# Effectiveness of integrase strand transfer inhibitors among treatment-experienced patients in a clinical setting

Thibaut Davy-Mendez[a,b], Sonia Napravnik[a,b], Oksana Zakharova[a], David A. Wohl[a,b], Claire E. Farel[a] and Joseph J. Eron[a,b]

**Objective:** Characterize virologic and immunologic outcomes of INSTI-based antiretroviral therapy (ART) in experienced patients with and without virologic failure.

**Design:** Prospective clinical cohort.

**Methods:** ART-experienced, INSTI-naive participants in the University of North Carolina Center for AIDS Research HIV Clinical Cohort (UCHCC) initiating an INSTI-containing regimen 2007–2016 were followed from INSTI initiation (baseline) to the earliest of: outcome of interest, loss to follow-up (LTFU, 1 year without clinical visit), or death. Outcomes of interest were virologic failure (first of two consecutive viral loads at least 200 copies/ml more than 2 weeks apart, or one viral load $\geq$200 before LTFU) and immune recovery (first $CD4^+$ $\geq$500 cells/$\mu$l). Patients with baseline viral load at least 50 copies/ml were given 24 weeks before meeting virologic failure criteria. Kaplan–Meier curves and Cox proportional hazards models compared INSTI regimens and patient characteristics.

**Results:** Of 773 patients, 32% were women, 59% African-American, and 42% had a viral load at least 50 copies/ml at INSTI initiation. After 2 years, 5% of patients with baseline viral load less than 50 copies/ml experienced virologic failure, compared with 35% of patients with baseline viral load at least 50 copies/ml ($P < 0.01$). Among patients with baseline viral load less than 50 copies/ml, dolutegravir/NRTIs was associated with longer time to virologic failure [adjusted hazard ratio (aHR) 0.11, 95% confidence interval (CI) 0.01–0.80], whereas among patients with baseline viral load at least 50 copies/ml, raltegravir/NRTIs was associated with longer time to virologic failure (aHR 0.35, 95% CI 0.18–0.68), both compared with elvitegravir/NRTIs. After 5 years suppressed, irrespective of baseline viral load, 61% of patients experienced immune recovery.

**Conclusion:** In this cohort, INSTI-containing regimens led to low virologic failure rates in patients switching ART while suppressed. Viremic patients initiating INSTIs were at high risk of virologic failure during follow-up.

*AIDS* 2019, **33**:1187–1195

**Keywords: antiretroviral therapy, HIV, integrase inhibitors, observational study, treatment-experienced**

## Introduction

Antiretroviral therapy (ART) regimens containing an integrase strand transfer inhibitor (INSTI) are recommended in treatment-naïve and treatment-experienced patients [1]. In clinical trials and observational studies, INSTI-based regimens lead to high rates of virologic success in naïve patients [2–4]. Efficacy of

[a]Department of Medicine, and [b]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.

Correspondence to Sonia Napravnik, PhD, Department of Medicine, University of North Carolina at Chapel Hill, 130 Mason Farm Road, Room 2132, Chapel Hill, NC 27599, USA.

Tel: +1 919 966 3875; fax: +1 919 966 8928; e-mail: napravs@med.unc.edu
Received: 7 November 2018; revised: 28 January 2019; accepted: 2 February 2019.

DOI:10.1097/QAD.0000000000002194

INSTI agents has also been demonstrated in ART-experienced patients in trials [5–7], yet few large observational studies have examined their effectiveness in experienced patients in the clinic setting [8–10].

INSTI agents have a high potency and more favorable safety and tolerability profiles than older ART agents [2,3,11]. When introduced in 2007, the INSTI agent raltegravir was active against viruses with resistance to prior drug classes. In 2012, elvitegravir became the first INSTI agent available in a single-tablet regimen. Dolutegravir, Food and Drug Administration (FDA)-approved in 2013, has a high barrier to resistance and is now also available as a single-tablet regimen [3]. Elvitegravir and dolutegravir are dosed once-daily, compared with twice-daily for raltegravir in treatment-experienced patients. These characteristics make INSTIs appealing treatment options for virologically suppressed patients who wish to simplify their ART and for patients with virologic failure, especially, with dolutegravir, in the context of poor regimen tolerability, preexisting resistance mutations, and suboptimal adherence. However, the anticipated benefits of INSTI agents in treatment-experienced patients should be confirmed in the clinic setting. In this study, we examined virologic and immunologic outcomes of INSTI-based therapy in ART-experienced patients with and without virologic failure.

## Methods

### Study population

Participants in the University of North Carolina Center for AIDS Research Clinical Cohort (UCHCC) were eligible for this study if they were ART-experienced, INSTI-naïve, had a complete ART history available, and initiated a first INSTI-containing regimen between 1 January 2007 and 31 December 2016 while in care at the University of North Carolina (UNC). Patients were excluded if they did not have an HIV RNA viral load measured in the 90 days prior to INSTI initiation, and a $CD4^+$ cell count measured between 180 days prior to and 90 days after INSTI initiation. The UCHCC prospectively collects laboratory results via electronic health records, and genotype tests and ART information via twice-yearly health record reviews. Patients were followed from INSTI initiation (baseline) until the earliest of: outcome of interest, death, loss to follow-up (LTFU), defined as 1 year without a clinic or laboratory visit, or administrative censoring on 31 August 2017. Patient were stratified by baseline viral load at least 50 copies/ml and less than 50 copies/ml, measured up to 90 days prior. Data collection for the UCHCC and secondary analysis for this study were both approved by UNC's Institutional Review Board, and patients provided written informed consent to participate in the UCHCC.

