J Antimicrob Chemother 2021; **76**: 2394–2399
doi:10.1093/jac/dkab200 Advance Access publication 2 July 2021

Journal of Antimicrobial Chemotherapy

Effectiveness of integrase strand transfer inhibitor-based regimens in HIV-infected treatment-naive individuals: results from a European multi-cohort study

Barbara Rossetti[1]*, Massimiliano Fabbiani [1], Domenico Di Carlo[2], Francesca Incardona[3,4], Ana Abecasis[5], Perpetua Gomes[6,7], Anna Maria Geretti[8], Carole Seguin-Devaux[9], Federico Garcia [10], Rolf Kaiser[11], Sara Modica[1], Adrian Shallvari[4], Anders Sönnerborg[12] and Maurizio Zazzi[13] on behalf of EuResist Network, INTEGRATE study group†

[1]Infectious Diseases Unit, University Hospital of Siena, Siena, Italy; [2]University of Milan 'La Statale', Milano, Italy; [3]EuResist Network, Roma, Italy; [4]I-PRO, Roma, Italy; [5]Global Health and Tropical Medicine (GHTM), Instituto de Higiene e Medicina Tropical—Universidade Nova de Lisboa, Lisbon, Portugal; [6]Laboratório de Biologia Molecular (LMCBM, SPC, CHLO-HEM), Lisbon, Portugal; [7]Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Instituto Universitário Egas Moniz, Caparica, Portugal; [8]Institute of Infection, University of Liverpool, Liverpool, UK; [9]Department of Infection and Immunity, Luxembourg Institute of Health, Luxembourg; [10]Hospital Universitario San Cecilio, Granada, Spain; [11]University of Cologne, Cologne, Germany; [12]Karolinska Institutet, Stockholm, Sweden; [13]University of Siena, Siena, Italy

*Corresponding author. E-mail: brossetti1982@gmail.com
†Members are listed in the Acknowledgements section.

Received 15 February 2021; accepted 16 May 2021

Background: INSTIs have become a pillar of first-line ART. Real-world data are needed to assess their effectiveness in routine care.

Objectives: We analysed ART-naive patients who started INSTI-based regimens in 2012–19 whose data were collected by INTEGRATE, a European collaborative study including seven national cohorts.

Methods: Kaplan–Meier analyses assessed time to virological failure (VF), defined as one viral load (VL) ≥1000 copies/mL, two consecutive VLs ≥50 copies/mL, or one VL ≥50 copies/mL followed by treatment change after ≥24 weeks of follow-up, and time to INSTIs discontinuation (INSTI-DC) for any reason. Factors associated with VF and INSTI-DC were explored by logistic regression analysis.

Results: Of 2976 regimens started, 1901 (63.9%) contained dolutegravir, 631 (21.2%) elvitegravir and 444 (14.9%) raltegravir. The 1 year estimated probabilities of VF and INSTI-DC were 5.6% (95% CI 4.5–6.7) and 16.2% (95% CI 14.9–17.6), respectively, and were higher for raltegravir versus both elvitegravir and dolutegravir. A baseline VL ≥100 000 copies/mL [adjusted HR (aHR) 2.17, 95% CI 1.55–3.04, $P < 0.001$] increased the risk of VF, while a pre-treatment CD4 count ≥200 cells/mm^3 reduced the risk (aHR 0.52, 95% CI 0.37–0.74, $P < 0.001$). Predictors of INSTI-DC included use of raltegravir versus dolutegravir (aHR 3.03, 95% CI 2.34–3.92, $P < 0.001$), use of >3 drugs versus 3 drugs (aHR 2.73, 95% CI 1.55–4.79, $P < 0.001$) and starting ART following availability of dolutegravir (aHR 0.64, 95% CI 0.48–0.83, $P = 0.001$). Major INSTI mutations indicative of transmitted drug resistance occurred in 2/1114 (0.2%) individuals.

Conclusions: This large multi-cohort study indicates high effectiveness of elvitegravir- or dolutegravir-based first-line ART in routine practice across Europe.

