



University of Southern Denmark

Long-term effectiveness of unboosted atazanavir plus abacavir/lamivudine in subjects with virological suppression

A prospective cohort study

Llibre, Josep M; Cozzi-Lepri, Alessandro; Pedersen, Court; Ristola, Matti; Losso, Marcelo; Mocroft, Amanda; Mitsura, Viktor; Falconer, Karolin; Maltez, Fernando; Beniowski, Marek; Vullo, Vincenzo; Hassoun, Gamal; Kuzovatova, Elena; Szlavik, János; Kuznetsova, Anastasiia; Stellbrink, Hans-Jürgen; Duvivier, Claudine; Edwards, Simon; Laut, Kamilla; Paredes, Roger; EuroSIDA Study

Published in:
Medicine

DOI:
[10.1097/MD.0000000000005020](https://doi.org/10.1097/MD.0000000000005020)

Publication date:
2016

Document version
Final published version

Document license
CC BY-ND

Citation for pulished version (APA):

Llibre, J. M., Cozzi-Lepri, A., Pedersen, C., Ristola, M., Losso, M., Mocroft, A., ... EuroSIDA Study (2016). Long-term effectiveness of unboosted atazanavir plus abacavir/lamivudine in subjects with virological suppression: A prospective cohort study. *Medicine*, 95(40), [e5020]. <https://doi.org/10.1097/MD.0000000000005020>

Terms of use

This work is brought to you by the University of Southern Denmark through the SDU Research Portal. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying this open access version

Long-term effectiveness of unboosted atazanavir plus abacavir/lamivudine in subjects with virological suppression

A prospective cohort study

Josep M. Llibre, MD, PhD^{a,b,*}, Alessandro Cozzi-Lepri, PhD^c, Court Pedersen, MD^d, Matti Ristola, MD^e, Marcelo Losso, MD^f, Amanda Mocroft, PhD^g, Viktor Mitsura, MD^h, Karolin Falconer, MD, PhDⁱ, Fernando Maltez, MD, PhD^j, Marek Beniowski, MD^k, Vincenzo Vullo, MD^l, Gamal Hassoun, MD^m, Elena Kuzovatova, MDⁿ, János Szlavik, MD^o, Anastasiia Kuznetsova, MD^p, Hans-Jürgen Stellbrink, MD^q, Claudine Duvivier, MD^r, Simon Edwards, MD^s, Kamilla Laut, MD^t, Roger Paredes, MD^{a,u}, on behalf of the EuroSIDA Study

Abstract

Effectiveness data of an unboosted atazanavir (ATV) with abacavir/lamivudine (ABC/3TC) switch strategy in clinical routine are scant.

We evaluated treatment outcomes of ATV + ABC/3TC in pretreated subjects in the EuroSIDA cohort when started with undetectable plasma HIV-1 viral load (pVL), performing a time to loss of virological response (TLOVR <50 copies/mL) and a snapshot analysis at 48, 96, and 144 weeks. Virological failure (VF) was defined as confirmed pVL >50 copies/mL.

We included 285 subjects, 67% male, with median baseline CD4 530 cells, and 44 months with pVL ≤50 copies/mL. The third drug in the previous regimen was ritonavir-boosted atazanavir (ATV/r) in 79 (28%), and another ritonavir-boosted protease inhibitor (PI/r) in 29 (10%). Ninety (32%) had previously failed with a PI. Proportions of people with virological success at 48/96/144 weeks were 90%/87%/88% (TLOVR) and 74%/67%/59% (snapshot analysis), respectively. The rates of VF were 8%/8%/6%. Rates of adverse events leading to study discontinuation were 0.4%/1%/2%. The multivariable adjusted analysis showed an association

Editor: Victor Asensi.

JML and AC-L are coauthors.

Authorship: JML has been a member of speakers' bureaus and received fees from lectures, educational activities, or for participating in advisory boards from Janssen-Cilag, Merck, Sharp & Dohme, ViiV Healthcare, Gilead Sciences, and Bristol-Myers Squibb. CP has received a research grant from Gilead, and has received fees for educational activities from Abbott, Glaxo Smith Kline, and Merck Sharp & Dohme. KF has received honoraria from Gilead Sciences and Bristol-Myers Squibb and research grants from Gilead Sciences. H-JS has received speaker honoraria from AbbVie, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead Sciences, and Janssen Cilag, and scientific advice from Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead Sciences, and Janssen Cilag. RP has served as a consultant or advisor to Gilead Sciences, Inc, and ViiV Healthcare, and has received research grants from ViiV Healthcare, Gilead Sciences, and MSD. JML led the design of the analysis on behalf of the EuroSIDA Study group, had full access to all the data in the study, and had final responsibility for the decision to submit for publication. EuroSIDA gathered and assured quality of the data collected from the participating sites. AC-L analyzed the data based on the statistical analysis plan. The manuscript was written by JML, edited by AC-L, and reviewed by the writing group members. The writing group vouches for the data, analysis, and content of the manuscript. The remaining authors disclose no conflicts of interest.

Funding: Primary funding for EuroSIDA is provided by the European Union's Seventh Framework Programme for research, technological development, and demonstration under EuroCoord grant agreement no. 260694. Current support also includes unrestricted grants by Bristol-Myers Squibb, Janssen R&D, Merck and Co. Inc, Pfizer Inc, Glaxo-Smith Kline LLC. The participation of centers from Switzerland was supported by The Swiss National Science Foundation (grant 108787). Study supported by grant [grant no. DNRF126] from the Danish National Research Foundation. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; or decision to submit the article for publication.

