Long-term Effectiveness of Recommended Boosted PI-Based Antiretroviral Therapy in Europe

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ABSTRACT

Objective: To evaluate the long-term response to antiretroviral treatment (ART) based on atazanavir/ritonavir (ATZ/r)-, darunavir/ritonavir (DRV/r)-, and lopinavir/ritonavir (LPV/r)-containing regimens.

Methods: Data were analyzed from 5,678 EuroSIDA-enrolled patients starting a DRV/r-, ATZ/r-, and LPV/r-containing regimens between 1 January 2000 and 30 June 2013. Separate analyses were performed for the following subgroups of patients: (a) ART-naïve subjects (8%) at ritonavir-boosted protease inhibitor (PI/r) initiation; (b) ART-experienced individuals (44%) initiating the new PI/r with viral load (VL) ≤500 copies/mL; and (c) ART-experienced patients (48%) initiating the new PI/r with VL >500 copies/mL. Virological failure (VF) was defined as two consecutive VL measurements >200 copies/mL after ≥24 weeks of PI/r initiation. Kaplan-Meier and multivariable Cox models were used to compare the risk of failure by PI/r-based regimens. The main analysis was performed by intention-to-treat (ITT) ignoring treatment switches.

Results: The time to VF favored DRV/r over ATZ/r, and both were superior to LPV/r (log-rank test, P <0.02) in all analyses. Nevertheless, the risk of VF in ART-naïve patients was similar regardless of the PI/r initiated after controlling for potential confounders. The risk of VF in both treatment-experienced groups was lower in DRV/r than in ATZ/r, which, in turn, was lower than in LPV/r-based ART.

Conclusions: Although confounding by indication and calendar year cannot be completely ruled out, in ART-experienced subjects the long-term effectiveness of DRV/r-containing regimens appears to be greater than that of ATZ/r and LPV/r.

Keywords: Darunavir/ritonavir, lopinavir/ritonavir, atazanavir/ritonavir, naïve-patients, ART-experienced patients.

Introduction

The new global 90-90-90 WHO targets call for 90% of all people with HIV to be diagnosed, 90% of people with HIV diagnosis to be treated, and 90% of treated subjects to have virological suppression by 2020 [1]. Standard antiretroviral treatment (ART) is still based on a combination of at least 3 antiretroviral drugs [2–4], it is generally expensive, and there are still many limitations to its use, especially in developing countries.

Consistent with ART optimizing principles, availability of fixed-dose combinations, tolerability, and the risk of resistance mutations, recent WHO recommendations for the limited resource setting include the use of non-nucleoside reverse transcriptase inhibitors and integrase strand-transfer inhibitors in first-line ART, and darunavir/ritonavir (DRV/r), lopinavir/ritonavir (LPV/r), and atazanavir/ritonavir (ATZ/r) as alternative drugs in second and third ART regimens [1]. Nevertheless, these drugs have different profiles of efficacy, safety, and tolerability [5–8].

Because the effectiveness of therapy in daily clinical practice usually differs from what is observed in clinical trials [9,10], it is important to analyse the experience with use of DRV/r, ATZ/r, and LPV/r in unselected HIV-infected patients. This study aimed to evaluate the long-term effectiveness of DRV/r-, ATZ/r-, and LPV/r-containing regimens initiated at various stages during participants' antiretroviral treatment history and the factors associated with virological failure (VF), treatment discontinuation, and CD4 cell count recovery in a large European cohort of HIV-1-infected patients.

