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Acta Clinica Belgica
International Journal of Clinical and Laboratory Medicine

ISSN: 1784-3286 (Print) 2295-3337 (Online) Journal homepage: https://www.tandfonline.com/loi/yacb20

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**To cite this article:** Stéphane De Wit, Eric Florence, Linos Vandekerkhove, Jean-Christophe Goffard, Bernard Vandercam, Eric Van Wijngaerden, Michel Moutschen, Rémy Demeester, Patrick Lacor, Marc Delforge, Maartje van Frankenhuijsen & Paul Lacante (2019) Long-term treatment with atazanavir (ATV) in real life in Belgium: a retrospective observational cohort of 2264 HIV patients , Acta Clinica Belgica, 74:3, 143-150, DOI: 10.1080/17843286.2018.1462753

**To link to this article:** https://doi.org/10.1080/17843286.2018.1462753

Published online: 02 May 2018.

ACTA CLINICA BELGICA
2019, VOL. 74, NO. 3, 143–150
https://doi.org/10.1080/17843286.2018.1462753

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ORIGINAL PAPER



# Long-term treatment with atazanavir (ATV) in real life in Belgium: a retrospective observational cohort of 2264 HIV patients*

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**ABSTRACT**

**Objectives:**: This 5-year follow-up study aimed to assess clinical outcomes of HIV-1 infected adults treated with atazanavir (ATV) in clinical practice in Belgium, to describe patient profiles and characteristics, as well as treatment safety.

**Methods:**: A multicenter, non-interventional, non-comparative, retrospective cohort study was performed in HIV-1 positive adult patients treated with ATV between 2006 and 2012. Data were collected from 8 AIDS reference centers' databases. All analyses were on-treatment. Sub-analyses were carried out in unboosted ATV treated patients and in females. The primary endpoint was defined as the time-to-treatment-discontinuation. Furthermore, virological suppression, immunological response, time to loss of virological response, reasons for ATV initiation, and discontinuation were also assessed.

**Results:**: 2264 ARV-naive and ARV-experienced patients (median age: 41 years) were included. Females and non-Caucasians were broadly represented (40 and 45%, respectively). The probability to remain on treatment was 0.78 (CI: 0.76; 0.78) for the first and 0.69 (CI: 0.66; 0.71) for the second year and was similar between males and females. Overall, 771 patients (34.1%) discontinued ATV over time, the median (Q1-Q3) time to discontinuation being 0.8 (0.3–1.5) year. In unboosted ATV-treated patients, results were comparable to the overall ATV population, except for a higher rate of discontinuation-over-time (45.1%).

**Conclusions:**: Clinical and safety data from this 5 year-cohort study show that the vast majority of patients remained on ATV treatment for the first and second years, overall as well as patients treated with unboosted ATV and females.

**KEYWORDS**
Atazanavir; HIV; Belgium; cohort

## Introduction

The use of antiretroviral (ARV) drugs reduces the mortality of HIV-infected individual patients and significantly improves patients' prognosis [1] thereby transforming HIV to a chronic disease. After almost 10 years of availability in Belgium, atazanavir (ATV) has been widely prescribed protease inhibitor (PI).Although ATV is not anymore a preferred regimen in most guidelines, its use remains significant in many settings, in particular in specific population such as pregnant women or women on oral contraceptives. The favorable safety profile and the antiviral activity of ATV boosted with ritonavir (ATV/r) was demonstrated in randomized controlled trials both in naïve [2–5] and in experienced patients [6].

Nevertheless, patients selected for those clinical trials have to meet strict inclusion criteria that may not exactly fit the routine clinical patient profile. Therefore, post-marketing studies are useful in describing outcomes in daily practice and in populations generally underserved in HIV clinical trials (like women and non-Caucasian populations).

This study aimed to assess the safety and clinical outcomes measured by the time to ATV treatment discontinuation in HIV-1 adults treated with ATV during a maximum 5-year period of time, and to describe patient characteristics and profiles, as well as treatment safety, in real-life settings in Belgium.

## Methods

### *Study design*

This observational multicenter cohort study conducted in Belgium was retrospective with a study period from 1 December 2006 to 31 December 2012.

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*The data have already been partially presented at the 14th EACS in Brussels, Belgium on 16–19 October 2013.
#Members of the Belgian HIV Research Consortium (BREACH).

### Objectives

The primary objective was to describe treatment outcomes with ATV in HIV-1 infected patients and in specific subpopulations, in daily clinical practice in Belgium.