^aInfectious Diseases and "Lluita contra la SIDA" Foundation, University Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain, ^bUniversitat Autònoma de Barcelona, Barcelona, Spain, ^cResearch Department of Infection and Population Health, University College London, London, UK, ^dOdense University Hospital, Department of Infectious Diseases, Odense, Denmark, ^eHelsinki University Hospital, Department of Infectious Diseases, Helsinki, Finland, ^fHospital General de Agudos JM Ramos Mejía, Department of Infectious Diseases, Buenos Aires, Argentina, ^gDepartment of Epidemiology and Medical Statistics, University College London, London, UK, ^hDepartment of Infectious Diseases, Gomel State Medical University, Gomel, Belarus, ⁱKarolinska University Hospital, Stockholm, Sweden, ^jCurry Cabral Hospital, Department of Infectious Diseases, Lisbon, Portugal, ^kSpecialistic Hospital, Outpatient Clinic for AIDS Diagnostics and Therapy, Chorzów, Poland, ^lPoliclinico Umberto 1, Rome, Italy, ^mRambam-Health Care Campus, Haifa, Israel, ⁿNizhny Novgorod Scientific and Research Institute of Epidemiology and Microbiology named after Academician I.N. Blokhina, Russia, ^oSzent László Hospital, Budapest, Hungary, ^pKharkov State Medical University, Ukraine, ^qICH Study Center, Hamburg, Germany, ^rInfectious Diseases Center Necker-Pasteur, APHP-Hôpital Necker-Enfants Malades, Paris, France, ^sMortimer Market Centre, UK, ^tCentre for Health & Infectious Diseases Research (CHIP), Department of Infectious Diseases, Section 2100, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, ^uIrsi-Caixa AIDS Research Institute, Badalona, Spain.

* Correspondence: Josep M. Llibre, HIV Unit, Hospital Universitari Germans Trias i Pujol, Ctra de Canyet, s/n, 08916 Badalona, Barcelona, Spain (e-mail: jmlibre@flsida.org).

Copyright © 2016 the Author(s). Published by Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2016) 95:40(e5020)

Received: 1 July 2016 / Received in final form: 31 August 2016 / Accepted: 3 September 2016

<http://dx.doi.org/10.1097/MD.00000000000005020>

between VF and nadir CD4+ (hazard ratio [HR] 0.63 [95% confidence interval [CI]: 0.42–0.93] per 100 cells higher), time with pVL ≤ 50 copies/mL (HR 0.87 [95% CI: 0.79–0.96] per 6 months longer), and previous failure with a PI (HR 2.78 [95% CI: 1.28–6.04]). Resistance selection at failure was uncommon.

A switch to ATV + ABC/3TC in selected subjects with suppressed viremia was associated with low rates of VF and discontinuation due to adverse events, even in subjects not receiving ATV/r. The strategy might be considered in those with long-term suppression and no prior PI failure.

Abbreviations: ABC/3TC = abacavir/lamivudine, ART = antiretroviral therapy, ATV/r = ritonavir-boosted atazanavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside analog reverse transcriptase inhibitors, PI/r = ritonavir-boosted protease inhibitor, pVL = plasma HIV-1 viral load, TDF = tenofovir disoproxil fumarate, VF = virological failure, ZDV = zidovudine.

Keywords: atazanavir, HIV-1, protease inhibitors: abacavir, simplification antiretroviral therapy

1. Introduction

Antiretroviral guidelines recommend switching a suppressive antiretroviral therapy (ART) in cases of toxicity, pharmacokinetic interactions, pregnancy, and for simplification purposes.^[1–4] Preferred options in guidelines to replace a ritonavir-boosted protease inhibitor (PI/r) include unboosted atazanavir (ATV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), and the integrase inhibitors raltegravir, dolutegravir, or elvitegravir/cobicistat, if full activity of the 2 nucleoside analog reverse transcriptase inhibitors (NRTI) can be guaranteed. Low-dose ritonavir (or cobicistat) inhibits P450 cytochrome enzymes (mainly CYP3A4) and drug transporter P-glycoprotein, and increases the plasma levels of the PI, thus making it possible to reduce the total daily dose and dosing intervals.^[5] However, it has the potential to cause multiple pharmacokinetic interactions with drugs that induce, inhibit, or are simply substrates of this metabolic pathway, and is generally associated with a poorer lipid profile. PI/r-based regimens are also typically associated with higher rates of discontinuation due to intolerance and toxicity as compared with ART regimens based on other drug classes.^[6,7]

ATV is the only PI that can be used without pharmacokinetic boosting. One randomized clinical trial demonstrated higher rates of virological failure (VF) with unboosted ATV in treatment-naïve subjects, although with less hyperbilirubinemia and a better lipid profile.^[8] Therefore, it is not recommended in treatment naïves.^[8,9]

However, in patients with virological suppression, clinical trials and a meta-analysis have demonstrated the noninferiority of unboosted ATV and the absence of major protease mutations in VF with respect to maintenance of ritonavir-boosted atazanavir (ATV/r), always combined with abacavir/lamivudine (ABC/3TC).^[10–14] The regimen proved beneficial not only in terms of lower rates of hyperbilirubinemia and improved lipid profiles, but also reduced consistently some inflammatory markers like lipoprotein-associated phospholipase A2 (LA-PLA2, but not interleukin-6 or high sensitivity C-reactive protein), considered an independent predictor of coronary heart disease by making atherosclerotic plaques in coronary vessels prone to rupture.^[15] This improvement could be related to low-density lipoprotein cholesterol decreases associated with ritonavir removal.^[16]