Introduction

ART confers substantial clinical benefits by drastically reducing HIV-related mortality and morbidity as well as improving the quality of life of people living with HIV, although eradication of HIV infection cannot be achieved.[1,2] Plasma HIV-1 RNA suppression also prevents transmission, reduces the risk of drug resistance and restores immunological function, reducing inflammation, immune activation and premature ageing.[3,4]

Integrase strand transfer inhibitor (INSTI)-based regimens are preferred for first-line ART, reflecting safety and efficacy demonstrated in clinical trials.[5–7] Two first-generation INSTIs (raltegravir and elvitegravir) and three second-generation INSTIs (dolutegravir, bictegravir and cabotegravir) have been approved.[8,9] Cabotegravir is administered as a once-monthly or bi-monthly, injectable, long-acting drug, in combination with rilpivirine.[10]

While randomized trials and small observational studies have demonstrated high virological efficacy, low risk of adverse events and low rates of discontinuation of INSTI-based regimens, there remains a need to monitor effectiveness on a large scale in real-life settings. In addition, in the context of increasing use, there is a need to monitor both treatment-emergent and transmitted drug resistance (TDR) to INSTIs.[11–17] The aim of this study was to determine the effectiveness of INSTI-based first-line ART across Europe, as measured by the rate of virological failure (VF) and INSTIs discontinuation (INSTI-DC) for any cause, and to investigate potential predictors of either outcome.

Methods

Study population

INTEGRATE is a large European collaboration enrolling HIV-1-positive individuals who started INSTI-based regimens at multiple clinical centres coordinated by the EuResist Network (https://www.euresist.org/integrate). We queried the EuResist integrated database to select ART-naive adults (≥18 years) who had started raltegravir, elvitegravir or dolutegravir as part of their first-line regimen between January 2012 and September 2019. Individuals were excluded if lacking a pre-treatment genotypic drug resistance test covering protease (PR) and reverse transcriptase (RT), or at least one plasma HIV-1 RNA measurement after 24 weeks of follow-up. The pre-treatment integrase genotype was also collected when available. Data collection in different cohorts was fully anonymized and performed in accordance with local regulations and approved by the local Ethics Committees as required. Informed consent was obtained from participating individuals in accordance with all relevant regulations. The study was performed in accordance with the Declaration of Helsinki (seventh revision) and the International Conference on Harmonization Good Clinical Practice guidelines.

Drug resistance

Genotypic resistance was determined by Sanger population sequencing using commercially available or homebrew systems as available at each participating centre. Drug resistance mutations indicative of TDR for NRTIs, NNRTIs, PIs and INSTIs were defined based on reference lists (https://hivdb.stanford.edu/pages/surveillance.html) using HIVdb version 8.8. Viral subtype was determined using the REGA 3.0 subtyping tool (http://dbpartners.stanford.edu:8080/RegaSubtyping/stanford-hiv/typingtool/).[18,19]

Statistical analysis

The objective of the analysis was to assess INSTI effectiveness, as defined by the primary endpoint of virological outcome and the secondary endpoint of durability. VF was defined as a single viral load ≥1000 copies/mL, two consecutive viral loads ≥50 copies/mL, or a single viral load ≥50 copies/mL followed by treatment change after ≥24 weeks of follow-up. The secondary outcome was defined as discontinuation for any reason of the INSTIs included in the first-line ART regimen (INSTI-DC). Changing any companion drug while maintaining the initial INSTI, or switching from a multiple to single-tablet regimen or *vice versa* while maintaining the same components of the regimen were not classified as discontinuation. Descriptive statistics were used to illustrate the individuals' baseline characteristics. Baseline was defined as the INSTI start date. Differences between categorical variables were tested by χ^2 test and those between continuous variables were tested by ANOVA. Kaplan–Meier analysis was used to determine the time to VF and to INSTI-DC and differences between Kaplan–Meier curves were evaluated by log-rank test. Cox regression models were used, after evaluating proportional hazard assumptions, to assess factors associated with VF and INSTI-DC. Each variable was included in univariable models and then the statistically significant variables ($P < 0.05$) were fitted simultaneously in a multivariable model. Individuals were censored at event, VF, or INSTI-DC, according to outcome, or at final follow-up, defined as last clinical visit, drop-out date, or date of death. In all models, an unknown category was used to account for missing data for categorical variables. Analyses were performed using R open source statistical environment v. 3.6.3.[20] All *P* values were two-sided and a *P* value <0.05 was defined as statistically significant.

