Treatment durability and virological response in treatment-experienced HIV-positive patients on an integrase inhibitor-based regimen: an Australian cohort study

Nicole L. De La Mata^{A,K}, David A. Cooper^A, Darren Russell^{B,C,D}, Don Smith^{E,F}, Ian Woolley^{G,H,I}, Maree O. Sullivan^{A,J}, Stephen Wright^A, and Matthew Law^A

^AKirby Institute, UNSW Australia, Wallace Wurth Building, Sydney, NSW 2052, Australia

^BSchool of Medicine and Dentistry, James Cook University, Townsville, Qld 4811, Australia

^CUniversity of Melbourne, Parkville, Vic. 3010, Australia

^DCairns Sexual Health Service, Cairns, Qld 4870, Australia

^EThe Albion Centre, Sydney, NSW 2010, Australia

^FSchool of Public Health and Community Medicine, UNSW Australia, Sydney, NSW 2052, Australia

^GMonash Health, Infectious Disease, Melbourne, Vic. 3168, Australia

^HMonash Health, Australia Department of Medicine, Melbourne, Vic. 3168, Australia

^IMonash University, Australia Department of Infectious Diseases, Melbourne, Vic. 3800, Australia

^JGold Coast Sexual Health Clinic, Miami, Qld 4215, Australia

Abstract

Background—Integrase inhibitors (INSTI) are a newer class of antiretroviral (ARV) drugs that offer additional treatment options for experienced patients. Our aim is to describe treatment durability and virological outcomes in treatment-experienced HIV-positive patients using INSTI-based regimens.

Methods—All patients in the Australian HIV Observational Database who had received an INSTI-based regimen 14 days as well as previous therapy were included in the study. We defined two groups of treatment-experienced patients: (1) those starting a second-line regimen with INSTI; and (2) highly experienced patients, defined as having prior exposure to all three main ARV classes, nucleoside reverse transcriptase inhibitor, nonnucleoside reverse transcriptase inhibitors and protease inhibitors, before commencing INSTI. Survival methods were used to determine time to viral suppression and treatment switch, stratified by patient treatment experience. Covariates of interest included age, gender, hepatitis B and C co-infection, previous antiretroviral treatment time, patient treatment experience and baseline viral load.

^KCorresponding author. ndelamata@kirby.unsw.edu.au.

Conflicts of interests

None declared.

Results—Time to viral suppression and regimen switching from INSTI initiation was similar for second-line and highly experienced patients. The probability of achieving viral suppression at 6 months was 77.7% for second-line patients and 68.4% for highly experienced patients. There were 60 occurrences of regimen switching away from INSTI observed over 1274.0 person-years, a crude rate of 4.71 (95% CI: 3.66–6.07) per 100 person-years. Patient treatment experience was not a significant factor for regimen switch according to multivariate analysis, adjusting for relevant covariates.

Conclusions—We found that INSTI-based regimens were potent and durable in experienced HIV-positive patients receiving treatment outside clinical trials. These results confirm that INSTI-based regimens are a robust treatment option.

Additional keywords

regimen switch; viral load; time to treatment switch

Introduction

Combination antiretroviral treatment is standard treatment for HIV-positive patients, with most current antiretroviral (ARV) drug regimens containing at least two classes of antivirals.^{1–3} However, treatment options need to be conserved as they may become depleted due to the genetic malleability of the HIV-1 virus.^{4–6} Cross-resistance between ARVs and the development of multidrug resistant viruses has necessitated the development of ARV agents active elsewhere in the lifecycle of the virus.^{7,8} The HIV-1 integrase is an enzyme that allows the viral DNA to integrate into the genome of the host cell. Integrase inhibitors INSTI rapidly reduce viral replication, and are not associated with several toxicities of other drugs.^{4,9,10}

Raltegravir (RAL) was the first integrase inhibitor of its class to be approved by the US Food and Drug Administration for treatment of HIV-1 infection, and became commercially available in 2007.^{11,12} As it used a new mechanism of action it was initially used in patients with drug resistance to other ARV classes. The proportion of patients with an undetectable viral load while undertaking RAL treatment with an optimised background therapy was comparable between treatment-experienced and naïve patients.^{7,13} In 2012, elvitegravir (EVG) was the second drug of the integrase inhibitors to be approved and was more convenient than RAL due to its once daily dosage when delivered in combination with a booster drug, cobicistat, to maintain potency.^{14–16} Dolutegravir (DTG) is the most recent integrase inhibitor approved in 2013. DTG is also administered once daily, does not require a booster drug and has continued to provide efficacy and safety in the treatment of both naïve and experienced HIV patients.^{17–19} Integrase inhibitors therefore present a class of HIV therapy that benefits patients with drug-resistant mutants as well as those experiencing drug-related toxicities.

The aim of this study is to describe the virological response and treatment durability of INSTI-based therapy in treatment-experienced HIV-positive patients receiving clinical care in routine practice outside of clinical trials. Further, we aim to describe whether patient

treatment experience will affect the virological response to an INSTI-based regimen or the occurrence of regimen switching away from an INSTI.