The efficacy of ATV combined with 2NRTIs in clinical practice has been analyzed in several cohorts, where the inclusion of difficult-to-treat patients (who are usually excluded in clinical trials) could reveal weaknesses of this regimen.^[17–21] Most of the studies have limitations in their methodological design that make it impossible to evaluate with certainty its efficacy. In some studies, ABC/3TC accounted for only 50% of the NRTI

backbone,^[14,17,19,22] with the remaining cases using tenofovir disoproxil fumarate (TDF) or zidovudine (ZDV) combined with 3TC/emtricitabine. TDF is formally advised against in combination with unboosted ATV owing to the existing pharmacokinetic interaction.^[17,23]

In addition, the toxicity and efficacy profiles of ZDV are significantly worse than that of ABC.^[24] Some studies included treatment-naïve patients in the analysis.^[20] Others included patients with detectable plasma HIV-1 viral load (pVL) at baseline, or had a short follow-up, or a small sample size with a mix of subjects also treated with ATV/r.^[14,19,21,23] Finally, most studies included patients with unknown HLA-B*5701 status, and could have a higher rate of discontinuation due to suspected abacavir hypersensitivity reactions.

Therefore, there is uncertainty around the efficacy and safety of unboosted ATV plus ABC/3TC outside the clinical trial setting when administered under optimal conditions.

2. Methods

We evaluated the treatment outcomes of unboosted ATV (400 mg once daily) + ABC/3TC in antiretroviral experienced subjects in the EuroSIDA cohort who started this regimen with an undetectable pVL (< 50 copies/mL), and previous ABC experience or assumed previous HLA-B*5701 testing. If there were more than one such episodes, only the first one was included. All subjects with at least 1 month of clinical follow-up were included. We performed a time to loss of virological response (TLOVR < 50 copies/mL and 200 copies/mL) and an FDA-recommended snapshot analysis at 48, 96, and 144 weeks (using the FDA definitions and recommended analysis plan).^[25] In brief the time windows were defined as follows: 42 to 54 weeks for week 48, 90 to 102 weeks for week 96, and 138 to 160 weeks for week 144. We used the pVL first hierarchy principle, meaning that people are classified according to the pVL value (success if pVL ≤ 50 copies, failure if pVL > 50) if pVL was available in each of the time windows. If pVL was missing in the time window, then patient's history before the beginning of the time window was examined (e.g., 0–42 weeks for week 48 window). If the subject discontinued ATV, ABC or 3TC because of adverse events, failure, or death or if they added any drug with unfavorable interactions with ATV before the window, they were defined as failure. Persons who discontinued because of loss to follow-up or disconnect from care were classified according to pVL value at time of last contact. If the person was still receiving unboosted ATV + ABC/3TC in the time window and pVL was missing, they were classified as “data not available.”

VF was defined as a confirmed pVL > 50 copies/mL (failure was defined at the time of the first of 2 consecutive values above the thresholds).

Table 1**Baseline characteristics of the subjects (n=285).**

Sex, male, n (%)	191 (67.0)
Mode of HIV transmission	
IDU	76 (26.7)
Male homosexual sex	98 (34.4)
Heterosexual sex	93 (32.6)
Ethnicity	
White	249 (87.4)
Asian	5 (1.8)
Black	19 (6.7)
Hepatitis coinfection (hepatitis C virus antibodies or HBsAg), n (%)	105 (36.8)
Calendar year of switching to atazanavir, median (IQR)	2008 (2006–2010)
Age, y, median (IQR)	46 (41–53)
CD4 count at switching to atazanavir, cells/mm ³ , median (IQR)	530 (357–700)
CD4 count nadir, cells/mm ³ , median (IQR)	168 (70–243)
Plasma HIV-1 RNA at first ART initiation, log copies/mL, median (IQR)	4.7 (4.0–5.2)
Time with plasma HIV-1 RNA ≤50 copies/mL, mo, median (IQR)	44 (23–68)
Third (anchor) drug in the previous regimen, n (%)	
ATV/r	79 (27.7)
Other PI/r	29 (10.2)
Other	177 (62.1)
Previously failed a protease inhibitor, n (%)	90 (31.6)

ART = antiretroviral therapy, ATV/r = ritonavir-boosted atazanavir, HBsAg = surface antigen of the hepatitis B virus, IDU = intravenous drug users, IQR = interquartile range, PI/r = ritonavir-boosted protease inhibitor.

A multivariable analysis was done to identify factors associated with VF by means of a Cox regression model which included a number of a priori chosen potential confounders: sex, mode of HIV transmission, calendar year of switching to unboosted ATV + ABC/3TC, age, CD4 count at time of switching and nadir CD4, pVL at time of starting ART, duration of viral suppression on previous regimen, history of drug exposure, evidence of previous VF to PI-based ART, bilirubin level at time of switch, and hepatitis C or B coinfection status. A VF to a prior PI was defined

as a single VL >500 copies/mL after at least 4 months from starting a PI and while still receiving the PI.

Follow-up accrued from the date of switching to the unboosted ATV-based regimen with a pVL ≤50 copies/L (baseline) to the date of viral rebound or last available pVL. Resistance test results available from samples tested in the time window of the estimated date of VF were extracted from the database and aminoacid sequences compared with that of *wild-type* HIV strain.

All participating cohorts followed local national guidelines/regulations regarding patient consent and/or ethical review.

