Poster No. P278

HIV Drug Therapy 2014 Glasgow

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Long term effectiveness of once-daily unboosted atazanavir plus abacavir/lamivudine as a switch strategy in subjects with virological suppression

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BACKGROUND

Use of unboosted atazanavir (ATV_{400}) is approved in the USA but not in Europe. Due to pharmacokinetic interactions it should not be used with tenofovir but it can be used with abacavir/lamivudine (ABC/3TC). However, effectiveness data of a regimen composed of ATV_{400} + ABC/3TC as a switch strategy in routine clinical practice however are scant. This regimen avoids pharmacokinetic interactions and results in a better lipid profile and lower rates of hyperbilirrubinemia.

METHODS

We evaluated treatment outcomes of ATV_{400} + ABC/3TC in pre-treated subjects in the EuroSIDA cohort with undetectable HIV-1 RNA, and previous ABC experience or assumed previous HLA-B*5701 testing. We performed a time to loss of virological response (TLOVR below 50 c/mL) and a snapshot analysis at 48, 96 and 144 weeks (using the FDA definitions and recommended analysis plan). Virological failure (VF) was defined as a confirmed plasma HIV-1 RNA >50 c/mL. A multivariable analysis was done to identify factors associated with the risk of virologic failure by means of a Cox regression model. Follow-up accrued from the date of switching to the ATV_{400}-based regimen with a VL≤50 copies/L (baseline) to the date of viral rebound or last available VL.

RESULTS

We included 264 subjects: 179 (68%) male, median age 46 (IQR 41, 53) years-old, 228 (86%) white, hepatitis B or C virus co-infection in 88 (33)%, median baseline CD4 at switch 540 cells (IQR 370 ,700), time with VL≤ 50 c/mL 45 (24, 69) months (**Table 1**). The median calendar year of switching was 2008 (2006, 2010). The 3rd drug in previous regimen was ATV/r in 75 (28.4%), and other PI/r in 24 (9.1). Of all people included, 87 (33.0%) had previously failed with a PI.

The virological response (TLOVR, composite endpoint failure or stop for any reason) was 90.2 (95%CI 85.9-93.5) at 48 weeks, and 89.0 (95%CI 84.6-92.5) at both 96 and 144 weeks (**Table 2**). The risk of pure VF > 50 c/mL was 7.9/7.0/6.3%, respectively. In the snapshot analysis HIV-RNA was below 50 c/ml in 74.6/70.1/56.8%, respectively, and >50 c/mL in 6.4/5.3/3.8%. Only 0.4/1.5/3.0% discontinued due to adverse events.
There was a high rate of discontinuations due to other reasons or with VL missing in window, due to due to the observational nature of the data.

In a multivariable analysis (**Table 3)** we observed an association between the risk of VF and nadir CD4 count (RH 0.65 [95% CI 0.44, 0.98] per 100 cells higher), time with VL ≤ 50 c/mL (RH 0.89 [0.81, 0.98] per 6 months longer), and previous failure with a PI (3.19 [1.45, 7.01]. There was no association with gender, age, hepatitis virus co-infection, CD4 count at time of switching, viral load at cART initiation, or third drug used in the previous regimen.

Two (0.8% of all cohort) out of 7 subjects with confirmed virological failure and genotyping data available harboured major protease mutations at failure (case 1 RT M41L/M184I/L210W/T215Y, PRO M46I/V82T; case 2 RT D67N/K70R/L74V/M184V/K219E, PRO M46L,I54V,V82A,L90M). However, there are no data on prior genotypic tests, and we can not confirm that those mutations were selected while on ATV_{400} + ABC/3TC.

CONCLUSIONS

A switch to ATV_{400} + ABC/3TC in selected subjects with HIV-RNA below 50 c/mL is associated with relatively low rates of VF and discontinuation due to adverse events (3% by week 144).
Use of this regimen might be considered in those with high CD4 count nadir, long-term suppression and without prior PI failure. Larger cohorts are required to further define the appropriate selection criteria.

LIMITATIONS

Observed rate of failure is difficult to relate to that of possible alternative strategies, due to the lack of a control group in our analysis.
The sample size was limited and only allowed detection of strong associations.
We assumed that people had been tested for HLA-B*5701 if they started abacavir after a certain calendar year, when the test was licensed, or had been successfully treated with abacavir before. However, confirmatory data are not available in the database. Therefore, some hypersensitivity reactions could still exist among the discontinuations due to adverse events in our series.