Methods

Data collection and participants

The Australian HIV Observational Database (AHOD) is an observational clinical cohort that began collecting data in 1999. There are 29 sites that transfer data electronically every 6 months. A more detailed description of the methodology for AHOD has been previously described elsewhere.²⁰ Briefly, data collected for AHOD includes basic demographics, hepatitis serology, CD4 and CD8 cell counts, HIV viral load, antiretroviral treatment history and cause of death. Genotypic resistance to ARV drug classes is not collected. Ethical approval for AHOD has been granted by the University of New South Wales Human Research Ethics Committee and other relevant institutional review boards. Written consent is also received from all the participants.

Analysis for the present study included all patients who had been on a treatment regimen containing an INSTI for longer than 14 days and had previously undertaken at least one other treatment regimen. For the purpose of this study, patients were followed from INSTI initiation until March 2014. There were two groups of treatment-experienced patients: (1) highly experienced patients; and (2) second-line patients. Highly experienced patients were those who had experienced all three of the main ARV classes (nucleoside reverse transcriptase inhibitor (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitor (PI)) before the initiation of an INSTI-based regimen. All other patients were considered second-line patients. The two patient treatment experience groups were each further divided into two groups, viral suppression and viral failure, according to the virological response to therapy before INSTI initiation. Patients were considered in the viral failure group if their most recent HIV viral load in the 6 months before initiating the INSTI-based regimen was greater than 50 copies/mL, all other patients were in the viral suppression group.

Statistical analysis

Virological response and regimen switching were assessed for the 36-month period after INSTI initiation. Virological response was measured as the time to viral suppression, defined as a viral load less than or equal to 50 copies/mL during the follow-up period, assessed in patients with viral failure before INSTI initiation. The endpoint for regimen switching was considered as the date when the INSTI-based regimen was changed to a non-INSTI-based regimen. Alterations to dosage or other ARV drugs within the INSTI-based regimen were not considered as a regimen switch. Patients were censored at the earliest date being either the date of death, last clinic visit or 36 months after the INSTI initiation. Kaplan–Meier curves were used to estimate the probability of the virological response and regimen switching from INSTI initiation, stratified by patient treatment experience. A log-rank test was used to determine whether the virological response and regimen switching was significantly different between patient treatment experience groups. The predictor variables used in this analysis were age at INSTI initiation, gender, hepatitis B virus (surface antigen)

co-infection, hepatitis C virus (antibody) co-infection, previous time on antiretroviral treatment (ART), patient treatment experience and viral load at INSTI initiation. All predictor variables were subsequently considered for the multivariate analysis (Cox proportional hazard model) to evaluate the risk factors for a regimen switch away from an INSTI.

Data were analysed using Stata ver. 12 (Stata Corporation, College Station, TX, USA).

Results

Patient characteristics

Of the 3971 AHOD patients, 598 treatment-experienced HIV-positive patients met the eligibility criteria. Of these 199 patients were identified as second-line patients, of whom 51 patients had viral failure before INSTI initiation (viral load >50 copies/mL; Fig. 1). Of the 148 second-line patients that began an INSTI-based regimen with viral suppression, 77 patients had specified a reason for ceasing the previous regimen. Reasons for stopping included toxicity (34%), trial-related (32%), patient or physician decision (20%), comorbidity (6%), treatment failure (4%) and other (unspecified; 4%).

The remaining 399 patients were considered to be highly experienced patients. Of these participants, 139 had viral failure before INSTI initiation (Fig. 1). Of the 260 highly experienced patients that began an INSTI-based regimen with viral suppression, 128 patients specified a reason for ceasing the previous regimen. Reasons for stopping included toxicity (52%), trial-related (4%), patient or physician decision (28%), comorbidity (5%), treatment failure (3%) and other (unspecified; 8%). Most patients initiated a RAL-based regimen ($n = 570$), the remaining patients initiated either a DTG-based ($n = 7$), EVG-based ($n = 3$) or EVG and cobicistat-based ($n = 18$) regimen.

Baseline characteristics of all patients are given in Table 1. Overall, the mode of HIV exposure was mainly through homosexual contact and most patients had previous mono or duo therapy experience. Second-line patients had a younger median age than highly experienced patients. The INSTI-based regimen consisted of three or more ARV classes for 75% of highly experienced patients and 44% of second-line patients. In highly experienced patients, there were 17 unique regimens with three or more ARV classes, whereby the four most initiated INSTI-based regimens were NRTI+PI+INSTI (52%), NRTI+NNRTI+INSTI (13%), NRTI+NNRTI+PI+INSTI (12%) and NNRTI+PI+INSTI (11%). In second-line patients, there were eight unique regimens with three or more ARV classes and the four most initiated INSTI-based regimens were NRTI+PI+INSTI (44%), NRTI+NNRTI+INSTI (22%), NRTI+INSTI+trial drug (16%) and NRTI+NNRTI+PI+INSTI (9%). A majority of patients had begun multiple new ARV drugs with the INSTI-based regimen, with 19% of second-line and 20% of highly experienced patients adding only an INSTI to the previous existing regimen.