### Definitions

We examined two outcomes: virologic failure and immune recovery. Virologic failure was defined as the first of two consecutive viral loads at least 200 copies/ml more than 2 weeks apart, or one viral load at least 200 copies/ml before being LTFU. Patients with baseline viral load at least 50 copies/ml were given 24 weeks on INSTI therapy before meeting criteria for virologic failure. Among patients with baseline $CD4^+$ less than 500 cells/μl, measured up to 6 months prior, immune recovery was defined as the first $CD4^+$ cell count at least 500 cells/μl after INSTI initiation. We categorized ART regimens according to INSTI agent raltegravir (RAL), elvitegravir (EVG), or dolutegravir (DTG), taken in combination with two or more nucleoside or nucleotide analog reverse transcriptase inhibitors (NRTIs). We also examined regimens including RAL with a protease inhibitor, with or without a pharmacoenhancer and with or without any NRTIs. Remaining regimens were categorized as 'other.' For patients receiving an INSTI in combination only with an NRTI backbone and who had a genotypic resistance test obtained in the 90 days prior to INSTI initiation, we estimated the activity of the NRTI backbone using the Stanford algorithm based on mutations from all previously available genotypes [12]. An NRTI backbone was considered fully active if no component drug had an intermediate or above resistance score. For patients with INSTI genotyping performed in the 90 days following virologic failure on the INSTI regimen, we described the presence of major (bolded) mutations listed in the 2017 IAS-USA list [13].

### Analyses

We compared baseline patient characteristics using Fisher's exact test, the Wilcoxon Rank-Sum test, and the Kruskal–Wallis test as appropriate. We estimated time from baseline to outcome of interest and compared INSTI regimens using Kaplan–Meier curves and Cox proportional hazards models, adjusting for age, sexual risk group, race/ethnicity, $CD4^+$ cell count, and number of prior antiretroviral agents, all measured at baseline. Time to virologic failure analyses among patients with baseline viral load at least 50 copies/ml were also adjusted for baseline viral load. Primary analyses were intention-to-treat and ignored changes in ART. In a secondary analysis of time to virologic failure, patients were censored if they had any change in ART regimen or discontinued ART for longer than 2 weeks. Dosage or formulation changes were not considered an ART regimen change. In time to immune recovery analyses, patients were censored at virologic failure. All *P* values are two-sided, and less than 0.05 was considered statistically significant. Analyses were conducted in SAS software, version 9.4 (SAS Institute, Inc, Cary, North Carolina, USA).

## Results

Of 933 eligible patients, we excluded 157 (17%) missing baseline viral load or $CD4^+$ cell count. These 157 patients

**Table 1. Patient characteristics stratified by HIV RNA viral load at integrase strand transfer inhibitor initiation.**

| | Viral load at least 50 copies/ml ($N = 327$) | Viral load less than 50 copies/ml ($N = 446$) | |
|---|---|---|---|
| Characteristic at INSTI initiation | *N* (%) or median (IQR) | *N* (%) or median (IQR) | $P$[a] |
| Sexual risk group | | | 0.58 |
| MSM | 137 (42%) | 198 (44%) | |
| Women | 104 (32%) | 145 (33%) | |
| Heterosexual men | 86 (26%) | 103 (23%) | |
| IDU | 29 (9%) | 49 (11%) | 0.40 |
| Race/ethnicity | | | <0.05 |
| African American | 207 (63%) | 243 (54%) | |
| White | 88 (27%) | 161 (36%) | |
| Hispanic/other | 32 (10%) | 42 (9%) | |
| Age (years) | 44 (35, 50) | 50 (41–56) | <0.01 |
| Calendar year | 2012 (2009–2014) | 2014 (2013–2015) | <0.01 |
| Years since first ART | 9 (4, 13) | 11 (5–16) | <0.01 |
| Prior ARV drugs | 6 (4, 9) | 5 (4–8) | <0.05 |
| Prior ART regimens | 4 (2, 7) | 3 (1–6) | <0.01 |
| Nadir $CD4^+$ cell count (cells/μl) | 81 (15–240) | 157 (48–304) | <0.01 |
| $CD4^+$ cell count (cells/μl) | 288 (113–495) | 636 (443–839) | <0.01 |
| HIV RNA ($log_{10}$ copies/ml) | 4.24 (2.98–4.94) | N/A | N/A |
| Last prior regimen anchor class | | | <0.01 |
| NNRTI | 107 (33%) | 183 (41%) | |
| PI | 179 (55%) | 232 (52%) | |
| NNRTI and PI | 11 (3%) | 15 (3%) | |
| EI[b] | 12 (4%) | 7 (2%) | |
| Other | 18 (5%) | 9 (2%) | |
| First INSTI regimen | | | <0.01 |
| EVG/COBI with at least two NRTI | 64 (20%) | 175 (39%) | |
| DTG with at least two NRTI | 61 (19%) | 141 (32%) | |
| RAL with at least two NRTI | 65 (20%) | 66 (15%) | |
| RAL with PI[c] | 70 (21%) | 31 (7%) | |
| Other[d] | 67 (20%) | 33 (7%) | |

ART, antiretroviral therapy; ARV, antiretroviral; COBI, cobicistat; DTG, dolutegravir; EI, entry inhibitor; EVG, elvitegravir; IDU, injection drug use; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; N/A, not applicable; NNRTI, nonnucleoside analog reverse transcriptase inhibitor; NRTI, nucleoside analog reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir.

[a]*P* value from Fisher's exact test for categorical variables and the Wilcoxon Rank-Sum test for continuous variables.

[b]May include another anchor drug.

[c]With or without any NRTI agent.

[d]Includes patients on RAL in combination with an NNRTI (17 with viral load ≥50 copies/ml and 14 with viral load <50 copies/ml), RAL with a PI and an NNRTI (27 with viral load ≥50 copies/ml and 7 with viral load <50 copies/ml), RAL with an EI (15 with viral load ≥50 copies/ml and 0 with viral load <50 copies/ml), and DTG with another anchor agent (8 with viral load ≥50 copies/ml and 12 with viral load <50 copies/ml), all with or without any NRTI agent.

