BMC Infectious Diseases

RESEARCH

Open Access

# Neuropsychiatric adverse events in people with HIV initiating a new integrase strand transfer inhibitor-based regimen in Italy: findings from the NEURO-INSTI study

Nicola Squillace[1*], Elena Delfina Ricci[2], Giancarlo Orofino[3], Gabriele Forcina[4], Laura Albini[4], Barbara Menzaghi[5], Giuseppe Vittorio De Socio[6], Stefania Piconi[7], Paolo Maggi[8], Giordano Madeddu[9], Giovanni Francesco Pellicanò[10], Eleonora Sarchi[11], Benedetto Maurizio Celesia[12], Filippo Lagi[13], Elena Salomoni[14], Antonio Di Biagio[15] and Paolo Bonfanti[1,16]

## Abstract

**Background** Although clinical trials reported a low and comparable rate of central nervous system (CNS)/neuropsychiatric (NP) disturbances among people with HIV (PWH) receiving integrase strand transfer inhibitors (INSTI) or other antiretroviral therapy (ART), higher rates of these disturbances have been reported in clinical practice. Our aim was to compare the occurrence of CNS-NP disorders in the different INSTI drugs.

**Methods** Using data from the SCOLTA project, a multicenter observational study following PWH who start antiretrovirals to identify adverse events (AEs) in real-life, we performed a retrospective analysis (NEURO-INSTI) to assess incidence rates (IRs) and 95% confidence intervals (95% CI) of CNS/NP AEs and related interruptions. Observation was truncated at the first occurrence of any CNS/NP AEs, even if not causing treatment discontinuation. IRs were calculated as number of first occurrences/100 person-years follow-up (PYFU). To identify risk factors for CNS/NP AEs occurrence, a Cox regression analysis for competing risks was used (hazard ratio, HR, and 95% CI), including variables associated with the outcome at a p level < 0.20 in the univariate analysis.

**Results** We analyzed a sample of 2,922 PWH (mean age 47.2 years, 74.7% males) enrolled in raltegravir (RAL), dolutegravir (DTG), elvitegravir (EVG), and bictegravir (BIC) INSTI-cohorts since 2007. Over a median observation time of 28 months (interquartile range 14–45), 126 CNS/NP AEs and 72 related discontinuations occurred; IRs were 1.59/100 PYFU (95% CI, 1.34–1.90) and 0.91/100 PYFU (95% CI 0.72–1.15), respectively. In multivariate models, intravenous drug use history (IVDUh), current abacavir use, RAL use, and psychiatric illnesses were associated with a higher risk of CNS/NP AEs. IVDUh and current abacavir use were also associated with treatment discontinuation. Using an INSTI as a first-line therapy and starting with CD4 ≥ 350 cell/μL also increased the likelihood of discontinuation.

*Correspondence:
Nicola Squillace
nicola.squillace@irccs-sangerardo.it; nicolasquillace74@gmail.com

Full list of author information is available at the end of the article

Compared to DTG, BIC and EVG showed lower risks of CNS/NP AEs (adjusted HR 0.27, 95% CI 0.10–0.74, and 0.51, 95% CI 0.22–1.20, respectively), while RAL showed a higher risk (aHR 2.52, 95% CI 1.57–4.05).

**Conclusions** Among PWH on INSTI treatment, IVDUh, concurrent psychiatric illness, abacavir and RAL use increased the risk of CNS/NP AEs occurrence. PWH on BIC were less likely to experience CNS/NP AEs and related treatment discontinuations.

**Keywords** CNS adverse events, Neurologic disorders, Psychiatric disorders, HIV, Integrase strand transfer inhibitors, Bictegravir, Dolutegravir

## Introduction

Central nervous system (CNS)/Neuro-Psychiatric Adverse Events (NP AEs) in people with HIV (PWH) have been recognized as a growing issue since the introduction of Integrase Strand Transfer Inhibitors (INSTIs), such as dolutegravir (DTG) and bictegravir (BIC). Recently, several studies evaluated the adverse effects of INSTIs because they are the most widely used class of antiretroviral drugs for HIV to date. These studies focused on CNS/NP AEs as the most frequent AEs in this drug class.

The rate of NP AEs varies according to the single INSTI drug and the type of study. In randomized clinical trials (RCTs), PWH on DTG showed a prevalence of NP AEs less than 1% [1], while rates ranging from 2.3 to 20.6% were reported in observational real-life studies [1, 2]. Discontinuation rates also varied in a wide range, from 0 to 13.8% [1, 3].On the other hand, BIC showed a prevalence of NP AEs of 0–1% in RCTs [2], while in real-life studies rates from 0.8 to 25.6% were observed [4–6]. Observational studies provide invaluable insights into the intricate interplay between exposures, risk factors, and health outcomes within authentic, real-world settings, differing significantly from the controlled interventional designs of randomized clinical trials [7, 8]. No study described a highly significant difference between NP AEs among different INSTI drugs.

Described risk factors for discontinuation both in RCT and observational studies were usually age (≥ 50 vs. < 50 years old), female sex, CD4 < 350 vs. ≥ 350, being antiretroviral treatment (ART)-naïve as compared to ART-experienced, and combination with abacavir (ABC) [1, 3].

Our aim was to evaluate the incidence of CNS/NP AEs occurring during the treatment with INSTIs in a real-life cohort, and the CNS/NP AEs-related INSTI discontinuation, especially as regards BIC- and DTG-based regimens.

## Methods

NEURO-INSTI Study is a real-life, observational, retrospective analysis using medical record data retrieved from the CISAI-SCOLTA Project, a prospective cohort database. The SCOLTA project is a multicenter observational study started in 2002 and following prospectively PWH who start to take new antiretroviral drugs, to identify toxicities and adverse events in a real-life setting [9]. The SCOLTA project uses an online pharmacovigilance program and involves 25 Italian Infectious Disease Centers (www.cisai.it).

Briefly, both ART-naïve and ART-experienced PWH can be included in SCOLTA, if they are ≥ 18 years old, and are able and willing to give their consent to study entry. PWH were invited to be enrolled if they were starting for the first time a treatment including a newly marketed antiretroviral drug. Clinical data collected include sex, age, ethnicity, weight, height, CDC stage, and previous ART history. Laboratory data include HIV-RNA, CD4 + T cell count, and biochemical data and are prospectively collected anonymously in a central database every six months (Fig. 1S). AEs are prospectively collected as soon as they are clinically observed.

Common Terminology Criteria for Adverse Events was used to define the severity and only grade 3–4 (moderate and/or severe) were considered as clinically significant [10].

CNS/NP AEs reported included altered mental status, cognitive, behavioral, or attentional disturbances (poor concentration, slow thinking), sleep disturbances and insomnia, nervousness, restlessness, depression, headaches, dizziness, seizures, and muscle-skeletal pain or paresthesia. Two CNS/NP AEs-related outcomes were considered, distinguishing between any occurrence (limited to grades 3–4) and causing treatment discontinuation (any grade).

This analysis includes PWH initiating or switching to an INSTI-based regimen recorded in the CISAI-SCOLTA database from March 2007 to October 2022, with at least one follow-up visit or discontinuation of the INSTI-based regimen before 6 months of observation. Each patient is considered as a different observation if included in a different INSTI cohort, and their baseline information was updated at the date of new INSTI initiation.

PWH were enrolled and followed in different calendar periods according to the cohort: 2007–2014 for RAL; 2014–2017 for EVG; 2014-ongoing for DTG; and 2019-ongoing for BIC. As regards the currently ongoing cohorts, in this analysis, the enrollment was truncated in

October 2022 and the follow-up continued until August 2023.

