ORIGINAL PAPER

Clinical experience with dolutegravir: efficacy, safety, tolerability

Isabel Furtado*, Sofia R. Valdoleiros*, Joana Fragoso, Olga Vasconcelos, Maria João Gonçalves, Rui Sarmento-Castro

Department of Infectious Diseases, Centro Hospitalar Universitário do Porto, Porto, Portugal

*These authors contributed equally to this work.

Abstract

Introduction: Dolutegravir (DTG) is an effective antiretroviral drug, associated with rapid virologic responses. Intermittent viremia has been linked to a higher risk of virologic failure and immune activation.

Material and methods: A retrospective, observational study of human immunodeficiency virus type 1 (HIV-1) infected adults who have started DTG between May 2015 and May 2017 was conducted, aiming to evaluate virologic responses. Baseline, 4-, 12-, 24-, and 48-week data were analyzed, including incidence of blips and low-level viremia (LLV), immunological progression and tolerability. The population was divided into three groups, including antiretroviral treatment (ART)-naïve, ART-experienced without virological failure (HIV-RNA < 200 copies/ml) at switch to DTG, and ART-experienced with virological failure (HIV-RNA ≥ 200 copies/ml) at switch to DTG.

Results: Within the 227-patient population, 55 (24.2%) were ART-naïve and 172 (75.7%) switched from other regimens. Virologic suppression (< 50 copies/ml) at 48-week was observed in 92.7%, 88.4%, and 75% of naïve, ART-experienced without virological failure at switch, and ART-experienced with virological failure at switch patients, respectively. During follow-up, 4.9% of ART-experienced without virological failure patients had blips above 50 copies/ml, and 0.6% of them maintained LLV above 50 copies/ml.

Conclusions: The use of dolutegravir in naïve patients was associated with a 92.7% rate of viral suppression at week 48. Experienced non-failing patients rarely developed intermittent viremia above 50 copies/ml.

HIV AIDS Rev 2022; 21, 1: 10-16
DOI: https://doi.org/10.5114/hivar.2022.112580

Key words: dolutegravir, HIV, antiretroviral agents, HIV integrase strand-transfer inhibitors, low-level viremia, viral blips, virologic failure.

Introduction

Dolutegravir (DTG) is an antiretroviral drug of the integrase strand-transfer inhibitor (INSTI) class, approved for human immunodeficiency virus (HIV) treatment in Portugal since early 2015. Due to its efficacy, high genetic barrier, favorable pharmacokinetics, safety profile, and few drug interactions [1-3], along with its use in a single-tablet regimen, absence of boosting, and food-independent absorption [4], DTG has become one of the recommended and most used drugs for HIV treatment.

Address for correspondence: Dr. Isabel Furtado, Department of Infectious Diseases, Centro Hospitalar Universitário do Porto, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal, e-mail: isabelfurtadops@gmail.com

Article history:
Received: 08.09.2020
Received in revised form: 05.04.2021
Accepted: 07.04.2021
Available online: 10.01.2022

DTG is effective for treatment of both antiretroviral treatment (ART) naïve and experienced patients, and is now a part of first-line therapies for ART-naïve patients, according to most of international recommendations [5-7]. For ART-experienced patients, with evidence of genotypic resistance to other integrase inhibitors, it appears to be as effective if given twice daily [8].

Clinical trials and real-life cohorts show that DTG usually has few side effects, and is normally better tolerated than most of other antiretrovirals [2, 3, 8-11]. Although neuropsychiatric, gastrointestinal symptoms, and rash are the most common side effects reported in real-life cohorts, discontinuation rates are low, varying between 4% to 8% [1, 12, 13].

DTG can also be associated with biochemical effects, of which creatinine elevation is the most common, yet not associated with a real reduction in glomerular function [14]. Transaminase elevation, neutropenia, and increments in glycemia are also described. DTG displays a favorable neutral metabolic profile [15,16], with lower rise of total cholesterol, low-density lipoprotein cholesterol, and triglycerides when compared to efavirenz and boosted protease inhibitors (PI) [17].