Virological response

A total of 51 second-line patients and 139 highly experienced patients were included in the virological response analysis. The most recent viral load result within the 6 months before

switching to an INSTI-based regimen indicated viral failure for all of these patients viral load >50 copies/mL. Further, 31 second-line patients and 95 highly experienced patients had a second viral load test result available from the 6 months before INSTI initiation that also confirmed viral failure. The median days between the most recent viral load result and initiation of the INSTI-based regimen was 33 days (interquartile range: 15–63). The median duration until viral suppression was 69 days for second-line patients and 66 days for highly experienced patients. At 36 months follow up, 67.7% (95% confidence interval (CI): 51.3–84.2) of second-line patients and 61.1% (95% CI: 51.0–71.2) of highly experienced patients experiencing viral failure before INSTI initiation had maintained viral suppression. Comparatively, 86.3% (95% CI: 76.8–95.7) of second-line patients and 74.1% (95% CI: 66.7–81.5) of highly experienced patients experiencing viral suppression before INSTI initiation, had maintained viral suppression at 36 months follow-up.

For second-line patients experiencing viral failure before INSTI initiation the probability of achieving viral suppression at 3 months was 55.4% (95% CI: 41.8–69.9) at 6 months was 77.7% (95% CI: 64.8–88.4) and at 12 months was 90.0% (95% CI: 78.8–96.7). For highly experienced patients experiencing viral failure before INSTI initiation, the probability of achieving viral suppression at 3 months was 56.4% (95% CI: 48.2–65.0), at 6 months was 68.4% (95% CI: 60.3–76.2) and at 12 months was 87.6% (95% CI: 80.8–92.8; Fig. 2). The virological response to the INSTI-based regimen was not significantly different between the patient treatment experience groups (P -value = 0.586).

Regimen switching

All 598 patients had sufficient follow-up data to be included in the regimen switching analysis. The median follow-up from INSTI initiation for second-line patients was 2.1 years and for highly experienced patients was 3.0 years. Overall, there were 60 occurrences of regimen switches away from an INSTI observed over 1274.0 person-years of follow up, a crude rate of 4.71 (95% CI: 3.66–6.07) per 100 person-years (Table 2). Although not significant, the rate of regimen switching was slightly higher in second-line patients, at 5.23 (95% CI: 3.38–8.11) per 100 person-years, than in highly experienced patients, at 4.48 (95% CI: 3.29–6.11) per 100 person-years.

The probability of regimen switching to a non-INSTI-based regimen for second-line patients experiencing viral suppression before INSTI initiation was 5.4% (95% CI: 2.6–11.1%) at 12 months and 3.4% (95% CI: 8.4–21.9%) at 24 months, however those with viral failure before INSTI initiation had a probability of regimen switching of 6.3% (95% CI: 2.1–18.3%) at 12 months and 6.3% (95% CI: 2.1–18.3%) at 24 months. For highly experienced patients, the probability of regimen switching to a non-INSTI-based regimen for those with viral suppression and viral failure before INSTI initiation was 3.8% (95% CI: 2.0–7.1%) and 9.7% (95% CI: 5.8–16.2%) at 12 months and 8.3% (95% CI: 5.3–12.9%), and 10.6% (95% CI: 6.4–17.2%) at 24 months, respectively (Fig. 3). Patient treatment experience did not significantly alter the occurrence of regimen switching to a non-INSTI-based regimen (P -value = 0.778).

Predictive factors of regimen switching

Multivariate analysis did not find a significant association between the occurrence of a regimen switch away from an INSTI and age, hepatitis C virus co-infection, hepatitis C virus co-infection, previous time on ART, patient treatment experience or pre-INSTI viral load. Gender was the only significant factor associated with the occurrence of a regimen switch away from an INSTI, where female patients had a hazard ratio of 2.53 (95% CI: 1.10–5.82) compared with male patients Table 2. Of the 60 patients who altered their regimen away from an INSTI, 27 patients did not give a reason for the switch, 17 patients switched due to patient or physician decision, six patients switched due to trial-related issues and six patients experienced toxicity or treatment failure. Fifty-two patients had a viral load result within the 6-month period before the regimen switch, 28 patients had undetectable viraemia (<50 copies/mL) and 24 patients had detectable viraemia (>50 copies/mL). During the 36-month follow-up period from INSTI initiation, 11 out of the 598 patients died, of which five were second-line patients and six were highly experienced patients. Among these 11 patients, the cause of death included cancer (2), cardiovascular disease (1), renal failure (1), pulmonary disease (1), AIDS (1) and unknown causes (5).

Discussion

Our findings suggest that previous treatment experience of other non-INSTI classes of ARV does not significantly affect the virological response to an INSTI-based regimen. Further, regimen switching away from an INSTI was not significantly affected by the degree of prior patient treatment experience as measured by the number of drug classes. Risk factors associated with the occurrence of a regimen switch away from an INSTI did not suggest that patient treatment experience was significant.