The SCOLTA Project focuses on newly marketed drugs, enrolling PWH that start a new treatment in the clinical practice and following them over the years until they discontinue the drug, or the cohort closed (which happens before). A cohort closes when the drug has been so widely used that all safety aspects have been plausibly investigated, or when a new standard of treatment makes the drug out-of-date and its use infrequent (such as was the case of RAL). Thus, the timeframe of our INSTI cohorts follows the commercialization of each drug in Italy. For the same reason, the decision to discontinue an INSTI and switch the PWH to another INSTI is also likely affected by the availability of such an opportunity. For example, RAL treatment was maintained also if causing AEs because this drug was prescribed to PWH with very few treatment options, that explains the higher IR for CNS/NP AE and the lower IR for CNS/NP AE-related discontinuation.

### Statistical analysis

All continuous variables were described using mean, standard deviation (SD), median, and interquartile range (IQR) as appropriate. Frequency (%) was used for categorical and ordinal variables. Regarding CNS/NP AE, we calculated the incidence rate (IR) for the occurrence of any event and for discontinuation due to this type of event. In all analyses, observation time for subjects without the given AE was the length of time in the study (i.e., from start of INSTI treatment up until the last follow-up or treatment discontinuation because of reasons other than CNS/NP AE). For subjects with the given AE, the time was calculated from the start of INSTI treatment up until the first occurrence of the CNS/NP AE.

The IRs and the relative 95% confidence intervals (CI) were calculated as the ratio between the number of events and the observation time on the total study population, per 100 person-year follow-up (PYFU) and by stratifying according to the baseline characteristics (e.g., age ≥ 50 years-old, history of psychiatric disorders or current use of psychiatric drugs). The Rate Ratio (RR, 95% CI) was estimated using the MidP exact method.

A Cox regression model of proportional hazards was used to calculate the hazard ratio (HR) and 95% CI associated with the exposures: HR > 1.0 indicated a higher risk of the outcome, HR < 1.00 a lower risk. The multivariate Cox regression analysis included all variables associated with the outcome at a p-level < 0.20. No imputation was done for missing data, as the missing at random assumption may not hold. A separate category for each covariate with missing information was included if data was missing in more than 1% of subjects.

No sensitivity analyses were conducted or multiple imputation strategies performed, since in our sample only BMI presented a substantial amount of missing data, mainly in patients from centers where height was not routinely recorded: missing status was not at random but also not linked to the treatment.

Considering that patients are at risk of CNS/NP AEs occurrence and ART discontinuation due to CNS/NP AEs, as well as to discontinuation due to other reasons (other AEs, treatment failure, clinical events), a competing risk model accounting for competing risk of discontinuation due to any other reasons than CNS/NP AEs was generated [11]. This model was preferred to non-competing risk models (such as the Kaplan-Meier survival analysis or Cox regression non-competing model), that would not account for data censoring due to discontinuations for other reasons.

Regarding the switch group of patients, since any CNS/NP AEs observed at the onset of the new INSTI-based regimen could result from the "tail effect" of the previous drug (e.g., in the case of drugs with long half-lives), a sensitivity analysis was performed by comparing the IRs of people who switched from a different INSTI (exposed) or switched from a non-INSTI drug ART drug (unexposed).

## Results

Since the opening of the first INSTI cohort (RAL, March 2007) in the SCOLTA Project, 2,922 PWH were enrolled until October 2022. The mean age was 47.2 years (SD 11.6), and the number of women was 738 (25.4%). Six hundred and twenty (21.2%) took an INSTI as the first-line treatment and 2,302 (78.8%) as a switch from a previous ART regimen, which included another INSTI in 705 (30.6%) PWH.

As shown in Table 1, PWH on BIC and DTG were usually older and with higher weight than PWH on EVG and RAL. PWH on RAL were usually experienced, with CDC stage C, and with lower CD4 cell count. They had also been on ART for more years and began their first ART in the 1985–2000 period.

The overall IR for any CNS/NP AEs was 1.59/100 PYFU (95% CI 1.34–1.90), whereas the IR for discontinuations was 0.91/100 PYFU (95% CI 0.72–1.15).

Tables 2 and 3 show the rate of CNS/NP AEs and discontinuation, respectively, and their association with demographic and clinical characteristics.

### CNS/NP AE occurrence

In the competing risk model for CNS/NP AE occurrence, sex at birth, age (below or over 50), Intravenous Drug Use history (IVDUh), CDC stage, year of first ART, backbone including tenofovir alafenamide (TAF) or ABC, NP disturbances at baseline, and cohort of INSTI were all associated with p-value < 0.20 at the univariate analysis and

**Table 1** Baseline characteristics of people with HIV enrolled in the SCOLTA project INSTI cohorts ($n = 2922$)

| | Bictegravir | Dolutegravir | Elvitegravir | Raltegravir | *P* |
|---|---|---|---|---|---|
| | ***N* = 735** | ***N* = 1339** | ***N* = 338** | ***N* = 510** | |
| **Age**, **years** (mean ± SD) | 48.4 ± 12.2 | 47.9 ± 12.1 | 43.7 ± 10.8 | 46.0 ± 9.3 | < 0.0001 |
| **Males** (n, %) | 560 (76.2%) | 1019 (76.1%) | 261 (77.2%) | 344 (67.4%) | 0.0005 |
| **Caucasian** (n, %) | 648 (88.2%) | 1204 (89.9%) | 305 (90.2%) | 474 (92.9%) | 0.05 |
| **Weight**, **Kg** (mean ± SD) | 74.6 ± 14.6 | 71.4 ± 13.7 | 71.0 ± 12.3 | 68.4 ± 14.4 | < 0.0001 |
| **BMI**, **Kg/m$^2$** (mean ± SD) | 25.3 ± 4.5 | 24.3 ± 4.1 | 23.9 ± 3.3 | 23.7 ± 4.0 | < 0.0001 |
| BMI ≤ 30.0 Kg/m$^2$ | 515 (70.1%) | 1090 (81.4%) | 294 (87.0%) | 421 (82.6%) | |
| BMI > 30.0 Kg/m$^2$ | 78 (10.6%) | 98 (7.3%) | 14 (4.1%) | 29 (5.7%) | |
| Missing value | 142 (19.3%) | 151 (11.3%) | 30 (8.9%) | 60 (11.8%) | < 0.0001 |
| **Risk factor for HIV acquisition (n, %)** | | | | | |
| Heterosexual | 285 (38.8%) | 497 (37.1%) | 125 (37.0%) | 178 (34.9%) | |
| IDU | 94 (12.8%) | 211 (15.8%) | 56 (16.6%) | 183 (35.9%) | |
| MSM | 201 (27.4%) | 484 (36.2%) | 125 (37.0%) | 104 (20.4%) | |
| other | 155 (21.1%) | 147 (11.0%) | 32 (9.5%) | 45 (8.8%) | < 0.0001 |
| **Naive** (n, %) | 156 (21.2%) | 335 (25.0%) | 101 (29.9%) | 28 (5.5%) | < 0.0001 |
| **CDC stage** (n, %) | | | | | |
| **A** | 388 (52.8%) | 726 (54.2%) | 172 (50.9%) | 157 (30.8%) | |
| **B** | 186 (25.3%) | 323 (24.1%) | 88 (26.0%) | 157 (30.8%) | |
| **C** | 151 (20.5%) | 287 (21.4%) | 78 (23.1%) | 196 (38.4%) | < 0.0001 |
| **CD4 (cells/**μL**)** (median, IQR) | 546 (337–786) | 577 (347–825) | 472 (256–730) | 340 (190–536) | < 0.0001 |
| **CD4 < 350 cells/**μL | 192 (26.1%) | 350 (26.1%) | 122 (36.1%) | 265 (52.0%) | |
| **CD4 ≥ 350 cells/**μL | 593 (73.9%) | 989 (73.9%) | 216 (63.9%) | 245 (48.0%) | < 0.0001 |
| **Detectable HIV RNA (ART-experienced)** (n, %) | 93 (16.1%) | 155 (15.4%) | 64 (27.0%) | 269 (55.8%) | < 0.0001 |
| **Years of ART (ART-experienced)** (n, %) (median, IQR) | 8.0 (3.3–16.2) | 10.5 (5.0-17.9) | 8.0 (2.8–16.3) | 11.8 (6.8–14.1) | < 0.0001 |
| **Year of first treatment (n, %)** | | | | | |
| 1985–2000 | 104 (14.2%) | 302 (22.6%) | 71 (21.0%) | 344 (67.4%) | |
| 2001–2010 | 143 (19.5%) | 342 (25.5%) | 88 (26.0%) | 160 (31.4%) | |
| 2011-today | 488 (66.4%) | 694 (51.8%) | 178 (52.7%) | 6 (1.2%) | < 0.0001 |
| **ABC-including regimen** (n, %) | 0 | 451 (33.7%) | 0 | 40 (7.8%) | < 0.0001 |
| **TAF-including regimen** (n, %) | 735 (100) | 151 (11.3%) | 0 | 0 | < 0.0001 |
| **Switched from a previous INSTI** (n, %) | 399 (54.3%) | 270 (20.2%) | 36 (10.6%) | 0 | < 0.0001 |
| **Psychiatric comorbidity** (n, %) | 62 (8.4%) | 101 (7.5%) | 25 (7.4%) | 51 (10.0%) | 0.34 |