Methods

Study population and data collection

The EuroSIDA study is a prospective, observational cohort of more than 22,000 HIV-positive subjects in 105 centers in 35 European countries, Israel, and Argentina, which has been described in detail previously [11,13–15]. The study population of the present analysis included all EuroSIDA-enrolled patients initiating an ATZ/r-, DRV/r-, or LPV/r-containing regimen between 1 January 2000 and 30 June 2013 who also had at least one additional clinical visit. Patients were included if they satisfied the inclusion criteria for one of the following groups: (a) ART-naive, i.e., previously untreated subjects at the time of boosted protease inhibitor (PI/r) initiation; (b) ART-switching, i.e., ART-experienced individuals initiating the new PI/r with VL ≤500 copies/mL; and (c) ART-salvage, i.e., ART-experienced patients initiating the new PI/r with VL >500 copies/mL, including patients who were on voluntary ART-interruption. Prior exposure to PI/r was allowed. Data were collected at the date of DRV/r, ATZ/r, or LPV/r initiation (baseline) and during the follow-up period, according to the EuroSIDA study protocol. Data collected for this analysis included demographic characteristics (age, gender, ethnicity, route of HIV-infection transmission), AIDS stage at time of PI/r initiation, hepatitis C and B virus (HCV/HBV) co-infections, HIV-1 RNA levels, CD4+ cell counts, CD4+ nadir at baseline, number of previous failures of treatment to specific drug classes, previous exposure to PI, nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbones included in PI/r regimen, and genotypic test results performed before DRV/r, ATZ/r, or LPV/r initiation (when available).

The primary endpoint of this analysis was the median time to VF after DRV/r, ATZ/r, or LPV/r initiation. VF was defined as two consecutive VL ≥200 copies/mL at 24 weeks or at any time after achieving HIV-1 RNA ≤50 copies/mL. The date of the first VL ≥200 copies/mL was used to define the time at which VF had occurred. The secondary endpoints were time to the composite endpoint of VF or PI/r discontinuation, and time to achieve a gain of CD4+ T cell count ≥200 cells/mm^3 above baseline levels while the person remained with a viral load ≤200 copies/mL.

Prior approval was given by the Ethics Committee of each participating center for the study, which is being carried out according to the stipulations of the Declaration of Helsinki (Seoul, 2008). All patients gave their written informed consent prior to participation.

Statistical analysis

For descriptive purposes, Europe was divided into six regions: north (Denmark, United Kingdom, Ireland, the Netherlands, Norway, Finland, and Sweden); east (Belarus, Estonia, Latvia, Lithuania, Russia, and Ukraine); west central (Austria, Belgium, France, Germany, Luxembourg, and Switzerland); east central (Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Serbia, and Slovakia); and south (Greece, Italy, Spain, Portugal, and Israel). Argentina was analyzed separately. Variables with a normal distribution were described as mean (SD) and compared using the *t*-test. Median and IQR were used to describe variables that did not follow a normal distribution, which were compared using a non-parametric test. Percentages were compared using the X^2 test or an exact binomial test when appropriate. Separate analyses were performed in the ART-naïve and each of the two ART-experienced groups.

Kaplan-Meier analysis was used to determine the median time to VF and the proportion of patients who experienced VF up to five years from starting the PI/r-based regimen. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated and a proportional hazards Cox regression model was performed to identify factors associated with each of the three considered outcomes. Multivariable models were fitted using 0.05 as the significance level in univariable analysis for a covariate to be included in the final multivariable model. The relationship between the final set of included covariates was checked and removed when collinearity was detected. Effectiveness was evaluated by an intention to treat (ITT) analysis ignoring treatment switches of PI/r (genuine ITT analysis). Sensitivity analyses were performed with any discontinuation of PI/r counted as failure (ITT: Switching=Failure; ITT: S=F), counting as failures only discontinuations of PI/r due to toxicity (ITT: switch for Toxicity=Failure; ITT: T=F), and with data censored at the date of PI/r discontinuation (on-treatment analysis, OT). In addition, in the pre-treated population subgroup that had initiated the new PI/r-containing regimen with VL >500 copies/mL, sensitivity analyses were also performed on those subjects initiating PI/r after 2004 and with genotyping tests available.

Statistical analysis was performed using SAS (Statistical Analysis Software, Cary, NC, USA, version 9.3).