At 12 months, there was a 90.0% and 87.6% probability of achieving undetectable viraemia for second-line and highly experienced patients receiving an INSTI-based regimen with viral failure before INSTI initiation, respectively. Patient treatment experience did not significantly affect the virological response to a regimen containing an INSTI. The high efficacy of INSTIs in patients with previous treatment experience has been shown in numerous clinical trials and cohorts, including BENCHMRK and SALIR (SALvage in Italy with Raltegravir).^{7,10,21–23} In the BENCHMRK studies, 62% of treatment-experienced patients undertaking a RAL-based therapy achieved viral suppression (<50 copies/mL) at week 16.⁷ Additionally, the SALIR observational cohort reported that 92% of the salvage patients undertaking a RAL-based therapy had undetectable viraemia by week 96.²³ Another observational cohort found 64% of patients with documented genotypic resistance to at least one of the three main ARV drug classes reached viral loads less than 50 copies/mL at week 24.¹⁰ As genotypic resistance data was not collected in our database, we are unable to comment on the efficacy of INSTI in treatment-experienced patients with known drug resistances. However, our findings do highlight the potential of INSTI-based regimens to offer effective treatment alternatives for treatment-experienced patients, with the ability to maintain potency despite virological failure under previous regimens.^{24–27}

Patient treatment experience and viral load at INSTI initiation were not significant risk factors for regimen switching. At 36-month follow-up, 90% of second-line and highly

experienced patients remained on an INSTI-based regimen. Likewise in the SALIR-Extension observational study, 77.5% of treatment-experienced patients were still receiving a RAL-based therapy after 4 years follow-up.²⁸ Every 100 person-years, approximately five switches occurred in second-line patients and four switches occurred in highly experienced patients. This rate was much lower than the overall observed rate of ART changes in treatment-experienced patients in AHOD, where around 45 second-line changes and 60 third-line changes occur every 100 person-years.²⁹ However, these rates considered ART change as the addition of any ARV drug to the existing regimen and may overestimate the regimen switches between ARV drug classes.

Six of the 60 patients who had switched regimens reported drug toxicity or treatment failure as the reason for ceasing the INSTI-based regimen. These few reports of adverse events are reflective of the high tolerability of INSTI-based regimens.²⁷ RAL has not been shown to result in serious adverse events and, in comparison with efavirenz, has caused fewer adverse events.³⁰ In BENCHMRK trials, the RAL-based regimens were well tolerated and adverse events were comparable to the placebo group.⁹ Other clinical trials have also shown a low occurrence of discontinuation due to adverse events in both EVG- (3.1%) and RAL-based (4.2%) regimens at week 96.³¹ In the present study, 17 of the 60 patients switched to regimens not containing an INSTI due to patient or physician decision. This may suggest that patients prefer regimens that are more convenient. INSTIs are required to be combined with a background therapy which may not be as convenient as other treatment options and could influence patients or physicians to move away from an INSTI-based regimen, particularly for patients who are responding to treatment.^{21,24,30} Other studies have noted poorer adherence in treatment-experienced patients undertaking a twice-daily RAL-based regimen (65.3%) compared with once-daily EVG-based regimen (78.3%).³¹ Therefore, there may also be a preference to switch to more convenient regimens to potentially achieve better adherence. Despite INSTI-based regimens being well tolerated and unlikely to result in adverse events, there may be a tendency for treatment-experienced patients to switch to regimens that are more convenient.

The multivariate analysis suggested that female patients are 2.5 times more likely to switch away from an INSTI-based regimen compared with male patients. This should be cautiously interpreted as there has been limited evidence to suggest that INSTI-based regimens are less durable in treatment-experienced female patients than male.^{21,23} Instead, it may be reflective of the limitations of this study as female patients were not well represented ($n = 32$) and 95% CI for the hazard ratio is wide. Further research focussed on the durability of INSTI-based regimens for females are needed to confirm a true association. Another limitation was the lack of genotypic drug resistance data for the patients included in the analysis. Genotypic drug resistance data would have allowed for more accurate classification of treatment-experienced patients, particularly as a majority of patients had previous mono or duo therapy experience and therefore were at an increased risk for drug resistance. However, patients were grouped based on previous ARV drug class exposure and viral load at INSTI initiation to account for the potential presence of resistance to drug classes.

We defined viral failure as occurring if a single viral load result was above 50 copies/mL. Many patients experience intermittent episodes of detectable low-level viraemia, known as

'blips', which spontaneously returns to undetectable levels without intervention.³² Relying upon single readings increases the chances of falsely identifying viral failure due to the occurrence of 'blips'. Although we were limited by the data available to verify viral failure with two readings for all patients, most patients with viral failure had a second viral load >50 copies/mL to confirm failure (second-line patients: 61%; highly experienced patients: 68%) and the rate of 'blips' in AHOD has been previously evaluated to be relatively low at 50.3 (95% CI: 46.7–54.1) per 1000 person-years.³³ Further, many other studies prefer to define viral failure at a higher threshold of 400 copies/mL instead of 50 copies/mL as viral load at extremely low levels does rely upon sensitive assays.³⁴ However, our study used data from a developed country with suitable access to sensitive assays and the given definition would be more suitable for defining treatment failure.³⁵

There were also limitations stemming from our study design. We used observational data to evaluate the use of INSTI in treatment-experienced patients. Although observational data can follow large numbers of patients over many years, a major disadvantage is the inability to control for other confounding factors. Randomised clinical trials are advantageous as they are able to reduce the effects of confounding factors by random assignment. However, as previously discussed, our findings are consistent with other randomised clinical trials evaluating INSTI use in treatment-experienced patients. Another disadvantage with cohort studies is the potential for high loss-to-follow-up rates, which can significantly affect the outcome. Loss-to-follow-up rates have previously been evaluated in AHOD and remain relatively low at 9.8 per 100 person-years.³⁶

Treatment-experienced HIV-positive patients are faced with limited further-treatment options as resistance to one or more of the main ARV classes or failure to respond to current alternative treatment options become increasingly common.³⁷ INSTIs are a relatively new class of HIV therapy that are becoming an attractive treatment option for treatment-experienced patients due to their high efficacy, durability and tolerability.^{9,24,38–40} Our study has shown that INSTI-based regimens remain potent and durable in HIV-positive patients outside of clinical trials, regardless of previous treatment experience. This encourages and strengthens the role of INSTI-based regimens as a robust treatment option for treatment-experienced patients.

