Outcomes of Heavily Experienced HIV-Infected Patients Receiving Salvage Raltegravir-Based Therapy

Jesús Enrique Patiño Escarcina (gsus.patino@gmail.com)
Federal University of Bahia: Universidade Federal da Bahia https://orcid.org/0000-0003-2948-5550
Eduardo Martins Netto
Federal University of Bahia: Universidade Federal da Bahia
Carlos Brites
Federal University of Bahia: Universidade Federal da Bahia

Research Article

Keywords: Raltegravir, Salvage therapy, Treatment experienced patients

Posted Date: February 28th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-757669/v2

Abstract

Objectives

To assess real-life virologic success, long-term survival, and adverse events in treatment-experienced patients initiating either raltegravir or other third-line drugs (darunavir/ritonavir, maraviroc or etravirine) for salvage regimens in a Brazilian cohort of heavily treated patients.

Results

We included 168 patients initiating salvage regimens, 123 on raltegravir and 45 on other drugs (darunavir/ritonavir, maraviroc or etravirine). Of these, 90 patients were matched by Propensity score (PS) methods to account for clinical differences at the time of the switch from failing ART regimens, 45 patients from each group. During follow-up, virologic suppression (PVL<50 copies/mL) was similar for both groups (77.8% vs. 82.2%, p=0.73). During a mean follow-up of 1.09 (SD = 0.32) years, mortality rates (4.04 vs 6.18 persons per 100 person-years; p=0.67), drug toxicity (0.00 vs 2.06 persons per 100 person-years; p=0.49), treatment interruption (8.07 vs 0.00 persons per 100 person-years; p=0.06), virologic failure (2.02 vs 4.12 persons per 100 person-years; p=0.61) and loss of follow-up (6.05 vs 4.12 persons per 100 person-years; p=0.70) were similar for both groups. Our findings suggest similar survival and virologic success rates for raltegravir and other drugs for salvage regimens, with similar drug toxicity rates, treatment interruption, virologic failure, and loss of follow-up.

Introduction

Effective antiretroviral therapy (ART) increases survival and decreases the risk of AIDS-related illness [1–4]. Nevertheless, nearly 15% of patients fail to achieve virologic suppression [5–7] leading to treatment failure or resistance to ART [8], limiting options for further therapy [9]. Factors such as comorbidities, tolerability, adherence, and cross-resistance within antiretrovirals (ARVs) determine treatment success in heavily treatment-experienced patients [10–17]. The introduction of new ARVs such as fusion inhibitors, new boosted protease inhibitors, CCR5 antagonists, and recently integrase inhibitors, improve success in treatment-experienced patients [18–21]. However, these agents differ in their tolerability, their toxicity and their efficacy to maintain virologic suppression. There is limited information on real-life experience with these agents, and the construction of suitable 'salvage' regimens for heavily experienced patients remains a complex and challenging issue worldwide [14, 22–25].

The Brazilian Unified Health System (*Sistema Único de Saúde*, SUS) and the national AIDS Program provide free access to ART and establish guidelines for their use [26]. Raltegravir is an option for salvage regimens [26, 27], as it demonstrated its efficacy, tolerability and safety profile for treatment-experienced patients under optimal conditions [21, 28–31]. However, raltegravir has a low genetic barrier to resistance [32], and treatment interruptions could affect its efficacy [33, 34]. This study aimed to assess real-life

virologic success, long-term survival, and adverse events in treatment-experienced patients initiating either raltegravir or other third-line drugs for salvage regimens.

Methods

Patients and setting

The Complexo Hospitalar Prof. Edgard Santos (COM-HUPES) at the Federal University of Bahia (UFBA) is a referral center for people with HIV in Salvador, Brazil. This retrospective study was conducted from March 2008 to December 2016, on adults (>18 years old), with virologic failure (two consecutive HIV RNA tests >1,000 copies/ml after at least six months of continuous therapy) initiating salvage regimens after a genotypic antiretroviral resistance test (GRT). Salvage regimens prescription took into consideration the genotypic resistance testing, treatment history, toxicity or allergy to ARV, and were based on third-line ARV according to Brazilian guidelines (raltegravir, darunavir/ritonavir, maraviroc, etravirine, and enfuvirtide) [35].