Results

A total of 5,678 out of 18,913 HIV-infected individuals enrolled in the EuroSIDA study up to September 30, 2013, met the inclusion criteria for this analysis.

ART-naïve subgroup

Of these 5,678, a total of 431 (8%) were ART-naïve patients of which 220 (51%) were receiving LPV/r, 119 (28%) were on ATZ/r, and 92 (21%) were on DRV/r-based regimens. The median (IQR) time of follow-up was 28 (11-57) months. Table 1 presents the baseline characteristics of this subgroup of patients. Median (IQR) CD4+ cell counts and HIV VL were 261 (164-352) cells/mm^3 and 79,271 (780-8,415,274) copies/mL, respectively. Genotypic resistance tests before PI/r initiation were available for 111 (26%) subjects.

Of the 431 patients included, 79 (18%) experienced VF during the follow-up. Of the 184 (42.7%) subjects with the composite endpoint of VF or PI/r discontinuation, PI/r was discontinued in 148 (80.4%). In the genuine ITT analysis, the median time to VF was longer (log rank, p = 0.004) for patients who initiated DRV/r-based treatment in comparison to those patients initiating ATZ/r or LPV/r (Figure 1A). Similarly, patients initiating DRV/r also had the longest median time to failure compared to ATZ/r or LPV/r in the ITT: S=F and ITT: T=F sensitivity analyses (Figures 1B and 1C), but not in the OT analysis (supplementary data, Figure 1A).

After adjustment for confounding variables, the multivariable Cox proportional hazard model showed no differences between DRV/r, ATZ/r, or LPV/r in the ITT analysis and when we examined the composite endpoint of VF or PI/r discontinuation (Figure 1D). Nevertheless, patients with AIDS diagnosis at time of initiation of their first PI/r-based ART were significantly more likely to experience VF (HR: 2.97, 95% CI: 1.26-7.03, p = 0.01), and female gender (vs male HR: 2.08, 95% CI: 1.20-3.63, p = 0.01 were associated with a higher risk in the ITT: S=F sensitive analysis (supplementary data, Figure 2).

No differences were found with regard to the probability of gaining a CD4+ cell count ≥200 cells/mm^3 in the Cox proportional hazard model (Figure 1D) when comparing the three PI/r treatment groups.

ART-switching subgroup

A total of 2,507 (44%) subjects had been switched to DRV/r, ATZ/r, or LPV/r with HIV VL ≤500 copies/mL. Of these, 1031 (41%) started a LPV/r-based, 824 (33%) started an ATZ/r-based, and 652 (26%) started a DRV/r-based regimens. The median (IQR) time of follow-up was 40 (17-68) months, and the median (IQR) CD4+ cell count was 468 (317-652) cells/mm^3. The median (IQR) number of previous PI previously experienced was 2 (1-3) and historical genotypic resistance tests before switching to PI/r were available for 1171 (47%) patients (Table 2). The median (IQR) duration of continuous viral suppression prior to baseline was 56 (32-84) months.

Out of the 2,507 patients included in this subgroup, 408 (16%) experienced VF during the follow-up. Of the 1278 (51.0%) subjects with the composite endpoint, PI/r was discontinued in 1042 (81.5%). In the ITT analysis, the median time to VF was longer (log rank, p <0.0001) for patients who initiated a DRV-switch strategy (Figure 2A), with a risk of developing VF of 5.8% [95% CI 3.6, 8.0] by 3 years compared to those who initiated ATZ/r (13.8 % [95% CI 11.4, 16.3]) or LPV/r (21.1 % [95% CI 18.5, 23.7]). Similar differences

were observed in the sensitivity ITT: S=F, ITT: T=F, and OT analyses (Figures 2B, 2C, and supplementary Figure 1B, respectively).