3. Results

We included 285 subjects: 191 (67%) male, median age 46 (interquartile range [IQR] 41–53) years; 249 (87%) white; hepatitis B or C virus coinfection in 105 (37%); median baseline CD4 at switch 530 cells (IQR 357–700); time with pVL ≤50 copies/mL 44 (IQR 23–68) months (Table 1). The third or anchor drug in the baseline regimen before the switch was ATV/r in 79 (27.7%), and another PI/r in 29 (10.2%). Of all people included, 90 (31.6%) had previously failed with a PI in their regimen, a median 98 months before (IQR 66–121).

The virological response (TLOVR, composite endpoint including failure or stop for any reason) was 89.8% (95% confidence interval [CI]: 85.7–93.1) at 48 weeks, 87.4% (95% CI: 82.9–91.0) at 96 weeks, and 88.4% (95% CI: 84.1–91.9) at 144 weeks (Table 2). The rate of pure VF (confirmed pVL >50 copies/mL) was 7.8%/7.7%/6.2%, respectively. These rates decreased to 4.3%/3.4%/3.9%, respectively, using the more common definition of VF as a confirmed pVL >200 copies/mL. In the snapshot analysis, pVL was ≤50 copies/mL in 74.4%/67.0%/58.6%, respectively, and >50 copies/mL in 6.3%/5.6%/3.9%, and 0.4%/0.7%/2.1% discontinued due to adverse events. There was one newly diagnosed myocardial infarction (0.4%) reported after the switch to the unboosted ATV-based regimen and during the study period (1.3 per 1000 patients/y of follow-up). Two (0.7%) subjects discontinued the regimen due to kidney adverse events, as reported by the treating physician. One of them also showed a single value of estimated glomerular

Table 2**Outcomes of efficacy at 48, 96, and 144 weeks (FDA snapshot analysis and sensitivity analyses; 285 subjects unless otherwise specified).**

Disposition, n (%)	Week 48	Week 96	Week 144
HIV-RNA ≤50 copies/mL	212 (74.4)	191 (67.0)	167 (58.6)
HIV-RNA >50 copies/mL*	18 (6.3)	16 (5.6)	11 (3.9)
No virological data in window			
Discontinued due to adverse events [†]	1 (0.4)	2 (0.7)	6 (2.1)
Discontinued due to other reasons [‡]	10 (3.5)	18 (6.3)	16 (5.6)
On study but missing pVL in window	44 (15.4)	58 (20.4)	85 (29.8)
Other endpoints, n (%)			
Pure virological failure [§] (OT), threshold 50 copies/mL	18 (7.8)	16 (7.7)	11 (6.2)
Pure virological failure [§] (OT), threshold 200 copies/mL	10 (4.3)	7 (3.4)	7 (3.9)
Composite failure or stop due to adverse events [†]	19 (6.7)	18 (6.3)	17 (6.0)
Composite failure or stop due to other reasons [‡]	28 (9.8)	34 (11.9)	27 (9.5)
Composite failure or stop due to any reason (TLOVR)	29 (10.2)	36 (12.6)	33 (11.6)
Composite failure or stop due to any reason or pVL missing	73 (25.6)	94 (33.0)	118 (41.4)

OT = on treatment analysis, pVL = plasma HIV-1 viral load, TLOVR = time to loss of virological response.

* 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 who are ≥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 pVL in week 48 window, N = 184 persons with pVL in week 96 window, and N = 144 persons with pVL in week 144 window.

Table 3
Factors associated with virological failure in a multivariable analysis.

	Unadjusted HR (95% CI)	P	Adjusted* HR (95% CI)	P
Sex				
Female vs male	0.68 (0.31–1.52)	0.351	1.02 (0.36–2.94)	0.965
Mode of HIV transmission				
IDU	1.00		1.00	
Homosexual contacts	1.72 (0.71–4.15)	0.228	2.06 (0.54–7.91)	0.292
Heterosexual contacts	0.93 (0.34–2.55)	0.881	1.09 (0.28–4.24)	0.905
Hepatitis coinfection*				
No	1.00		1.00	
Yes	0.85 (0.40–1.81)	0.673	1.68 (0.52–5.39)	0.387
Calendar year of switching to ATV				
Per more recent	0.87 (0.74–1.02)	0.076	0.94 (0.79–1.14)	0.547
Age				
Per 10 y older	0.92 (0.64–1.31)	0.630	1.05 (0.71–1.56)	0.810
CD4 count at switching to ATV				
≤300 vs >300	0.79 (0.36–1.76)	0.570	1.27 (0.51–3.15)	0.601
CD4 count nadir				
Per 100 cells higher	0.71 (0.51–0.99)	0.043	0.63 (0.42–0.93)	0.020
Viral load at first ART initiation				
>100,000 vs ≤100,000 copies/mL	1.18 (0.49–2.84)	0.714	0.90 (0.34–2.35)	0.828
Time with pVL ≤50 copies/mL				
Per 6 mo longer	0.89 (0.81–0.97)	0.007	0.87 (0.79–0.96)	0.004
Third drug in previous regimen				
ATV/r	1.00		1.00	
Other PI/r	2.32 (0.71–7.60)	0.165	1.55 (0.42–5.65)	0.507
Other	1.56 (0.63–3.86)	0.333	1.18 (0.45–3.10)	0.741
Previously failed a PI				
Yes vs no	2.05 (1.03–4.05)	0.040	2.78 (1.28–6.04)	0.010

ART = antiretroviral therapy, ATV = atazanavir, ATV/r = ritonavir-boosted atazanavir, CI = confidence interval, HR = hazard ratio, IDU = intravenous drug users, PI/r = ritonavir-boosted protease inhibitor, pVL = plasma HIV-1 RNA.

