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

A prospective cohort study

Josep M. Llibre, MD, PhD; a Alessandro Cozzi-Lepri, PhD; b Court Pedersen, MD; c Matti Ristola, MD; d Marcelo Losso, MD; e Amanda Mocroft, PhD; f Viktor Mitsura, MD; g Karolin Falconer, MD, PhD; h Fernando Maltez, MD, PhD; i Marek Beniowski, MD; j Vincenzo Vullo, MD; k Gamal Hassoun, MD; l Elena Kuzovatova, MD; m János Szlavik, MD; n Anastassia Kuzenetsova, MD; o Hans-Jürgen Stellbrink, MD; p Claudine Duvivier, MD; q Simon Edwards, MD; r Hans-Jürgen Stellbrink, MD; s Roger Paredes, MD; t Kamilla Laut, MD; 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...
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 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-naive subjects, although with less hyperbilirubinemia and a better lipid profile.\(^8\) Therefore, it is not recommended in treatment naive.\(^6\)\(^,\)\(^9\)

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-naive patients in the analysis.\(^20\) Othres 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, 48 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).
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-based ART, Hepatitis C virus (HCV) coinfection, calendar year of switching to atazanavir, hepatitis B virus (HBV) coinfection, and hepatitis C (HCV) coinfection status. 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-based ART, Hepatitis C virus (HCV) coinfection, calendar year of switching to atazanavir, hepatitis B virus (HBV) coinfection, and hepatitis C (HCV) coinfection status.

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

| Characteristics                                      | n   | (%)  |
|------------------------------------------------------|-----|------|
| Male                                                  | 191 | 67   |
| Female                                                | 94  |      |
| IDU                                                   | 76  | 26.25|
| 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                                              | 105 | 36.8 |
| Calendar year of switching to atazanavir, median (IQR)| 2008 (2006–2010) |
| Age, y, median (IQR)                                  | 46  | 15–53|
| CD4 count at switching to atazanavir, cells/mm³, median (IQR)| 530 (357–700) |
| CD4 count nadir, cells/mm³, 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, median (IQR)| 44  | 23–68|
| Third (anchor) drug in the previous regimen, n (%)    |     |      |
| ATV/r                                                 | 79  | 27.7 |
| Other PIs/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.

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

| Disposition                                           | Week 48 | Week 96 | Week 144 |
|-------------------------------------------------------|---------|---------|----------|
| HIV-RNA <50 copies/mL                                 | 212     | 191     | 167      |
| HIV-RNA >50 copies/mL                                 | 18      | 16      | 11       |
| No virological data in window                         |         |         |          |
| Discontinued due to adverse events                    | 1       | 0.4     | 6        |
| Discontinued due to other reasons                     | 10      | 3.5     | 16       |
| On study but missing pVL in window                    | 44      | 15.4    | 85       |
| Other endpoints, n (%)                                |         |         |          |
| Pure virological failure (OT, threshold 50 copies/mL)  | 18      | 7.8     | 11       |
| Pure virological failure (OT, threshold 200 copies/mL) | 10      | 4.3     | 7        |
| Composite failure or stop due to adverse events       | 19      | 6.7     | 17       |
| Composite failure or stop due to other reasons        | 28      | 9.8     | 27       |
| Composite failure or stop due to any reason (TLOVR)   | 29      | 10.2    | 33       |
| Composite failure or stop due to any reason or pVL missing | 73      | 25.6    | 118      |

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

1 Includes patients who discontinued due to 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.
2 Other includes withdrawal consent, loss to follow-up, pregnancy, physician decision.
3 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.

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/µL (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 ATVR in 79 (27.7%), and another PIs in 29 (10.2%). Of all people included, 90 (31.6%) had previously failed 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 63.3%/55.6%/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 patient-years 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...
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: 0.92–8.49] per 6 months) 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 M46I/L54V/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.

VF rates in the real clinical setting are bound to be lower than those seen in trials. However, using the threshold of 50 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. 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. 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. 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. 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), inflammation, or thrombogenesis (hsCRP, interleukin-6, and D-dimer) generally remained stable, there is currently not enough evidence to recommend a switch to ATV plasma levels and liver.

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. The interpretation of this result was that hepatitis coinfection was a marker for disordered lifestyle due to intravenous drug use and nonadherence. 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.

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. 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 patients 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 Paduro, 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 Jerstoft, T Katzenstein, Rigshospitalet, Copenhagen; NFMøller, C Pedersen, Odense University Hospital, Odense; L Ostedgaard, Skejby Hospital, Aarhus, U B Dragsted, Roskilde Hospital, Roskilde; L N Nielsen, Hillerod Hospital, Hillerod. Estonia: (K Zímer), West-Tallinn Central Hospital, Tallinn; Jelena Smidt, Nakkusosasandise Kliinik, Kohila-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 Fontes, Hôpital de l’Archet, Nice; F Dabis, D Neau, Unité INSERM, Bordeaux, C Duvrier, Hôpital Necker-Enfants Malades, Paris. Germany: (J Rockstroh), Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; D 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, Ippokration General Hospital, Athens. Hungary: (J Szlák), Szent László Hospital, Budapest. Iceland: (M Gorthredsson), Landspitali University Hospital, Reykjavik. Ireland: (G Mulcahy), St. James’s Hospital, Dublin. Israel: (I Yust), D Turner, M Burke, Ichilov Hospital, Tel Aviv; E Shahar, G Hassoun, Rambam Medical
[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, Bhati 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(9):e108187.

[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-naive HIV-infected patients treated for 144 weeks with abacavir/lamivudine/atazanavir with or without ritonavir in ARIES. AIDS Res Hum Retroviruses 2012;29:350–48.

[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, Torri 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 atazanavir/ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 2004;48:2091–6.

[21] Soriano V, García-Gasco P, Vispo E, et al. Efficacy and safety of replacing lopinavir with atazanavir in HIV-infected patients with undetectable plasma viremia: final results of the SLOAT trial. J Antimicrob Chemother 2008;61:200–5.

[22] Taburet AM, Peketty 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.

[23] DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. Clin Infect Dis 2004;39:1038–46.

[24] 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.

[25] 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 (AH24-097) 48-week results. Clin Infect Dis 2007;44:1484–92.

[26] Mailolas J, Podzamczer 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.

[27] 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.

[28] 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.

[29] Bräutigam 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.

[30] 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.