Switching to LPV/r (HR: 2.56; 95% CI 1.62, 4.05; p <0.001) or ATZ/r (HR: 1.98; 95% CI 1.27, 3.08; p <0.001) was associated with a higher risk of VF in comparison to DRV/r in the multivariable Cox proportional hazard model according to the ITT analysis (Figure 2D). In addition, intravenous drug use, higher HIV-1 RNA at baseline, black ethnicity, having historic genotyping tests available, and number of prior failures to non-PI based ART were independent predictors of an increased hazard of VF. The association with baseline VL was confirmed when it was explored using a categorical variable (ARH: 1.64; 95% CI 1.22, 2.21; p = 0.001 and ARH: 1.87; 95% CI 1.39, 2.53; p <0.001 comparing the VL≤ 50 copies/mL stratum with 51-200 and 201-500 copies/mL, respectively). By contrast, younger patients, with higher CD4+ cell count at switching, and having initiated DRV/r, ATZ/r, or LPV/r more recently were all associated with a lower hazard of VF (supplementary data, Figure 4).

The use of DRV/r, ATZ/r, or LPV/r, however, was not found to be predictive of CD4 count response in the multivariable Cox proportional hazard model (Figure 2D).

ART-salvage subgroup

A total of 2,740 (48%) patients began DRV/r, ATZ/r, or LPV/r with HIV-1 RNA ≥500 copies/mL. Of these, 1,893 (69%) started a LPV/r-based, 594 (22%) started an ATZ/r-based, and 253 (9%) started a DRV/r-based regimens. Their median (IQR) time of follow-up was 35 (12-72) months. Median (IQR) CD4+ cell counts and HIV VL were 260 (156-380) cells/mm^3 and 31,482 (501-7,943,282) copies/mL, respectively. The median (IQR) number of PI previously experienced was 2 (1-3) and genotypic resistance tests were available for 1,268 (46%) subjects (Table 2).

Out of the 2,740 patients included, 942 (34%) experienced VF during the follow-up. Of the 1812 (66%) subjects with the composite endpoint, PI/r was discontinued in 1267 (70%). In the ITT analysis, the median time to VF was longer (log rank, p <0.001) for patients who initiated DRV/r-based treatment as salvage ART-regimen (Figure 3A), with a risk of developing VF of 14.2% (95% CI 8.6, 19.9) by 3 years compared to patients who initiated ATZ/r (20.6% [95% CI 17.1, 24.1]) or LPV/r (37.9% [95% CI 35.6, 40.2]). Similarly, patients initiating DRV/r also showed longer time to failure compared to those initiating ATZ/r or LPV/r in sensitivity analyses (Figures 3B, 3C and supplementary data: Figure 1C), and in the analyses restricted to subjects with a pre-treatment genotype available (supplementary data, Figure 5) or initiating boosted PI after 2004 (supplementary data, Figure 6).

In addition, patients who initiated LPV/r- (HR: 1.61; 95% CI 1.02, 2.54; p = 0.040) had a higher risk of VF than those who initiated DRV/r in the multivariable Cox proportional hazard model (Figure 3D). Furthermore, having acquired HIV infection through heterosexual sex (compared to men who have sex with men, higher HIV-1 RNA at salvage regimen initiation, and number of prior failures to respond to PI/r-based ART were associated with increased risk of VF. By contrast, younger patients, higher CD4+ cell count at ART-rescue, and having started DRV/r, ATZ/r, or LPV/r in more recent years were associated with a lower hazard of VF (supplementary data, Figure 7).

When we examined the composite endpoint of VF or PI/r discontinuation, starting LPV/r- or ATZ/r-based regimens as salvage ART was associated with a higher risk (HR: 3.12, 95% CI: 2.28-4.28, *p* <0.001 and HR: 2.09, 95% CI:1.52-2.88, *p* <0.001, respectively) than DRV/r in the ITT: S=F sensitive analysis. Similar results were also observed in the ITT: T=F (supplementary data, Figure 7).

