

Effectiveness of switching to darunavir/cobicistat in virologically-suppressed HIV-positive patients receiving ritonavir-boosted protease inhibitor-based regimen: the “STORE” Study

Running head: DRV/c in virally suppressed HIV-positive patients

Gori, Andrea<sup>1,2</sup>; Antinori, Andrea<sup>3</sup>; Vergori, Alessandra<sup>3</sup>; Cossu, Maria Vittoria<sup>4</sup>; Menzaghi, Barbara<sup>5</sup>; Sterrantino, Gaetana<sup>6</sup>; Rusconi, Stefano<sup>7</sup>; Cattelan, Annamaria<sup>8</sup>; Castelli, Francesco<sup>9</sup>; Gianotti, Nicola<sup>10</sup>; Orofino, Giancarlo<sup>11</sup>; Ripamonti, Diego<sup>12</sup>; Savinelli, Stefano<sup>13</sup>; Manzillo, Elio<sup>14</sup>; Santantonio, Teresa Antonia<sup>15</sup>; Celesia, Benedetto Maurizio<sup>16</sup>; Cauda, Roberto<sup>17,18</sup>; Maserati, Renato<sup>19</sup>; D'arminio Monforte, Antonella<sup>20</sup>; Stingone, Christof<sup>21</sup>; Bonora, Stefano<sup>22</sup>; Uglietti, Alessia<sup>23</sup>; Termini, Roberta<sup>23</sup>; Rucci, Francesco<sup>24</sup>; Mancusi, Daniela<sup>23</sup>

<sup>1</sup>University Milano-Bicocca, Clinic of Infectious Diseases; "San Gerardo" Hospital - ASST Monza

<sup>2</sup>Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Infectious Diseases Unit Milano, Italy

<sup>3</sup>National Institute for Infectious Diseases "Lazzaro Spallanzani" IRCCS HIV/AIDS Department Roma, Italy

<sup>4</sup>ASST Fatebenefratelli-Sacco 1st Division of Infectious Diseases Milano, Italy

<sup>5</sup>Azienda Socio-Sanitaria Territoriale della Valle Olona-Busto Arsizio, Infectious Diseases Busto Arsizio, Italy

<sup>6</sup>Reparto Malattie Infettive e Tropicali, Dipartimento di Medicina Clinica e Sperimentale, Università di Firenze, Italy

<sup>7</sup>Infectious Diseases Unit, DIBIC Luigi Sacco, University of Milan, Italy

<sup>8</sup>Azienda Ospedaliero-Universitaria di Padova Division of Infectious and Tropical Diseases Padova, Italy

<sup>9</sup>University of Brescia and ASST Spedali Civili, Department of Infectious and Tropical Diseases  
Brescia, Italy

<sup>10</sup>IRCCS San Raffaele Scientific Institute, Dipartimento di Malattie Infettive Milano, Italy

<sup>11</sup>Amedeo di Savoia Hospital Unit of Infectious Diseases Torino, Italy

<sup>12</sup>FROM Research Foundation, Papa Giovanni XXIII Hospital, Bergamo, Italy

<sup>13</sup>Sapienza University Department of Public Health and Infectious Disease Roma, Italy

<sup>14</sup>A.O.R.N. Cotugno VIII Divisione di Malattie Infettive Napoli, Italy

<sup>15</sup>University of Foggia Department of Clinical and Experimental Medicine Foggia, Italy

<sup>16</sup>ARNAS "Garibaldi" UOC Malattie Infettive Catania, Italy

<sup>17</sup>Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma Italia, UOC Malattie Infettive

<sup>18</sup>Università Cattolica del Sacro Cuore, Roma Italia, Istituto di Clinica Malattie Infettive

<sup>19</sup>Fondazione Policlinico San Matteo Clinica Malattie Infettive Pavia, Italy

<sup>20</sup>ASST Santi Paolo e Carlo Dipartimento di Scienze della Salute Milano Italy

<sup>21</sup>University of Roma "Tor Vergata" Department of Medicine of Systems Roma Italy