ABC: abacavir; ART: antiretroviral treatment; BMI: body mass index; IDU: intravenous drug use; INSTI: integrase strand transferase inhibitor; IQR: interquartile range; MSM: men having sex with men; SD: standard deviation; TAF: tenofovir alafenamide

were included in the multivariate model. Adjusted HR (aHR) of CNS/NP AEs did not significantly differ by age, sex, CDC stage, and year of first treatment.

On the contrary, some factors were associated with higher risk for CNS/NP AEs: IVDUh (aHR 1.83, 95% CI 1.17–2.86), ABC-including regimen (aHR 1.72, 95% CI 1.13–2.72), and psychiatric comorbidity (aHR 1.69, 95% CI 1.02–2.80). Using DTG as the reference category, BIC and EVG showed a lower risk of CNS/NP AEs and RAL a higher risk, with an aHR 2.52 (95% CI 1.57–4.05) (Table 2).

### CNS/NP AE-related discontinuations

The factors associated with treatment discontinuation were partially different (Table 3). The multivariate model included age at study entry, body mass index (BMI), IVDUh, naïve status, CD4 (< 350 or ≥ 350 cells/μL), backbone including TAF or ABC, and cohort of INSTI. As observed for the occurrence, IVDUh and ABC-containing regimens were associated with a higher risk of treatment discontinuation for CNS/NP AEs. On the other hand, ART-naïve PWH and CD4 ≥ 350 cells/μL, not associated with CNS/NP AEs occurrence, were associated with a higher risk of discontinuation. BIC and EVG showed a lower risk of CNS/NP AEs, whereas the high incidence of CNS/NP AEs in PWH on RAL did not translate into higher treatment interruptions (Table 3; Fig. 2S). Although CNS/NP AE occurrence was significantly higher in RAL than DTG-treated PWH, the aHR for discontinuation was 0.75 (95% CI 0.33–1.69), showing no difference.

### Preplanned sub-group analysis

To explore the chance that switching from a previous INSTI-based treatment could result in a CNS/NP AE due to a "tail effect" but erroneously ascribed to the currently

**Table 2** Number of any CNS adverse events: incidence rates, rate ratios and crude and adjusted hazard risks in PWH starting a new INSTI-based treatment, by characteristics at baseline

| | ***N*** **(%)** | **PYFU** ***N*** **= 7902.66** | **Any CNS AEs** ***N*** **= 126** | **IR AEs / 100 PYFU (95% CI)** | **RR (95% CI)** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)** |
|---|---|---|---|---|---|---|---|
| Female | 738 (25.3) | 1964.52 | 38 | 1.93 (1.41–2.66) | Ref. M | | |
| Male | 2184 (74.7) | 5938.14 | 88 | 1.48 (1.20–1.83) | 1.30 (0.89–1.91) | 1.28 (0.87–1.87) | 1.23 (0.83–1.81) |
| Age < 50 years | 1655 (56.6) | 4422.71 | 68 | 1.54 (1.21–1.95) | Ref. <50 | | |
| Age ≥ 50 years | 1267 (43.4) | 3479.95 | 58 | 1.67 (1.29–2.16) | 1.08 (0.76–1.54) | 1.12 (0.79–1.59) | 1.29 (0.89–1.88) |
| Caucasian | 2631 (90.0) | 7270.06 | 117 | 1.61 (1.34–1.93) | Ref. Caucasian | | |
| Other | 291 (10.0) | 632.6 | 9 | 1.42 (0.74–2.73) | 0.88 (0.45–1.74) | 0.73 (0.37–1.43) | - |
| BMI ≤ 30.0 Kg/m$^2$ | 2320 (79.4) | 6315.32 | 107 | 1.69 (1.40–2.05) | Ref. BMI ≤ 30 | | |
| BMI > 30.0 Kg/m$^2$ | 219 (7.5) | 582.13 | 7 | 1.20 (0.57–2.52) | 0.71 (0.33–1.52) | 0.71 (0.33–1.53) | - |
| Missing value | 383 (13.1) | 1005.21 | 12 | 1.19 (0.68–2.10) | 0.70 (0.39–1.28) | 0.69 (0.38–1.26) | - |
| Intravenous drug use history no | 2378 (81.4) | 6382.17 | 81 | 1.27 (1.02–1.58) | Ref. No IDU | | |
| Intravenous drug use history yes | 544 (18.6) | 1520.48 | 45 | 2.96 (2.21–3.96) | 2.33 (1.62–3.36) | 2.42 (1.68–3.49) | **1.83 (1.17–2.86)*** |
| ART experienced | 2302 (78.8) | 6416.23 | 102 | 1.59 (1.31–1.93) | Ref. ART exp. | | |
| ART naïve | 620 (21.2) | 1486.43 | 24 | 1.62 (1.08–2.41) | 1.02 (0.55–1.58) | 0.89 (0.57–1.38) | - |
| CDC stage | | | | | | | |
| A | 1443 (49.4) | 3856 | 44 | 1.14 (0.85–1.53) | Ref. A | | |
| B | 754 (25.8) | 2110.38 | 39 | 1.85 (1.35–2.53) | 1.62 (1.05–2.49) | 1.70 (1.11–2.61) | 1.30 (0.82–2.06) |
| C | 712 (24.4) | 1913.11 | 43 | 2.25 (1.67–3.03) | 1.97 (1.29-3.00) | 1.99 (1.31–3.03) | 1.40 (0.89–2.19) |
| CD4 < 350 cells/mL | 929 (31.8) | 2325.77 | 43 | 1.85 (1.37–2.49) | Ref < 350 | | |
| CD4 ≥ 350 cells/mL | 1993 (68.2) | 5393.05 | 83 | 1.54 (1.24–1.91) | 0.83 (0.58–1.20) | 0.89 (0.61–1.28) | - |
| Year of first treatment | | | | | | | |
| 1985–2000 | 821 (28.1) | 2493.39 | 52 | 2.09 (1.59–2.74) | Ref. 1985–2000 | | |
| 2001–2010 | 733 (25.1) | 2075.56 | 37 | 1.78 (1.29–2.46) | 0.85 (0.56–1.30) | 0.80 (0.53–1.23) | 1.29 (0.80–2.10) |
| 2011-today | 1366 (46.7) | 3325.88 | 37 | 1.11 (0.81–1.54) | 0.53 (0.35–0.81) | 0.44 (0.29–0.68) | 1.29 (0.74–2.26) |
| Regimen without ABC and TAF | 1545 | 4360.19 | 76 | 1.74 (1.39–2.18) | Ref. no | | |
| Regimen with ABC | 491 | 1922.58 | 35 | 1.82 (1.31–2.54) | 1.04 (0.70–1.56) | 1.38 (0.93–2.06) | **1.72 (1.13–2.72)** |
| Regimen with TAF | 886 | 1619.89 | 15 | 0.93 (0.56–1.54) | 0.53 (0.30–0.92) | 0.37 (0.22–0.65) | 1.27 (0.56–2.89) |
| Treatment cohort | | | | | | | |
| Bictegravir | 735 (25.2) | 1302.38 | 8 | 0.61 (0.31–1.23) | 0.44 (0.21–0.92) | 0.26 (0.12–0.54) | **0.27 (0.10–0.74)** |
| Dolutegravir | 1339 (45.8) | 4516.86 | 63 | 1.40 (1.09–1.78) | Ref. DTG | | |
| Elvitegravir | 338 (11.6) | 776.21 | 6 | 0.77 (0.35–1.72) | 0.55 (0.24–1.28) | 0.38 (0.16–0.88) | 0.51 (0.22–1.20) |
| Raltegravir | 510 (17.5) | 1307.2 | 49 | 3.75 (2.83–4.96) | 2.69 (1.85–3.90) | 2.15 (1.48–3.11) | **2.52 (1.57–4.05)*** |
| PWH without psychiatric comorbidity | 2683 (91.8) | 7256.28 | 107 | 1.48 (1.22–1.78) | Ref. No | | |
| PWH with psychiatric comorbidity | 239 (8.2) | 646.37 | 19 | 2.94 (1.88–4.61) | 1.99 (1.22–3.25) | 2.04 (1.25–3.32) | **1.69 (1.02–2.80)** |