*Hepatitis C antibodies or HBsAg+.

filtration rate decrease to <60 mL/min/1.73 m² (CKD-Epi formula).

There was a high rate of discontinuations due to other reasons (not related to VF, toxicity, or death), mainly due to physician’s decision, or with pVL missing values in the window, due to the observational nature of the data.

In a multivariable analysis (Table 3), we observed an association between nadir CD4+ count (hazard ratio [HR] 0.63 [95% CI: 0.42–0.93] per 100 cells higher), time with pVL ≤50 copies/mL before the switch (HR 0.87 [95% CI: 0.79–0.96] per 6 months longer), and previous failure with a PI (HR 2.78 [95% CI: 1.28–6.04]) with the risk of VF. There was no evidence of an association with sex, mode of HIV transmission, age, hepatitis virus coinfection, calendar year of switching to ATV, CD4+ cell count at time of switching to ATV, pVL at first ART initiation, or third drug used in the previous regimen. Regarding the latter, there were no differences in VF rates comparing those who were receiving ATV/r before the switch to unboosted ATV, with those who were receiving other PI/r, or non-PI-based regimens.

Two (0.7% of all cohort) out of 8 subjects with confirmed VF and genotyping data available around the date of failure harbored major protease mutations. One case presented mutations M46I/V82T (associated with intermediate ATV resistance, together with M41L/M184I/L210W/T215Y in the reverse transcriptase), and the other one showed M46L/I54V/V82A/L90M (high-level ATV resistance, with D67N/K70R/L74V/M184V/K219E in the reverse transcriptase). However, there were no genotypic test results available at the time of switching to unboosted ATV in these 2 subjects, and one of them had documented prior failures to a PI-based regimen. So, we are unable to establish whether the mutations detected at time of failure were selected while receiving

unboosted ATV + ABC/3TC or if they were indeed already present before switching. A third subject harbored an isolated M184V at failure (no genotypic resistance tests before unboosted ATV initiation available). No subject selected the key ATV mutations I50L, I84V or N88S at failure.

4. Discussion

In this analysis of data of patients enrolled in a large cohort of HIV-infected individuals in Europe, a switch to a regimen including unboosted ATV plus ABC/3TC in subjects with suppressed viremia was associated with low rates of VF or discontinuation due to adverse events at 48, 96, and 144 weeks. Resistance selection at VF was uncommon, particularly in subjects without previous PI failures. Results were consistent when either a TLOVR or the new FDA snapshot definition for treatment failure was used.

These data are in agreement with those of previous randomized clinical trials and support the efficacy of the regimen also in routine clinical practice, even if we used a more strict VF definition in our analysis (a threshold of 50 copies/mL of HIV-1 RNA) instead of the more commonly used limit of 200 copies/mL.^[10–13] VF rates in the real clinical setting are bound to be higher than those seen in trials. However, using the threshold of 200 copies/mL we identified rates of VF closer to those seen in clinical trials. The regimen also showed a good safety profile, supporting previous similar findings.^[19,20] We found no significant differences regarding sex in the multivariable analysis.

In our cohort subjects had previously been treated with abacavir or had a negative HLA-B*5701 allele, therefore the risk of discontinuation due to suspected ABC hypersensitivity

reactions was likely to be small. Interestingly, nephrolithiasis was not reported as a cause of ATV discontinuation, although there were 2 discontinuations due to renal toxicity as reported by the treating physician.

One-third of the study subjects came from a previous PI/r strategy. Of note, we found no significant differences in the risk of VF when comparing people who had ATV/r, other PI/r or other drugs included in their previous regimen. Our data increase our understanding of the possible consequences in people switching to an unboosted ATV-based regimen but coming from treatments not including ATV/r.

The withdrawal of low-dose ritonavir in people treated with ATV/r has been associated with the reduction of hyperbilirubinemia and improvements in the lipid profile in previous studies, and has the potential to prevent pharmacokinetic interactions.^[10–12,14,26,27] These concerns are of particular importance in the HIV-infected population currently in care as background cardiovascular risk, the proportion of elderly patients, and those prone to drug-related toxicities are typically on the rise.^[28] In studies where the switch included a change from TDF to ABC, a significant improvement in markers of bone turnover and kidney tubule dysfunction was also demonstrated.^[12] In contrast, data on the change in inflammatory/cardiovascular markers following a switch to ATV have been controversial. Although LA-PLA2 values (a surrogate marker for metabolic syndrome and incident cardiovascular disease) were shown to decrease significantly, biomarkers of cardiovascular disease, inflammation, or thrombogenesis (hsCRP, interleukin-6, and D-dimer) generally remained stable.^[12,15,16,29] Therefore, there is currently not enough evidence to recommend a switch to an unboosted ATV-based regimen if the main goal is to try to reduce patients' level of inflammation.

Nadir CD4+ cell count, baseline pVL at first ART initiation, time with undetectable pVL before the switch, and previous failures with a PI were independently associated with VF to the study regimen in our analysis. Our findings are useful to guide the selection of patients who might benefit from this switching strategy.