<sup>22</sup>Unit of Infectious Diseases, Department of Medical Sciences, Amedeo di Savoia Hospital,  
University of Torino, Torino, Italy

<sup>23</sup>Janssen-Cilag SpA, Medical Affairs Department, Infectious Diseases Cologno Monzese, Italy

<sup>24</sup>Department of Oncology and Onco-Hematology, Postgraduate school of Clinical Pharmacology  
and Toxicology, University of Milan

**Corresponding author:**

Dr. Daniela Mancusi, MSc, Biotechnologist Medical Affairs Department, Infectious Diseases,  
Janssen-Cilag SpA Via Michelangelo Buonarroti, 23, 20093 Cologno Monzese (Milano) - Italy

mobile: + 39 345 9581944, E-mail address: [dmancusi@its.jnj.com](mailto:dmancusi@its.jnj.com)

**Tables:** 1

**Figures:** 1

**Word count:** 1978

**Contact information for reprint requests:** as above

**Funding:** Janssen-Cilag SpA

**Conflict of Interest Statement:**

AG received a grant from Janssen-Cilag, ViiV Healthcare, MSD, BMS, Abbvie, Gilead Sciences, Novartis, Pfizer, Astellas, AstraZeneca and Angelini; he received consulting fees or honorarium from Janssen-Cilag, ViiV Healthcare, MSD, BMS, Abbvie, Gilead Sciences, Novartis, Pfizer, Astellas, AstraZeneca and Angelini.

AA received a grant from Gilead Sciences, ViiV Healthcare and Janssen-Cilag; he received consulting fees or honorarium from ViiV Healthcare, Janssen-Cilag and Merck.

SR received grants research support, compensation for CME activities or advisory boards from ViiV Healthcare, MSD, Gilead Sciences and Janssen

SB has received grants, travel grants and consultancy fees from Abbvie, BMS, MSD, Gilead, Janssen-Cilag, and ViiV.

AV, MVC, BM, GS, AC, FC, NG, GO, DR, SS, EM, TAS, BMC, RC, RM, ADM, CS, FR have no conflicts of interest that are directly relevant to the content of this article

AU, RT and DM are Janssen employees.

## Abstract

**Objective:** This study investigates the effectiveness and tolerability of switching to darunavir/cobicistat (DRV/c)-based antiretroviral regimen (ART) from a ritonavir-boosted protease inhibitor (PI/r)-based regimen in virologically suppressed human immunodeficiency virus (HIV)-positive patients. DRV trough values were also investigated.

**Setting:** Prospective, multicenter, single-country, non-interventional, cohort study.

**Methods:** This study included patients on a PI/r-based ART for at least twelve months having plasma HIV-1 RNA <50 copies/mL for at least six months. Primary endpoint: HIV-1 RNA <50 copies/mL at  $48 \pm 6$  weeks from baseline. A secondary analysis was performed using the time to loss of virological response (TLOVR) algorithm. Biochemical parameters including DRV trough samples were collected as per clinical practice and measured using high-performance liquid chromatography.

**Results:** Of 336 patients enrolled, 282 completed the study: 70.8% had plasma HIV-1 RNA <50 copies/mL at 48 weeks; using the TLOVR algorithm, 82.7% maintained virological suppression. Virological failure (VF) was observed in 6 patients (1.8%). Adverse event (AE)-related discontinuations were 4.5%. After 48 weeks, we found a significant improvement in both triglycerides (median, 130.0 mg/dL to 113.5 mg/dL,  $p=0.0254$ ) and HDL cholesterol (48 to 49 mg/dL,  $p<0.0001$ ) but no change in other biomarkers. DRV trough concentrations in 56 subjects showed a median value of 2862.5 (1469.5–4439.0) ng/mL, higher in females than in males (4221 ng/mL vs. 2634 ng/mL,  $p=0.046$ ).

**Conclusions:** In stable HIV-1 positive virologically suppressed patients, the switch to DRV/c-based ART was beneficial in terms of low rates of VF and AEs due to its high tolerability and improvement in triglycerides.