ABC: abacavir; ART: antiretroviral treatment; BMI: body mass index; CI: confidence interval; CNS: central nervous system; HR: hazard ratio; IDU: intravenous drug use; IR: incidence rate; PWH: people with HIV; PYFU: person-year follow-up; RR: rate ratio; TAF: tenofovir alafenamide

Cox multivariate model for CNS AE occurrence includes sex at birth, age < 50 or ≥ 50 at study entry, IDU history, CDC stage, year of first ART, backbone including TAF or ABC, NP disturbances at baseline, and cohort of INSTI (all associated with p-value < 0.20 at the univariate analysis). Bold results are associated to the outcome with $p < 0.05$. *an asterisk states that the results are associated to the outcome with $p < 0.01$

prescribed INSTI, we compared PWH by groups of previous ART-regimen. As regards any CNS/NP AEs, the IR in PWH exposed or unexposed to INSTI in the previous regimen did not support the hypothesis of a "tail effect" of previous INSTI exposure, since the IRs were 1.00/100 PYFU (95% CI 0.62–1.61) in INSTI-exposed PWH, and 1.76/100 PYFU (95% CI 1.46–2.12) in INSTI-unexposed ones, with an RR of 0.57 (95% CI 0.34–0.95, $p = 0.03$). This suggested a lower incidence of CNS/NP AEs in previously INSTI-exposed PWH. The result could be due to the higher tolerance to INSTI in PWH experienced to this class of drugs, possibly because they did not change treatment for moderate/severe adverse events. On the other hand, a possible explanation may also be that INSTI-exposed PWH who discontinued for AE were prescribed a different drug class after the switch, excluding PWH prone to any type of AEs.

**Table 3** Number of CNS adverse events leading to treatment discontinuation: incidence rates, rate ratios and crude and adjusted hazard ratios for competing risks, in PWH starting a new INSTI-based treatment, by characteristics at baseline

| | ***N*** **(%)** | **PYFU** ***N*** **= 7902.66** | **CNS AEs** ***N*** **= 72** | **IR** **AEs / 100 PYFU (95% CI)** | **RR** **(95% CI)** | **Crude HR (95% CI)** | **Adjusted HR (95% CI)** |
|---|---|---|---|---|---|---|---|
| Female | 738 (25.3) | 1964.52 | 20 | 1.02 (0.66–1.58) | Ref. M | | |
| Male | 2184 (74.7) | 5938.14 | 52 | 0.87 (0.67–1.15) | 1.16 (0.69–1.95) | 1.13 (0.68–1.90) | - |
| Age < 50 years | 1655 (56.6) | 4422.71 | 31 | 0.70 (0.49-1.00) | Ref. <50 | | |
| Age ≥ 50 years | 1267 (43.4) | 3479.95 | 41 | 1.18 (0.87–1.60) | 1.68 (1.05–2.68) | 1.74 (1.09–2.78) | 1.66 (0.99–2.80) |
| Caucasian | 2631 (90.0) | 7270.06 | 68 | 0.94 (0.74–1.19) | Ref. Caucasian | | |
| Other | 291 (10.0) | 632.6 | 4 | 0.63 (0.24–1.68) | 0.68 (0.25–1.85) | 0.56 (0.20–1.53) | - |
| BMI ≤ 30.0 Kg/m$^2$ | 2320 (79.4) | 6315.32 | 64 | 1.01 (0.79–1.30) | Ref. BMI ≤ 30 | | |
| BMI > 30.0 Kg/m$^2$ | 219 (7.5) | 582.13 | 2 | 0.34 (0.09–1.37) | 0.34 (0.08–1.38) | 0.34 (0.08–1.38) | 0.40 (0.10–1.61) |
| Missing value | 383 (13.1) | 1005.21 | 6 | 0.60 (0.27–1.33) | 0.59 (0.26–1.56) | 0.58 (0.25–1.34) | 0.72 (0.30–1.78) |
| Intravenous drug use history no | 2378 (81.4) | 6382.17 | 48 | 0.77 (0.58–1.02) | Ref. No IDU | | |
| Intravenous drug use history yes | 544 (18.6) | 1520.48 | 23 | 1.51 (1.00-2.58) | 1.97 (1.20–3.23) | 2.02 (1.23–3.32) | **2.39 (1.41–4.05)*** |
| ART experienced | 2302 (78.8) | 6416.23 | 50 | 0.78 (0.59–1.03) | Ref. ART exp. | | |
| ART naïve | 620 (21.2) | 1486.43 | 22 | 1.48 (0.97–1.25) | 1.90 (1.13–3.11) | 1.67 (1.01–2.75) | **2.42 (1.39–4.23)*** |
| CDC stage | | | | | | | |
| A | 1443 (49.4) | 3856 | 35 | 0.91 (0.65–1.26) | Ref. A | | |
| B | 754 (25.8) | 2110.38 | 20 | 0.95 (0.61–1.47) | 1.04 (0.60–1.81) | 1.09 (0.63–1.88) | - |
| C | 712 (24.4) | 1913.11 | 17 | 0.89 (0.55–1.43) | 0.98 (0.55–1.75) | 0.98 (0.55–1.75) | |
| CD4 < 350 cells/mL | 909 (31.1) | 2325.77 | 16 | 0.69 (0.42–1.12) | Ref < 350 | | |
| CD4 ≥ 350 cells/mL | 1979 (67.7) | 5393.05 | 56 | 1.04 (0.80–1.35) | 1.51 0.87–2.63) | 1.62 (0.93–2.82) | **1.86 (1.03–3.34)** |
| Year of first treatment | | | | | | | |
| 1985–2000 | 821 (28.1) | 2493.39 | 20 | 0.80 (0.52–1.24) | Ref. 1985–2000 | | |
| 2001–2010 | 733 (25.1) | 2075.56 | 18 | 0.87 (0.55–1.38) | 1.08 (0.57–2.04) | 1.03 (0.54–1.94) | - |
| 2011-today | 1366 (46.7) | 3325.88 | 34 | 1.02 (0.73–1.43) | 1.27 (0.73–2.21) | 1.08 (0.62–1.88) | |
| Regimen without ABC and TAF | 1545 | 4360.19 | 28 | 0.64 (0.44–0.93) | Ref. no | | |
| Regimen with ABC | 491 | 1922.58 | 29 | 1.51 (1.05–2.17) | 2.35 (1.40–3.95) | 3.09 (1.85–5.15) | **2.38 (1.40–4.07)*** |
| Regimen with TAF | 886 | 1619.89 | 15 | 0.93 (0.56–1.54) | 1.44 (0.77–2.70) | 1.04 (0.55–1.94) | 1.56 (0.64–3.81) |
| Treatment cohort | | | | | | | |
| Bictegravir | 735 (25.2) | 1302.38 | 8 | 0.61 (0.31–1.23) | 0.52 (0.25–1.10) | 0.32 (0.15–0.66) | **0.34 (0.12–0.94)** |
| Dolutegravir | 1339 (45.8) | 4516.86 | 53 | 1.17 (0.90–1.54) | Ref. DTG | | |
| Elvitegravir | 338 (11.6) | 776.21 | 3 | 0.39 (0.12–1.20) | 0.33 (0.10–1.05) | 0.23 (0.07–0.73) | 0.37 (0.11–1.22) |
| Raltegravir | 510 (17.5) | 1307.2 | 8 | 0.61 (0.31–1.22) | 0.52 (0.25–1.10) | 0.41 (0.20–0.87) | 0.75 (0.33–1.69) |
| PWH without psychiatric comorbidity | 2683 (91.8) | 7256.28 | 65 | 0.90 (0.70–1.14) | Ref. No | | |
| PWH with psychiatric comorbidity | 239 (8.2) | 646.37 | 7 | 1.08 (0.52–2.27) | 1.21 (0.55–2.64) | 1.22 (0.56–2.67) | - |