Acknowledgments

AHOD is funded as part of the Asia Pacific HIV Observational Database, a program of The Foundation for AIDS Research and is supported in part by a grant from the USA National Institutes of Health's National Institute of Allergy and Infectious Diseases Grant No. U01-AI069907 and by unconditional grants from Merck Sharp & Dohme, Gilead Sciences, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen-Cilag, VINSTIV Healthcare.

Appendix

Australian HIV Observational Database contributors asterisks indicate steering committee members in 2014.

New South Wales: D Ellis, General Medical Practice, Coffs Harbour; M Bloch, S Agrawal, T Vincent, Holdsworth House Medical Practice, Darlinghurst; D Allen, JL Little, Holden Street Clinic, Gosford; D Smith, R Hawkins, K Allardice, Lismore Sexual Health & AIDS

Services, Lismore; D Baker*, V Ieroklis, East Sydney Doctors, Surry Hills; DJ Templeton*, CC O'Connor, S Phan, RPA Sexual Health Clinic, Camperdown; E Jackson, K McCallum, Blue Mountains Sexual Health and HIV Clinic, Katoomba; M Grotowski, S Taylor, Tamworth Sexual Health Service, Tamworth; D Cooper, A Carr, F Lee, K Hesse, St Vincent's Hospital, Darlinghurst; R Finlayson, S Gupta, Taylor Square Private Clinic, Darlinghurst; R Varma, J Shakeshaft, Nepean Sexual Health and HIV Clinic, Penrith; K Brown, V McGrath, S Halligan, N Arvela Illawarra Sexual Health Service, Warrawong; L Wray, R Foster, H Lu, Sydney Sexual Health Centre, Sydney; D Couldwell, Parramatta Sexual Health Clinic; DE Smith*, V Furner Albion Street Centre; Clinic 16 – Royal North Shore Hospital, S Fernando; Dubbo Sexual Health Centre, Dubbo; J Watson*, National Association of People living with HIV/AIDS; C Lawrence*, National Aboriginal Community Controlled Health Organisation; B Mulhall*, Department of Public Health and Community Medicine, University of Sydney; M Law*, K Petoumenos*, S Wright*, H McManus*, C Bendall*, M Boyd*, The Kirby Institute, University of NSW. Northern Territory: N Ryder, R Payne, Communicable Disease Centre, Royal Darwin Hospital, Darwin. Queensland: M O'Sullivan, S White, Gold Coast Sexual Health Clinic, Miami; D Russell, S Doyle-Adams, C Cashman, Cairns Sexual Health Service, Cairns; D Sowden, K Taing, K McGill, Clinic 87, Sunshine Coast-Wide Bay Health Service District, Nambour; D Orth, D Youds, Gladstone Road Medical Centre, Highgate Hill; M Kelly, D Rowling, N Latch, Brisbane Sexual Health and HIV Service, Brisbane; B Dickson*, CaraData. South Australia: W Donohue, O'Brien Street General Practice, Adelaide. Victoria: R Moore, S Edwards, R Woolstencroft Northside Clinic, North Fitzroy; NJ Roth*, H Lau, Prahran Market Clinic, South Yarra; T Read, J Silvers*, W Zeng, Melbourne Sexual Health Centre, Melbourne; J Hoy*, K Watson*, M Bryant, S Price, The Alfred Hospital, Melbourne; I Woolley, M Giles*, T Korman, J Williams*, Monash Medical Centre, Clayton. Western Australia: D Nolan, J Robinson, Department of Clinical Immunology, Royal Perth Hospital, Perth. New Zealand: G Mills, C Wharry, Waikato District Hospital Hamilton; N Raymond, K Bargh, Wellington Hospital, Wellington.

AHOD reviewers: D Sowden, J Hoy, L Wray, I Woolley, K Morwood, N Roth, K Choong, CC O'Connor, MA Boyd.