**Keywords:** darunavir/cobicistat, darunavir/ritonavir, effectiveness, HIV, STORE, virologically suppressed

## Introduction

The current treatment of HIV-positive patients requires lifelong administration of combination antiretroviral (ARV) drugs, which is extremely effective and well-tolerated, but several factors may decrease its long-term efficacy. As patient adherence is crucial to maintain the efficacy and immunological benefits of ARV treatment,<sup>1</sup> it is essential to adopt effective and well-tolerated ARV strategies, including a reduced number of pills. Regarding this latter point, the adoption of fixed-dose combinations (FDCs), and single-tablet regimens (STRs) has a decisive role in improving patient compliance and adherence to ART.<sup>2</sup>

For the above reason, a coformulation of the protease inhibitor (PI) darunavir (DRV) with the pharmacoenhancer cobicistat has been developed<sup>2</sup>. Cobicistat, at the dose of 150 mg q.d, while not having antiviral activity, is more selective in terms of enzyme inhibition thus reducing the number of clinically relevant DDIs compared with the previous pharmacoenhancer ritonavir (RTV).<sup>3</sup> This FDC, reducing the pill burden, allows to improve adherence to ART.<sup>4</sup> To date, few clinical trials have studied DRV/c in a real-world clinical setting. Most data on DRV/c were obtained from the phase 3 Study GS-US-216-0130,<sup>5</sup> but real-life data were available only in 2017.<sup>6</sup>

The primary aim of this study was to describe the effectiveness of DRV/c-based regimens in terms of maintenance of virological suppression after 48±6 weeks from study enrollment. Furthermore, we described steady-state DRV trough values in a subgroup of patients, if collected per clinical practice.

## Methods

This study, named S**T**art Of REzolsta (STORE), was a prospective, multicenter, non-interventional cohort study conducted between 2016 and 2018 with HIV-1-infected adult outpatients referred to the Italian Infectious Disease Hospital departments. All patients were on stable RTV-boosted ART with PIs for at least twelve months, and virologically suppressed (HIV-1 RNA < 50 copies/mL) for at least six months. Patients were offered to enter this study once their treating physician had

considered them eligible for DRV/c-based treatment as per the DRV/c Summary of Product Characteristics.<sup>7</sup>

Main exclusion criteria were: (1) estimated glomerular filtration rate (eGFR) <70 mL/min if any co-administered agent (e.g. emtricitabine-FTC, lamivudine-3TC, tenofovir disoproxil fumarate-TDF, or adefovir dipivoxil) required dose adjustment based on creatinine clearance, (2) pregnancy or breastfeeding at the time of enrollment, (3) history of allergy or intolerance to sulfonamides, (4) receiving DRV/r 600/100 bis in die (bid) or PI/r monotherapy, (5) being treated with directly active agents against hepatitis C virus (HCV) within one year of enrollment, (6) scheduled chemotherapy.

Ethics approval was obtained by each Institutional Review Board, and patients signed a written informed consent before being enrolled. The trial was registered on ClinicalTrials.gov (NCT02926456).

This study collected only data available per clinical practice. Patients were observed prospectively for 48±6 weeks after starting the DRV/c-based regimen. The end of the study was defined as the last visit within the study for the last patient enrolled.

The primary endpoint, defined as HIV-1 RNA <50 copies/mL measured as per the FDA Snapshot algorithm, was measured at 48±6 weeks from baseline. A secondary analysis was performed using the time to loss of virological response (TLOVR) algorithm.<sup>8</sup> Virological failure (VF) was defined as the last plasma HIV-1 RNA value in the 48-week window ≥50 copies/mL, as well as discontinuation before the end of the study for any reason with last available viral load (VL) ≥50 copies/mL. Secondary endpoints included changes in CD4 and CD8 cell counts, in serum lipid levels, and in the values of routinely collected laboratory exams.

Four visits were scheduled during the study following the clinical practice: Visit 1 (enrollment), Visit 2 (4-8 weeks from the start of DRV/c), Visit 3 (24±6 weeks from the start of DRV/c) and Visit 4 (48±6 weeks). The results here described are related to Visit 4.