Hepatitis C virus coinfection was associated with increased risk of VF in a previous analysis.^[19] The interpretation of this result was that hepatitis coinfection was a marker for disordered life-style due to intravenous drug use and nonadherence.^[30] Our data do not confirm this association and are consistent with other studies showing no impact of HCV coinfection on ATV plasma levels and liver fibrosis.^[31]

Our study has a number of limitations. First of all, it is an observational study and therefore we cannot rule out channeling in (confounding by indication) and channeling out (reasons for stopping ATV are not random) biases. Also, there was a high rate of discontinuations due to reasons unrelated to efficacy and of people with missing pVL values in the snapshot windows, a common finding in observational studies, which could result in underreporting of toxicity and failure. In addition, this is a single treatment analysis with no control group as it is difficult to identify suitable control groups of switching strategies in the observational setting. It is therefore difficult to put our estimates of VF into context as the rate of switching in people who did not switch is counterfactual (e.g., missing data) and unclear which other estimates could be used as comparator.

On the contrary, strengths of our analysis include the proportion of female patients, of subjects with hepatitis B or C coinfection or of intravenous drug use, and with a lower nadir CD4+ cell count in our study population compared with pivotal

randomized clinical trials evaluating the strategy.^[10,12] Our analysis also provides further long-term data on the efficacy of unboosted ATV when used in combination with the optimal NRTI background of ABC/3TC in subjects who were not treated with ATV/r—and particularly not treated with PIs—at baseline.

In summary, our analysis of the data of this large prospective cohort suggests that a switch to unboosted ATV + ABC/3TC regimen with a pVL ≤ 50 copies/mL is associated with a low risk of VF and discontinuation due to adverse events, and confirms outcome data previously seen in randomized clinical trials. This risk was smallest in patients with no prior evidence of VF to a PI, those with a high CD4+ nadir cell count and with long-term viral suppression. These data may also have interest in resource-limited countries where all 3 components are available as FDA-certified generic or low-cost treatments. Additional work is needed to further guide the selection of people who are likely to benefit from this strategy and inform antiretroviral treatment guidelines.

Acknowledgments

The EuroSIDA Study group: The multicentre study group, EuroSIDA (national coordinators in parenthesis). Argentina: (M Losso), M Kundro, Hospital JM Ramos Mejia, Buenos Aires. Austria: (N Vetter), Pulmologisches Zentrum der Stadt Wien, Vienna; R Zangerle, Medical University Innsbruck, Innsbruck. Belarus: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; D Paduto, Regional AIDS Centre, Svetlogorsk. Belgium: (N Clumeck), S De Wit, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent. Bosnia-Herzegovina: (V Hadziosmanovic), Klinicki Centar Univerziteta Sarajevo, Sarajevo. Bulgaria: (K Kostov), Infectious Diseases Hospital, Sofia. Croatia: (J Begovac), University Hospital of Infectious Diseases, Zagreb. Czech Republic: (L Machala), D Jilich, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. Denmark: G Kronborg, T Benfield, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, Rigshospitalet, Copenhagen; NFMØller, C Pedersen, Odense University Hospital, Odense; L Ostergaard, Skejby Hospital, Aarhus, U B Dragsted, Roskilde Hospital, Roskilde; L N Nielsen, Hillerød Hospital, Hillerød. Estonia: (K Zilmer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosakond Sisekliinik, Kohtla-Järve. Finland: (M Ristola), I Aho, Helsinki University Central Hospital, Helsinki. France: (J-P Viard), Hôtel-Dieu, Paris; P-M Girard, Hospital Saint-Antoine, Paris; L Cotte, Hôpital de la Croix Rousse, Lyon; C Pradier, E Fontas, Hôpital de l'Archet, Nice; F Dabis, D Neau, Unité INSERM, Bordeaux, C Duvivier, Hôpital Necker-Enfants Malades, Paris. Germany: (J Rockstroh), Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; C Stefan, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. Georgia: (N Chkhartishvili) Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi. Greece: (J Kosmidis), P Gargalianos, G Xylomenos, P Lourida, Athens General Hospital; H Sambatakou, Ippokraton General Hospital, Athens. Hungary: (J Szilávik), Szent László Hospital, Budapest. Iceland: (M Gottfredsson), Landspítali University Hospital, Reykjavik. Ireland: (F Mulcahy), St. James's Hospital, Dublin. Israel: (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; E Shahar, G Hassoun, Rambam Medical