References

1. Daniel V, Susal C, Melk A, Weimer R, Kropelin M, Zimmermann R, et al. Reduction of viral load and immune complex load on CD4+ lymphocytes as a consequence of highly active antiretroviral treatment (HAART) in HIV-infected hemophilia patients. *Immunol Lett.* 1999; 69:283–289. [PubMed: 10482364]
2. Hejdeman B, Lenkei R, Leandersson AC, Hultstrom AL, Wahren B, Sandstrom E, et al. Clinical and immunological benefits from highly active antiretroviral therapy in spite of limited viral load reduction in HIV type 1 infection. *AIDS Res Hum Retroviruses.* 2001; 17:277–286. [PubMed: 11242515]
3. World Health Organization. Geneva: WHO; 2013. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach.
4. Hazuda DJ, Felock P, Witmer M, Wolfe A, Stillmock K, Grobler JA, et al. Inhibitors of strand transfer that prevent integration and inhibit HIV-1 replication in cells. *Science.* 2000; 287:646–650. [PubMed: 10649997]

5. Kumarasamy N, Madhavan V, Venkatesh KK, Saravanan S, Kantor R, Balakrishnan P, et al. High frequency of clinically significant mutations after first-line generic highly active antiretroviral therapy failure: implications for second-line options in resource-limited settings. *Clin Infect Dis*. 2009; 49:306–309. [PubMed: 19522657]
6. Jansson J, Wilson DP, Carr A, Petoumenos K, Boyd MA. Currently available medications in resource-rich settings may not be sufficient for lifelong treatment of HIV. *AIDS*. 2013; 27:1245–1251. [PubMed: 23276809]
7. Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med*. 2008; 359:339–354. [PubMed: 18650512]
8. Sabin CA, Hill T, Lampe F, Matthias R, Bhagani S, Gilson R, et al. Treatment exhaustion of highly active antiretroviral therapy (HAART) among individuals infected with HIV in the United Kingdom: multicentre cohort study. *BMJ*. 2005; 330:695–698. [PubMed: 15749728]
9. Eron JJ, Cooper DA, Steigbigel RT, Clotet B, Gatell JM, Kumar PN, et al. 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. [PubMed: 23664333]
10. Caby F, Valin N, Marcelin AG, Schneider L, Andrade R, Guiguet M, et al. Raltegravir as functional monotherapy leads to virological failure and drug resistance in highly treatment-experienced HIV-infected patients. *Scand J Infect Dis*. 2010; 42:527–532. [PubMed: 20222846]
11. Marcelin AG, Delaugerre C, Beaudoux C, Descamps D, Morand-Joubert L, Amiel C, et al. A cohort study of treatment-experienced HIV-1-infected patients treated with raltegravir: factors associated with virological response and mutations selected at failure. *Int J Antimicrob Agents*. 2013; 42:42–47. [PubMed: 23562640]
12. Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, Andrade-Villanueva JF, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naïve adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet*. 2013; 382:700–708. [PubMed: 23830355]
13. Wirten M, Simon A, Schneider L, Tubiana R, Malet I, Ait-Mohand H, et al. Raltegravir has no residual antiviral activity *in vivo* against HIV-1 with resistance-associated mutations to this drug. *J Antimicrob Chemother*. 2009; 64:1087–1090. [PubMed: 19717396]
14. Shah BM, Schafer JJ, Desimone JA Jr. Dolutegravir: a new integrase strand transfer inhibitor for the treatment of HIV. *Pharmacotherapy*. 2014; 34:506–520. [PubMed: 24347095]
15. Lampiris HW. Elvitegravir: a once-daily, boosted, HIV-1 integrase inhibitor. *Expert Rev Anti Infect Ther*. 2012; 10:13–20. [PubMed: 22149610]
16. Wills T, Vega V. Elvitegravir: a once-daily inhibitor of HIV-1 integrase. *Expert Opin Investig Drugs*. 2012; 21:395–401.
17. Patel DA, Snedecor SJ, Tang WY, Sudharshan L, Lim JW, Cuffe R, et al. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naïve HIV-1-infected patients: a systematic review and network meta-analysis. *PLoS One*. 2014; 9:e105653. [PubMed: 25188312]
18. Fantauzzi A, Turriziani O, Mezzaroma I. Potential benefit of dolutegravir once daily: efficacy and safety. *HIV AIDS*. 2013; 5:29–40.
19. Osterholzer DA, Goldman M. Dolutegravir: a next-generation integrase inhibitor for treatment of HIV infection. *Clin Infect Dis*. 2014; 59:265–271. [PubMed: 24723281]
20. The Australian HIV Observational Database. Rates of combination antiretroviral treatment change in Australia, 1997–2000. *HIV Med*. 2002; 3:28–36. [PubMed: 12059948]
21. Squires KE, Bekker LG, Eron JJ, Cheng B, Rockstroh JK, Marquez F, et al. Safety, tolerability, and efficacy of raltegravir in a diverse cohort of HIV-infected patients: 48-week results from the REALMRK Study. *AIDS Res Hum Retroviruses*. 2013; 29:859–870. [PubMed: 23351187]
22. Rockstroh JK, Lennox JL, DeJesus E, Saag MS, Lazzarin A, Wan H, et al. Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naïve human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. *Clin Infect Dis*. 2011; 53:807–816. [PubMed: 21921224]