Where the concentrations of plasma ARVs were routinely measured, the values of cobicistat-boosted DRV trough concentrations ( $24\pm 3$  h after last drug intake) were registered throughout the study and measured using high-performance liquid chromatography.

No data were available regarding the  $C_{\text{trough}}$  of ritonavir-boosted PIs taken before the switch. To assess the adequacy of DRV exposure, half-maximal effective concentration ( $EC_{50}$ ), adjusted for protein binding for both wild-type (55 ng/mL) and drug-resistant (550 ng/mL) HIV-1 was used.

A sample size of 300 patients was set with a pre-specified target of 30% female patients. The original sample size calculation was based on feasibility criteria and assumed a 10% dropout rate.

Patient characteristics were described using standard descriptive statistics. Continuous variables are presented as mean values  $\pm$  standard deviation (SD) or median value and interquartile range and categorical variables as numbers and percentages. Data are presented as median and 25th-75<sup>th</sup> ( $Q_1$ - $Q_3$ ) percentiles. Non-parametric Mann-Whitney, Wilcoxon signed-rank, and Kruskal-Wallis tests were used for the analysis.

## Results

### *Baseline*

In this study, 348 patients were enrolled and 336 were included in the final analysis. Among the 336 patients, 282 completed the study, while 54 (16%) discontinued before week 48. The baseline characteristics are shown in Table 1. Female patients had longer duration of infection (16.9 vs. 13.2 years,  $p=0.0006$ ), longer ART use (13.9 vs. 10.7 years,  $p=0.0002$ ) and longer duration of viral suppression (5.8 vs. 4.7 years,  $p=0.011$ ); they acquired HIV through heterosexual contacts more frequently than males (72.9% vs. 26.6%,  $p<0.0001$ ). DRV/r was the most common PI used before enrollment ( $N=274$ , 81.5%) followed by ATV/r ( $N=33$ , 9.8%) and lopinavir/r ( $N=21$ , 6.3%). Most patients (59.6%) were receiving two additional drugs besides boosted-PIs: 16.7% received abacavir/3TC, 42.9% TDF/FTC.

### ***Efficacy***

Out of the 282 patients who completed the study, 242 had a VL measurement within the Visit 4 (V4) window (48±6 weeks). Of these patients, 238/242 (98.34%) had a VL <50 copies/mL. During the study period, 6 patients experienced VF; five out of them were deemed incompletely adherent by the treating clinicians.

According to the FDA snapshot analysis, 238 patients (70.8%) had a virological response with plasma HIV-1 RNA <50 copies/mL at V4. Considering the TLOVR algorithm, 278 patients (82.7%) maintained virological suppression. Both rates were higher in male patients than in females (FDA snapshot: 72.5% vs. 67.3%,  $p=0.329$ ; TLOVR: 85.6% vs. 76.6%,  $p=0.0430$ ). The Kaplan-Meier curve, depicting the risk of withdrawal from the study for different reasons, is represented in Figure 1. Considering the patients who completed the study, including the ones having a VL measurement out of V4 window (N=282), 98% of them were virologically suppressed. At baseline, female patients showed a higher median CD4<sup>+</sup> T lymphocyte cell count (704 vs. 617 cells/mm<sup>3</sup>,  $p=0.0149$ , Kruskal-Wallis test), a higher median CD4/CD8 ratio (0.9 vs. 0.7,  $p=0.0003$ ), and lower median CD8<sup>+</sup> T cell count (758 vs. 893 cells/mm<sup>3</sup>,  $p=0.0235$ ). After 48 weeks, the difference between males and females in either CD4<sup>+</sup> or CD8<sup>+</sup> cell counts was lost ( $p=0.36$  and  $p=0.06$ , respectively).

### ***Safety***

AEs and serious adverse events (SAEs) were experienced by 69/336 (20.5%) and 17/336 (5.1%) patients, respectively. During the study, 120 AEs were reported; the most common were infections (6.8%), gastrointestinal events (6.8%, mostly nausea), and events involving the central nervous system (4.2%, mostly headache). No SAEs were considered ART-related. Fifteen patients were withdrawn from the study due to safety reasons, including one pregnancy and two patients with non-drug-related SAEs (hepatitis A and anaplastic lymphoma). The remaining 12 patients were



withdrawn primarily due to gastrointestinal AEs, which were all grade 1 or 2 and deemed as either possibly or very likely to be related to DRV/c.