The main goal of HIV treatment is the suppression of peripheral viremia, therefore reducing HIV-related morbidity and mortality at all stages of HIV infection [6]. Maximal and durable suppression of HIV viremia delays or prevents the selection of drug-resistance mutations, preserves or improves CD4+ T-lymphocyte cell number, reduces or prevents HIV transmission, and may also decrease inflammation and immune activation, believed to contribute to higher rates of cardiovascular and other end-organ damage [6]. Viral blips are isolated low-level detectable HIV RNA that occur during long-term monitoring of patients on ART with a previously suppressed viral load (VL) [6,18]. Most viral blips are not clinically significant. However, several studies suggest that patients with viral blips may be at increased risk for virologic failure [19-23]. On the other hand, low-level viremia (LLV), defined as low repetitive measurable plasma viremia (< 200 copies/ml), has been shown to be associated with a higher risk of resistance [24], of immune activation [24] and persistence of inflammatory status [25-31], which is associated with metabolic disorders, cardiovascular disease, bone complications, neurocognitive decline, and frailty [32-34]. However, the significance of intermittent viremia is still controversial and there is currently no consensus on the optimal management of LLV, with most guidelines relying on expert opinion [35].

Material and methods

This retrospective, observational study was conducted among HIV-1-infected adults (older than 18 years of age), who started DTG between May 2015 and May 2017. Patients were identified through our hospital's pharmacy registries, and data were collected by consultation of medical records.

The following data were collected: 1) population demographics, including age, gender, ethnicity, mode of acquisition of the infection; 2) comorbidities, such as other viral infections (hepatitis C, hepatitis B), previous cardiovascular, renal or bone disease, and previous dyslipidemia; 3) outcome, including viral response, CD4+ T-lymphocyte cell count, creatinine, transaminases, cholesterol and triglycerides at week 0, 4, 12, 24 and 48, as well as adherence to treatment, tolerability, side effects, and other relevant outcomes.

Patients were categorized into three groups: 1) naïve to treatment; 2) treatment-experienced without virological failure at switch to DTG (VL < 200 copies/ml), and 3) ART-experienced with virological failure at switch (VL ≥ 200 copies/ml).

Patients with irregular or unknown adherence to treatment, transferring care from or to other centers during follow-up, with less than 50% of clinical or analytic evaluations, and with major events (such as cancer) capable of influencing outcome values were excluded from the study.

Viral blips were defined as isolated and transient low-level increases in VL above 50 copies/ml that were preceded and followed by undetectable viremia. LLV was defined as low, persistent, measurable plasma viremia, above 50 and under 200 copies/ml.

Statistical analysis was performed with IBM SPSS Statistics® software, version 25 (IBM Co., NY, USA).

Results

Baseline characteristics

A total of 292 patients were started on DTG, of which 65 were excluded (Figure 1). Of the 227 included patients, 161

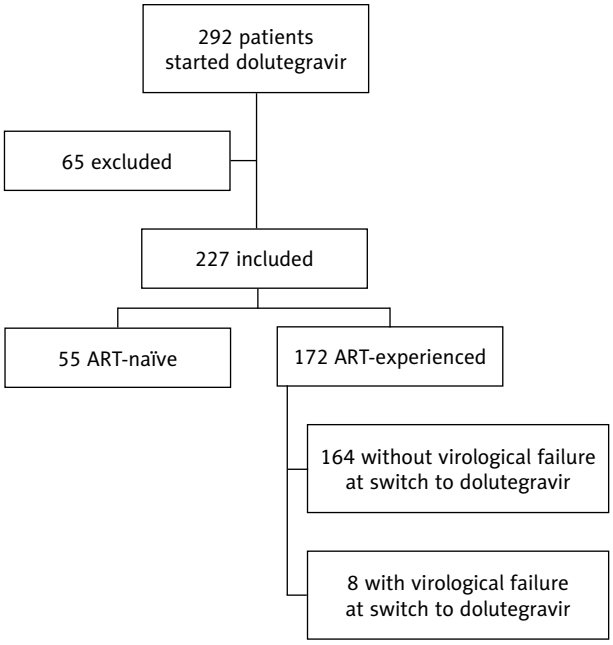

Figure 1. Included and excluded patients of the study

Table 1. Baseline characteristics of antiretroviral therapy (ART)-naïve, ART-experienced without virological failure at switch, and ART-experienced with virological failure at switch patients