The use of DRV/r, ATZ/r, or LPV/r was not found to be predictive of CD4 count response in the multivariable Cox proportional hazard model (Figure 3D), although a higher CD4 nadir, HIV RNA, and the availability of a genotyping test were all factors associated with a better chance of CD4 count recovery (supplementary data, Figure 3).

Discussion

In this analysis, when we examined endpoints that counted PI/r discontinuation as treatment failures, there was a clear superiority of DRV/r over LPV/r and ATZ/r. Indeed, although the risk of VF was similar in DRV/r, ATZ/r, and LPV/r in ART-naïve patients, the risk of PI/r discontinuation due to any reason was lowest for DRV/r. In the treatment-experienced patients who initiated PI/r either as the result of a switching strategy with suppressed viral load or as a salvage treatment, patients who experienced VF and the risk of VF or PI/r discontinuation was lower for DRV/r- compared to both LPV/r and ATZ/r.

In ART-naïve patients, the antiviral efficacy of ATZ/r has been shown to be similar to that of DRV/r and LPV/r in randomized studies [5,16,17]. However, ATZ/r shows higher rates of jaundice and hyperbilirrubinemia than DRV/r and LPV/r [5,17], a worse lipid profile than DRV/r [16,18], albeit with less gastrointestinal toxicity, and a better lipid profile than LPV/r. [5] In addition, DRV/r is superior to LPV/r in virological response [19], with a higher genetic barrier [6,20], higher efficacy in patients of different gender, age, race, or co-infection status [21], and fewer discontinuations due to adverse events [6]. In our analysis, we found no significant differences in the risk of VF between the three drugs. It must be noted, however, that the number of VF events was especially small with DRV/r, so the analysis of the ART-naïve population was likely underpowered. In contrast and coinciding with literature [6,17], we observed that the risk of PI/r discontinuation for any reason was >2.5 times higher in patients who started LPV/r- than in those initiating a DRV/r-based ART, while no significant difference was observed when ATZ/r and DRV/r regimens were compared. In addition, the study design and limited number of ART-naïve patients, including those with HIV VL >100,000 copies/mL and low CD4 cell count levels, might partly explain why prior AIDS diagnosis and female gender, but not the recognized CD4 cell count and HIV-RNA, were identified as predictive factors of virological response and clinical outcomes in ART-naïve patients [22–25]. Therefore, we believe that these results should be interpreted with caution.

In treatment-experienced patients, DRV/r and ATZ/r have been shown to be suitable for switching strategies with suppressed viral load [26–29], while DRV/r has been demonstrated to be the most effective PI/r in ART salvage strategies [7,30,31]. Regarding LPV/r, its posology, as well as a worse tolerance profile compared to DRV/r and ATZ/r [5,6], currently make it difficult to use in switching strategies. Nevertheless, LPV/r continues to have a role in second-line regimens in resource-limited settings [1]. Consistently, our results show a lower risk of experiencing VF and treatment discontinuation

for any reason or due to toxicity in patients starting DRV/r compared to those initiating ATZ/r or LPV/r, reflecting the well-known better efficacy and safety profile of DRV/r, and of ATZ/r compared with LPV/r-based regimens]5–7]. However, confounding by indication for switching cannot be ruled out.

As expected, having genotyping tests available and the number of prior failures of treatment with non-PI and PI-based ART were identified as predictors of virological response in patients from both subgroups of treatment-experienced patients. Having a history of genotypic testing might be considered a proxy of poor adherence or reflect selected testing for people perceived at increased risk of detection of resistance and risk of failure. Other characteristics such as age (older patients), female gender, men who have sex with women, black ethnicity, and co-infection with HCV were also identified in our study as factors associated with the risk of VF and treatment discontinuation in the ART-experienced patients. Similar results have been previously reported [24,32–39], and they may be the result of confounding due to differences in sociodemographic characteristics [35].

