ATV and RAL during multiple blood sampling throughout a 36 hour period.

Liver impairment has been showed to enhance plasma concentration of several drugs. A recent study observed a higher RAL C_{trough} among 5 HIV-HCV co-infected patients with moderate-severe hepatic disease, compared to healthy controls [23]. These data suggest the necessity for assessing ARVs plasma concentrations in individuals with impaired liver function.

Our patient showed a limited immune recovery following HAART initiation: despite the persistent virological suppression below 40 HIV-1 RNA cp/ml, a CD4+ T-cells nadir of 40 cells/ μ l (10.1%) was reached one year after starting treatment. However, at month 6 after ATV introduction, CD4+ T-cells count doubled its value up to 120 cells/ μ l (24%) and after starting RAL/ATV dual-therapy, continued growing steadily, reaching the highest value (198 CD4+ T-cells/ μ l, 29.7%) in the last assessment. It is still under debate if HIV/HCV co-infection is associated with impaired CD4+ T cell recovery [24]. Recently, increased rates of CD4+ T-cell apoptosis in HCV-infected HIV-positive patients have been identified as a potential mechanism for enhanced mortality in patients with HIV/HCV co-infection. This may be related to a synergistic mechanism between the up-regulation of Fas expression on CD4+ T-cells observed in co-infected patients, and HIV-induced elevated levels of cellular and soluble Fas [25].

Conclusion

The present paper reports the clinical utility of performing TDM in a patient with poor adherence, history of drug and alcohol abuse, multiple co-morbidities and concurrent medications. Furthermore, a stable virologic control and immune recovery during RAL/ATV dual-therapy taken every other day has been observed in the case described. Further studies are recommended in order to identify the factors that could enable a reduction in ARV dosing frequency in case of difficult management of HIV-infected patients due to low adherence to therapy.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interest

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the manuscript. EG was involved in drafting the manuscript and reviewing the literature. PDN, AC and AO were responsible for the primary management of the patient and helped to draft the manuscript. MT and NT performed therapeutic drug monitoring. RB and CT provided the figures and helped to draft the manuscript. PN revised the final manuscript and EN has given the final approval of the version to be published. All authors have read and approved the final manuscript.

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