Results

Study population

A total of 2976 ART-naive individuals were included, of whom 1901 (63.9%) started dolutegravir, 631 (21.2%) elvitegravir and 444 (14.9%) raltegravir between 2012 and 2019 (median 2016) (Table S1, available as Supplementary data at *JAC* Online). Baseline demographic and clinical characteristics are detailed in Table 1. The cohort was diverse both in terms of HIV-1 subtypes and risk groups. Notably, individuals in the raltegravir group had higher baseline viral load and lower CD4 cell counts with respect to the elvitegravir and dolutegravir groups. The vast majority of individuals received 3 drugs (94.5%) while low proportions received <3 drugs (1.4%) and >3 drugs (4.1%). Companion drugs included NRTIs in 99.1% of patients, PIs in 4.8%, NNRTIs in 0.6% and the entry inhibitors maraviroc or enfuvirtide in 0.5%. Among 43 individuals treated with <3 drugs, 25 (58.1%) started raltegravir ($n = 14$) or dolutegravir ($n = 11$) plus a PI and 15 (34.9%) started dolutegravir + lamivudine or emtricitabine or tenofovir disoproxil fumarate, whereas 3 (7.0%) received other two-drug combinations. Among the 122 individuals treated with >3 drugs, 103 (84.5%) received a PI, mainly boosted darunavir with raltegravir (62, 60.1%) and dolutegravir (25, 24.3%) and boosted atazanavir with raltegravir (8, 7.8%).

Drug resistance

PR and RT genotype before introduction of INSTI-containing regimen were available for all participants as per inclusion criteria, whereas integrase genotype was available in 1019 individuals (34.2%). The overall prevalence of any TDR was 9.6%. In particular, NRTI, NNRTI, PI and INSTI resistance mutations were detected in 117 (3.9%), 136 (4.6%), 72 (2.4%) and 2 (0.2%) individuals, respectively. The most common TDR mutations detected were the thymidine analogue mutations (TAMs) T215rev ($n = 58$; 1.9%) and M41L ($n = 40$, 1.3%), M184IV ($n = 26$; 0.9%) for NRTIs, K103NS ($n = 86$; 2.9%) for NNRTIs and M46I/L ($n = 25$; 0.8%) for PIs. The two INSTI TDR cases showed R263K in one and N155H in the other, both without contemporary resistance detected to other classes.

Virological outcomes and risk factors for VF

During 3520 person-years of follow-up (PYFU), VF occurred in 169 individuals with an estimated cumulative probability at 1 year of

Table 1. Baseline characteristics of population

	Total population ($N = 2976$)	According to INSTI used			
		DTG-based ($n = 1901$)	EVG-based ($n = 631$)	RAL-based ($n = 444$)	*P* value
Age (years), median (IQR)	39 (31–48)	39 (31–48)	38 (30–45)	40 (32–49)	0.001*
Female gender, *n* (%)	629 (21.1)	442 (23.3)	73 (11.6)	114 (25.7)	<0.001*
Non-B viral subtype, *n* (%)	1369 (46.0)	861 (45.3)	450 (71.3)	252 (56.8)	<0.001**
Risk factor, *n* (%)					<0.001*
MSM	1183 (39.8)	700 (36.8)	316 (50.1)	167 (37.6)	
heterosexual contacts	867 (29.1)	614 (32.3)	128 (20.3)	125 (28.2)	
injecting drug users	119 (4.0)	84 (4.4)	19 (3.0)	16 (3.6)	
other/unknown	807 (27.1)	503 (26.5)	168 (26.6)	136 (30.6)	
Non-Caucasian ethnicity, *n* (%)	602 (20.2)	463 (24.4)	68 (10.8)	71 (16.0)	<0.001**
Calendar year of HIV diagnosis, median (IQR)	2016 (2014–17)	2016 (2015–17)	2014 (2013–16)	2013 (2012–15)	<0.001**
Calendar year of therapy start, median (IQR)	2016 (2015–17)	2016 (2015–17)	2016 (2014–17)	2014 (2013–15)	<0.001**
Baseline HIV-1 RNA, $\log_{10}$ copies/mL, median (IQR)	5.0 (4.4–5.6)	4.9 (4.3–5.5)	4.7 (4.1–5.2)	5.1 (4.3–5.8)	<0.001**
Baseline HIV-1 RNA ≥100 000 copies/mL, *n* (%)	1422 (47.8)	924 (48.6)	237 (37.6)	261 (58.8)	<0.001**
Baseline CD4 cell count (cells/mm^3), median (IQR)	323 (148–498)	310 (128–490)	368 (258–539)	272 (104–510)	<0.001**
Baseline CD4 cell count <200 cells/mm^3, *n* (%)	865 (29.1)	596 (31.4)	110 (17.4)	159 (35.8)	<0.001**
NRTI, *n* (%)	2949 (99.1)	1890 (99.4)	631 (100)	428 (96.4)	<0.001***
TDF or TAF + 3TC or FTC	1897 (64.3)	914 (48.4)	631 (100)	352 (82.2)	<0.001**
ABC + 3TC	1012 (34.3)	955 (50.5)	0	57 (13.3)	<0.001**
others	40 (1.4)	21 (1.1)	0	19 (4.4)	<0.001**
NNRTI, *n* (%)	17 (0.6)	4 (0.2)	0	13 (2.9)	<0.001***
PI, *n* (%)	143 (4.8)	35 (1.8)	2 (0.3)	106 (23.9)	<0.001***
EI, *n* (%)	15 (0.5)	4 (0.2)	0	11 (2.5)	<0.001***