Our analysis has a number of limitations. First, we cannot rule out confounding by indication and calendar year as our patients were not randomized to the evaluated strategies. One crucial unmeasured possible confounder is indeed ART adherence, which has been shown to guide treatment choices and to be a predictor of treatment response and survival in HIV-infected patients [40,41]. Moreover, the better tolerance profile as well as the once daily dosage could have favored a better adherence of DRV/r and ATV/r compared to LPV/r [5,6]. Secondly, participants were from multiple countries showing a great diversity of socioeconomic and demographic characteristics, as well as differences in access to care, medical insurance, prevalence of immigration, co-morbidities and incidence of mental health disorders in PWID patients, pharmacokinetic or pharmacodynamic factors, and composition of the ART, some of which we tried to control for in the analysis, but residual confounding is still possible. These limitations, however, are inherent to the design of a continent-wide multicenter observational study subject to different local guidelines for the management of chronic HIV infection. Nevertheless, results from the multivariable Cox proportional hazard model were adjusted by clinical sites.

Despite limitations, the key strengths of our study are the inclusion of an unselected population of HIV-infected individuals routinely seen for care across Europe and the fact that we show robust estimates of the rates of treatment failure up to five years after the date of initiation. Our results suggest that in routine clinical practice, DRV/r-based regimens are independently associated with less risk of experiencing VF and any discontinuation or toxicity, showing a higher long-term effectiveness than that of ATZ/r- and LPV/r-based regimens, especially in ART-experienced patients. Findings from this study may be reasonably extrapolated to people living with HIV infection in European and other developed countries. Moreover, from the point of view of the new 90-90-90 WHO targets, our findings suggest that DRV/r-containing regimens may be considered a preferred PI/r option relative to other PI/r. DRV/r, however, is the most expensive PI currently available. Therefore, policies to reduce DRV/r cost and improve its accessibility in developing countries are still necessary.

In summary, assuming no unmeasured confounding factors, the long-term effectiveness of boosted PI-containing regimens in ART-experienced subjects appears to be greater in people receiving DRV/r than in

those receiving ATZ/r and LPV/r. The same tendency was observed in ART-naïve patients, although the analysis was likely to be underpowered in this population. Strategies to improve clinical care and treatment response continue to be necessary in some subsets of the HIV-infected population such as women, intravenous drug users, hepatitis co-infected and ethnic minorities.

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Conflict of interest notifications

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References

[1] World Health Organisation. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection: What's new? 2015;(November):1–16.

[2] European AIDS Clinical Society (EACS). EACS Guidelines. Vol. October. 2016. Version 8.1.

[3] DHHS Panel on Antiretroviral Guidelines for Adults and adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Department of Health and Human Services. Downloaded from http://aidsinfo.nih.gov/guidelines on 1/20/2017.

[4] Günthard HF, Saag MS, Benson CA, Rio C, Eron JJ, Gallant JE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society–USA Panel. *JAMA* 2016; **316**: 191–210.

[5] Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* 2008; **372**: 646–55.

[6] Ortiz R, Dejesus E, Khanlou H, Voronin E, van Lunzen J, Andrade-Villanueva J, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *AIDS* 2008; **22**: 1389–97.

[7] Madruga JV, Berger D, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. *Lancet* 2007; **370**: 49–58.

[8] Eron J, Yeni P, Gathe J, Estrada V, DeJesus E, Staszewski S, et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet* 2006; **368**: 476–82.

[9] López-Martínez A, Nathan MO, Caro-Vega Y, Crabtree-Ramírez B, Sierra-Madero J. Different Baseline Characteristics and Different Outcomes of HIV-Infected Patients Receiving HAART Through Clinical Trials Compared With Routine Care in Mexico. *J Acquir Immune Defic Syndr* 2012; **59**: 155–60.