were demographically and clinically comparable with patients who met inclusion criteria. Additionally, we excluded three (<1%) patients who initiated an INSTI with only one or no NRTI. Our study population included 773 patients who were 32% women, 43% MSM, and 59% African-American patients, and at baseline had a median age of 47 years [interquartile range (IQR) 38–54), $CD4^+$ cell count of 509 cells/μl (IQR 274–739), and prior exposure to 6 (IQR 4–8) antiretrovirals. At baseline, 327 (42%) patients had a viral load at least 50 copies/ml, with a median viral load of 4.24 $log_{10}$ copies/ml (IQR 2.98–4.94). Compared with patients with baseline viral load less than 50 copies/ml, patients with baseline viral load at least 50 copies/ml were more likely African American (63 vs. 54%), younger (median age 44 vs. 50 years), had initiated ART more recently (median 9 vs. 11 years), yet been exposed to more agents (median 6 vs. 5) (Table 1, all $P < 0.05$). Patients with baseline viral load at least 50 copies/ml had lower $CD4^+$ cell counts, both nadir (median 84 vs. 158 cells/μl) and baseline (288 vs. 636 cells/μl), than patients with viral load less than 50 copies/ml (both $P < 0.05$). In both viral load groups, a majority of patients were switching from a protease inhibitor-based regimen and at least one-third from an NNRTI-based regimen. Patients with baseline viral load less than 50 copies/ml most commonly initiated a first INSTI regimen containing EVG/COBI (39%) or DTG (31%) in combination with NRTIs. In contrast, the most common first INSTI regimens among patients with viral load at least 50 copies/ml were EVG/COBI/NRTIs (20%), DTG/NRTIs (19%), RAL/NRTIs (20%), and RAL/PI (21%). When further stratifying patients with baseline viral load at least 50 copies/ml by INSTI regimen, those receiving EVG/COBI/NRTIs were the youngest and least treatment-experienced group, with a median age of 36 years (IQR 28–48) and prior antiretroviral drug exposure of four agents (IQR 3–6) (Table 2, both $P < 0.01$).

## Time to virologic failure

Among patients with baseline viral load less than 50 copies/ml, 2 and 5% experienced virologic failure

**Table 2. Characteristics of patients with HIV RNA viral load at least 50 copies/ml at integrase strand transfer inhibitor initiation, stratified by antiretroviral therapy regimen.**

| Characteristic at INSTI initiation | EVG/COBI + ≥2 NRTIs (*N* = 64) *N* (%) or median (IQR) | DTG + ≥2 NRTIs (*N* = 61) *N* (%) or median (IQR) | RAL + ≥2 NRTIs (*N* = 65) *N* (%) or median (IQR) | RAL + PI[a] (*N* = 70) *N* (%) or median (IQR) | Other (*N* = 67) *N* (%) or median (IQR) | *P*[b] |
|---|---|---|---|---|---|---|
| Sexual risk group | | | | | | 0.10 |
| MSM | 36 (56%) | 26 (43%) | 30 (46%) | 19 (27%) | 26 (39%) | |
| Women | 16 (25%) | 18 (30%) | 21 (32%) | 28 (40%) | 21 (31%) | |
| Heterosexual men | 12 (19%) | 17 (28%) | 14 (22%) | 23 (33%) | 20 (30%) | |
| IDU | 4 (6%) | 6 (10%) | 6 (9%) | 7 (10%) | 6 (9%) | 0.95 |
| Race/ethnicity | | | | | | |
| African American | 46 (72%) | 37 (61%) | 33 (51%) | 48 (69%) | 43 (64%) | 0.16 |
| White | 11 (17%) | 16 (26%) | 26 (40%) | 15 (21%) | 20 (30%) | |
| Hispanic/other | 7 (11%) | 8 (13%) | 6 (9%) | 7 (10%) | 4 (6%) | |
| Age (years) | 36 (28, 48) | 45 (36, 57) | 42 (33, 48) | 45 (38, 53) | 47 (42, 52) | <0.01 |
| Calendar year | 2014 (2013, 2015) | 2015 (2014, 2016) | 2011 (2009, 2012) | 2009 (2008, 2010) | 2009 (2008, 2011) | <0.01 |
| Years since first ART | 5 (2, 10) | 8 (4, 13) | 9 (2, 13) | 10 (5, 14) | 12 (9, 15) | <0.01 |
| Prior ARV drugs | 4 (3, 6) | 5 (3, 8) | 5 (4, 8) | 8 (6, 12) | 10 (7, 13) | <0.01 |
| Prior ART regimens | 2 (1, 4) | 3 (2, 5) | 3 (2, 5) | 5 (4, 9) | 9 (4, 15) | <0.01 |
| Nadir $CD4^+$ cell count (cells/μl) | 227 (63, 355) | 152 (33, 312) | 135 (46, 297) | 28 (9, 108) | 22 (9, 15) | <0.01 |
| $CD4^+$ cell count (cells/μl) | 388 (187, 541) | 357 (191, 545) | 315 (141, 541) | 203 (56, 397) | 178 (69, 326) | <0.01 |
| HIV RNA ($log_{10}$ copies/ml) | 4.04 (2.84, 4.60) | 3.75 (2.71, 4.94) | 4.05 (2.92, 4.77) | 4.35 (3.29, 5.17) | 4.51 (3.49, 4.90) | 0.20 |
| Last prior regimen anchor class | | | | | | <0.01 |
| NNRTI | 27 (42%) | 29 (48%) | 26 (40%) | 17 (24%) | 8 (12%) | |
| PI | 34 (53%) | 29 (48%) | 32 (49%) | 45 (64%) | 39 (58%) | |
| NNRTI and PI | 1 (2%) | 1 (2%) | 1 (2%) | 0 (0%) | 8 (12%) | |
| EI[c] | 0 (0%) | 0 (0%) | 0 (0%) | 4 (6%) | 8 (12%) | |
| Other | 2 (3%) | 2 (3%) | 6 (9%) | 4 (6%) | 4 (6%) | |
| Genotype performed at INSTI initiation | 22 (34%) | 22 (36%) | 22 (34%) | 31 (44%) | 25 (37%) | 0.74 |
| Fully active NRTI backbone[d] | 20 (91%) | 17 (77%) | 18 (82%) | N/A | N/A | 0.60 |

ART, antiretroviral therapy; ARV, antiretroviral; COBI, cobicistat; DTG, dolutegravir; EI, entry inhibitor; EVG, elvitegravir; IDU, injection drug use; INSTI, integrase strand transfer inhibitor; IQR, interquartile range; N/A, not applicable; NNRTI, nonnucleoside analog reverse transcriptase inhibitor; NRTI, nucleoside analog reverse transcriptase inhibitor; PI, protease inhibitor; RAL, raltegravir.