Factor	ART-naïve patients (*n* = 55), *n* (%)	ART-experienced without virological failure at switch patients (*n* = 164), *n* (%)	ART-experienced with virological failure at switch patients (*n* = 8), *n* (%)	Total population (*n* = 227), *n* (%)
Gender				
Male	41 (74.5)	114 (69.5)	6 (75.0)	161 (70.9)
Female	14 (25.5)	50 (30.5)	2 (25.0)	66 (29.1)
Ethnicity				
White European	48 (87.3)	162 (98.8)	7 (87.5)	217 (95.6)
African Black	4 (7.3)	1 (0.6)	1 (12.5)	6 (2.6)
Asian	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.4)
Arabic	1 (1.8)	0 (0.0)	0 (0.0)	1 (0.4)
Unknown	1 (1.8)	1 (0.6)	0 (0.0)	2 (0.9)
Routes of HIV transmission				
IVDU	3 (5.5)	54 (32.9)	4 (50.0)	61 (26.9)
Heterosexual	25 (45.5)	53 (32.3)	3 (37.5)	81 (35.7)
MSM	19 (34.5)	20 (12.2)	0 (0.0)	39 (17.1)
Bisexual	0 (0.0)	2 (1.2)	0 (0.0)	2 (0.8)
Transfusion	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.4)
Vertical	0 (0.0)	1 (0.6)	1 (12.5)	2 (0.8)
Unknown	8 (14.5)	33 (20.1)	0 (0.0)	41 (18.1)
CDC stage				
A	37 (67.3)	67 (40.8)	3 (37.5)	107 (47.1)
B	7 (12.7)	19 (11.6)	1 (12.5)	27 (11.9)
C	6 (10.9)	39 (23.8)	2 (25.0)	47 (20.7)
Unknown	5 (9.1)	39 (23.8)	1 (12.5)	46 (20.2)
Viral co-infection				
Anti-HCV positive	3 (5.6)	59 (40.4)	4 (57.1)	66 (31.9)
HBsAg-positive	0 (0.0)	4 (2.8)	0 (0.0)	4 (1.9)
Cardiovascular disease				
Yes	4 (7.3)	50 (30.5)	1 (12.5)	55 (24.2)
No	48 (87.3)	101 (61.6)	6 (75.0)	155 (68.3)
Unknown	3 (5.4)	13 (7.9)	1 (12.5)	17 (7.5)
Kidney disease				
Yes	2 (3.6)	32 (19.5)	1 (12.5)	35 (15.4)
No	50 (90.9)	119 (72.6)	7 (87.5)	176 (77.5)
Unknown	3 (5.5)	13 (7.9)	0 (0)	16 (7.1)
Bone disease				
Yes	3 (5.5)	27 (16.5)	1 (12.5)	31 (13.7)
No	48 (87.3)	124 (75.6)	6 (75.0)	178 (78.4)
Unknown	4 (7.3)	13 (7.9)	1 (12.5)	18 (7.9)
Dyslipidemia				
Yes	5 (9.1)	72 (43.9)	2 (25.0)	79 (34.8)
No	46 (83.6)	81 (49.4)	5 (62.5)	132 (58.1)
Unknown	4 (7.3)	11 (6.7)	1 (12.5)	16 (7.1)

ART – antiretroviral therapy, IVDU – intravenous drug users, MSM – men who have sex with men, HIV – human immunodeficiency virus, HCV – hepatitis C virus

(70.9%) were males and 66 (29.1%) were females. The mean age was 45.9 (range, 19-80) years old, and most of the patients were Caucasian European (95.6%). Eighty-one patients (35.7%) were heterosexual, 61 (26.9%) were intravenous drug users, and 39 (17.1%) were men who have sex with men (MSM).