The secondary objective was to describe the profiles and characteristics of HIV infected patients who received ATV treatment.

### Patients

Patients were included in the study if they met the following criteria: HIV-1 positive, ≥18 years of age, having taken at least one dose of ATV between 1 December 2006 (date of reimbursement in Belgium) and 31 March 2012. Concerning patients who took ATV treatment several times, only the first episode was taken into account.

Patients on ATV participating in clinical trials and/or medical need programs were excluded.

### Data collection

The data of eligible patients were extracted from existing databases in 8 participating AIDS reference centers (ARCs) working under the umbrella of the Belgian HIV Research Consortium (BREACH). The data were anonymized on site and pooled into one common database for data cleaning and statistical analysis.

Data recorded were demographics (age, gender, ethnicity), disease characteristics (mode of transmission, age at diagnosis, time span between diagnosis and initiation of ARV, CD4 nadir, HCV co-infection, previous and current AIDS event, co-morbidities) at ATV initiation, full ARV history, body weight, body mass index (BMI), concomitant treatments, antiretroviral regimen after ATV discontinuation, tobacco use, laboratory tests (lipids, bilirubin, creatinine, estimated glomerular filtration rate [eGFR], CD4 cell counts, HIV viral load [VL]), and adverse events (AEs). These follow up data were collected at leastv annually for 5 years. Laboratory data analyses were performed on patients having baseline values and post-baseline values at a minimum of one selected time-point.

### Statistical analysis

Descriptive analyses on demography and primary endpoint were carried out on the complete ATV population set, defined as all subjects treated with a minimum of one dose of ATV during the recorded period and having at least one assessment after ATV initiation. Additional analyses were carried out on 2 defined subsets: female subjects and subjects having a record of unboosted ATV treatment during the ATV treatment period. Analyses including the first endpoint analysis were conducted on 4 sub-groups according to the gender, treatment status at ATV initiation (ARV-naive [stratified by VL< or ≥100.000 copies/mL]/ARV-experienced [stratified by VL< or ≥50 copies/mL] patients), baseline CD4 count (<350 per $mm^3$/≥350 per $mm^3$) and tenofovir disoproxil fumarate (TDF) exposure (i.e. at least one dose of TDF)/non-TDF exposure during ATV treatment period.

Continuous variables were expressed as the number of observations, number of missing data, mean, standard deviation (SD), median, minimum and maximum values, and quartiles (Q1, Q3). Categorical values were presented by counts, percentages expressed on available data, and number of missing data.

The primary endpoint defined as the time to first permanent ATV treatment discontinuation (defined as an ATV discontinuation period of ≥90 days), and the time to loss of virological response were assessed using Kaplan-Meier (KM) estimates of survival and log-rank tests. Point estimates and corresponding 2-sided 95% confidence intervals (CI) were provided at various time-points. Furthermore, secondary endpoints including virological response (VL < 50 copies/mL), immunological response, reasons for ATV initiation and discontinuation, and lab test parameters were assessed. All analyses were done on-treatment; the treatment duration was defined as the time between the treatment initiation date until treatment discontinuation date or until the last evaluation date for the patients who did not discontinue their treatment. A complete case analysis was used in this study as missing data were not imputed. Regarding changes from baseline by time-point, data from patients having baseline values and at least one post-baseline value at one of the time-points (0.5, 1, 2, 3, 4 or 5 years) were analyzed. Finally, concerning the end of follow-up analysis, the last value available on-treatment was used, and only data from patients having both baseline value and end of follow-up value were analyzed .

Due to the limited availability of AEs data and the retrospective nature of the data collection, incidence of AEs by their seriousness, severity, and treatment relationship was not reported. However, AEs leading to discontinuation were analyzed overall. In addition, univariate and multivariate regression analyses were performed to determine predictive factors of the time to ATV treatment discontinuation using log-rank tests and Cox regression models.

Statistical analyses were performed using SAS® Version 9.1.3 (SAS® Institute, Inc., Cary, North Carolina, USA).