[a]With or without any NRTI agent.

[b]*P* values from the Monte Carlo estimate of Fisher's exact test for categorical variables and the Kruskal–Wallis test for continuous variables.

[c]May include another anchor drug.

[d]Restricted to patients on a single anchor agent and with a genotype performed at INSTI initiation. On the basis of mutations from all available genotype testing prior to INSTI initiation, interpreted according to the Stanford algorithm. NRTI backbones in which no agent had a resistance score of intermediate or above were considered fully active.

after 1 and 2 years, respectively, compared with 23 and 35% among patients with baseline viral load at least 50 copies/ml (log-rank $P < 0.01$). The differences in time to virologic failure by baseline viral load persisted after stratifying by calendar period of INSTI initiation 2007–2010, 2011–2013, and 2014–2016 (Supplemental Digital Content 1, Figure, http://links.lww.com/QAD/B461, all $P < 0.01$). Time to virologic failure differed by INSTI regimen in both viral load groups (Fig. 1a and b, both log-rank $P < 0.05$). Among patients with baseline viral load at least 50 copies/ml, RAL/NRTIs was associated with longer time to virologic failure compared with EVG/COBI/NRTIs, with an adjusted hazard ratio (aHR) of 0.35 [95% confidence interval (CI) 0.18–0.68), whereas there was no association with any other regimen (Table 3). Among patients with baseline viral load less than 50 copies/ml, DTG/NRTIs was associated with longer time to virologic failure compared with EVG/COBI/NRTIs, with an aHR of 0.11 (95% CI 0.01–0.80), but there was no association with any other regimen. Regardless of baseline viral load, older age was associated with longer time to virologic failure, with an aHR of 0.74 (95% CI 0.61–0.89) and 0.67 (95% CI 0.46–0.98) per 10-year increase among patients with baseline viral load at least 50 copies/ml and less than 50 copies/ml, respectively. Among patients with baseline viral load at least 50 copies/ml, a longer time to virologic failure was associated with higher baseline $CD4^+$ cell count (aHR per 100-cell increase 0.82, 95% CI 0.75–0.91) and exposure to fewer antiretrovirals (aHR per one-drug increase 1.07, 95% CI 1.01–1.12), but not among patients with baseline viral load less than 50 copies/ml. Among patients with baseline viral load at least 50 copies/ml, a one-unit increase in $log_{10}$ RNA copies/ml was associated with increased virologic failure rates in unadjusted analyses, with a hazard ratio of 1.35 (95% CI 1.16–1.57), but not in adjusted models (aHR 1.14, 95% CI 0.96–1.34). Patients with baseline viral load more than 10 000 ($N = 182$), compared with those with baseline viral load 50–10 000 ($N = 145$), had a hazard ratio of 1.78 (95% CI 1.23–2.58) in unadjusted models and 1.19 (95% CI 0.80–1.78) in adjusted models. Prior