Serum creatinine showed a small expected median (Q<sub>1</sub>-Q<sub>3</sub>) increase during the first 4-8 weeks [from 0.8 (0.7–1) mg/dL to 0.9 (0.8–1) mg/dl] and subsequently remained stable. This was paralleled by a slight decrease in eGFR [from 98.5 (85.6–106.1) mL/min per 1.73 m<sup>2</sup> to 94 (80.1–103.4) mL/min per 1.73 m<sup>2</sup>]. We observed a significant decrease in triglycerides [130.0 (97–180) mg/dL at baseline and 113.5 (83–165.5) mg/dL at week 48, p=0.0254] and a slight increase in HDL cholesterol [48.0 (39–57) mg/dL at baseline and 49.0 (41-60) mg/dL at week 48, p=<0.0001].

We did not observe significant changes in the other biochemical markers (lipid, glucidic, hepatic profile).

### ***Pharmacokinetics***

DRV trough concentrations were collected from 56 patients. These patients were mostly of European ancestry (n=53, 94.6%) and male (n=39, 69.6%), with a median age of 49 (38–54) years and BMI of 24.1 (21.9-26.8) kg/m<sup>2</sup>. No concomitant drug had a predicted significant effect on DRV exposure according to the Liverpool Interaction Website).<sup>9</sup>

Median DRV C<sub>trough</sub> values were 2862.5 (1469.5–4439) ng/mL; values were higher in females than in males [4221 (2741–5622) ng/mL vs. 2634 (1430–3752) ng/mL, p=0.046, Mann-Whitney U-test]. BMI did not differ between genders. No correlation of C<sub>trough</sub> values with BMI, age, or patient-reported side effects was observed.

At the time of sampling, all patients were virologically suppressed. No DRV C<sub>trough</sub> was below the threshold of 55 ng/mL, while 6 patients had DRV C<sub>trough</sub> values below 550 ng/mL, despite maintaining virological suppression.

## Discussion

In this study, we describe the effectiveness of switching to DRV/c in people living with HIV on boosted PI/r-based regimens. We observed a low rate of VFs and few discontinuations due to side effects. Antiviral efficacy was maintained in the majority of patients, with rates comparable to those in other PI-based regimens. Furthermore, in our observational setting, the FDA snapshot analysis may have underestimated the virological results: 40 patients had results outside the 48-week window, leading to an apparent lower rate of virological suppression. However, the TLOVR algorithm showed a satisfactory rate of HIV-1 RNA suppression at week 48 (82.7%). In addition, confirmed VFs were uncommon (1.8%), and no treatment-emergent resistance-associated mutations were reported.

In this study, the DRV/c-based ART was well-tolerated; 4.5% (15/336) of study patients stopped the study drug due to AEs. After excluding SAEs or special situations unrelated to DRV (such as lymphoma, hepatitis A, and pregnancy), the majority of side effects were related to the gastrointestinal system (specifically, nausea), as previously reported.<sup>5</sup> The observed discontinuation rate is not quite different from what has been observed in recent studies, where stable patients were switched to other ARV drugs.<sup>10-12</sup> Laboratory abnormalities were not observed, except an expected small serum creatinine increase, attributed to the well-known MATE1 inhibition by cobicistat.<sup>7</sup> Serum lipid levels were stable with a small but significant improvement in HDL cholesterol and a decrease in triglyceride levels, as already reported elsewhere.<sup>6</sup> The data regarding a neutral-positive impact on the lipid profile in our observational trial support DRV/c as a therapeutic option for both dyslipidemic and normolipidemic HIV-patients.

The real-life setting of this study is relevant and explains some of the observed results. Notably, we enrolled a high proportion of women (31.8%), often underrepresented in clinical trials. This allowed us to notice some differences in virological efficacy, lower in female patients, while the immunological profile was quite similar between genders.