ABC: abacavir; ART: antiretroviral treatment; BMI: body mass index; CI: confidence interval; CNS: central nervous system; HR: hazard ratio; IDU: intravenous drug use; IR: incidence rate; PWH: people with HIV; PYFU: person-year follow-up; RR: rate ratio; TAF: tenofovir alafenamide

Cox multivariate model for discontinuations CNS AE-related includes age < 50 or ≥ 50 at study entry, BMI ≤ 30.0 or > 30.0 kg/m$^2$, IDU history, naïve status, CD4 < 350 or ≥ 350 cells/mm$^3$, backbone including TAF or ABC, and cohort of INSTI (all associated with p-value < 0.20 at the univariate analysis). Bold results are associated to the outcome with $p < 0.05$. *an asterisk states that the results are associated to the outcome with $p < 0.01$

Excluding ART-naïve people, the IR for INSTI-unexposed was 1.80 / 100 PYFU (95% CI 1.46–2.23) and the RR 0.56 (95% CI 0.33–0.94). However, considering that PWH on RAL were all in the INSTI-unexposed group (because they were enrolled when RAL was marketed first and no one could have been exposed to other INSTIs), we also calculated the IR for unexposed to INSTI excluding the RAL group. The IR for INSTI-unexposed ART-experienced PWH was 1.04 (95% CI 0.75–1.44) for an RR of 0.96 (95% CI 0.54–1.72, $p = 0.90$).

As regards discontinuations, the IRs were 0.82/100 PYFU (95% CI 0.49–1.39) in INSTI-exposed and 0.93/100 PYFU (95% CI 0.72–1.21) in INSTI-unexposed, with no significant difference (RR 0.88, 95% CI 0.49–1.58, $p = 0.68$). Excluding ART-naïve people, the IR in INSTI-unexposed PWH was 0.76 (95% CI 0.55–1.76) with a corresponding RR of 1.08 (95% CI 0.58-2.00, $p = 0.80$); excluding all people in the RAL cohort, IR for interruptions was 0.80 (95% CI 0.56–1.17) and the corresponding RR 1.02 (95% CI 0.54–1.94, $p = 0.95$).

### Drug-drug interactions

We explored the potential drug-drug interactions in PWH on concurrent antiepileptic drugs ($n = 88$, 3.0%),

metformin ($n = 57$, 2.0%) and beta-blockers ($n = 173$, 5.9%). The distribution of these concurrent treatments (Table 2S) was not significantly different across INSTI cohorts as regards metformin and beta-blockers, whereas use of antiepileptic drugs was significantly more frequent in the RAL cohort (6.1%). CNS/NP AE were also more frequent in PWH on these drugs at the univariate analysis (HR 2.65, 95% CI 1.34–5.25) but they did not lead to discontinuation (HR 0.49, 95% CI 0.07–3.51) and lost their statistical significance if included in the adjusted model (any CNS/NP AE aHR 1.50, 95% CI 0.75–1.98; discontinuation due to CNS/NP AE aHR 0.41, 95% CI 0.05–3.20) (Table 1S).

#### Overall discontinuations

As regards discontinuations due to other reasons, overall AEs represented the most frequent cause ($n = 196$, 6.7%), followed by simplification ($n = 188$, 6.4%). Virologic failures were: 31/510 (6.1%), 16/338 (4.7%), 16/1339 (1.1%) and 4/735 (0.5%) for RAL, EVG, DTG and BIC, respectively. Discontinuations due to pregnancy were low: women with HIV who discontinued for pregnancy were: 0/166 on RAL, 3/77 (3.9%) on EVG, 7/320 (2.2%) on DTG and 2/175 (1.1%) on BIC. Treatment interruptions due to any reasons are reported in Table 2S of supplementary materials and the overall durability is shown in Fig. 3S.

## Discussion

In this sample of PWH treated with INSTI-based regimens, we found an overall low incidence of grade 3–4 CNS/NP AEs.

The incidence of CNS/NP AEs was associated with IVDUh, use of ABC in the backbone, and psychiatric comorbidity. The IVDUh and current ABC use were also associated with higher likelihood of treatment discontinuation. Risk factors for discontinuation were also being on the first-line ART treatment and entering the study with a CD4 level ≥ 350 cell/μL.

As regards IVDUh, the relationship could be due to the known higher prevalence of mental disorders in PWH with IVDUh [12, 13] or to the higher probability of stopping /switching ART in general in PWH that have a IVDUh [14, 15]. The development of new CNS/NP AEs in patients with previous drug dependence diagnosis could probably trigger the physician's decision to switch.