### Ethics

The study was carried out in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Epidemiology Practices and applicable local regulatory requirements. The study protocol had been approved by the ethics committee of all participating ARCs. The patient's confidentiality was ensured

**Table 1.** Baseline demographics and disease characteristics overall and by sub-groups.

| Characteristics | | Females (*N* = 877) | Unboosted (*N* = 457) | Overall (*N* = 2264) |
|---|---|---|---|---|
| Age (years) | N available (missing) | 877 (0) | 457 (0) | 2263 (1) |
| | Median | 37.7 | 42.2 | 40.6 |
| | Q1; Q3 | 31.2; 44.7 | 34.5; 48.6 | 33.4; 48.0 |
| Gender (*n*, %) | N available (missing) | 877 (0) | 457 (0) | 2264 (0) |
| | Male | – | 245 (53.6) | 1386 (61.2) |
| | Female | 877 (100.0) | 212 (46.4) | 877 (38.7) |
| | Missing | – | – | 1 (0.0) |
| Ethnicity (*n*, %) | N available (missing) | 860 (17) | 448 (9) | 2225 (39) |
| | Caucasian | 179 (20.8) | 224 (50.0) | 1231 (55.3) |
| | Sub-Saharan African | 641 (74.5) | 206 (46.0) | 905 (40.7) |
| | Asian | 32 (3.7) | 11 (2.5) | 61 (2.7) |
| | Other | 8 (0.9) | 7 (1.6) | 28 (1.3) |
| Mode of HIV transmission (*n*, %) | N available (missing) | 848 (29) | 445 (12) | 2216 (48) |
| | Heterosexual contact | 689 (81.3) | 231 (51.9) | 1046 (47.2) |
| | Homo/bisexual | 1 (0.1) | 125 (28.1) | 776 (35.0) |
| | Injecting drug user | 14 (1.7) | 8 (1.8) | 35 (1.6) |
| | Perinatal | 11 (1.3) | 5 (1.1) | 16 (0.7) |
| | Other | 20 (2.4) | 14 (3.1) | 47 (2.1) |
| | Unknown | 113 (13.3) | 62 (13.9) | 296 (13.4) |
| HCV co-infection (*n*, %) | N available (missing) | 628 (249) | 326 (131) | 1586 (678) |
| | Positive | 35 (5.6) | 18 (5.5) | 120 (7.6) |
| Tobacco use (*n*, %) | N available (missing) | 856 (21) | 448 (9) | 2218 (46) |
| | Yes | 132 (15.4) | 124 (27.7) | 669 (30.2) |
| | No | 614 (71.7) | 246 (54.9) | 1252 (56.4) |
| | Unknown | 110 (12.9) | 78 (17.4) | 297 (13.4) |
| Age at HIV diagnosis (years) | N available (missing) | 695 (182) | 374 (83) | 1845 (419) |
| | Median | 30.7 | 34.2 | 33.5 |
| | Q1; Q3 | 26.0; 37.2 | 27.7; 42.6 | 27.8; 41.3 |
| Time span between HIV diagnosis and initiation of ARV (years) | N available (missing) | 660 (217) | 362 (95) | 1782 (482) |
| | Median | 0.7 | 1.2 | 1.0 |
| | Q1; Q3 | 0.1; 3.6 | 0.2; 4.0 | 0.2; 3.7 |
| CD4 nadir (count per mm3) | N available (missing) | 804 (73) | 377 (80) | 2091 (173) |
| | Median | 217.0 | 225.0 | 234.0 |
| | Q1; Q3 | 119.5; 314.0 | 122.0; 321.0 | 129.0; 332.0 |
| Prior AIDS event (*n*, %) | N available (missing) | 877 (0) | 457 (0) | 2264 (0) |
| | Yes | 144 (16.4) | 81 (17.7) | 390 (17.2) |
| | No | 466 (53.1) | 242 (53.0) | 1120 (49.5) |
| | Unknown | 267 (30.4) | 134 (29.3) | 754 (33.3) |
| Baseline CD4 (count per mm3) | N available (missing) | 770 (107) | 360 (97) | 1988 (276) |
| | Median | 357.0 | 396.0 | 361.0 |
| | Q1; Q3 | 230.0; 517.0 | 256.5; 609.5 | 237.0; 538.5 |

as only anonymous data were collected for analysis. This study was strictly observational and did not impact the management of patients.

## Results

### Baseline patient characteristics

In total, 2264 HIV-infected patients were included. 38.8% were ARV treatment-naïve, and 61.2% ARV treatment-experienced, of those 50% were virologically suppressed (HIV-RNA < 50 copies/mL). The majority of patients were male (61.2%) and of Caucasian origin (55.0%). The median age was 40.6 years. At the start of ATV treatment, 17.2% of patients had experienced previous AIDS-defining events, and 7.6% were HCV co-infected. HIV transmission was mainly through sexual contacts (82.2%). The median baseline CD4 cell count was 361 cells/mm$^3$ (Table 1).