23. 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. [PubMed: 22808029]
24. Grinsztejn B, Nguyen BY, Katlama C, Gatell JM, Lazzarin A, Vittecoq D, et al. Safety and efficacy of the HIV-1 integrase inhibitor raltegravir (MK-0518) in treatment-experienced patients with multidrug-resistant virus: a phase II randomised controlled trial. *Lancet*. 2007; 369:1261–1269. [PubMed: 17434401]
25. Wittkop L, Breilh D, Da Silva D, Duffau P, Mercie P, Raymond I, et al. 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. [PubMed: 19336453]
26. Palmisano L. Role of integrase inhibitors in the treatment of HIV disease. *Expert Rev Anti Infect Ther*. 2007; 5:67–75. [PubMed: 17266455]
27. Hughes A, Barber T, Nelson M. New treatment options for HIV salvage patients: an overview of second generation PIs, NNRTIs, integrase inhibitors and CCR5 antagonists. *J Infect*. 2008; 57:1–10. [PubMed: 18556070]
28. Capetti A, Meraviglia P, Landonio S, Sterrantino G, Di Biagio A, Lo Caputo S, et al. Four years data of raltegravir-based salvage therapy in HIV-1-infected, treatment-experienced patients: the SALIR-E Study. *Int J Antimicrob Agents*. 2014; 43:189–194. [PubMed: 24315315]
29. Australian HIVOD. Rates of combination antiretroviral treatment change in Australia, 1997–2000. *HIV Med*. 2002; 3:28–36. [PubMed: 12059948]
30. Markowitz M, Nguyen BY, Gotuzzo E, Mendo F, Ratanasuwan W, Kovacs C, et al. Rapid and durable antiretroviral effect of the HIV-1 Integrase inhibitor raltegravir as part of combination therapy in treatment-naïve patients with HIV-1 infection: results of a 48-week controlled study. *J Acquir Immune Defic Syndr*. 2007; 46:125–133. [PubMed: 17721395]
31. Elion R, Molina JM, Ramon Arribas Lopez J, Cooper D, Maggiolo F, Wilkins E, et al. A randomized phase-3 study comparing once-daily elvitegravir with twice-daily raltegravir in treatment-experienced subjects with HIV-1 infection: 96-week results. *J Acquir Immune Defic Syndr*. 2013; 63:494–497. [PubMed: 23807156]
32. Nkoa Onana DF, Mewoli B, Ouattara DA. Excitability in the host–pathogen interactions of HIV infection and emergence of viral load blips. *J Theor Biol*. 2013; 317:407–417. [PubMed: 23108210]
33. Kanapathipillai R, McManus H, Kamarulzaman A, Lim PL, Templeton DJ, Law M, et al. The Significance of HIV ‘blips’ in resource-limited settings: is it the same? Analysis of the Treat Asia HIV Observational Database (TAHOD) and the Australian HIV Observational Database (AHOD). *PLoS One*. 2014; 9:e86122. [PubMed: 24516527]
34. Verhofstede C, Van Wanseele F, Reynaerts J, Mangelschots M, Plum J, Franssen K. Viral load assay sensitivity and low level viremia in HAART treated HIV patients. *J Clin Virol*. 2010; 47:335–339. [PubMed: 20138803]
35. Vrijens B, Goetghebeur E, de Klerk E, Rode R, Mayer S, Urquhart J. Modelling the association between adherence and viral load in HIV-infected patients. *Stat Med*. 2005; 24:2719–2731. [PubMed: 16118813]
36. McManus H, Petoumenos K, Brown K, Baker D, Russell D, Read T, et al. Loss to follow-up in the Australian HIV Observational Database. *Antivir Ther*. 2014; 20:731–741. [PubMed: 25377928]
37. Lagnese M, Daar ES. Antiretroviral regimens for treatment-experienced patients with HIV-1 infection. *Expert Opin Pharmacother*. 2008; 9:687–700. [PubMed: 18345948]
38. Katlama C, Murphy R. Emerging role of integrase inhibitors in the management of treatment-experienced patients with HIV infection. *Ther Clin Risk Manag*. 2009; 5:331–340. [PubMed: 19536321]
39. Steigbigel RT, Cooper DA, Teppler H, Eron JJ, Gatell JM, Kumar PN, et al. Long-term efficacy and safety of raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. *Clin Infect Dis*. 2010; 50:605–612. [PubMed: 20085491]

40. Correll T, Klibanov OM. Integrase inhibitors: a new treatment option for patients with human immunodeficiency virus infection. *Pharmacotherapy*. 2008; 28:90–101. [PubMed: 18154479]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Fig. 1.
Patient selection and inclusion for the analyses.

Fig. 2.

Time to viral suppression from integrase inhibitor (INSTI) initiation for those with viral failure at INSTI initiation, stratified by patient treatment experience. ^τLog rank test.

Fig. 3. Probability of switching from an integrase inhibitor (INSTI)-based regimen to a non-INSTI-based regimen, by patient treatment experience and viral load at INSTI initiation. (a) Regimen switches for patients without viral failure at INSTI initiation. (b) Regimen switches for patients with viral failure at INSTI initiation. ‡ Log rank test.