We also observed a higher percentage of interruption for CNS/NP AEs in naïve vs. experienced PWH as described in the literature [14, 16, 17]. This effect could not be related to INSTIs but only to the first regimen effect, independent from drug class. In a recent paper on 479 PWH in USA by Byrne ME et al. [17] to be an ART-naïve woman and to begin therapy with Protease Inhibitors vs. INSTI were risk factors for stopping treatment.

In our study, CD4 cell ≥ 350 cell/μL was associated with a higher probability of discontinuation. This is probably due to the fact that it is more frequent to switch therapy in PWH with a good immune status and undetectable viral load than in people with multiple virological failures and/or severe immune depression, who may have limited treatment options.

In presence of psychiatric comorbidity, PWH enrolled in this study showed more frequently CNS/NP AEs, but not discontinuations. A meta-analysis [2] summarizing the results of eighteen studies estimated that underlying psychiatric conditions were not associated with higher risk of CNS/NP AE occurrence nor related discontinuation. In a recent publication on women with post-traumatic stress disorders, starting but not switching to DTG or RAL was associated with a worsening of symptoms [18]. We cannot exclude that the "first therapy" effect could impact on reported CNS/NP AEs in people (not only women) with psychiatric comorbidity.

The development of CNS/NP AEs in ABC-containing regimens is described in the literature [3, 19] and our findings are consistently showing that both occurrence and discontinuation were more frequent in PWH on INSTI regimens including ABC. In vitro, a higher neurotoxicity of ABC vs. TDF was demonstrated, that could explain these results [20].

We found a high prevalence of RAL-associated CNS/NP AEs, but a very low rate of discontinuation in this group, probably because in this study PWH on RAL treatment were enrolled when RAL was first marketed and assigned to people with scarce therapeutic options. In fact, PWH on RAL were in CDC stage C, had lower CD4 levels and longer ART exposure, suggesting that in this subset few other therapeutic options were available.

We found less incident CNS/NP AEs in people treated with BIC than DTG showing a protective role of BIC vs. DTG. This result confirms data from real-life BIC use, that reported a low percentage of discontinuations due to CNS/NP AEs [3]. In this regard, a recent meta-analysis [3] split the effect of DTG in dual regimens (with rilpivirine or lamivudine, 3TC) and DTG in triple regimen with ABC, showing that the former still presented higher NP AE-related discontinuation rates than BIC with emtricitabine (FTC) and tenofovir alafenamide (TAF). Excluding ABC from DTG-based regimens seemed insufficient to reduce discontinuation rates due to CNS/NP AEs to the levels observed with BIC. On the contrary, it also appeared that discontinuation rates increase with follow-up time, and BIC treatments have in general a shorter time of observation [3]. Thus, it is possible that CNS/NP AEs accumulate over time and new ones appear during the treatment with BIC, as well as it happens in DTG-based regimens.

Both DTG and BIC demonstrated in vitro and in vivo a dysregulation of blood brain barrier (BBB) such as Efavirenz, with a significant higher Blood Brain Barrier permeability was observed in DTG vs. BIC [21]. In another in vivo study a higher proinflammatory role of DTG vs. BIC was demonstrated [22].

On the other hand, a higher concentration of DTG, due to polymorphism in the SLC22A2 gene [23] or for interactions with drugs that inhibits UDP glucuronosyltransferase [24], could contribute to the higher prevalence of CNS/NP AEs in PWH on DTG vs. BIC determining a higher concentration and, consequently, an increased Blood Brain Barrier permeability of DTG. These pathogenetic studies could explain the protective role of BIC vs. DTG.

In our study, CNS/NP AEs were infrequent in PWH treated with EVG/cobicistat (COBI), in line with an RCT demonstrating a complete reversibility of neurotoxicity of ABC + 3TC + DTG switching to EVG/COBI/FTC/TAF [25] and, thus, suggesting a neutral effect of EVG/COBI.

Regarding demographic characteristics of PWH in our study, we found higher IR of CNS/NP AEs and CNS/NP AE-related discontinuations in women and PWH aged ≥ 50 years. However, these associations were not significant, except for discontinuation in PWH aged ≥ 50 years, that showed a borderline increased risk. This is inconsistent with some data of literature [26–29]. However, we have to consider that, in this analysis, we have only taken in account the CNS/NP AE-related treatment discontinuation, whereas in the paper by Bonfanti et al., discontinuation for any reasons was analyzed [26]. Another possible explanation could be that the median age of all the cohorts was less than 50 years with most PWH younger than 60 years.

Pregnancy has certainly had an impact in the last years for stopping DTG, lacking data for neonatal safety. In a recent study of Italian Cohort Naïve to Antiretrovirals (ICONA) a higher risk of discontinuation was also observed excluding drug interruptions for pregnancy [30]. In this cohort, however, female sex was associated to be migrant, late presenters and with an older age that are known risk factors for poor adherence. We can affirm that female sex in Italian cohorts is often associated with other risk factors for switching or stop therapy independently of drug regimen.

Older age could be associated with a higher rate of comorbidities and consequent drug-drug interactions (DDI), that could have been difficult to manage in the first years of INSTI commercialization. In recent years, much data on safety and Drug-Drug-Interactions of INSTI became available, making the management of complex situations easier.

### Study limitations

This study has some potential limitations. First, the Infectious Diseases Clinics involved in the SCOLTA study do not formally represent the Italian Clinics at the national level, because they are only the centers that decided to participate in this study, even if they were well distributed on the national territory and included centers of different size. Second, the study participants were representative of PWH in need of initiating a new ART drug in the considered periods with a possible time-bias due to different decades of starting ART, instead of all PWH followed in the participating Infectious Diseases Clinics. Third, PWH enrolled in the INSTI cohorts had different baseline characteristics: even if we accounted for the significantly different variables, we cannot exclude a residual effect on the outcome. Lastly, we cannot exclude the potentially confounding effect of unmeasured variables, such as socio-economic status and unreported active drugs use. Despite these limits, our study has the strength to describe a large, real-life cohort of PWH consecutive enrolled on INSTI-based regimens, followed up prospectively in multiple centers across Italy, in a research network specifically designed to improve post-marketing surveillance of adverse reactions to antiretrovirals.

## Conclusions

In our study, the risk of CNS/NP AEs development was significantly higher in PWH on RAL and was associated with IVDUh, ABC use and psychiatric comorbidities. However, CNS/NP AE incidence is low, and even lower INSTI therapy discontinuation due to CNS/NP AEs. The low incidence of interruptions confirms that PWH change ART only for moderate/severe events promoting the clinical relevance of our findings.

The risk factors associated with treatment interruptions are previous IVDUh ABC use, being naïve to ART and CD4 > 350 cell/μL. BIC might be associated with a lower risk of CNS/NP AEs and related discontinuations and could be considered a preferred option in PWH with risk factors for CNS/NP AEs occurrence. Further data is needed to confirm the protective role of BIC, in particular at the light of shorter observation time in this cohort.