In this study, the CD4/CD8 ratio increased in both males and females and this may show a positive impact on the immune outcome associated with the use of DRV/c.

Few real-life data on cobicistat-boosted DRV  $C_{\text{trough}}$  values have been published. In this study, the measurements of DRV  $C_{\text{trough}}$  have shown DRV exposure to be similar to that observed in patients receiving low-dose RTV, but higher than that reported in other studies assessing DRV exposure when administered with cobicistat.<sup>13-15</sup>

Six out of the 56 samples showed DRV  $C_{\text{trough}}$  values below the target concentration for drug-resistant viruses (550 ng/mL), and none showed DRV  $C_{\text{trough}}$  values below the target concentration for wild-type viruses (55 ng/mL), confirming the high inhibitory quotient obtained by DRV. The data showing higher DRV concentrations in female patients is partially unexplained, but it was consistent with earlier studies.<sup>16-17</sup> The significant difference between males and females in our study could be ascribed to the small sample size.

The main limitation of this study is that it is a single-arm study with no comparison.

In conclusion, stable HIV-positive patients receiving boosted PIs may benefit from switching to DRV/c in terms of low rates of VF and AEs due to its high tolerability and in terms of reduced levels of certain lipid biomarkers, particularly triglycerides.

### **Acknowledgments**

We thank all the patients and all the clinicians participating in this study.

## References

1. Altice F, Evuarherhe O, Shina S et al. Adherence to HIV treatment regimens: systematic literature review and meta-analysis. *Patient Prefer Adherence* 2019 13:475-490.
2. Curran A, Pérez-Valero I, Moltó J. Rezolsta® (darunavir/cobicistat): First boosted protease inhibitor co-formulated with cobicistat. *AIDS Rev.* 2015; 17:114-120.
3. Tseng A, Hughes CA, Wu J et al. Cobicistat versus ritonavir: similar pharmacokinetic enhancers but some important differences. *Ann Pharmacother* 2017; 51:1008-1022.
4. Capetti A, Cossu MV, Rizzardini G. Darunavir/cobicistat for the treatment of HIV-1: a new era for compact drugs with high genetic barrier to resistance. *Expert Opin Pharmacother* 2015; 16(17):2689-702.
5. Tashima K, Crofoot G, Tomaka FL et al. Cobicistat-boosted darunavir in HIV-1-infected adults: week 48 results of a Phase IIIb, open-label single-arm trial. *AIDS Res Ther* 2014; 11(39).
6. Echeverría P, Bonjoch A, Puig J et al. Significant improvement in triglyceride levels after switching from ritonavir to cobicistat in suppressed HIV-1-infected subjects with dyslipidaemia. *HIV Med* 2017; 18(10):782-786.
7. [https://www.ema.europa.eu/en/documents/product-information/rezolsta-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/rezolsta-epar-product-information_en.pdf)
8. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Guidance for Industry. Antiretroviral Drugs Using Plasma HIV RNA Measurements – Clinical Considerations for Accelerated and Traditional Approval, October 2002. Available at [www.fda.gov/cder/guidance/index.htm](http://www.fda.gov/cder/guidance/index.htm)
9. [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)
10. Orkin C, Molina JM, Negredo E et al. Efficacy and safety of switching from boosted protease inhibitors plus emtricitabine and tenofovir disoproxil fumarate regimens to single-