Out of the 2264 individual patient baseline characteristics, approximately three quarters (74.5%) of the 877 females were of sub-Saharan African origin. At baseline, HIV-RNA was <50 copies/mL in 42.4% of women.

### Previous and concomitant medications

Regarding the 1386 ARV-experienced patients, 41.8% had previously received a PI, 21.6% a non-nucleoside reverse-transcriptase inhibitor (NNRTI), and 32.8% were both PI and NNRTI-experienced. About a fifth (20.5%) had to switch their previous treatment(s) to ATV because of gastrointestinal intolerance (Table 2) [7]. A large proportion of patients (78.1%) received TDF concomitantly in their ATV-based regimen.

### Efficacy endpoints on the overall ATV-treated population

#### ATV treatment discontinuation

The estimated probability of loss of virological suppression varied from 9 to 15% after 1 year and 2 years of treatment, respectively. The probability to remain on treatment was 0.78 (CI: 0.76; 0.80) and 0.69 (CI: 0.66; 0.71) for the first and second years, respectively, and similar according to baseline CD4 count status and gender (respectively, $p$ = 0.8896 and $p$ = 0.4066; log-rank test) (Figure 1). Conversely, the ATV treatment

**Table 2.** Reasons for ATV initiation (D:A:D Classification).

| Reasons for initiation (*n*, %) | Females (*N* = 592) | Overall (*n* = 1386) |
|---|---|---|
| N available (missing) | 473 (119) | 1119 (267) |
| Toxicity – Gastro-intestinal tract | 82 (17.3) | 229 (20.5) |
| Simplified treatment available | 62 (13.1) | 150 (13.4) |
| Patient's wish/decision | 63 (13.3) | 121 (10.8) |
| Physician's decision | 47 (9.9) | 105 (9.4) |
| Toxicity, predominantly from nervous system | 23 (4.9) | 98 (8.8) |
| Treatment failure (i.e. virological, immunological, and/or clinical failure) | 27 (5.7) | 80 (7.1) |
| Dyslipidaemia | 24 (5.1) | 78 (7.0) |
| Abnormal fat redistribution | 31 (6.6) | 56 (5.0) |
| Hypersensitivity reaction | 19 (4.0) | 49 (4.4) |
| Other causes | 13 (2.7) | 46 (4.1) |
| Toxicity, not mentioned above | 14 (3.0) | 35 (3.1) |
| Pregnancy | 33 (7.0) | 33 (2.9) |
| Availability of more effective treatment (not specifically failure or side effect) | 10 (2.1) | 31 (2.8) |
| Virological failure | 13 (2.7) | 29 (2.6) |
| Non-compliance | 12 (2.5) | 20 (1.8) |
| Toxicity – Liver | 9 (1.9) | 18 (1.6) |
| Structured Treatment Interruption (STI) | 6 (1.3) | 11 (1.0) |
| Toxicity, predominantly from kidneys | 3 (0.6) | 11 (1.0) |
| Side effects – any of the above but unspecified | 2 (0.4) | 8 (0.7) |
| Concern of cardiovascular disease | 1 (0.2) | 4 (0.4) |
| Partial virological failure | 1 (0.2) | 4 (0.4) |
| Pregnancy – prevention of mother to child transmission | 4 (0.8) | 4 (0.4) |
| Toxicity, predominantly from endocrine system | 2 (0.4) | 4 (0.4) |
| Drug interaction | 3 (0.6) | 3 (0.3) |
| Hematological toxicity (anemia…) | 3 (0.6) | 3 (0.3) |
| Pregnancy – toxicity concerns | 3 (0.6) | 3 (0.3) |
| Cardiovascular disease | 1 (0.2) | 2 (0.2) |
| Co morbidity | 1 (0.2) | 1 (0.1) |
| Diabetes | – | 1 (0.1) |
| Hyperlactataemie/lactic acidosis | – | 1 (0.1) |
| Toxicity – Pancreas | 1 (0.2) | 1 (0.1) |

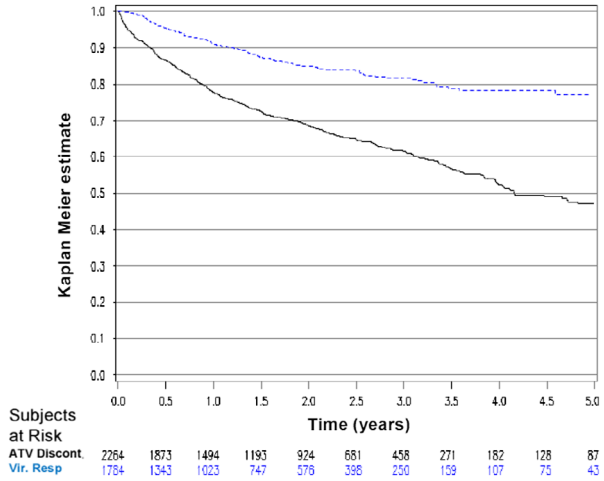


**Figure 1.** Over time probability to remain on treatment (black line) and probability of not showing loss of virological response (blue line) (overall ATV population).