ABC, abacavir; DTG, dolutegravir; EI, entry inhibitor; EVG, elvitegravir; FTC, emtricitabine; NRTI, nucleos(t)ide reverse transcriptase inhibitor; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.
*Statistically significant for dolutegravir versus elvitegravir and elvitegravir versus raltegravir.
**Statistically significant for all comparisons between drugs.
***Statistically significant for dolutegravir versus raltegravir and elvitegravir versus raltegravir.

5.6% (95% CI 4.5–6.7). Individuals treated with raltegravir showed a significantly higher estimated probability of 1 year VF (9.0%, 95% CI 4.9–12.9) versus both elvitegravir (5.2%, 95% CI 3.0–7.4) and dolutegravir (5.1%, 95% CI 3.8–6.5) (*P* by log-rank test = 0.007) (Figure 1a). In the regression model, a pre-treatment viral load ≥100000 copies/mL increased the risk of VF with an adjusted HR (aHR) of 2.17 (95% CI 1.55–3.04, $P < 0.001$), whereas a pre-treatment CD4 count ≥200 cells/mm^3 reduced the risk (aHR 0.52, 95% CI 0.37–0.74, $P < 0.001$) after adjusting for time-dependent availability of raltegravir, elvitegravir and dolutegravir, number of drugs co-administered, type of INSTI, NRTI or PI including regimen. In a separate analysis, TDR for at least one class had no impact on VF (Table S2). VFs according to study definitions across the different treatment groups are detailed in Table S3.

Durability and risk factors for INSTIs-DC

During 8780 PYFU, INSTI-DC occurred in 800 individuals with an estimated cumulative probability at 1 year of 16.2% (95% CI 14.9–17.6). Individuals treated with raltegravir showed a significantly higher estimated probability of 1 year INSTI-DC (39.9%, 95% CI 35.1–44.3) versus both elvitegravir (12.8%, 95% CI 10.2–15.4) and dolutegravir (11.8%, 95% CI 10.4–13.3) (*P* by log-rank test <0.001) (Figure 1b). Among 708 individuals with known viral load at the time of INSTI-DC, 241 (34%) showed a viral load ≥50 copies/mL [103/1901 (5.4%) with dolutegravir, 92/444 (20.7%) with raltegravir and 46/631 (7.3%) with elvitegravir] whilst 467 (66%) showed a viral load <50 copies/mL [203/1901 (10.7%) with dolutegravir, 178/444 (40.1%) with raltegravir and 86/631 (13.6%) with elvitegravir]. In the regression analysis, after adjusting for pre-treatment viral load and CD4 cell counts, inclusion of NNRTI or PI or entry inhibitors in the regimen, and TDR for at least one class, INSTI-DC was associated with use of raltegravir versus dolutegravir (aHR 3.03, 95% CI 2.34–3.92, $P < 0.001$), use of >3 drugs versus 3 drugs (aHR 2.73, 95% CI 1.55–4.79, $P < 0.001$) and starting ART after versus before dolutegravir availability (aHR 0.64, 95% CI 0.48–0.83, $P = 0.001$); there was evidence to suggest that the time-dependent availability of dolutegravir, elvitegravir and raltegravir modulated the likelihood of INSTI-DC (Table S4). INSTI-DCs across the different treatment groups are detailed in Table S3.