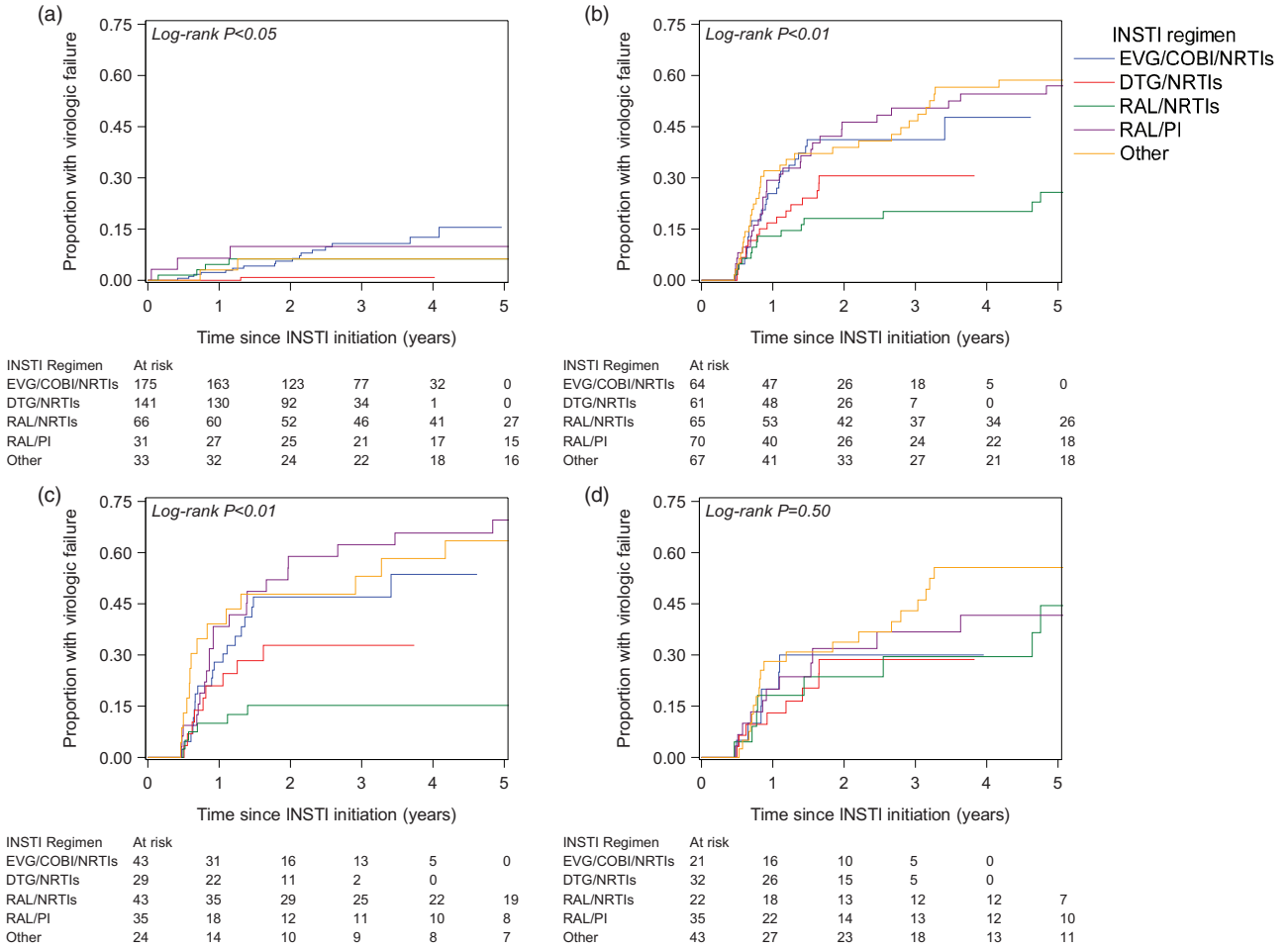


**Fig. 1. Time from integrase strand transfer inhibitor initiation to virologic failure stratified by integrase strand transfer inhibitor regimen: (a) among patients with HIV viral load less than 50 copies/ml at INSTI initiation, (b) among patients with viral load at least 50 copies/ml at INSTI initiation, (c) among patients with viral load at least 50 copies/ml and aged less than 45 years at INSTI initiation, and (d) among patients with viral load at least 50 copies/ml and aged 45 years or more at INSTI initiation. INSTI, integrase strand transfer inhibitor.**

**Table 3. Factors associated with time to virologic failure, stratified by HIV RNA viral load at integrase strand transfer inhibitor initiation.**

| | Viral load ≥50 copies/ml | | Viral load <50 copies/ml | |
|---|---|---|---|---|
| Characteristic at INSTI initiation | Unadjusted HR[a] (95% CI) | Adjusted HR[b] (95% CI) | Unadjusted HR[a] (95% CI) | Adjusted HR[b] (95% CI) |
| INSTI regimen | | | | |
| EVG/COBI with ≥2 NRTI | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| RAL with ≥2 NRTI | 0.43 (0.22–0.81) | 0.35 (0.18–0.68) | 0.63 (0.23–1.75) | 0.77 (0.27–2.23) |
| DTG with ≥2 NRTI | 0.68 (0.37–1.25) | 0.80 (0.42–1.50) | 0.08 (0.01–0.60) | 0.11 (0.01–0.80) |
| RAL with PI | 1.10 (0.65–1.85) | 0.59 (0.33–1.08) | 0.78 (0.22–2.75) | 1.03 (0.26–4.10) |
| Other | 1.22 (0.73–2.03) | 0.76 (0.41–1.39) | 0.51 (0.12–2.23) | 0.89 (0.18–4.36) |
| Sexual risk group | | | | |
| MSM | 0.74 (0.48–1.16) | 0.58 (0.35–0.93) | 0.74 (0.26–2.09) | 0.61 (0.20–1.83) |
| Women | 1.09 (0.70–1.68) | 0.79 (0.49–1.25) | 1.53 (0.58–4.02) | 1.35 (0.50–3.61) |
| Heterosexual men | 1 (ref.) | 1 (ref.) | 1 (ref.) | 1 (ref.) |
| African American race | 1.41 (0.97–2.06) | 1.13 (0.77–1.68) | 1.55 (0.72–3.38) | 1.25 (0.53–2.96) |
| Age, per 10-year increase | 0.84 (0.73–0.98) | 0.74 (0.61–0.89) | 0.68 (0.49–0.94) | 0.67 (0.46–0.98) |
| $CD4^+$, per 100-cell increase | 0.78 (0.72–0.85) | 0.82 (0.75–0.91) | 0.95 (0.84–1.08) | 0.96 (0.84–1.10) |
| Number of prior ARVs, per 1-drug increase | 1.06 (1.02–1.11) | 1.07 (1.01–1.12) | 0.97 (0.86–1.09) | 0.99 (0.86–1.12) |
| HIV RNA, per $\log_{10}$ increase | 1.35 (1.16–1.57) | 1.14 (0.96–1.34) | N/A | N/A |

ARV, antiretroviral; CI, confidence interval; COBI, cobicistat; DTG, dolutegravir; EVG, elvitegravir; HR, hazard ratio; INSTI, integrase strand transfer inhibitor; N/A, not applicable; RAL, raltegravir; Ref., referent.

[a]Estimates from separate Cox proportional models including only one characteristic.

[b]Estimates from Cox proportional hazards models including all variables in the table, except HIV RNA for patients with baseline viral load less than 50 copies/ml.

ART duration was not associated with time to virologic failure in unadjusted or adjusted models (results not shown).

We further stratified analyses of patients with baseline viral load at least 50 copies/ml by age less than 45 years or at least 45 years at INSTI initiation. In Kaplan–Meier curves, we observed differences in time to virologic failure by INSTI regimen with longer time for RAL/NRTIs in the younger group (Fig. 1c, log-rank $P < 0.05$), but not in the older group (Fig. 1d, log-rank $P = 0.50$). These findings were also observed in multivariable analyses stratified by age, with an adjusted hazard ratio comparing RAL/NRTIs to EVG/COBI/NRTIs of 0.21 (95% CI 0.08–0.51) in the younger group and 0.99 (0.33–2.96) in the older group.

Twenty-one patients had INSTI genotypes obtained at virologic failure on the INSTI regimen. Out of four patients on a DTG-containing regimen, none (0%) had a major INSTI mutation. Out of nine patients on a RAL-containing regimen, 1 (11%) developed N155H. Out of eight patients on an EVG-containing regimen, one (13%) developed N155H, two (25%) developed E92Q.