[10] Freemantle N, Blonde L, Bolinder B, Gerber RA, Hobbs FDR, Martinez L, et al. Real-World Trials to Answer Real-World Questions. *Pharmacoeconomics* 2005; **23**: 747–54.

[11] Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, D'Arminio Monforte A, et al. Decline in the AIDS and death rates in the EuroSIDA study: An observational study. *Lancet* 2003; **362**: 22–9.

[12] From the Centers for Disease Control and Prevention.1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults. *JAMA* 1993; **269:** 729–30.

[13] Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, et al. Serious fatal and

nonfatal non-AIDS-defining illnesses in Europe. *J Acquir Immune Defic Syndr* 2010; **55**: 262–70.

[14] Kowalska JD, Friis-Møller N, Kirk O, Bannister W, Mocroft A, Sabin C, et al. The Coding Causes of Death in HIV (CoDe) Project. *Epidemiology* 2011; **22**: 516–23.

[15] Kowalska JD, Mocroft A, Ledergerber B, Florence E, Ristola M, Begovac J, et al. A Standardized Algorithm for Determining the Underlying Cause of Death in HIV Infection as AIDS or non AIDS Related: Results from the EuroSIDA Study. *HIV Clin Trials* 2011; **12:** 109–17.

[16] Martinez E, Gonzalez-Cordon A, Ferrer E, Domingo P, Negredo E, Gutierrez F, et al. Differential Body Composition Effects of Protease Inhibitors Recommended for Initial Treatment of HIV Infection: A Randomized Clinical Trial. *Clin Infect Dis* 2014; **60**: 811–20.

[17] Lennox JL, Landovitz RJ, Ribaudo HJ, Ofotokun I, Na LH, Godfrey C, et al. Efficacy and Tolerability of 3 Nonnucleoside Reverse Transcriptase Inhibitor–Sparing Antiretroviral Regimens for Treatment-Naive Volunteers Infected With HIV-1. *Ann Intern Med* 2014; **161**: 461-71.

[18] Saumoy M, Ordonez-Llanos J, Martinez E, Ferrer E, Domingo P, Ribera E, et al. Atherogenic properties of lipoproteins in HIV patients starting atazanavir/ritonavir or darunavir/ritonavir: a substudy of the ATADAR randomized study. *J Antimicrob Chemother* 2015; **70**: 1130–8.

[19] Mills AM, Nelson M, Jayaweera D, Ruxrungtham K, Cassetti I, Girard PM, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS* 2009; **23**: 1679–88.

[20] Lathouwers E, De Meyer S, Dierynck I, Van de Casteele T, Lavreys L, de Béthune MP, et al. Virological characterization of patients failing darunavir/ritonavir or lopinavir/ritonavir treatment in the ARTEMIS study: 96-week analysis. *Antivir Ther* 2011; **16**: 99–108.

[21] Fourie J, Flamm J, Rodriguez-French A, Kilby D, Domingo P, Lazzarin A, et al. Effect of Baseline Characteristics on the Efficacy and Safety of Once-Daily Darunavir/Ritonavir in HIV-1–Infected, Treatment-Naïve ARTEMIS Patients at Week 96. *HIV Clin Trials* 2015; **12**: 313–22.

[22] Mellors JW, Muñoz A, Giorgi J V, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997; **126**: 946–54.

[23] Mocroft A, Furrer HJ, Miro JM, Reiss P, Mussini C, Kirk O, et al. The Incidence of AIDS-Defining Illnesses at a Current CD4 Count ≥ 200 Cells/L in the Post-Combination Antiretroviral Therapy Era. *Clin Infect Dis* 2013; **57**: 1038–47.

[24] Paredes R, Mocroft A, Kirk O, Lazzarin A, Barton SE, van Lunzen J, et al. Predictors of virological success and ensuing failure in HIV-positive patients starting highly active antiretroviral therapy in Europe: results from the EuroSIDA study. *Arch Intern Med* 2000; **160**: 1123–32.