### Abbreviations

| | |
|---|---|
| CNS | Central nervous system |
| NP | Neuropsychiatric disturbances |
| HIV | Human Immunodeficiency Virus |
| PWH | People with HIV |
| INSTI | Integrase strand transfer inhibitors |
| ART | Antiretroviral therapy |
| SCOLTA | Surveillance Cohort Long-Term Toxicity Antiretrovirals |
| AEs | Adverse Events |
| IR | Incidence Rates |
| CI | Confidence Intervals |
| PYFU | Person-years follow-up |
| HR | Hazard Ratio |
| RAL | Raltegravir |
| DTG | Dolutegravir |

| | |
|---|---|
| EVG | Elvitegravir |
| BIC | Bictegravir |
| IVDUh | IntraVenous Drug Use history |
| RCTs | Randomized clinical trials |
| ABC | Abacavir |
| CISAI | Coordinamento Italiano per lo Studio dell'Allergia in Infezione da HIV |
| SD | Standard deviation |
| IQR | Interquartile range |
| RR | Rate Ratio |
| CDC | Centers for Disease Control and Prevention |
| TAF | Tenofovir Alefenamide |
| aHR | Adjusted Hazard Ratio |
| TDF | Tenofovir disoproxil fumarate |
| COBI | Cobicistat |
| 3TC | Lamivudine |
| FTC | Emtricitabine |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-11090-3.

Supplementary Material 1

Supplementary Material 2

**Acknowledgements**

Paolo Bonfanti (Monza), Antonio Di Biagio (Genova). Data Management and Analysis: Elena Delfina Ricci (Milano). Health Informatic Service: L.D. Magnoni, M. Bonetto (Genova, Healthropy); M. Giacomini (Genova, DIBRIS), E. Sarchi, G. Chichino, C. Bolla (Alessandria); (A) Saracino, D. Fiordelisi (Bari); L. Calza (Bologna); (B) Menzaghi, M. Farinazzo, F. Franzetti (Busto Arsizio); G. Angioni, M. Buffa (Cagliari); P. Maggi, (A) Masiello, F. Simeone (Caserta); G. Bruno, (B) M. Celesia (Catania); (C) Grosso (Cesena); K. Falasca (Chieti); L. Pusterla, G. Chieffo (Como); A. Mastroianni, G. Guadagnino (Cosenza); S. Carradori (Ferrara); F. Vichi, E. Salomoni (Firenze); C.V. Martinelli, F. Lagi (Firenze); S. Ferrara (Foggia); A. Di Biagio, C. Dentone, L. Taramasso, M. Bassetti (Genova); E. Pontali, A. Parisini, F. Del Puente (Genova); C. Molteni, A. Pandolfo, S. Piconi (Lecco); S. Rusconi, M. Franzetti (Legnano); G. F. Pellicanò, G. Nunnari (Messina); L. Valsecchi, L. Cordier, S. Parisini, G. Rizzardini (Milano); F. Conti (Milano); A. Bandera, A. Gori (Milano); (D) Motta, M. Merli, M. Puoti (Milano); P. Bonfanti, N. Squillace, M. Rossi, (E) Pollastri, N. Corti (Monza); S. Martini (Napoli); V. Esposito, M.A. Carleo (Napoli); O. Bargiacchi, P.L. Garavelli (Novara); A. Cascio, M. Trizzino (Palermo); R. Gulminetti, L. Pagnucco (Pavia); G. V. De Socio, G. Gamboni, D. Altobelli, D. Francisci (Perugia); E. Mazzotta, G. Parruti (Pescara); S. Cicalini, R. Bellagamba, A. Antinori (Roma); P. Morelli (Humanitas); G. Cenderello (Sanremo); G. Madeddu, M. S. Mameli (Sassari); G. Orofino, M. Guastavigna (Torino); M. Lanzafame, A. Delama (Trento); A. Londero, A. Giacinta, C. Tascini (Udine); G. Battagin, V. Manfrin (Vicenza).

**Author contributions**

N.S. have drafted the work. N.S. and E.D.R. and P.B.contributed to the conception and design of the project. E.D.R. performed the anlaysisN.S. and E.D.R. and P.B. contributed to the interpretation of the dataN.S. and E.D.R.and G.O. and B.M. and G.V.D.S. and S.P. and P.M., G.M.and G.F.P and E.S. and B.M.C. and F.L. and E.S. and A.D.B. AND P.M. contributed to the acquisition of the data and to the revision of the manuscript G.F. and L.A. contributed to the revision of manuscript.

**Funding**

The NEURO-INSTI Study is sponsored and funded by Gilead Sciences. The sponsor, Gilead Sciences, played a role in the study design, and preparation of the manuscript.

**Data availability**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**

The SCOLTA Project was conducted in accordance with the Declaration of Helsinki. The ethical approval was originally obtained by the Ethics Committee of the L.Sacco Hospital, where the principal investigator (dr. Rizzardini) was working at the time. Amendments were requested in 2013, 2019, 2020 and 2023: with this last amendment, the role of Principal Investigator was taken by dr. Bonfanti (IRCCS San Gerardo Monza), and the reference Ethics Committee changed. The original study protocol was approved on 18 September 2002, and three amendments were approved on 13 June 2013, 20 December 2019, 12 May 2020 and 12 June 2023 by the coordinating center at Hospital "L. Sacco"-University of Milan, Milan (Italy), and thereafter by all participating centers. Written consent for study participation was obtained from all participants, and the study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and by Italian national laws. All patients starting one of the drugs included in the surveillance program in participating centers are consecutively asked to participate in the study after signing a written informed consent.

**Competing interests**

N.S. received grants for educational activity, speaker's fee, advisory board, research projects and for conferences'attending by Gilead Sciences and speaker's fee and grant for attending conferences by ViiV Healthcare. P.M. received: Grant for publication, Advisory board fees, Conference hospitality: Gilead Science; Advisory board fees: ViiV Healthcare; Advisory board fees, Conference hospitality: MSD, Advisory board fees, Conference hospitality: Janssen. P.B. received advisory board fees by Viiv, Gilead, MSD and AstrazenecaB.M.C. reported honoraria for presentations and scientific advice from Gilead Sciences, ViiV Healthcare, Janssen-Cilag, Mylan, GSK vaccines and Merck Sharp & Dohme and researchgrants for his institution from Gilead Sciences, ViiV Healthcare GSK vaccines and Merck Sharp &and Dohme. G.V.D.S. received speaker's fees from Gilead Sciences and ViiV HealthcareF. Lparticipated on advisory boards sponsored by ViiV Healthcare, Janssen and recevide research grant from Gilead A.D.B. has received speakers' honoraria from Gilead, ViiV and Janssen-Cilag, has been an advisor for ViiV, Gilead and MSD, and has received grant for research from Gilead Sciences and ViiV healthcare.All the other authors declared no conflicts of interests.

**Author details**

[1]Infectious Disease Unit, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
[2]Fondazione A.S.I.A. Onlus, Buccinasco, MI, Italy
[3]Division I of Infectious and Tropical Diseases, ASL Città di Torino, Turin, Italy
[4]Gilead Sciences Srl, Milan, Italy
[5]Unit of Infectious Diseases, ASST della Valle Olona– Busto Arsizio (VA), Milan, Italy
[6]Unit of Infectious Diseases, Santa Maria Hospital, Perugia, Italy
[7]Unit of Infectious Diseases, A. Manzoni Hospital, Lecco, Italy
[8]Infectious Diseases Unit, Università della Campania "Luigi Vanvitelli", AORN Sant'Anna e San Sebastiano, Caserta, Italy
[9]Unit of Infectious Diseases, Department of Medicine, Surgery and Pharmacy, University of Sassari, Sassari, Italy
[10]Unit of Infectious Diseases, Department of Human Pathology of the Adult and the Developmental Age 'G. Barresi', University of Messina, Messina, Italy
[11]Infectious Diseases Unit, S.Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy
[12]Unit of Infectious Diseases, Garibaldi Hospital, Catania, Italy
[13]AOU Infectious and Tropical Diseases, Careggi Hospital, Florence, Italy
[14]Unit of Infectious Diseases, SOC 1 USLCENTRO FIRENZE, Santa Maria Annunziata Hospital, Florence, Italy
[15]Infectious Diseases Unit, Department of Health's Sciences, Ospedale Policlinico San Martino– IRCCS, University of Genoa, Genoa, Italy
[16]University of Milano-Bicocca, Monza, Italy