Table 1

Baseline Characteristics of the subjects

Baseline Characteristics of the subjects	Total: 264
Gender, male	179 (67.8%)
Mode of HIV Transmission	
IDU	66 (25.0%)
Homosexual contacts	95 (36.0%)
Heterosexual contacts	88 (33.3%)
Ethnicity	
White	228 (86.4%)
Asian	5 (1.9%)
Black	19 (7.2%)
Hepatitis co-infection (Yes, HCVAb+ or HBsAg+)	88 (33.3%)
Calendar year of switching to ATZ; median (IQR)	2008 (2006, 2010)
Age, years; Median (IQR)	46 (41, 53)
CD4 count at switching to ATZ, cells/mm3; Median (IQR)	540 (370, 700)
CD4 count nadir, cells/mm3; Median (IQR)	167 (70, 244)
Viral load at cART, log copies/mL; median (IQR)	4.8 (4.0, 5.2)
Time with VL<=50, months; Median (IQR)	45 (24, 69)
Third drug in previous regimen	
ATV/r	75 (28.4%)
Other PI/r	24 (9.1%)
Other	165 (62.5%)
Previously failed a PI *(Yes)*	*87 (33.0%)*

Table 2

Efficacy analyses (n=264)

Efficacy analyses (n=264)	Week 48	Week 96	Week 144
Disposition, n(%)			
HIV-RNA below 50 copies/mL	197 (74.6%)	185 (70.1%)	150 (56.8%)
HIV-RNA >50 copies/mL #	17 (6.4%)	14 (5.3%)	10 (3.8%)
No virological data in window			
Discontinued due to AE *	1 (0.4%)	4 (1.5%)	8 (3.0%)
Discontinued due to other reasons **	8 (3.0%)	11 (4.2%)	11 (4.2%)
On study but missing VL in window	41 (15.5%)	50 (18.9%)	85 (32.2%)
Other endpoints, n(%)			
Pure virological failure (OT) &	17 (7.9%)	14 (7.0%)	10 (6.3%)
Composite -failure or stop due to AE *	18 (6.8%)	18 (6.8%)	18 (6.8%)
Composite -failure or stop due to other reasons **	25 (9.5%)	25 (9.5%)	21 (8.0%)
Composite -failure or stop due to any reason (TLOVR)	26 (9.8%)	29 (11.0%)	29 (11.0%)
Composite -failure or stop due to any reason or VL missing	67 (25.4%)	79 (29.9%)	114 (43.2%)

Includes patients who changed any component of background therapy to a new drug class or changed background components that were not permitted per protocol or changed any background drug in the regimen because of lack of efficacy (perceived or documented) before window, patients who discontinued study drug or study before window for lack or loss of efficacy and patients with HIV-RNA ≥ 50 copies/mL in the window.
* Includes patients who discontinued because of adverse event or death at any time point from Day 1 through the time window if this resulted in no virological data on treatment during the specified window.
** Other includes withdrew consent, loss to follow-up, pregnancy, physician decision.
& Denominator N=204 persons with VL in wk 48 window, N=184 with VL in wk 96 window, and N=144 persons with VL in wk 144 window

Table 3

Factors associated with virological failure, multivariable analysis (relative hazards of TLOVR)

	Unadj. RH (95% CI)	p-value	Adjusted* RH (95% CI)	p-value
Gender				
Female vs. male	0.76 (0.34, 1.69)	0.497	1.02 (0.34, 3.02)	0.975
Mode of HIV Transmission				
IDU	1.00		1.00	
Homosexual contacts	1.73 (0.67, 4.47)	0.255	1.34 (0.30, 5.98)	0.705
Heterosexual contacts	1.16 (0.41, 3.26)	0.778	1.13 (0.28, 4.57)	0.863
Hep co-infection, HCVAb or HBsAg				
No	1.00		1.00	
Yes	0.71 (0.32, 1.60)	0.413	1.36 (0.39, 4.76)	0.626
Calendar year of switching to ATV				
per more recent	0.85 (0.71, 1.02)	0.082	0.93 (0.74, 1.16)	0.503
Age				
per 10 years older	1.02 (0.71, 1.45)	0.933	1.17 (0.78, 1.77)	0.451
CD4 count at switching to ATV				
<=300 vs. >300	1.33 (0.51, 3.46)	0.560	2.00 (0.71, 5.69)	0.191
CD4 count nadir				
per 100 cells higher	0.71 (0.51, 1.00)	0.053	0.65 (0.44, 0.98)	0.038
Viral load at cART				
>100,000 vs. <=100,000 c/mL	1.61 (0.63, 4.08)	0.318	1.27 (0.46, 3.53)	0.646
Time with VL<=50				
per 6 months longer	0.91 (0.84, 0.99)	0.032	0.89 (0.81, 0.98)	0.021
Third drug in previous regimen				
ATV/r	1.00		1.00	
Other PI/r	2.47 (0.75, 8.08)	0.136	1.56 (0.42, 5.84)	0.506
Other	1.43 (0.57, 3.56)	0.446	1.08 (0.40, 2.92)	0.880
Previously failed a PI				
Yes vs. No	2.43 (1.20, 4.93)	0.014	3.19 (1.45, 7.01)	0.004

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Funding: Primary support for EuroSIDA is provided by the European Commission BIOMED 1 (CT94-1637), BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773), the 6th Framework (LSHP-CT-2006-018632), and the 7th Framework (FP7/2007-2013, EuroCoord n° 260694) programmes. Current support also includes unrestricted grants by Janssen R&D, Merck and Co. Inc., Pfizer Inc., GlaxoSmithKline LLC. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 108787).

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