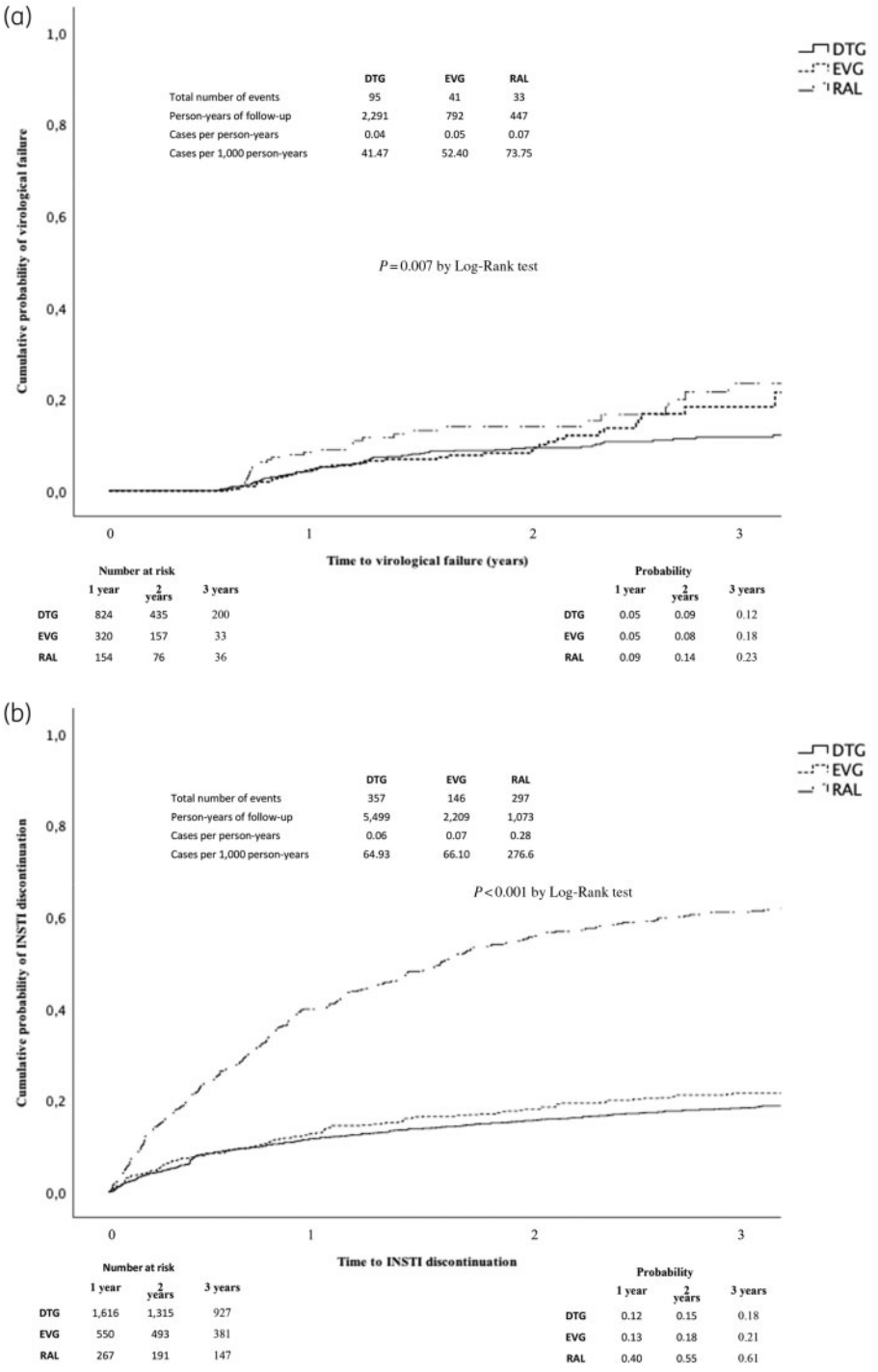

Figure 1. Kaplan–Meier curves showing virological failure according to INSTIs (a) and INSTIs discontinuation (b). DTG, dolutegravir; EVG, elvitegravir; RAL, raltegravir.