- tablet darunavir, cobicistat, emtricitabine, and tenofovir alafenamide at 48 weeks in adults with virologically suppressed HIV-1 (EMERALD): a phase 3, randomised, non-inferiority trial. *Lancet HIV* 2018; 5: e23-e34.
11. Daar ES, DeJesus E, Ruane P et al. Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48-week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. *Lancet HIV* 2018; 5:e347-e356.
  12. Trottier B, Lake JE, Logue K et al. Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIIVING): a 48-week, randomized, non-inferiority, open-label, Phase IIIb study. *Antivir Ther* 2017; 22(4):295-305.
  13. Kakuda TN, Opsomer M, Timmers M, Itebeke K, Van De CT, Hillewaert V, et al. Pharmacokinetics of darunavir in fixed-dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers. *J Clin Pharmacol*. 2014 Aug;54(8):949-957.
  14. Kakuda T, Sekar V, Vis P et al. Pharmacokinetics and pharmacodynamics of darunavir and etravirine in HIV-1-infected, treatment-experienced patients in the Gender, Race, and Clinical Experience (GRACE) Trial. *AIDS Res Treat* 2012; 2012:186987.
  15. Moltó J, Curran A, Miranda C et al. Pharmacokinetics of darunavir/cobicistat and etravirine alone and co-administered in HIV-infected patients. *J Antimicrob Chemother*. 2018; 73(3):732-737.
  16. Madruga JV, Berger D, McMurchie M 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(9581):49-58.

17. Cahn P, Fourie J, Grinsztejn B et al. Week 48 analysis of once-daily vs. twice-daily darunavir/ritonavir in treatment-experienced HIV-1-infected patients. *AIDS* 2011; 25(7):929-39.

## Tables

**Table 1. Main demographic and HIV-associated patient characteristics at baseline.**

## Figures

**Figure 1. Kaplan-Meier curves depicting the risk of remaining in the study according to different causes of discontinuation**

Abbreviations: AE=adverse event; VF = virological failure

		<b>Male</b>	<b>Female</b>	<b>Total</b>
<b>Number</b>		229 (68.2%)	107 (31.8%)	336 (100%)
<b>Age; years</b>		49.6 (9.9)	48.5 (9.1)	49.2 (9.6)
<b>Age above 50 years</b>		114 (49.8%)	46 (43%)	160 (47.6%)
<b>Ethnicity: European</b>		218 (95.2%)	100 (93.5%)	318 (94.6%)
<b>African</b>		8 (3.5%)	4 (3.7%)	12 (3.6%)
<b>Other</b>		3 (1.3%)	3 (2.8%)	6 (1.8%)
<b>Body mass index: Kg/m<sup>2</sup></b>		24.0 (3.2)	23.4 (4)	23.8 (3.5)
<b>Mode of transmission*</b>	<b>Intravenous Drug User</b>	49 (21.4%)	16 (15.0%)	65 (19.3%)
	<b>Men who have sex with men</b>	83 (36.2%)	1 (0.9%)	84 (25.0%)
	<b>Heterosexual</b>	61 (26.6%)	78 (72.9%)	139 (41.4%)
	<b>Unknown</b>	40 (17.5%)	13 (12.1%)	53 (15.8%)
<b>Anti HCV-positive</b>		67 (29.3%)	25 (23.4%)	92 (27.4%)
<b>HBsAg-positive</b>		17 (7.4%)	4 (3.7%)	21 (6.3%)
<b>Anti HCV and HBsAg-Positive</b>		10 (4.4%)	1 (0.9%)	11 (3.3%)
<b>CD4+ T lymphocyte at baseline: n/mm<sup>3</sup></b>		655.7 (310.9)	753.1 (331.5)	685 (320)
<b>CD4+ T lymphocyte at nadir: n/mm<sup>3</sup></b>		208.3 (170)	226.4 (154)	213.8 (165.3)
<b>Time from first HIV-1 positive test: years</b>		13.2 (9.5)	16.9 (8.9)	14.4 (9.5)
<b>Time from the start of the first ARV treatment: years</b>		10.7 (7.6)	13.9 (7.4)	11.7 (7.6)
<b>Time from the start of the first ARV treatment PI/r based: years</b>		6.9 (5.7)	8.4 (5.7)	7.4 (5.7)
<b>Time from viral suppression (HIV-1 RNA &lt; 50 copies/mL): years</b>		4.7 (4)	5.8 (4.4)	5.1 (4.2)

**Table 1. Main demographic and HIV-associated patient characteristics at baseline.** Data are provided as number (percentage) or average (standard deviation) and stratified per gender.

\* Note. The mode of transmission could be more than one.

**Figure 1. Kaplan-Meier curves depicting the risk of remaining in the study according to different causes of discontinuation**