[25] Study Group on Death Rates at High CD4 Count in Antiretroviral Naive Patients, Lodwick RK, Sabin CA, Porter K, Ledergerber B, van Sighem A, et al. Death rates in HIV-positive antiretroviral-naive patients with CD4 count greater than 350 cells per microL in Europe and North America: a pooled cohort observational study. *Lancet* 2010; **376**: 947–56.

[26] Santos JR, Llibre JM, Berrio-Galan D, Bravo I, Miranda C, Perez-Alvarez S, et al. Monotherapy with boosted PIs as an ART simplification strategy in clinical practice. *J Antimicrob Chemother* 2015;

70: 1124–9.

[27] Arribas JR, Horban A, Gerstoft J, Fätkenheuer G, Nelson M, Clumeck N, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. *AIDS* 2010; **24**: 223–30.

[28] Squires KE, Young B, DeJesus E, Bellos N, Murphy D, Zhao HH, 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.

[29] Gatell J, Salmon-Ceron D, Lazzarin A, van Wijngaerden E, Antunes F, Leen C, 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 (AI424-097) 48-week results. *Clin Infect Dis* 2007; **44**: 1484–92.

[30] Katlama C, Haubrich R, Lalezari J, Lazzarin A, Madruga J V, Molina JM, et al. Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: pooled 48 week analysis of two randomized, controlled trials. *AIDS* 2009; **23**: 2289–300.

[31] Clotet B, Bellos N, Molina JM, Cooper D, Goffard JC, Lazzarin A, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet* 2007; **369**: 1169–78.

[32] Mocroft A, Gill MJ, Davidson W, Phillips AN. Predictors of a viral response and subsequent virological treatment failure in patients with HIV starting a protease inhibitor. *AIDS* 1998; **12:** 2161–7.

[33] Easterbrook PJ, Keruly JC, Creagh-Kirk T, Richman DD, Chaisson RE, Moore RD. Racial and ethnic differences in outcome in zidovudine-treated patients with advanced HIV disease. Zidovudine Epidemiology Study Group. *JAMA* 1991; **266**: 2713–8.

[34] Lagakos S, Fischl MA, Stein DS, Lim L, Volberding P. Effects of zidovudine therapy in minority and other subpopulations with early HIV infection. *JAMA*1991; **266:** 2709–12.

[35] Simbiri KO, Hausman A, Wadenya RO, Lidicker J. Access Impediments to Health Care and Social Services Between Anglophone and Francophone African Immigrants Living in Philadelphia with Respect to HIV/AIDS. *J Immigr Minor Heal* 2010; **12**: 569–79.

[36] van Leth F, Andrews S, Grinsztejn B, Wilkins E, Lazanas MK, Lange JM, et al. The effect of baseline CD4 cell count and HIV-1 viral load on the efficacy and safety of nevirapine or efavirenz-based first-line HAART. *AIDS* 2005; **19**: 463–71.

[37] Saunders P, Goodman A, Smith C, Marshall N, O'Connor J, Lampe F, et al. Does gender or mode of HIV acquisition affect virological response to modern antiretroviral therapy (ART)?. *HIV Med* 2016; **17**: 18-27.

[38] Pulido F, Hill A, Van Delft Y, Moecklinghoff C. Impact of hepatitis C co-infection on response to antiretroviral treatment. *AIDS Rev* 2012; **14**: 124–31.

[39] Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet* 2000; **356**: 1800–5.

[40] García de Olalla P, Knobel H, Carmona A, Guelar A, López-Colomés JL, Caylà JA. Impact of Adherence and Highly Active Antiretroviral Therapy on Survival in HIV-Infected Patients. *J Acquir Immune Defic Syndr* 2002; **30**: 105–10.

[41] Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, et al. Adherence to Protease Inhibitor Therapy and Outcomes in Patients with HIV Infection. *Ann Intern Med* 2000; **133**: 21–30.