Discussion

This large European multi-cohort study provides real-world evidence for the high efficacy and durability of INSTI-based first-line ART regimens started between 2012 and 2019 in Europe, highlighting a greater virological efficacy and durability of elvitegravir- or dolutegravir-based regimens compared with those based on raltegravir.

The three INSTI treatment groups differed in most of their baseline characteristics. Individuals receiving elvitegravir were younger and more frequently males than those receiving other INSTIs. Non-B viral subtypes were well represented in the whole dataset, but significantly more prevalent in the elvitegravir group with respect to the others. HIV acquisition risk was also associated

with treatment group, with MSM more likely to receive elvitegravir than heterosexual participants. As expected, the use of the different INSTIs was affected by the sequential availability of raltegravir first, then elvitegravir and finally dolutegravir. The higher baseline CD4 cell counts in the dolutegravir and elvitegravir groups versus raltegravir group probably reflects the sequential availability of the three INSTIs in a large observational time together with the increasing trend in recent years to start ART at earlier stages of infection, following the demonstration of improved clinical outcome and reduced transmission of infection.[1,2] Given the need for lifelong treatment, current availability of more treatment options led to an optimized sequential INSTIs use, considering drug–drug interactions, pre-existing resistance-associated mutations and clinical setting of ART initiation.

Consistent with common understanding, [5–7,21] a higher pre-treatment viral load and lower pre-treatment CD4 cell count were associated with an increased risk of VF after starting first-line ART with an INSTI-based regimen. Interestingly, the impact of higher pre-treatment viral load was confirmed even among those treated with dolutegravir- or elvitegravir-including regimens (data not shown), without any effect of the specific NRTI backbone among those receiving a dolutegravir-based ART regimen.

INSTIs were primarily used in accordance with standard practice, with the vast majority of individuals receiving an INSTI in combination with two NRTIs. The NRTI backbones associated with the different INSTIs reflected the availability of elvitegravir- and dolutegravir-based single-tablet regimens, but there was no significant impact of the different NRTI backbones on the outcome measures. A minority of patients received less common regimens, including two-drug combinations or combinations including more than three agents. As expected, the latter presented at baseline higher viral load (5.9 copies/mL, IQR 5.3–6.5) and more frequently carried TDR; NNRTI-TDR was reported in 8.2% and NRTI-TDR in 4.9%, corresponding to 10 and 6 cases, respectively. Regimens including >3 drugs were associated with an increased likelihood of subsequent INSTI-DC. Overall, raltegravir was discontinued more often than elvitegravir and dolutegravir, likely reflecting the earlier availability of raltegravir, the lack of raltegravir-including fixed-dose combinations and the twice-daily administration of this drug at least in the earlier treatments. The effect of this last potential confounder was not measurable due to a lack of information regarding raltegravir posology. Interestingly, the rates of discontinuation were not different for elvitegravir- versus dolutegravir-based INSTI regimens, despite the higher genetic barrier of the latter and the higher potential for drug–drug interactions with boosted elvitegravir-including regimens. It is possible that the mandatory use of elvitegravir as single-tablet regimen made elvitegravir as effective as dolutegravir, which was used in mixed formulations, both as a single agent and in fixed-dose combination with abacavir and lamivudine. Unfortunately, this information was not available in the case file.

Based on current reported rates of TDR to different antiretrovirals, current international guidelines recommend genotypic drug-resistance testing in ART-naive persons focusing on testing for mutations in the RT and PR genes.[5–7] There is no recommendation for baseline integrase sequencing as transmission of INSTI resistance-associated mutations remains anecdotal. In this study, 136 (4.6%) patients started an INSTI-based regimen in the presence of pre-treatment resistance, most frequently TAMs, but this did not impact on virological efficacy, similarly to previous studies enrolling individuals with pre-treatment resistance.[17] First-generation INSTIs (raltegravir and elvitegravir) have been used earlier and for longer than dolutegravir in PLWH and are more likely to select for INSTI resistance at VF due to their low genetic barrier. By contrast, dolutegravir and the other second-generation bictegravir have a much higher genetic barrier, thus their use should further limit both selection and transmission of INSTIs resistance.

