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 (ATV400) 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 ATV400 + 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 hyperbilirubinemia.

METHODS
We evaluated treatment outcomes of ATV400 + 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 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 ATV400-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/rr 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 25.4/29.9/43.2%, respectively. 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/V92A/L90M). However, there are no data on prior genotypic tests, and we can't confirm that those mutations were selected while on ATV400 + ABC/3TC.

CONCLUSIONS
A switch to ATV400 + 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.