Virological response to unboosted atazanavir in combination with tenofovir and lamivudine in HIV-1-infected patients who had achieved virological suppression: a therapeutic drug monitoring and pharmacogenetic study

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Abstract

Background: Virological response in those switched to regimens containing unboosted atazanavir (ATV) and tenofovir/lamivudine guided by therapeutic drug monitoring (TDM) in HIV-infected patients having achieved virological suppression is rarely investigated.
Methods: We enrolled patients with plasma HIV RNA load<200 copies/mL who switched to unboosted ATV plus 2 NRTIs between 2010 to 2012. Plasma ATV concentrations were measured using high-performance liquid chromatography, and single-nucleotide polymorphisms (SNPs) of *MDR1*, *PXR*, and *UGT1A1* genes were determined. Primary endpoint was plasma HIV RNA lad<200 copies/ml at week 48 after switch.
Results: During the study period, 69 receiving unboosted ATV with tenofovir/lamivudine (TDF-based) and 128 unboosted ATV with 2 other NRTIS (non-TDF-based) were enrolled. There were no statistically significant differences in the distributions of SNPs of *MDR1* (positions 2677 and 3435), *PXR* genotypes (position 63396), and *UGT1A1*28*. Recommended ATV concentrations were achieved in 93.5% and 85.0% of TDF- and non-TDF-based group, respectively. By week 48, 91.9% of TDF-based group and 92.1% of non-TDF-based group achieved virological suppression in intention-to-treat analysis. After follow-up for 84.6 weeks (IQR, 45.1-99.0), 28 (14.2%) experienced virological failure: 19 (7 and 12 in TDF and non-TDF group, respectively) due to regimen changes and 9 (1 and 8 for TDF and non-TDF groups, respectively) due to viral rebound. There was no significant difference in time to viral rebound (*P*=0.86) between the 2 groups.
Conclusions: Under the guidance of TDM, switch therapy with unboosted ATV combined with TDF/3TC achieved similar virological response to that with unboosted ATV with 2 other NRTIs in patients having achieved virological suppression.

Methods

1. Patients who had achieved plasma HIV RNA load<200 copies/ml for more than 3 months were enrolled and the antiretroviral regimens were switched to unboosted atazanavir (ATV) plus 2 NRTIs..
2. Plasma ATV concentrations (C12 and C24) were determined using HPLC.
3. Distributions of SNPs of *MDR1* (positions 2677 and 3435), *PXR* genotypes (position 63396), and *UGT1A1*28* were determined
4. Primary outcome of interest was virological response defined as plasma HIV RNA load<200 copies/ml at week 48.

Results

1. Between 2010 and 2012, 197 HIV-infected male patients were enrolled: 69 in TDF group and 128 in non-TDF group (Table 1).
2. Fig.1 shows the virological responses at wk 24 and 48.
3. Fig. 2 shows the time to virological failure during the follow up; viral rebound was noted in 1.5% and 6.3% of the TDF and non-TDF group, respectively (*P*=0.16).
4. Fig. 3 show the decrease of total cholesterol and triglyceride levels after switch
5. Fig. 4 show the plasma ATV levels after switch to unboosted ATV plus 2 NRTIs.

Table 1. Characteristics of the patients switched to unboosted ATV plus 2 NRTIs

	All (n=197)	TDF (n=69)	Non-TDF (n=128)	*p* value
Age, median (IQR) years	41.2 (35.6-47.1)	39.2 (35.5-44.7)	42.3 (35.8-47.5)	0.07
BMI, median (IQR) kg/m²	22.4 (20.8-24.7)	22.1 (20.4-24.5)	22.5 (21.1-24.6)	0.35
MSM, n (%)	145 (73.6)	56 (81.2)	89 (69.5)	
Heterosexual	42 (21.3)	9 (13.0)	33 (25.8)	
HBsAg-positive, n (%)	47 (24.5)	24 (37.5)	23 (18.0)	0.004
CD_4 cell count, median (IQR),	529.9 (391.5-707.0)	523.1 (369.6-709.9)	535.1 (393.0-695.6)	0.71
HIV-1 RNA <40 copies/mL, n (%)	175 (88.8)	63 (91.3)	112 (87.5)	0.42
ART regimens before switch				<0.001
Atazanavir + 2 NRTIs	79 (40.1)	53 (76.8)	26 (20.3)	
PI (non-atazanavir) + 2 NRTIs	43 (21.8)	4 (5.8)	39 (30.5)	
NNRTI + 2 NRTIs	63 (33.0)	11(15.9)	55 (43.0)	
UGT1A1*28 (n=117) TA6 /TA6	91 (77.8)	41 (77.3)	50 (78.1)	0.92
TA6/TA7	26 (22.2)	12 (22.6)	14 (21.9)	

Figure 1. Virological responses at weeks 24 and 48 for the two groups of patients

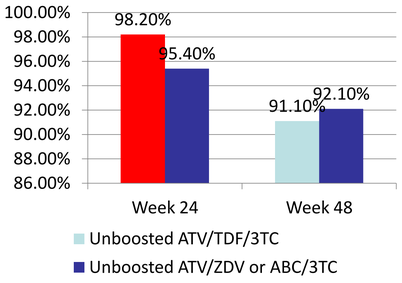


Figure 2. Time to virological failure in the two groups of patients

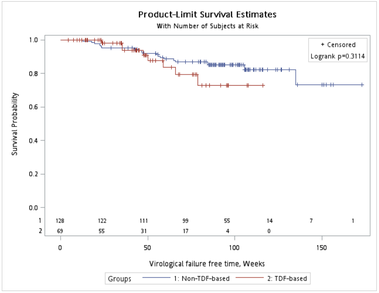


Figure 3. Changes of cholesterol and triglyceride levels in the two groups

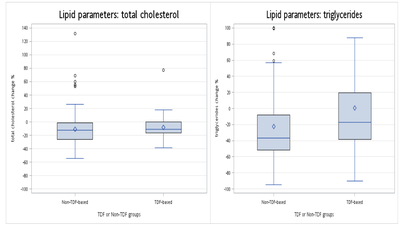
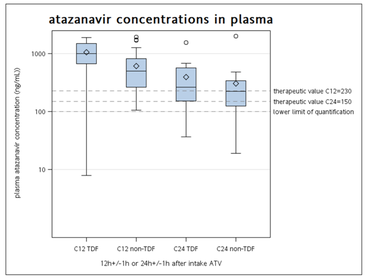


Figure 4. Plasma atazanavir concentrations



Conclusions

In highly selected patients who had achieved virological suppression, switch to unboosted ATV combined with TDF/3TC does not compromise the virological response, as compared to those switched to unboosted ATV with 2 other NRTIs, with the information provided by therapeutic drug monitoring .