### Sensitivity analyses of virologic failure

In a sensitivity analysis censoring all patients after 3 years, estimates were similar to the main findings. Stratifying patients by baseline viral load at least 200 copies/ml ($N = 282$) or less than 200 ($N = 491$) instead of 50 copies/ml, estimates were also comparable to our primary results. In further sensitivity analyses censoring patients who changed or discontinued ART, our results were consistent with our ITT findings, although the estimates were less precise, with an adjusted hazard ratio of 0.37 (95% CI 0.12–1.13) comparing RAL/NRTIs to EVG/COBI/NRTIs among patients with baseline viral load at least 50 copies/ml . There were too few virologic failure events among patients with baseline viral load less than 50 copies/ml, after censoring patients at ART changes, to allow us to estimate hazard ratios comparing different regimens. We also conducted analyses restricted to patients with baseline viral load at least 50 copies/ml, who initiated an INSTI in combination with an NRTI backbone and had a genotype at INSTI start. In this patient group, adjusting for NRTI backbone activity as well as age, sexual risk group, race, $CD4^+$ cell count, viral load, and number of prior agents, the aHR compared with EVG/COBI was 0.50 (95% CI 0.18–1.35) for DTG and 0.14 (95% CI 0.04–0.51) for RAL. In this patient group, incomplete activity of the NRTI backbone was associated with shorter time to failure, with an unadjusted hazard ratio of 3.02 (95% CI 1.33–6.91). When we also included patients with NRTI resistance based on earlier genotypes, results comparing EVG/COBI to RAL were similar. Finally, in an analysis restricted to patients with baseline viral load at least 50 copies/ml who initiated EVG/COBI/NRTIs or RAL/NRTIs in the years 2012–2016, the aHR comparing RAL to EVG was similar to the main findings.

### Time to immune recovery

Among patients with baseline viral load at least 50 copies/ml and less than 50 copies/ml, 246 (75%) and 134 (30%) had a baseline $CD4^+$ cell count less than 500 cells/μl, with median $CD4^+$ cell counts (IQR) of 202 (72–329) and 360 (256–426), respectively. The median age (IQR) of these patients was 44 years (36–50) and 51 years (42–57), respectively. In unadjusted analyses (Supplemental Digital Content 2, Figure, http://links.lww.com/QAD/B461), we observed differences in time to immune recovery by nadir $CD4^+$ cell count ($P < 0.01$), but not by baseline viral load, INSTI regimen, or age group. After 5 years of INSTI therapy, censoring patients with virologic failure, 61% in both viral load groups reached $CD4^+$ cell counts at least 500 cells/μl. Almost 80% of patients with nadir $CD4^+$ cell count greater than 200 cells/μl experienced immune recovery after 5 years, compared with 44% in those with nadir $CD4^+$ cell count less than 50 cells/μl.

## Discussion

In this clinical cohort study of ART-experienced patients initiating INSTI-based therapy, INSTI regimens were highly effective among patients who switched with undetectable HIV RNA levels, with 95% of patients remaining virologically suppressed after 2 years. Suppressed patients who switched to DTG had a significantly lower rate of failure compared with EVG, although the confidence interval around the point estimate was wide. On the other hand, patients with detectable viremia at INSTI initiation had high virologic failure rates, associated with younger age and lower $CD4^+$ cell counts at baseline. Viremic patients switching to RAL in combination with NRTIs had a lower risk of failure compared with EVG. This difference persisted in additional analyses adjusted for NRTI backbone activity, and among patients less than 45 years old, but not among patients 45 years or older. Irrespective of baseline viral load or regimen type, patients on INSTIs experienced good immune recovery, with only observed differences by degree of prior immunosuppression.

Clinical trials have demonstrated that patients with suppressed viral loads maintain high rates of virologic suppression after switching to INSTI-containing regimens [5,14,15]. Some observational studies have also shown good virologic outcomes in suppressed patients switching to RAL [16–18], one study in patients switching to EVG [9], and one in patients switching to DTG [19]. One cohort study reported low failure rates over 2 years after switching while suppressed to an INSTI-based regimen, including RAL, DTG, and EVG,

though it did not compare INSTI agents [10]. Some studies have shown good virologic outcomes on RAL or DTG in heterogeneous groups constituting both suppressed and unsuppressed patients [8,20,21]. However, most prior studies were small (50–150 patients), had short follow-up (24–48 weeks), or included only one INSTI (most often RAL); none compared INSTI agents.

In this larger study, we found high rates of maintained suppression among patients initiating RAL, DTG, and EVG through 5 years of follow-up. Further, we observed lower virologic failure rates among suppressed patients switching to DTG compared with EVG, both in combination with NRTIs. This difference may be linked to patient adherence and to DTG's higher barrier to resistance [2,3]. As a majority of patients switched from a protease inhibitor-based regimen, which also have high barriers to resistance [22,23], it is possible that patients with suboptimal adherence who were able to maintain virologic suppression on a protease inhibitor experienced failure after switching to an agent less forgiving of missed doses such as EVG. Our study also observed good $CD4^+$ recovery for patients who achieved and maintained suppression on INSTI-based regimens. Improvements in $CD4^+$ cell counts have been reported in both clinical trials and observational studies after switching to RAL-based regimens [6,8], and in clinical trials after switching to DTG- and EVG-based regimens [5,14]. Our study shows a $CD4^+$ recovery in patients switching to EVG and DTG in the clinical setting as well.

High virologic failure rates in patients initiating INSTI therapy with detectable viral loads was not a surprising result. Although in clinical trials INSTI-based regimens lead to good suppression rates among patients with virologic failure, poor adherence to treatment has been shown to lead to continued lack of virologic control [6,7]. Patients in our study who had previously failed several regimens, including potent ones initiated in recent years, may have been nonadherent to the new INSTI-based treatment. Two observational studies reporting 48-week outcomes of switching from a failing regimen to RAL found failure rates of 15 and 35% [17,24], whereas another two studies found a failure rate of 20% at 24 weeks [18,25]. Only one study of RAL reported high suppression rates after 2 years in patients switching from a failing regimen [26]. Our study confirms most prior reports observing high virologic failure rates following RAL initiation among patients virologically detectable at time of regimen switch, and to our knowledge is the first to report the high virologic failure risk among virologically detectable patients switching to DTG or EVG in a clinical care setting.