**Table 3.** Reasons for ATV discontinuation (DAD Classification).

| Reasons for discontinuation (*n*, %) | Females (*N* = 877) | Overall (*n* = 2264) |
|---|---|---|
| N available (missing) | 231 (51) | 627 (144) |
| Patient wish/decision | 41 (17.7) | 86 (13.7) |
| Physician decision | 27 (11.7) | 63 (10.0) |
| Simplified treatment available | 16 (6.9) | 54 (8.6) |
| Toxicity – gastrointestinal tract | 20 (8.7) | 54 (8.6) |
| Toxicity – liver | 15 (6.5) | 51 (8.1) |
| Other causes | 19 (8.2) | 47 (7.5) |
| Abnormal fat redistribution | 16 (6.9) | 34 (5.4) |
| Toxicity, predominantly from kidneys | 4 (1.7) | 30 (4.8) |
| Toxicity, not mentioned above | 5 (2.2) | 27 (4.3) |
| Non-compliance | 13 (5.6) | 25 (4.0) |
| Virological failure | 5 (2.2) | 23 (3.7) |
| Drug interaction | 7 (3.0) | 20 (3.2) |
| Treatment failure (i.e. virological, immunological, and/or clinical failure) | 2 (0.9) | 18 (2.9) |
| Hypersensitivity reaction | 9 (3.9) | 16 (2.6) |
| Availability or more effective treatment (not specifically failure or side effect) | 4 (1.7) | 15 (2.4) |
| Side effects – any of the above but unspecified | 8 (3.5) | 13 (2.1) |
| Toxicity, predominhantly from nervous system | 3 (1.3) | 10 (1.6) |
| Dyslipidaemia | 6 (2.6) | 9 (1.4) |
| Death | 1 (0.4) | 8 (1.3) |
| Pregnancy | 6 (2.6) | 7 (1.1) |
| Study treatment | 1 (0.4) | 5 (0.8) |
| Partial virological failure | – | 3 (0.5) |
| Cardiovascular disease | – | 2 (0.3) |
| Diabetes | 2 (0.9) | 2 (0.3) |
| Clinical progression | – | 1 (0.2) |
| Hyperlactaemiae/lactic acidosis | – | 1 (0.2) |
| Pregnancy – prevention of mother to child transmission | 1 (0.4) | 1 (0.2) |
| Structured treatment interruption (STI) | – | 1 (0.2) |
| Toxicity, predominantly from endocrine system | – | 1 (0.2) |

discontinuation significantly differed by baseline treatment status, as ARV-treatment experienced patients with <50 HIV-RNA copies/mL at ATV initiation stayed longer on treatment than other patients ($p = 0.0186$ log-rank test). Using a multivariate analysis, treatment status at start of ATV still remained significant to predict discontinuation of ATV ($p = 0.002$). The probability to discontinue was higher for ARV-experienced patients with ≥50 HIV-RNA copies/mL (hazard ratio [HR]: 1.4) compared to ARV-naive patients with HIV-RNA VL <100.000 copies/mL (HR: 1.0); HR of other baseline status at ATV initiation being equal or close to 1. Gender and baseline CD4 count were not significant predictors of treatment discontinuation.

Patients were on ATV treatment for a median (Q1; Q3) time of 1.6 (0.8; 2.8) year, and the median (Q1; Q3) time to ATV discontinuation was 0.8 (0.3; 1.5) year. Over all follow-up period, 771 patients (34.1%) discontinued ATV treatment, mainly due to patient or physician decision (13.7 and 10.0%, respectively), simplified treatment availability (8.6%), and gastrointestinal and hepatic side effects (respectively, 8.6 and 8.1%) (Table 3. Reasons for ATV discontinuation (D:A:D Classification)) [7]. Renal AEs led to discontinuation in 30 patients (4.8%).