Concerning co-morbidities, 14 (6.8%) patients had active hepatitis C virus (HCV) co-infection, and 38 (18.4%) had past HCV infection. Only four (1.9%) patients had chronic hepatitis B virus (HBV) co-infection; 11 (5.3%) had an isolated HBc antibody. Fifty-five (24.2%) cases presented with a cardiovascular disease, 35 (15.4%) had a kidney disease, and 31 (13.7%) had a bone disease before the treatment. Dyslipidemia prior to starting DTG was present in 79 patients (34.8%). Other baseline characteristics of the population are depicted in Table 1.

Clinical outcomes in antiretroviral treatment-naïve patients

Within the 227-patient cohort, 55 were naïve to treatment, of which 44 (80%) were started on regimens with abacavir/lamivudine (ABC/3TC), and nine (16.4%) with emtricitabine/tenofovir disoproxil (FTC/TDF). Two patients started other regimens (DTG plus darunavir/ritonavir and DTG plus darunavir/ritonavir plus zidovudine/lamivudine). Baseline mean CD4+ cell count (428 cells/ml) increased to 775 cells/ml by week 48 (Figure 2). Baseline mean HIV-1 RNA VL was 568,573 copies/ml. By week 4, 21 patients showed undetectable VL < 50 copies/ml, and four patients had HIV-1 VL > 200 copies/ml. By week 48, 92.7% of the patients had HIV-1 VL < 50 copies/ml (Figure 3). Of the 26 patients with a baseline HIV-1 VL over 100,000 copies, only three patients presented detectable VL above 50 copies/ml by week 48. Fifteen of the 26 patients were started with regimens containing ABC/3TC. During the 48-week follow-up, no patients had viral blips over 50 copies/ml, and none maintained LLV.

Treatment history and clinical outcomes in antiretroviral treatment-experienced without virological failure patients

Of the 172 ART-experienced patients, 164 had VL < 200 copies/ml at switch to DTG. 127 (78%) were previously on regimens that included a NRTI-backbone and nine patients (5.5%) were on NRTI-sparing regimens; the previous ART-regimen of 27 patients was unknown; one patient was taking lamivudine plus darunavir/ritonavir (DRV/r) plus tipranavir. Of the 127 patients who were previously on regimens with a NRTI-backbone, 62 had a regimen with a boosted-PI, 46 had a non-nucleoside reverse-transcriptase inhibitor (NNRTI), and 19 an INSTI. Reasons for switching ART included adverse effects (52.4%), therapy simplification (35.2%), drug-drug interaction (6.7%), and detectable viral load (5.7%).

Of the 164 ART-experienced patients without virological failure who switched to a DTG regimen, 113 (68.9%) started an ABC/3TC backbone and 22 (13.4%) FTC/TDF. A total of 29 patients (17.6%) started NRTI-sparing combinations. Baseline CD4+ T cell count was 734 cells/ml, remaining stable throughout the first 48 weeks, with a slight increase (780 cells/ml) at the end of follow-up (Figure 2). HIV-1 VL was < 50 copies/ml by week 48 in 145 patients (88.4%) (Figure 3). During the 48-week follow-up, 4.9% of the 164 patients had viral blips over 50 copies/ml, and 0.6% maintained LLV.

Treatment history and clinical outcomes in antiretroviral treatment-experienced with virological failure patients

Of the 172 ART-experienced patients, eight had VL ≥ 200 copies/ml at switch to DTG. Of these eight, four

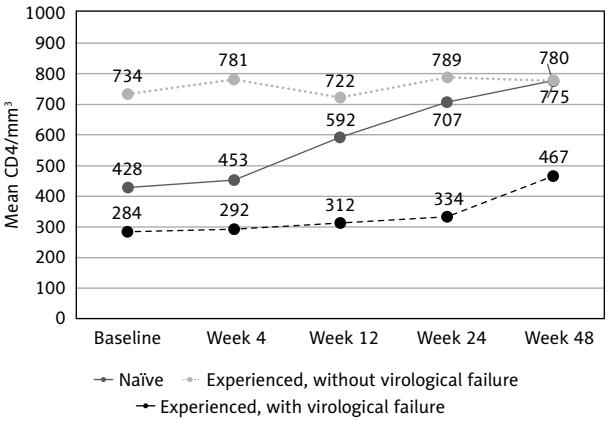

Figure 2. Mean CD4+ T lymphocyte cell count (cells/ml) at baseline, weeks 4, 12, 24 and 48 in antiretroviral therapy (ART)-naïve, ART-experienced without virological failure, and ART-experienced with virological failure at switch patients