The lower failure rate associated with RAL/NRTIs compared with EVG was an unexpected finding. As a single-tablet regimen with once-daily dosing, adherence to EVG/COBI/FTC/TDF could be expected to be higher than adherence to RAL/NRTIs, which has a higher pill burden and required two daily doses until recently. There are several possible explanations for this result. Co-formulation of EVG with the pharmacoenhancer COBI may have led to poorer tolerance of the regimen [2]. Our estimates could be affected by residual confounding because of channeling bias, if healthcare providers opted to prescribe the once-daily single-tablet regimen (EVG) to patients believed to be less likely to adhere. Among patients with some but incomplete adherence, it is also possible that a twice-daily regimen with some missed doses may lead to better virologic outcomes than a once-daily regimen with some missed doses [27]. Younger patients may be more likely to adhere partially to treatment, explaining lower failure rates with RAL/NRTIs vs. EVG in this age group. In a German study, patients with intermittent adherence reported most commonly skipping doses because they 'felt bad' or planned on consuming alcohol or drugs [28]. Older patients, on the other hand, are less likely to miss doses [29]. Patients in our study's older group who were nonadherent may have had severe obstacles to adherence, such as substance use, leading to very low adherence levels and no observed difference in failure rates by regimen. Analyses restricted to 2012–2016 were similar to the main findings, suggesting that confounding by calendar time, such as better adherence in early users of RAL, is unlikely to explain regimen differences. Additionally, it is possible that patients in the RAL and EVG groups had different antiretroviral resistance profiles. In subgroup analyses of patients with a genotype at INSTI initiation, adjusting for reduced activity of the NRTI backbone, we continued to observe the RAL and EVG difference, suggesting that detected resistance could not account for the observed differences.

The appeal of INSTIs for treatment-experienced patients is likely to persist with the approval of additional once-daily single-tablet regimens (STR) containing EVG, DTG, or the new INSTI bictegravir (BIC), especially in combination with tenofovir alafenamide [30]. Our findings highlight the need to continue to study INSTI outcomes in clinical settings among treatment-experienced patients, including additional follow-up time, heterogeneous patient populations, BIC use, and STR INSTI use. Comparative effectiveness studies are also needed to assess differences between INSTIs and other new STRs, such as those containing darunavir or rilpivirine, particularly in the context of incomplete patient adherence and preexisting drug resistance [31,32]. In addition, drug resistance and toxicities of INSTI agents should continue to be monitored in clinical populations [33]. Finally, ongoing efforts supporting patient adherence are needed, given the high virologic failure rates we observed among patients with detectable viral loads at INSTI initiation. Patients facing persistent challenges to adherence may benefit from interventions leading to even modest improvements in adherence, and from future therapies with long-acting injectable agents.

This study's strengths include longitudinal follow-up of treatment-experienced patients on three INSTI agents including two approved in recent years, providing what is, to our knowledge, the largest and longest observational study of INSTI use in ART-experienced patients and the only one to compare INSTI agents. Our cohort also captures granular data, such as complete treatment histories and genotypic resistance tests, which added valuable information to the analyses. However, our study is limited by small sample sizes, which affected our ability to obtain precise estimates, and by the lack of information on adherence or reasons for switching from a prior regimen. This study was conducted at a single center in a high-income nation and may not be directly generalizable to other settings.

In conclusion, INSTI-based regimens can be highly effective in ART-experienced patients with current virologic control. However, in patients who have detectable viremia, INSTI effectiveness is likely limited by other treatment factors, such as adherence. Treatment-experienced patients who remain suppressed on INSTI regimens experience good immunologic outcomes.

## Acknowledgements

Sources of funding: This study was funded by the University of North Carolina at Chapel Hill Center for AIDS Research, an NIH-funded program (Grant Award Number P30 AI50410). Traineeship for T.D. was provided by the National Institute of Allergy and Infectious Diseases (Grant Award Number T32 AI007001).

### Conflicts of interest

J.J.E. has received research grants from Janssen, Gilead Sciences, and ViiV Healthcare and has served as a consultant to Merck & Co., Janssen, Gilead Sciences, and ViiV Healthcare. D.A.W. has received research grants from Gilead Sciences and Merck & Co. and has served as a consultant to Gilead Sciences, Janssen, ViiV Healthcare, and Merck & Co. T.D.-M., S.N., C.E.F., and O.Z. have nothing to declare.

## References

1. Saag MS, Benson CA, Gandhi RT, Hoy JF, Landovitz RJ, Mugavero MJ, *et al*. **Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel.** *JAMA* 2018; **320**:379–396.
2. Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, *et al*. **Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks.** *Lancet* 2012; **379**:2439–2448.
3. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F, *et al*., SINGLE Investigators. **Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection.** *N Engl J Med* 2013; **369**:1807–1818.
4. Davy-Mendez T, Eron JJ, Zakharova O, Wohl DA, Napravnik S. **Increased persistence of initial treatment for HIV infection with modern antiretroviral therapy.** *J Acquir Immune Defic Syndr* 2017; **76**:111–115.
5. Arribas JR, Pialoux G, Gathe J, Di Perri G, Reynes J, Tebas P. **Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial.** *Lancet Infect Dis* 2014; **14**:581–589.
6. Eron JJ, Cooper DA, Steigbigel RT, Clotet B, Gatell JM, Kumar PN, *et al*., BENCHMRK Study Teams. **Efficacy and safety of raltegravir for treatment of HIV for 5 years in the BENCHMRK studies: final results of two randomised, placebo-controlled trials.** *Lancet Infect Dis* 2013; **13**:587–596.
7. Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, Andrade-Villanueva JF, *et al*., extended SAILING Study Team. **Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, noninferiority SAILING study.** *Lancet* 2013; **382**:700–708.
8. Buchacz K, Wiegand R, Armon C, Chmiel JS, Wood K, Brooks JT, Palella FJ Jr. **Long-term immunologic and virologic responses on raltegravir-containing regimens among ART-experienced participants in the HIV Outpatient Study.** *HIV Clin Trials* 2015; **16**:139–146.
9. Perrier M, Charpentier C, Peytavin G, Lê M, Blondel L, Visseaux B, *et al*. **Switch as maintenance to elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate: week 48 results in a clinical cohort.** *J Antimicrob Chemother* 2017; **72**:1745–1751.
10. Gianotti N, Poli A, Nozza S, Galli L, Galizzi N, Ripa M, *et al*. **Durability of switch regimens based on rilpivirine or on integrase inhibitors, both in association with tenofovir and emtricitabine, in HIV-infected, virologically suppressed patients.** *BMC Infect Dis* 2017; **17**:723.
11. Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JV, Berger DS, *et al*., STARTMRK investigators. **Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial.** *Lancet* 2009; **374**:796–806.
12. Tang MW, Liu TF, Shafer RW. **The HIVdb system for HIV-1 genotypic resistance interpretation.** *Intervirology* 2012; **55**:98–101.
13. Wensing AM, Calvez V, Gunthard HF, Johnson VA, Paredes R, Pillay D, *et al*. **2017 update of the drug resistance mutations in HIV-1.** *Top Antivir Med* 2017; **24**:132–133.
14. Trottier B, Lake JE, Logue K, Brinson C, Santiago L, Brennan C, *et al*. **Dolutegravir/abacavir/lamivudine versus current ART in virally suppressed patients (STRIIVING): a 48-week, randomized, noninferiority, open-label, Phase IIIb study.** *Antivir Ther* 2017; **22**:295–305.
15. Troya J, Montejano R, Ryan P, Gómez C, Matarranz M, Cabello A, *et al*., GESIDA-8715 Study Group. **Raltegravir plus abacavir/lamivudine in virologically suppressed HIV-1-infected patients: 48-week results of the KIRAL study.** *PLoS One* 2018; **13**:e0198768.
16. Caby F, Schneider L, Blanc C, Soulié C, Tindel M, Peytavin G, *et al*. **Efficacy of raltegravir switching strategies in HIV-infected patients with suppressed viraemia according to the genotypic sensitivity score.** *Infection* 2014; **42**:295–301.
17. Naumann U, Moll A, Schleehauf D, Lutz T, Schmidt W, Jaeger H, *et al*. **Similar efficacy and tolerability of raltegravir-based antiretroviral therapy in HIV-infected patients, irrespective of age group, burden of comorbidities and concomitant medication: Real-life analysis of the German 'WIP' cohort.** *Int J STD AIDS* 2017; **28**:893–901.
18. Scherrer AU, von Wyl V, Fux CA, Opravil M, Bucher HC, Fayet A, *et al*., Swiss HIV Cohort Study. **Implementation of raltegravir in routine clinical practice: selection criteria for choosing this drug, virologic response rates, and characteristics of failures.** *J Acquir Immune Defic Syndr* 2010; **53**:464–471.