After ATV discontinuation, 85.9% of patients (662/771) were switched to other ARV drugs, including PIs in 52.1% of cases (55.7% on boosted darunavir), NNRTIs in 23.2% (61.5% on efavirenz and 27.4% on nevirapine), and raltegravir or maraviroc in 14.9%.

In women, the probability to remain on treatment was 0.79 (95% CI: 0.76; 0.81) and 0.70 (CI: 0.67; 0.73) for the first and second years, respectively, compared to 0.77 (95% CI: 0.75; 0.80) and 0.68 (95% CI: 0.65; 0.70)

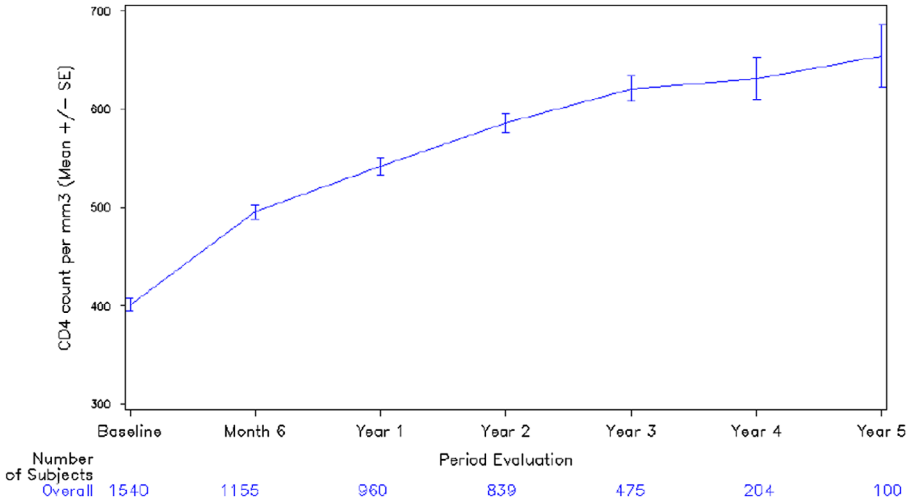


**Figure 2.** Evolution of CD4 count over time (overall ATV population).

in men ($p$ = 0.4066). Slightly less women (282, 32.2%) discontinued the ATV regimen compared to men (489, 35.3%); the most frequent reasons for discontinuation being the participant's or physician's wish/decision (14.5 and 11.5%, respectively).

The same trends were observed in unboosted ATV treated patients. The probability to remain on treatment was 0.77 (95% CI: 0.73; 0.81) and 0.67 (95%CI: 0.62; 0.71) for the first and second years, respectively, and was also comparable between males/females, and between the different baseline CD4 categories (respectively, $p$ = 0.7855 and $p$ = 0.7152; log-rank test). Finally, multivariate analyses carried out in patients with unboosted ATV gave the same results as those found in the overall population.

### *Virological and immunological efficacy*

Respectively, 81.1% (792/977), 83.5% (405/485), and 91.8% (89/97) of patients achieved virological suppression <50 HIV-RNA copies/mL after 1, 3. and 5 years of follow-up for the overall group. At the end of follow-up (i.e. at treatment discontinuation or at the latest available record time-point), the proportion of patients virologically suppressed increased from 33.4 at to 76.6% with HIV-RNA <50 copies/mL and from 42.4 to 91.3% with HIV-RNA <400 copies/mL. These findings were observed overall and regardless of gender with no marked difference between both groups at the end of follow-up: 75.2% of males vs. 78.9% of females with HIV-RNA <50 copies/mL and 90.9% of males vs. 91.9% of females with HIV-RNA <400 copies/mL. The same was true for patients concomitantly treated or not with TDF. In contrast, by treatment status, a greater proportion of patients with a virological response was found in ART treatment-experienced patients with a HIV-RNA VL <50 copies/mL at baseline. Indeed, loss of virological response was observed in 205 patients over time (time to loss of virological response defined as 2 consecutive plasma HIV RNA levels > 50 copies/mL after virological control). No differences were found by gender and by CD4 category (< or ≥ 350 cells/mm$^3$ at baseline). Conversely, there was a significant difference in time to loss of virological response according to treatment status with a greater probability of not showing loss of virological failure in ARV-experienced patients with HIV-RNA <50 copies/mL at baseline than in other patients ($p$ < 0.0001 log-rank).