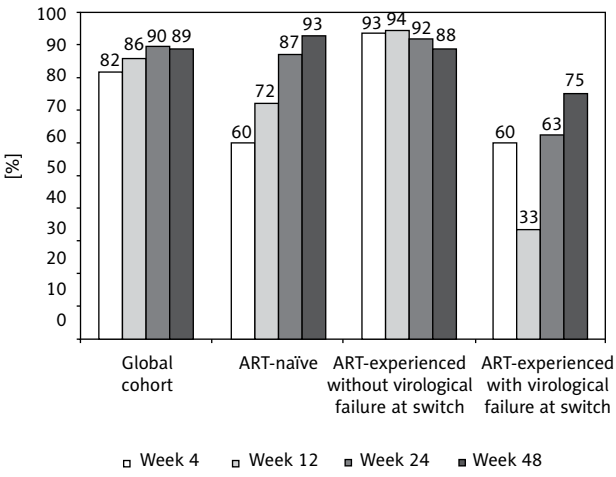

Figure 3. Rates of virologic suppression throughout the follow-up period

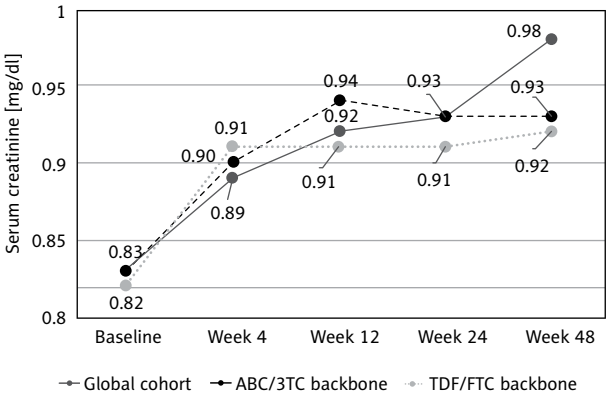

Figure 4. Serum creatinine (mg/dl) evolution from baseline to week 48 in the overall cohort and in the patients on an ABC/3TC backbone or a TDF/FTC backbone

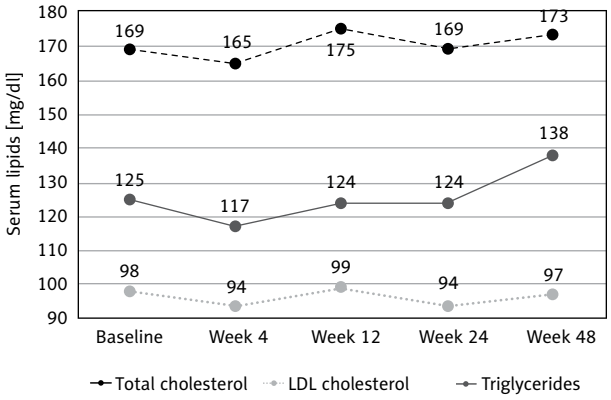

Figure 5. Serum lipids evolution from baseline to week 48 in the total cohort

were previously on NNRTI, two on an INSTI, and one on a NRTI-sparing regimen with etravirine and DRV/r. There was no information regarding previous regimen in one patient.

Three patients started DTG-simple regimens with a NRTI-backbone, including two patients with ABC/3TC and one with FTC/TDF. NNRTI-sparing combinations were started in two patients, with DTG plus DRV/r. The other three patients started DTG in salvage regimens with 3TC + DRV/r, 3TC + ETV + DRV/r, and FTC/TDF + DRV/r.

Baseline mean CD4+ cell count (284 cells/ml) increased to 467 cells/ml by week 48 (Figure 2).