19. Todd S, Rafferty P, Walker E, Hunter M, Dinsmore WW, Donnelly CM, *et al*. **Early clinical experience of dolutegravir in an HIV cohort in a larger teaching hospital.** *Int J STD AIDS* 2017; **28**:1074–1081.
20. Capetti AF, Cossu MV, Orofino G, Sterrantino G, Cenderello G, De Socio GV, *et al*. **A dual regimen of ritonavir/darunavir plus dolutegravir for rescue or simplification of rescue therapy: 48 weeks' observational data.** *BMC Infect Dis* 2017; **17**:658.
21. Capetti AF, Sterrantino G, Cossu MV, Orofino G, Barbarini G, De Socio GV, *et al*. **Switch to dolutegravir plus rilpivirine dual therapy in cART-experienced subjects: an observational cohort.** *PLoS One* 2016; **11**:e0164753.
22. Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, *et al*., CASTLE Study Team. **Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study.** *Lancet* 2008; **372**:646–655.
23. Mills AM, Nelson M, Jayaweera D, Ruxrungtham K, Cassetti I, Girard PM, *et al*. **Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis.** *AIDS* 2009; **23**:1679–1688.
24. Mata-Marin JA, Smeke AE, Rodriguez MR, Chávez-García M, Banda-Lara MI, Rios AM, *et al*. **Effectiveness and risk factors for virological outcome of raltegravir-based therapy for treatment-experienced HIV-infected patients.** *Drugs R D* 2017; **17**:225–231.
25. Wittkop L, Breilh D, Da Silva D, Duffau P, Mercié P, Raymond I, *et al*., ANRS CO3 Aquitaine Cohort. **Virological and immunological response in HIV-1-infected patients with multiple treatment failures receiving raltegravir and optimized background therapy, ANRS CO3 Aquitaine Cohort.** *J Antimicrob Chemother* 2009; **63**:1251–1255.
26. Capetti A, Landonio S, Meraviglia P, Di Biagio A, Lo Caputo S, Sterrantino G, *et al*. **96 Week follow-up of HIV-infected patients in rescue with raltegravir plus optimized backbone regimens: a multicentre Italian experience.** *PLoS One* 2012; **7**:e39222.
27. Eron JJ Jr, Rockstroh JK, Reynes J, Andrade-Villanueva J, Ramalho-Madruga JV, Bekker LG, *et al*. **Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 noninferiority trial.** *Lancet Infect Dis* 2011; **11**:907–915.
28. Boretzki J, Wolf E, Wiese C, Noe S, Balogh A, Meurer A, *et al*. **Highly specific reasons for nonadherence to antiretroviral therapy: results from the German adherence study.** *Patient Prefer Adherence* 2017; **11**:1897–1906.
29. Langebeek N, Gisolf EH, Reiss P, Vervoort SC, Hafsteinsdóttir TB, Richter C, *et al*. **Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis.** *BMC Med* 2014; **12**:142.
30. Gallant J, Lazzarin A, Mills A, Orkin C, Podzamczer D, Tebas P, *et al*. **Bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled noninferiority trial.** *Lancet* 2017; **390**:2063–2072.
31. Eron JJ, Orkin C, Gallant J, Molina JM, Negredo E, Antinori A, *et al*., AMBER study group. **A week-48 randomized phase-3 trial of darunavir/cobicistat/emtricitabine/tenofovir alafenamide in treatment-naive HIV-1 patients.** *AIDS* 2018; **32**:1431–1442.
32. DeJesus E, Ramgopal M, Crofoot G, Ruane P, LaMarca A, Mills A, *et al*. **Switching from efavirenz, emtricitabine, and tenofovir disoproxil fumarate to tenofovir alafenamide coformulated with rilpivirine and emtricitabine in virally suppressed adults with HIV-1 infection: a randomised, double-blind, multicentre, phase 3b, noninferiority study.** *Lancet HIV* 2017; **4**:e205–e213.
33. Davy-Mendez T, Eron JJ, Brunet L, Zakharova O, Dennis AM, Napravnik S. **New antiretroviral agent use affects prevalence of HIV drug resistance in clinical care populations.** *AIDS* 2018; **32**:2593–2603.