### *CD4 cell count over time*

CD4 cell count gradually increased over time from baseline (median: 361 cell/mm$^3$; $n$ = 1836) to the end of follow-up (median: 540 cell/mm$^3$; $n$ = 1836), with a median increase of 42.2% (Figure 2). This trend was observed with no notable differences between males and females (median change between baseline and end of follow-up in CD4 cell count of 45.4 vs. 38.4%, respectively). In contrast, a greater immunological response was seen in treatment-naive patients compared to ARV-experienced patients.

### *Safety parameters*

BMI, cardiovascular, and lipid parameters remained unchanged throughout the observation period. An increase in total bilirubin occurred during the follow-up at 6 months of ATV regimen (0.54 ± 0.44 mg/dL at baseline ($n$ = 1261) to 2.13 ± 1.38 mg/dL at 6 months ($n$ = 934)), and levels then remained stable until the end of the follow-up period. Similarly, the proportion of patients presenting with hyperbilirubinemia of more than 2 times the upper limit of normal (≥ 3 mg/dL) increased from 0.6% at baseline to 20.9% at 6 months, 17.1% at 1 year and 21.4% at 5 years.

Regarding renal parameters, estimated glomerular filtration rate (eGFR) values based on MDRD formula were calculated, and collected eGFR values were categorized per grade (G0-G1: ≥ 60; G2: [30; 60]; G3: [15;

30]; and G4: <15 mL/min). As a general comment data on eGFR should be interpreted cautiously, as no control group was available. Among the 878 patients with an available baseline value and at least one post-baseline value, a minority of patients experienced a worsening in their mean eGFR: 6.8% ($n = 60$) and 0.5% ($n = 4$) had a worsening equal to 1 grade and higher than 1 grade, respectively. The median MDRD calculated eGFR (mL/min/1.73 $m^2$) value (Q1; Q3) slightly decreased from baseline (99.2 (86.3; 115.1)) to 92.7 (79.3; 107.3) at 1 year with a median change of −6.4%. The maximum decrease in median MDRD calculated eGFR (−13%) was observed after 4 years of follow-up. A change in eGFR from baseline to the end of follow-up up to −10% was showed by 46.6% of patients ($n = 625$), while 27.3% ($n = 367$) had a decrease ranging from −10 to −20%, 16.5% ($n = 221$) from −20 to −30%, and 9.6% ($n = 129$) of more than −30%. Comparing patients with worsening (> 1 Grade) and without worsening in eGRF, lower baseline MDRD calculated eGFR value (79.1 vs. 102.6 mL/min/17.73 $m^2$) and older age (52.2 vs. 41.5 years) were identified as significant predictive risk factors of eGRF worsening ($p < 0.0001$, $t$-test). Finally, no relevant change over time was observed for serum creatinine levels.

## Subgroup of patients with unboosted ATV

Data from 457 patients receiving unboosted ATV-based regimen were also analyzed. Baseline characteristics of this subgroup were similar to those of the overall population. In addition, similar findings concerning virological and immunological efficacy were observed and the probability to remain on ATV treatment was also high: 0.77 (95% CI: 0.73; 0.81) and 0.67 (95% CI: 0.62; 0.71) at the first and second years after treatment initiation. Few patients (12.3%, $n = 56$) experienced virological failure over time, and a large proportion of patients were also virologically suppressed (defined as HIV-RNA VL <50 copies/mL after two consecutive measurements) at the end of follow-up (75.1% with HIV-RNA <50 copies/mL and 86.8% with HIV-RNA <400 copies/mL). At the end of follow-up, the improvement in immunological response was lower than in the overall population with the CD4 cell count increased by 29.2%. Compared to the overall population, slightly more patients discontinued unboosted ATV treatment (45.1%, $n = 206$) with a median (Q1; Q3) time to discontinuation of 1.0 (0.4; 2.2) year. No major concerns were identified in this subgroup. Except for a similar decrease in the median MDRD calculated eGFR (−4.2% at 6 months to −11.5% at 5 years), the remaining laboratory safety parameters were either unchanged or very little changed.

## Discussion

This study is the first observational study collecting data on the therapeutic value and describing characteristics of a large population of patients receiving ATV in daily practice in Belgium since the introduction of the drug on the market. The majority of patients included (61.2%) were previously experienced with ARVs, with previous PI or PI/NNRTI containing combination in nearly two patients out of three; the switch to ATV being mainly linked to the occurrence of gastro-intestinal disorders.

The virological suppression rate using a 50 HIV-RNA copies/mL threshold remained high (91.8%) 5 years (91.8%) after starting ATV, illustrating durable virological effectiveness. Viral suppression was calculated on the whole population this including patients who were still or not anymore on ATV. This can thus be seen as an intent to treat analyses. In addition, the patients enrolled achieved a significant immunological recovery with a median CD4 cell count increase of 42.2%.