The mean baseline HIV-1 viral load was 87,977 copies/ml. At week 48, six patients (75%) showed VL under 50 copies/ml (Figure 3), two patients (25%) had a mean baseline HIV-1 VL over 100,000 copies/ml, and only one of them had VL < 50 copies/ml by week 48.

Clinical outcomes in patients with VL above 100,000 copies/ml

In our cohort, 26 patients had a baseline VL above 100,000 copies/ml. Twenty-four (92.3%) were naïve to treatment and two (7.7%) were experienced. Of these patients, 23 (88.5%) had VL < 50 copies/ml at week 48. Seventeen (65.4%) of these patients started ABC/3TC-containing regimens, and six (23.1%) started TDF/FTC-containing regimens.

Creatinine profile and metabolic outcomes

Apart from patients with chronic kidney disease prior to ART initiation, mean serum creatinine increased from 0.83 mg/dl at baseline to 0.98 mg/dl at the end of follow-up ($p < 0.05$). All the patients followed the same trend independently of the backbone chosen (Figure 4).

The metabolic profile of the overall cohort showed no significant changes, with a non-significant increase in the serum triglycerides throughout the evaluation period (Figure 5).

Safety and tolerability

Overall, ten patients (4.4%) reported side effects, and three patients reported more than one. Gastrointestinal symptoms were the most frequent side effect ($n = 6$), followed by sleep disturbances ($n = 4$), anxiety ($n = 1$), headache ($n = 1$), and ejaculation disturbance ($n = 1$).

Three patients discontinued DTG due to intolerable side effects, including diarrhea, insomnia, and anxiety leading to suicide attempt. Two patients stopped DTG due to intention of pregnancy, and one patient due to drug-drug interactions (primidone). Two of these patients switched to other INSTI (raltegravir), two patients switched to a PI, and two other patients to a NNRTI.

Discussion and conclusions

DTG has shown to be an effective antiretroviral treatment, with virologic suppression rates at week 48 below 50 copies/ml in more than 90% of patients [1, 2, 12]. The results of naïve and experienced without virological failure at switch patients in our study are consistent with these findings, showing a suppression rate below 50 copies/ml of 92.7% and 88.4% at week 48, respectively. However, in experienced with virological failure patients, the suppression rate < 50 copies/ml was lower (75.0%).

The significance of intermittent viremia is still a matter of debate. On one hand, viral blips are frequent on patients on ART and, in most cases, not clinically significant, although a shorter monitoring time is usually warranted. Blips might only represent methodological inaccuracies and intercurrent infections; even immunizations can cause temporary increases in VL [36-39]. On the other hand, LLV has been linked to a higher risk of virologic failure [19-24] and to immune activation [25-31]. The precise consequences and factors responsible for this phenomenon are still controver-

sial, but persistent inflammation caused by HIV has been linked to metabolic disorders, cardiovascular diseases, bone complications, neurocognitive decline, and frailty [32-34], raising the question of whether the current definition of viral load suppression is sufficient or ideal. We found blip rates of 4.0% and LLV rates of 0.4% in a global cohort. Blip rates of 4.9% were observed in ART-experienced without virological failure patients. In our cohort, intermittent viremia was not associated with specific clinical data or resistance.

In the current study, DTG has also shown to be a safe antiretroviral treatment, with few side effects. It is, however, of notice that one patient discontinued DTG due to a suicide attempt. Dolutegravir-related neuropsychiatric toxicity has been a matter of debate, particularly amongst older HIV patients [40]. A slight increase was observed in the mean serum creatinine from baseline to week 48, which was expected. As previously described [41], metabolic profile showed no significant changes, with only a slight increase in the serum triglycerides throughout evaluation period.

Our study had several limitations. First, it was a retrospective observational study, which relied on clinical registries to evaluate adherence and major clinical events. Secondly, the observation time was only 48 weeks, whereas for evaluation of blips and LLV a longer period would allow further conclusions. Lastly, we did not compare DTG-containing ART regimens with other regimens, which would be essential to determine whether our findings are clinically significant. Therefore, further investigations should focus on a longer observation period and comparing with other ART regimens, ideally in a larger sample size.