Received: 27 February 2025 / Accepted: 7 May 2025
Published online: 27 May 2025

**References**

1. Hoffmann C, Llibre JM. Neuropsychiatric adverse events with dolutegravir and other integrase strand transfer inhibitors. AIDSRev. 2019;21:1768.
2. Senneker T, Tseng A. An update on neuropsychiatric adverse effects with second-generation integrase inhibitors and nonnucleoside reverse transcriptase inhibitors. Curr Opin HIV AIDS. 2021;16:309–20.
3. Pérez-Valero I, Corona D, Martínez N, López-Cavanillas M, Lluis C, Luque I. Real-world discontinuations due to neuropsychiatric symptoms in people living with HIV treated with second-generation integrase inhibitors: a systematic review. Expert Rev Anti-infective Therapy. 2023;21:655–65.
4. Troya J, Pousada G, Micán R, Galera C, Sanz J, De Los Santos I, et al. Real-life data of immune recovery using bictegravir/emtricitabine/tenofovir Alafenamide in virologically suppressed people living with HIV. Results at 48–96 weeks of RETROBIC study. J Antimicrob Chemother. 2024;79:595–607.
5. Esser S, Brunetta J, Inciarte A, Levy I, D'Arminio Monforte A, Lambert JS, et al. Twelve-month effectiveness and safety of bictegravir/emtricitabine/tenofovir Alafenamide in people with HIV: Real-world insights from bicstar cohorts. HIV Med. 2024;25:440–53.
6. Hidalgo-Tenorio C, Sequera S, Vivancos MJ, Vinuesa D, Collado A, Santos IDL, et al. Bictegravir/emtricitabine/tenofovir Alafenamide as first-line treatment in Naïve HIV patients in a rapid-initiation model of care: BIC-NOW clinical trial. Int J Antimicrob Agents. 2024;63:107164.
7. Jeffries N, Zaslavsky AM, Diez Roux AV, Creswell JW, Palmer RC, Gregorich SE, et al. Methodological approaches to Understanding causes of health disparities. Am J Public Health. 2019;109:S28–33.
8. Gilmartin-Thomas JF, Liew D, Hopper I. Observational studies and their utility for practice. Aust Prescr. 2018;41:82–5.
9. Bonfanti P, Martinelli C, Ricci E, Carradori S, Parruti G, Armignacco O, et al. An Italian approach to postmarketing monitoring: preliminary results from the SCOLTA (Surveillance cohort Long-Term toxicity Antiretrovirals) project on the safety of Lopinavir/Ritonavir. JAIDS J Acquir Immune Defic Syndr. 2005;39:317–20.
10. Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
11. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94:496–509.
12. Norman T, Power J, Clifton B, Murray J, Bourne A. People living with HIV who inject or have injected non-prescription drugs: evidence of substantial differences in health inequalities and experiences of clinical care. Drug Alcohol Rev. 2023;42:1517–28.
13. Degenhardt L, Bharat C, Glantz MD, Sampson NA, Scott K, Lim CCW, et al. The epidemiology of drug use disorders cross-nationally: findings from the who's world mental health surveys. Int J Drug Policy. 2019;71:103–12.
14. Eaton EF, Tamhane A, Davy-Mendez T, Mathews WC, Moore RD, Saag MS, et al. Trends in antiretroviral therapy prescription, durability and modification: new drugs, more changes, but less failure. AIDS. 2018;32:347–55.
15. Moore D, Zhang W, Yip B, Genebat M, Lima V, Montaner J, et al. Non-medically supervised treatment interruptions among participants in a universally accessible antiretroviral therapy programme. HIV Med. 2010;11:299–307.
16. Cicconi P, Cozzi-Lepri A, Castagna A, Trecarichi E, Antinori A, Gatti F, et al. Insights into reasons for discontinuation according to year of starting first regimen of highly active antiretroviral therapy in a cohort of antiretroviral-naïve patients. HIV Med. 2010;11:104–13.
17. Byrne ME, Resnik JB, Horberg MA, Greenberg AE, Castel AD, Monroe AK. Factors associated with time to initial antiretroviral therapy discontinuation in the DC cohort. AIDS Res Hum Retroviruses. 2024;40:671–9.
18. Kamkwalala AR, Wang K, O'Halloran J, Williams DW, Dastgheyb R, Fitzgerald KC, et al. Starting or switching to an integrase Inhibitor-Based regimen affects PTSD symptoms in women with HIV. AIDS Behav. 2021;25:225–36.
19. Abers MS, Shandera WX, Kass JS. Neurological and psychiatric adverse effects of antiretroviral drugs. CNS Drugs. 2014;28:131–45.
20. Robertson K, Liner J, Meeker RB. Antiretroviral neurotoxicity. J Neurovirol. 2012;18:388–99.
21. Huang C, Hoque T, Bendayan R. Antiretroviral drugs Efavirenz, dolutegravir and bictegravir dysregulate blood-brain barrier integrity and function. Front Pharmacol. 2023;14:1118580.
22. Huang C, Hoque MT, Qu QR, Henderson J, Bendayan R. Antiretroviral drug dolutegravir induces inflammation at the mouse brain barriers. FASEB J. 2024;38:e23790.
23. Borghetti A, Calcagno A, Lombardi F, Cusato J, Belmonti S, D'Avolio A, et al. *SLC22A2* variants and dolutegravir levels correlate with psychiatric symptoms in persons with HIV. J Antimicrob Chemother. 2019;74:1035–43.
24. Cattaneo D, Minisci D, Cozzi V, Riva A, Meraviglia P, Clementi E, et al. Dolutegravir plasma concentrations according to companion antiretroviral drug: unwanted drug interaction or desirable boosting effect?? Antivir Ther. 2017;22:353–6.
25. Perez Valero I, Cabello A, Ryan P, De La Fuente-Moral S, Santos I, Vivancos MJ, et al. Randomized trial evaluating the neurotoxicity of dolutegravir/abacavir/lamivudine and its reversibility after switching to Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide: GESIDA 9016. Open Forum Infect Dis. 2020;7:ofaa482.
26. Bonfanti P, Madeddu G, Gulminetti R, Squillace N, Orofino G, Vitiello P, et al. Discontinuation of treatment and adverse events in an Italian cohort of patients on dolutegravir. AIDS. 2017;31:455–7.
27. Borghetti A, Baldin G, Capetti A, Sterrantino G, Rusconi S, Latini A, et al. Efficacy and tolerability of dolutegravir and two nucleos(t)ide reverse transcriptase inhibitors in HIV-1-positive, virologically suppressed patients. AIDS. 2017;31:457–9.
28. Elzi L, Erb S, Furrer H, Cavassini M, Calmy A, Vernazza P, et al. Adverse events of raltegravir and dolutegravir. AIDS. 2017;31:1853–8.
29. Hoffmann C, Welz T, Sabranski M, Kolb M, Wolf E, Stellbrink H, et al. Higher rates of neuropsychiatric adverse events leading to dolutegravir discontinuation in women and older patients. HIV Med. 2017;18:56–63.
30. D'arminio Monforte A, Tavelli A, Sala M, Mondi A, Rusconi S, Antinori S, et al. Long-term outcome of dolutegravir-containing regimens according to sex: data from the ICONA study. J Antimicrob Chemother. 2023;78:933–45.

## Publisher's note