The strengths of the study are the large number of individuals, the international representativeness of the real-life setting and the enrolment of individuals typically not included in randomized trials due to the presence of baseline resistance. Another advantage is the wide calendar time span analysed, encompassing years 2012–19 and including 8780 PYFU. The main limitations are the lack of detailed information on the reason for INSTI-DC and on adherence to treatment, the relatively small number of individuals with the pre-treatment integrase genotype and the lack of genotypic data at VF. Finally, female gender of non-Caucasian ethnicity was poorly represented, being only one-fifth of the general population and just over one-tenth of the patients treated with elvitegravir. As with any observational study, our analysis may be affected by unmeasured potential confounders as the choice of ART drugs is influenced by many factors, including co-morbidities or concomitant medications.

In conclusion, INSTI-based antiretroviral regimens are effective for first-line ART, even in presence of TDR for the accompanying drugs. However, the rate of discontinuation is much higher than the rate of VF. Future analyses should expand the proportion of cases with baseline integrase genotype, include bictegravir and analyse the reasons for INSTI-DC to define the full potential of second-generation INSTI-based regimens in the clinical setting.

Acknowledgements

Members of the INTEGRATE study group

A. Abecasis, Global Health and Tropical Medicine (GHTM), Instituto de Higiene e Medicina Tropical – Universidade Nova de Lisboa, Lisbon, Portugal. M. Bobkova, Gamaleya Federal Center for Epidemiology and Microbiology of Russia. C. Seguin-Devaux, Department of Infection and Immunity, Luxembourg Institute of Health, Luxembourg. M. Fabbiani, University Hospital of Siena, Siena, Italy. F. Garcia, Hospital Universitario San Cecilio, Granada, Spain. A. M. Geretti, University of Liverpool, UK. P. Gomes, Laboratório de Biologia Molecular (LMCBM, SPC, CHLO-HEM), Lisbon, Portugal and Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Instituto Universitário Egas Moniz, Caparica, Portugal. F. Incardona, EuResist Network, Roma, Italy – IPRO, Roma, Italy. R. Kaiser, University of Cologne, Cologne, Germany. R. Paredes, Irsicaixa, Spain. B. Rossetti, University Hospital of Siena, Siena, Italy. M. Sayan, Kocaeli University, Medical Faculty, Turkey. A. Sönnerborg, Karolinska Institutet, Stockholm, Sweden. A. M. Vandamme, REGA Institut KU Leuven, Belgium. M. Zazzi, University of Siena, Siena, Italy.

Funding

The INTEGRATE project received an unconditioned grant from GILEAD Sciences Europe Ltd. This study was also funded by the Swedish Research Council (2016–01675; A. Sönnerborg), the European Union by the CARE H2020 project under grant agreement no. 825673, the Stockholm County Council (ALF 20190451 and CIMED 20200645; A.

Sönnerborg) and the Fundação para a Ciência e Tecnologia, Portugal (INTEGRIV Project PTDC/SAU-INF/31990/20170 and GHTM-UID/Multi/04413/2013; A.A.).

Transparency declarations

B.R. received speakers' honoraria and support for travel to meetings from Gilead Sciences, Janssen-Cilag, Merck Sharp & Dohme (MSD), ViiV Healthcare, and fees for attending advisory boards from ViiV Healthcare, Janssen-Cilag, MSD, Gilead Sciences, Bristol-Myers Squibb (BMS). M.Z. received research support from Gilead Sciences and ViiV Healthcare, and fees for attending advisory boards from ViiV Healthcare, Janssen-Cilag, MSD, Gilead Sciences. A. Sönnerborg received research support from Gilead Sciences and fees for attending advisory boards from GSK and Gilead Sciences. A.A. received speakers' honoraria and support for travel to meetings from Gilead Sciences. A.M.G. received personal fees from Roche Pharma Research & Early Development and fees and research funding paid to the institution from Gilead, ViiV and Janssen, outside of the submitted work; Roche Pharma Research & Early Development played no role in the study. All other authors: none to declare.