Ethical statement

All procedures of the study were in accordance with ethical standards of the responsible committee on human experimentation (institutional and national), and with the Helsinki Declaration of 1975, revised in 2000. The requirement to obtain informed written consent from each individual was waived, as the study was limited to the review of existing medical records. To ensure confidentiality, each case was anonymized with a random identification number.

Conflict of interest

The authors declare no conflict of interest.

References

1. Todd S, Rafferty P, Walker E, et al. Early clinical experience of dolutegravir in an HIV cohort in a larger teaching hospital. Int J STD AIDS 2017; 28: 1074-1081.
2. van Lunzen J, Maggiolo F, Arribas JR, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. Lancet Infect Dis 2012; 12: 111-118.
3. Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. Lancet 2013; 381: 735-743.
4. Comi L, Maggiolo F. Abacavir + dolutegravir + lamivudine for the treatment of HIV. Expert Opin Pharmacother 2016; 17: 2097-2106.
5. Churchill D, Waters L, Ahmed N, et al. British HIV association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015. HIV Med 2016; 17 Suppl 4: s2-s104.
6. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. Available at: https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf.
7. EACS. European AIDS Clinical Society. Guidelines version 9.0. 2017. Available at: https://www.eacsociety.org/media/guidelines_9.0-english.pdf.
8. Eron JJ, Clotet B, Durant J, et al. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. J Infect Dis 2013; 207: 740-748.
9. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med 2013; 369: 1807-1818.
10. Stellbrink HJ, Reynes J, Lazzarin A, et al. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS 2013; 27: 1771-1778.
11. Curtis L, Nichols G, Stainsby C, et al. Dolutegravir: clinical and laboratory safety in integrase inhibitor-naive patients. HIV Clin Trials 2014; 15: 199-208.
12. Cid-Silva P, Llibre JM, Fernández-Bargiela N, et al. Clinical experience with the integrase inhibitors dolutegravir and elvitegravir in HIV-infected patients: efficacy, safety and tolerance. Basic Clin Pharmacol Toxicol 2017; 121: 442-446.
13. Elzi L, Erb S, Furrer H, et al. Adverse events of raltegravir and dolutegravir. AIDS 2017; 31: 1853-1858.
14. Koteff J, Borland J, Chen S, et al. A phase 1 study to evaluate the effect of dolutegravir on renal function via measurement of iohexol and para-aminohippurate clearance in healthy subjects. Br J Clin Pharmacol 2013; 75: 990-996.
15. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naive HIV-1-positive individuals: 96 week results from FLAMINGO. J Int AIDS Soc 2014; 17 (4 Suppl 3): 19490.
16. Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet 2013; 382: 700-708.
17. Patel DA, Snedecor SJ, Tang WY, et al. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naive HIV-1-infected patients: a systematic review and network meta-analysis. PLoS One 2014; 9: e105653.
18. Sungkanuparph S, Overton ET, Seyfried W, Groger RK, Fraser VJ, Powderly WG. Intermittent episodes of detectable HIV viremia in patients receiving nonnucleoside reverse-transcriptase inhibitor-based or protease inhibitor-based highly active antiretroviral therapy regimens are equivalent in incidence and prognosis. Clin Infect Dis 2005; 41: 1326-1332.
19. Gunthard HF, Wong JK, Ignacio CC, et al. Human immunodeficiency virus replication and genotypic resistance in blood and lymph nodes after a year of potent antiretroviral therapy. J Virol 1998; 72: 2422-2428.
20. Nettles RE, Kieffer TL, Simmons RP, et al. Genotypic resistance in HIV-1-infected patients with persistently detectable low-level viremia while receiving highly active antiretroviral therapy. Clin Infect Dis 2004; 39: 1030-1037.