Center, Haifa; H Elinav, M Haouzi, Hadassah University Hospital, Jerusalem; D Elbirt, ZM Sthoeger, AIDS Center (Neve Or), Jerusalem. Italy: (A D'Arminio Monforte), Istituto Di Clinica Malattie Infettive e Tropicale, Milan; R Esposito, I Mazzeo, C Mussini, Università Modena, Modena; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; M Zaccarelli, A Antinori, R Acinapura, M Plazzi, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan. Latvia: (B Rozentale), Infectology Centre of Latvia, Riga. Lithuania: (V Uzdaviniene) Vilnius University Hospital Santariskiu Klinikos, Vilnius; R Matulionyte, Center of Infectious Diseases, Vilnius University Hospital Santariskiu Klinikos, Vilnius. Luxembourg: (T Staub), R Hemmer, Centre Hospitalier, Luxembourg. The Netherlands: (P Reiss), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. Norway: (V Ormaasen), A Maeland, J Bruun, Ullevål Hospital, Oslo. Poland: (B Knysz), J Gasiorowski, M Inglot, Medical University, Wrocław; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; R Flisiak, A Grzeszczuk, Medical University, Białystok; M Parczewski, M Pynka, K Maciejewska, Medical University, Szczecin; M Beniowski, E Mularska, Ośrodek Diagnostyki i Terapii AIDS, Chorzów; T Smiatacz, M Gensing, Medical University, Gdansk; E Jablonowska, E Malolepsza, K Wojcik, Wojewodzki Szpital Specjalistyczny, Łódź; I Mozer-Lisewska, Poznan University of Medical Sciences, Poznan. Portugal: (M Doroana), L Caldeira, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon. Romania: (R Radoi), C Oprea, Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest. Russia: (A Rakhmanova) (deceased), Medical Academy Botkin Hospital, St Petersburg; A Rakhmanova, St Petersburg AIDS Centre, St Petersburg; T Trofimova, Novgorod Centre for AIDS, Novgorod, I Khromova, Centre for HIV/AIDS & Infectious Diseases, Kaliningrad; E Kuzovatova, Nizhny Novgorod Scientific and Research Institute, Nizhny Novgorod. Serbia: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. Slovakia: A Shunnar, D Staneková, Dérer Hospital, Bratislava. Slovenia: (J Tomazic), University Clinical Centre Ljubljana, Ljubljana. Spain: (JM Gatell), JM Miró, Hospital Clinic Universitari de Barcelona, Barcelona; S Moreno, J. M. Rodriguez, Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona; JM Laporte, Hospital Universitario de Alava, Vitoria-Gasteiz. Sweden: (K Falconer), A Thalme, A Sonnerborg, Karolinska University Hospital, Stockholm; A Blaxhult, Venhälsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö. Switzerland: (B Ledergerber), R Weber, University Hospital Zurich; M Cavassini, University Hospital Lausanne; A Calmy, University Hospital Geneva; H Furrer, University Hospital Bern; M Battegay, University Hospital Basel; P Schmid, Cantonal Hospital St. Gallen. Ukraine: (E Kravchenko), Kiev Centre for AIDS, Kiev; V Frolov, G Kutsyna, I Baskakov, Luhansk State Medical University, Luhansk; A Kuznetsova, Kharkov State Medical University, Kharkov; G Kysel'yova, Crimean Republican AIDS centre, Simferopol; M Sluzhynska, Lviv Regional HIV/AIDS Prevention and Control CTR, Lviv. United Kingdom: (B Gazzard), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, E Simons, S Edwards, Mortimer Market Centre, London; A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London Hospital, London; J Weber, G Scullard, Imperial College School

of Medicine at St. Mary's, London; A Clarke, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh. The following centers have previously contributed data to EuroSIDA: Hôpital de la Pitié-Salpêtrière, Paris, France; Bernhard Nocht Institut für Tropenmedizin, Hamburg, Germany; 1st I.K.A Hospital of Athens, Athens, Greece; Ospedale Riuniti, Divisione Malattie Infettive, Bergamo, Italy; Ospedale di Bolzano, Divisione Malattie Infettive, Bolzano, Italy; Ospedale Cotugno, III Divisione Malattie Infettive, Napoli, Italy; Hospital Carlos III, Departamento de Enfermedades Infecciosas, Madrid, Spain; Odessa Region AIDS Center, Odessa, Ukraine. *EuroSIDA Steering Committee*: J Gatell, B Gazzard, A Horban, I Karpov, B Ledergerber, M Losso, A d'Arminio Monforte, C Pedersen, A Rakhmanova, M Ristola, A Phillips, P Reiss, J Lundgren, J Rockstroh, S De Wit. Chair: J Rockstroh, Vice-chair: S De Wit, Study Co-leads: A Mocroft, O Kirk. EuroSIDA Representatives to EuroCoord: O Kirk, A Mocroft, J Garup, P Reiss, A Cozzi-Lepri, R Thiebaut, J Rockstroh, D Burger, R Paredes, L Peters. EuroSIDA staff. Coordinating Centre Staff: O Kirk, L Peters, C Matthews, AH Fischer, A Bojesen, D Raben, D Kristensen, K Grønberg Laut, JF Larsen, D Podlekareva. Statistical Staff: A Mocroft, A Phillips, A Cozzi-Lepri, L Shepherd, A Schultze. Josep M Llibre, Alessandro Cozzi-Lepri, Court Pedersen, Matti Ristola, Marcelo Losso, Amanda Mocroft, Viktor Mitsura, Karolin Falconer, Fernando Maltez, Marek Beniowski, Vincenzo Vullo, Gamal Hassoun, Elena Kuzovatova, János Szlavik, Anastasiia Kuznetsova, Hans-Jürgen Stellbrink, Claudine Duvivier, Simon Edwards, Kamilla Laut, Roger Paredes for the EuroSIDA Study Group.

References

- [1] Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. May 2015. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed May 6, 2016.
- [2] Günthard HF, Aberg JA, Eron JJ, et al. Antiretroviral treatment of adult HIV infection. *JAMA* 2014;312:410–25.
- [3] European AIDS Clinical Society. Guidelines. Version 8.0 October 2015. Available at: <http://www.eacsociety.org/>. Accessed March 10, 2016.
- [4] Expert Panel of GeSIDA and the National AIDS Plan Document on antiretroviral therapy in adults infected by the human immunodeficiency virus (updated January 2015). *Enf Infect Microbiol Clin* 2015; 33:544–56.
- [5] Kempf D, Marsh K, Kumar G, et al. Pharmacokinetic enhancement of inhibitors of the human immunodeficiency virus protease by coadministration with ritonavir. *Antimicrob Agents Chemother* 1997; 41:654–60.
- [6] Lennox JL, Landovitz RJ, Ribaud HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naïve volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med* 2014; 161:461–71.
- [7] Clotet B, Feinberg J, Van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naïve adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet* 2014;383:2222–31.
- [8] Malan DR, Krantz E, David N, et al. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral therapy regimens in antiretroviral-naïve patients. *J Acquir Immune Defic Syndr* 2008;47:161–7.
- [9] Focà E, Ripamonti D, Motta D, et al. Unboosted atazanavir for treatment of HIV infection: rationale and recommendations for use. *Drugs* 2012;72:1161–73.
- [10] Squires KE, Young B, DeJesus E, et al. Similar efficacy and tolerability of atazanavir compared with atazanavir/ritonavir, each with abacavir/lamivudine after initial suppression with abacavir/lamivudine plus ritonavir-boosted atazanavir in HIV-infected patients. *AIDS* 2010; 24:2019–27.