Supplementary data

Tables S1 to S4 are available as Supplementary data at *JAC* online.

References

1 INSIGHT START Study Group, Lundgren JD, Babiker AG *et al.* Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373**: 795–807.

2 TEMPRANO ANRS Study Group, Danel C, Moh R, *et al.* A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373**: 808–22.

3 Kitahata MM, Gange SJ, Abraham AG *et al.* Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* 2009; **360**: 1815–26.

4 Cohen MS, Chen YQ, McCauley M *et al.* Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365**: 493–505.

5 US FDA. Antiretroviral Drugs Used in the Treatment of HIV Infection. https://www.fda.gov/individuals/hivtreatmentantiretroviral-drugs-used-treatment-hiv-infection.

6 EACS. EACS Guidelines Version 10.0. 2019. http://www.eacsociety.org/files/2020_guidelines-10.1-english.pdf.

7 WHO. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV World Health Organization; 2018. https://www.who.int/hiv/pub/guidelines/ARV2018update/en/.

8 Sax PE, Pozniak A, Montes ML *et al.* Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet* 2017; **390**: 2073–82.

9 Alejos B, Suarez-Garcıa I, Bisbal O *et al.* Choice of the initial antiretroviral treatment for HIV positive individuals in the era of integrase inhibitors. *PloS One* 2019; **14**: e0221598.

10 Cabenuva and Vocabria. [Product Monograph]. Laval, Quebec. Viiv Healthcare ULC. March 2020. https://viivhealthcare.com/content/dam/cf-viiv/viiv-healthcare/en_GB/medicines/CABENUVA-VOCABRIA-PM-26-Mar-2021.pdf.

11 Scévola S, Tiraboschi JM, Podzamczer D. Nothing is perfect: the safety issues of integrase inhibitor regimens. *Expert Opin Drug Saf* 2020; **19**: 683–94.

12 Lepik KJ, Yip B, Ulloa AC *et al.* Adverse drug reactions to integrase strand transfer inhibitors. *AIDS* 2018; **32**: 903–12.

13 Peñafiel J, de Lazzari E, Padilla M *et al.* Tolerability of integrase inhibitors in a real-life setting. *J Antimicrob Chemother* 2017; **72**: 1752–9.

14 Greenberg L, Ryom L, Wandeler G *et al.* Uptake and Discontinuation of Integrase Inhibitors (INSTIs) in a Large Cohort Setting. *J Acquir Immune Defic Syndr* 2020; **83**: 240–50.

15 Mills AM, Brunet L, Fusco JS *et al.* Virologic Outcomes Among ART-naïve Individuals Initiating Dolutegravir, Elvitegravir, Raltegravir or Darunavir: an Observational Study. *Infect Dis Ther* 2020; **9**: 41–52.

16 Scutari R, Alteri C, Vicenti I *et al.* Evaluation of HIV-1 integrase resistance emergence and evolution in patients treated with integrase inhibitors. *J Glob Antimicrob Resist* 2020; **20**: 163–9.

17 Yang LL, Li Q, Zhou LB *et al.* Meta-analysis and systematic review of the efficacy and resistance for human immunodeficiency virus type 1 integrase strand transfer inhibitors. *Int J Antimicrob Agents* 2019; **54**: 547–55.

18 Liu TF, Shafer RW. Web Resources for HIV type 1 Genotypic-Resistance Test Interpretation. *Clin Infect Dis* 2006; **42**: 1608–18.

19 Tzou PL, Rhee SY, Descamps D *et al.* Integrase strand transfer inhibitor (INSTI)-resistance mutations for the surveillance of transmitted HIV-1 drug resistance. *J Antimicrob Chemother* 2020; **75**: 170–82.

20 R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0. http://www.R-project.org/.

21 Mocroft A, Neesgard B, Zangerle R *et al.* Treatment outcomes of integrase inhibitors, boosted protease inhibitors and nonnucleoside reverse transcriptase inhibitors in antiretroviral-naive persons starting treatment. *HIV Med* 2020; **21**: 599–606.