Table 1
Demographic overview of the treatment-experienced patients starting an integrase inhibitor (INSTI)-based regimen

	Second-line				Highly experienced			
	Viral suppression		Viral failure		Viral suppression		Viral failure Salvage	
	n	%	n	%	n	%	n	%
Age								
30	6	4	2	4	1	<0.4	0	NA
31–40	28	19	6	12	17	7	10	7
41–50	56	38	23	45	90	35	62	45
51+	58	39	20	39	152	58	67	48
Median [IQR]	47.8	[41.4, 54.5]	48.1	[42.2, 53.4]	53.3	[46.9, 60.7]	50.1	[45.5, 55.0]
Sex								
Female	6	4	2	4	16	6	8	6
Male	142	96	49	96	243	93	131	94
Transgender	0	NA	0	NA	1	<0.4	0	NA
Mode of HIV exposure								
Homosexual contact	120	81	37	73	207	80	110	79
Heterosexual contact	23	16	10	20	28	11	15	11
IDU	2	1	0	NA	17	7	8	6
Other/Unknown	3	2	4	8	8	3	6	4
HCV (ever)								
No/not tested	131	89	47	92	225	87	121	87
Yes	17	11	4	8	35	13	18	13
HBV sAg (ever)								
No/not tested	145	98	48	94	244	94	138	99
Yes	3	2	3	6	16	6	1	1
Total time on treatment (years)								
0–5	86	58	29	57	24	9	23	17
6–10	36	24	10	20	60	23	22	16
>10	26	18	12	24	176	68	94	68

	Second-line				Viral suppression				Viral failure				Viral suppression				Viral failure Salvage			
	Viral suppression		Viral failure		Viral suppression		Viral failure		Viral suppression		Viral failure		Viral suppression		Viral failure		Viral suppression		Viral failure	
	n = 148		n = 51		n = 260		n = 139													
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Median [IQR]	4.4	[2.1, 8.8]	3.8	[1.2, 9.6]	12.7	[9.3, 15.9]	11.8	[8.6, 14.0]												
CD4 at INSTI initiation (cells/ μ l)																				
200	7	5	14	27	21	8	41	30												
201–350	11	7	12	24	34	13	35	25												
351–500	27	18	13	25	37	14	29	21												
501	72	49	12	24	115	44	34	24												
Missing	31	21	0	NA	53	20	0	NA												
Median [IQR]	572.0	[440.0, 778.0]	340.0	[190.0, 480.0]	540.0	[330.0, 792.0]	330.0	[180.0, 500.0]												
Viral load at INSTI initiation (copies/mL)																				
50	111	75	0	NA	200	77	0	NA												
51–10 000	0	NA	25	49	0	NA	85	61												
10 001	0	NA	26	51	0	NA	54	39												
Missing	37	25	0	NA	60	23	0	NA												
Median [IQR]	40.0	[37.0, 50.0]	18700.0	[375.0, 63000.0]	44.5	[39.0, 50.0]	5290.0	[600.0, 57600.0]												
Mono/duo therapy past																				
Yes	62	42	23	45	222	85	110	79												
No	86	58	28	55	38	15	29	21												
Year of HIV diagnosis																				
1990	23	16	11	22	115	44	56	40												
1990–1999	38	26	9	18	115	44	65	47												
2000	73	49	26	51	22	8	15	11												
Missing	14	9	5	10	8	3	3	2												
Year of ART initiation																				
1996–1999	37	25	17	33	217	83	116	83												
2000–2006	45	30	14	27	33	13	10	7												
2007–2013	66	45	20	39	10	4	13	9												

IDU, injecting drug use; IQR, interquartile range; HCV, hepatitis C virus co-infection; HBVsAG, hepatitis B virus (surface antigen) co-infection; ART, antiretroviral therapy; NA, not applicable

Table 2
Risk factors associated with regimen switching away from an integrase-inhibitor (INSTI)-based regimen

	Treatment switches	Person-years (pys)	Rate (per 100 pys)	95% CI	HR	Multivariate 95% CI	P
Total	598	60	1274.0	4.7	3.7, 6.1		
Age at INSTI initiation (years)							
30	9	1	14.9	6.7	1.0, 47.6	0.80	0.10, 6.65
31–40	61	5	107.3	4.7	1.9, 11.2	1	0.834
41–50	231	24	495.0	4.9	3.3, 7.2	1.18	0.47, 2.95
51+	297	30	656.9	4.6	3.2, 6.5	1.10	0.43, 2.84
Gender							
Male	566	53	1212.6	4.4	3.3, 5.7	1	0.842
Female	32	7	61.5	11.4	5.4, 23.9	2.53	1.10, 5.82
HBV surface antigen Co-infection							
Negative/not tested	575	58	1221.9	4.8	3.7, 6.1	1	0.029
Positive	23	2	52.2	3.8	1.0, 15.3	1.03	0.48, 2.22
HCV antibody co-infection							
Negative/not tested	524	52	1120.9	4.6	3.5, 6.1	1	0.941
Positive	74	8	153.1	5.2	2.6, 10.5	1.05	0.27, 4.11
Previous time on ART							
Per year					1.01	0.94, 1.07	0.844
Patient experience							
Second-line	199	20	382.1	5.2	3.4, 8.1	1	
Highly experienced	399	40	891.9	4.5	3.3, 6.1	0.79	0.39, 1.58
Viral load at INSTI initiation							
Failure (>50 copies/mL)	190	19	437.1	4.4	2.8, 6.8	1	0.500
Suppressed (≤ 50 copies/mL)	311	39	649.0	6.0	4.4, 8.2	1.30	0.75, 2.28
Missing	97	2	187.9	1.1	0.3, 4.3		0.351

Global *P*-value for the age at INSTI initiation is a test for trend.

pys, person years; CI, confidence interval; HR, hazard ratio; HBV, hepatitis B virus co-infection; HCV, hepatitis C virus co-infection; ART, antiretroviral therapy