- [11] Squires KE, Young B, DeJesus E, et al. ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine. *HIV Clin Trials* 2012;13:233–44.
- [12] Wohl DA, Bhatti L, Small CB, et al. Simplification to abacavir/lamivudine + atazanavir maintains viral suppression and improves bone and renal biomarkers in ASSURE, a randomized, open label, non-inferiority trial. *PLOS One* 2014;9:e96187.
- [13] Baril J, Conway B, Giguère P, et al. A meta-analysis of the efficacy and safety of unboosted atazanavir compared with ritonavir-boosted protease inhibitor maintenance therapy in HIV-infected adults with established virological suppression after induction. *HIV Med* 2014;15:301–10.
- [14] Ghosn J, Carosi G, Moreno S, et al. Unboosted atazanavir-based therapy maintains control of HIV type-1 replication as effectively as a ritonavir-boosted regimen. *Antivir Ther* 2010;15:993–1002.
- [15] Young B, Squires K, Ross LL, et al. Inflammatory biomarker changes and their correlation with Framingham cardiovascular risk and lipid changes in antiretroviral-naïve HIV-infected patients treated for 144 weeks with abacavir/lamivudine/atazanavir with or without ritonavir in ARIES. *AIDS Res Hum Retroviruses* 2012;29:350–8.
- [16] Packard CJ, O'Reilly DS, Caslake MJ, et al. Predictor of coronary heart disease. *N Engl J Med* 2000;343:1148–55.
- [17] Rodríguez-Nóvoa S, Morello J, Barreiro P, et al. Switch from ritonavir-boosted to unboosted atazanavir guided by therapeutic drug monitoring. *AIDS Res Hum Retroviruses* 2008;24:821–5.
- [18] Giuntini R, Martinelli C, Ricci E, et al. Efficacy and safety of boosted and unboosted atazanavir-containing antiretroviral regimens in real life: results from a multicentre cohort study. *HIV Med* 2010;11:40–5.
- [19] Pavie J, Porcher R, Torti C, et al. Efficacy and safety of a switch to unboosted atazanavir in combination with nucleoside analogues in HIV-1-infected patients with virological suppression under antiretroviral therapy. *J Antimicrob Chemother* 2011;66:2372–8.
- [20] de Wit S, Moutschen M, Vandekerckhove L, et al. Long-term use of unboosted atazanavir in real-life in Belgium: a retrospective observational cohort of 457 HIV-infected patients. In: 14TH European AIDS Conference of the European AIDS Clinical Society (EACS). October 16-19, 2013. Brussels, Belgium. Abstract PE8/15.
- [21] Santos JR, Moltó J, Llibre JM, et al. Unboosted atazanavir plus co-formulated lamivudine/abacavir as a ritonavir-sparing simplification strategy in routine clinical practice. *HIV Clin Trials* 2009;10:129–34.
- [22] Soriano V, García-Gasco P, Vispo E, et al. Efficacy and safety of replacing lopinavir with atazanavir in HIV-infected patients with undetectable plasma viraemia: final results of the SLOAT trial. *J Antimicrob Chemother* 2008;61:200–5.
- [23] Taburet AM, Piketty C, Chazallon C, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2004;48:2091–6.
- [24] DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naïve HIV-infected adults. *Clin Infect Dis* 2004;39:1038–46.
- [25] U.S. Department of Health and Human Services, Food and Drug Administration. Human immunodeficiency virus-1 infection: developing antiretroviral drugs for treatment guidance for industry. Available at: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm355128.pdf>. Accessed May 17, 2016.
- [26] Gatell J, Salmon-Ceron D, Lazzarin A, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (A1424-097) 48-week results. *Clin Infect Dis* 2007;44:1484–92.
- [27] Mallolas J, Podzamczar D, Milinkovic A, et al. Efficacy and safety of switching from boosted lopinavir to boosted atazanavir in patients with virological suppression receiving a LPV/r-containing HAART: the ATAZIP study. *J Acquir Immune Defic Syndr* 2009;51:29–36.
- [28] Martin-Iguacel R, Llibre JM, Friis-Moller N. Risk of cardiovascular disease in an aging HIV population: where are we now? *Curr HIV/AIDS Rep* 2015;12:375–87.
- [29] Persson M, Hedblad B, Nelson JJ, et al. Elevated Lp-PLA2 levels add prognostic information to the metabolic syndrome on incidence of cardiovascular events among middle-aged nondiabetic subjects. *Arterioscler Thromb Vasc Biol* 2007;27:1411–6.
- [30] Braitstein P, Justice A, Bangsberg DR, et al. Hepatitis C coinfection is independently associated with decreased adherence to antiretroviral therapy in a population-based HIV cohort. *AIDS* 2006;20:323–31.
- [31] Barreiro P, Rodríguez-Novoa S, Labarga P, et al. Influence of liver fibrosis stage on plasma levels of antiretroviral drugs in HIV-infected patients with chronic hepatitis C. *J Infect Dis* 2007;195:973–9.