Taking into account methodological challenges and limitations associated with observational retrospective studies, these findings are consistent with those from cohort data conducted in HIV infected patients, and confirmed the long-term efficacy of ATV in HIV type 1 (HIV1) positive patients observed in previous clinical studies [2–4,6,8–12].

Overall, the rate of ATV treatment discontinuation of 34.1% in this mixed population was limited over time and close to that previously shown (30%) in the REMAIN cohort of naive patients [9]. The most common reasons for discontinuations such as patient or physician decision and safety concerns were the same as those previously reported in the literature [8,13].

Virological and immunological effectiveness results appeared to be similar by gender in this study with a rate of discontinuation even lower in females than in males. Our results are in line with those which had previously shown that long-term efficacy and safety outcomes of ATV/ritonavir (ATV/r)-based regimens were similar by gender despite a higher risk of treatment discontinuation in women [10]. It is however in contrast with other studies showing that women on ATV/r, especially of non white ethnicity, had higher risk of virological failure than men [8,14,15]. We also observed that the probability to remain on treatment did not vary according to baseline CD4 count, while previous reports found increased rates of ARV discontinuation with higher baseline CD4 cell count [16]. In contrast, an increased probability of treatment discontinuation seemed to be associated with prior treatment status, especially in non-virologically controlled treatment-experimented patients. Detailed data on patient comorbidities needing pharmacological treatment were not available for the present analysis; therefore, the influence of ATV treatment on the possible comorbidities increase could not be completely evaluated.

Besides maintaining virological suppression combined with an immunological benefit, patients who were treated with ATV had a satisfactory biological safety. While several PIs, particularly indinavir and lopinavir,

were commonly associated with hypercholesterolemia and hypertriglyceridemia [17,18], our data showed a good long-term lipids safety profile of ATV as previously observed [19,20]. Hyperbilirubinaemia is the most common AE related to the use of ATV reported in the literature [8,11]. In this study, ATV intake resulted in a modest increase of bilirubinemia only seen at 6 months, which can be explained by a reversible elevation of indirect bilirubin levels by competitive inhibition of the uridine diphosphate glucuronosyltransferase [8,12]. Similarly, renal function seemed not to be affected by ATV administration as no significant increase in creatinine levels and low incidence of worsening in eGFR were found over time of ATV exposure. However, age and low baseline MDRD calculated eGFR were identified as risk factors of eGFR decline over time.

As previously reported in the literature [21] the virological and immunological responses as well as safety were comparable in unboosted patients treated with ATV, including naive and ART treatment-experienced patients, with those found in the overall population receiving ATV or ATV/r. Overall, the safety lab tests were satisfactory up to 5 years of ATV therapy. Of note, the presence or absence of ritonavir as part of the ATV-based antiretroviral regimen did not have an impact on the eGFR changes.

The main strength of this study is the high number of data collected from patients treated with ATV in Belgium. Because HIV treatment is mainly performed in HIV reference centers, databases from these centers contain the vast majority of patients treated with ATV in Belgium. Therefore, the sample of patients included in this study may represent a substantial part of the patient population receiving this regimen in Belgium. However, some limitations must be highlighted. Due to the heterogeneous and not pre-selected patient population, caution must be taken when drawing conclusions from this study. For the same reason, it was not possible to make any formal statistical comparisons between the results of this study and those from controlled clinical trials, or to combine them. For some variables, despite all efforts, a significant proportion of missing data were recorded. This is due to the retrospective multicentric design of the study. The distribution of missing data among the different centers was homogeneous. Reassuringly, missing variables did not impact on the major outcomes of the analysis. Finally, this large retrospective cohort of patients did not allow to provide sufficient information about the frequency and severity of AEs.

In conclusion, in real life settings, clinical and safety data obtained from this 5 year-cohort study conducted in ART-naive and experienced HIV-1 positive patients showed a high probability to remain on ATV treatment for the first and second years and a satisfactory lipid profile, overall and in each sub-population, i.e. patients treated with unboosted ATV-based regimens and females.

## Aknowledgement

The authors acknowledge the assistance of Romain Jegou, Business & Decision Life Sciences for statistical analysis, Valérie Patin for her Medical Writing Services.

## Disclosure statement

No potential conflict of interest was reported by the authors.

## Funding

Retrospective collection and analysis of data were supported by Bristol Myers Squibb.ORCID
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