21. Taiwo B, Gallien S, Aga E, et al. Antiretroviral drug resistance in HIV-1-infected patients experiencing persistent low-level viremia during first-line therapy. J Infect Dis 2011; 204: 515-520.
22. Laprise C, de Pokomandy A, Baril JG, Dufresne S, Trottier H. Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. Clin Infect Dis 2013; 57: 1489-1496.
23. Pernas B, Grandal M, Pertega S, et al. Any impact of blips and low-level viraemia episodes among HIV-infected patients with sustained virological suppression on ART? J Antimicrob Chemother 2016; 71: 1051-1055.
24. Maggiolo F, Callegaro A, Cologni G, et al. Ultrasensitive assessment of residual low-level HIV viremia in HAART-treated patients and risk of virological failure. J Acquir Immune Defic Syndr 2012; 60: 473-482.
25. Eastburn A, Scherzer R, Zolopa AR, et al. Association of low level viremia with inflammation and mortality in HIV-infected adults. PLoS One 2011; 6: e26320.
26. Taiwo B, Hunt PW, Gandhi RT, et al. CD8+ T-cell activation in HIV-1-infected patients experiencing transient low-level viremia during antiretroviral therapy. J Acquir Immune Defic Syndr 2013; 63: 101-104.
27. Reus S, Portilla J, Sanchez-Paya J, et al. Low-level HIV viremia is associated with microbial translocation and inflammation. J Acquir Immune Defic Syndr 2013; 62: 129-134.
28. Zoufaly A, Kiepe JG, Hertling S, et al. Immune activation despite suppressive highly active antiretroviral therapy is associated with higher risk of viral blips in HIV-1-infected individuals. HIV Med 2014; 15: 449-457.
29. Ruggiero A, Cozzi-Lepri A, Beloukas A, et al. Factors associated with persistence of plasma HIV-1 RNA during long-term continuously suppressive firstline antiretroviral therapy. Open Forum Infect Dis 2018; 5: ofy032.
30. Ryscavage P, Kelly S, Li JZ, Harrigan PR, Taiwo B. Significance and clinical management of persistent low-level viremia and very-low-level viremia in HIV-1-infected patients. Antimicrob Agents Chemother 2014; 58: 3585-3598.
31. Yukl SA, Gianella S, Sinclair E, et al. Differences in HIV burden and immune activation within the gut of HIV-positive patients receiving suppressive antiretroviral therapy. J Infect Dis 2010; 202: 1553-1561.
32. Nasi M, De Biasi S, Gibellini L, et al. Ageing and inflammation in patients with HIV infection. Clin Exp Immunol 2017; 187: 44-52.
33. Duprez DA, Neuhaus J, Kuller LH, et al. Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. PLoS One 2012; 7: e44454.
34. Margolick JB, Bream JH, Martinez-Maza O, et al. Frailty and circulating markers of inflammation in HIV+ and HIV– men in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr 2017; 74: 407-417.
35. Esber A, Polyak C, Kiweewa F, et al. Persistent low-level viremia predicts subsequent virologic failure: is it time to change the third 90? Clin Infect Dis 2019; 69: 805-812.
36. Jones LE, Perelson AS. Transient viremia, plasma viral load, and reservoir replenishment in HIV-infected patients on antiretroviral therapy. J Acquir Immune Defic Syndr 2007; 45: 483-493.
37. Easterbrook PJ, Ives N, Waters A, et al. The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to < 400 copies/ml. AIDS 2002; 16: 1521-1527.
38. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. AIDS 2004; 18: 2075-2079.
39. Kolber MA, Gabr AH, De La Rosa A, et al. Genotypic analysis of plasma HIV-1 RNA after influenza vaccination of patients with previously undetectable viral loads. AIDS 2002; 16: 537-542.
40. Elliot ER, Wang X, Singh S, et al. Increased dolutegravir peak concentrations in people living with human immunodeficiency virus aged 60 and over, and analysis of sleep quality and cognition. Clin Infect Dis 2019; 68: 87-95.
41. Quercia R, Roberts J, Martin-Carpenter L, Zala C. Comparative changes of lipid levels in treatment-naive, HIV-1-infected adults treated with dolutegravir vs. efavirenz, raltegravir, and ritonavir-boosted darunavir-based regimens over 48 weeks. Clin Drug Investig 2015; 35: 211-219.