All participants were examined every 3-6 months at COM-HUPES to record relevant clinical data. Demographic characteristics prior to initiation of salvage regimen, included sex, age, gender, and race. Clinical variables included alcohol use, cigarette smoking, illicit drug use, hemoglobin level, body mass index (BMI), years on ART, number of treatment failures, previously used ARVs, comorbidities and coinfections. Information on genotypic antiretroviral resistance testing, HIV-1 RNA viral load (PVL), CD4+/CD8+ cell count, and patient ART management information were manually extracted from the System for Control of Laboratory Tests (Sistema de Controle de Exames Laboratoriais – SISCEL), which monitors laboratory HIV surrogate markers, and the System for Control of Drug Logistics (Sistema de Controle Logístico de Medicamentos - SICLOM), which provides traceability of all ARVs prescribed, including the start date, refill dates, and ART changes. The Genotypic Sensitivity Score (GSS) was defined as the arithmetic sum of the individual score (1.0 for fully active, 0.5; partial, and 0.0 for inactive) for each drug used on salvage regimens. Mortality information, such as the date and diagnoses of death causes, was extracted manually from the National Mortality Information System (Sistema de Informações de Mortalidade - SIM), a high-quality database [36] in which death certificates have been registered and stored since 1979.

Different endpoints were analyzed during follow-up. Virological suppression, defined as the first PVL test that detected less than 50 copies/ml, was assessed one month after the start of salvage regimen and then every 3-6 months. Information on toxicity due to ART was classified according the Table for Grading the Severity of Adult and Pediatric Adverse Events [37]. Loss of follow-up was defined as any participant who was not reported dead by the SIM, did not seek medical attention at the COM-HUPES neither maintained contact with the service, and did not refill ART regularly in the last six months. Treatment interruption was considered to have occurred if the patient stopped refilling ART for more than three months without a known reason. Virologic failure was defined by two consecutive HIV RNA tests >1,000 copies/ml after at least six months of continuous therapy.

Propensity score analyses

Propensity score (PS) matching was used to balance the two nonrandomized treatment groups [38, 39] to avoid potential indication bias that could skew our results. PS, computed by multivariate logistic regression, was defined as the probability a patient had of been prescribed raltegravir given his or her clinical characteristics. Our final PS model included HIV-1 RNA PVL, a CD4 cell count below 100 cells per milliliter, and Genotypic Sensitivity Score of less than three as binary variables. Variables measured at baseline that were not included in the PS model because they did not improve model fit were age, episodes of previous treatment failure, malnutrition, and anemia. Patients with similar PS, receiving raltegravir or other drugs, were matched 1:1 using a nearest neighbor algorithm. Non-matched patients were excluded from subsequent analyzes.

Statistical analysis

Participants receiving raltegravir or other drugs (darunavir/ritonavir, maraviroc, or etravirine) were compared using Student's *t*-test, Pearson chi-square test, or Fisher's exact test. For the subgroup of PS-matched participants, a time-dependent survival analysis was performed (Kaplan-Meier method and Wilcoxon test to assess equality of survival curves) to compare the time from initiation of salvage regimens to virologic suppression or December 31, 2016, whichever occurred first. Patients without virologic suppression at the time of the last medical evaluation were censored. Also, cases of loss of follow-up, death, toxicity, or treatment interruption at the time of the last contact were censored. A Cox proportional hazard regression analysis to examine the adjusted association between salvage regimens and virologic suppression could not be performed because the proportional hazard assumptions were violated.

The occurrence of drug toxicity, treatment interruption, virological failure, loss of follow-up, and death from any cause during follow-up, were described as incidence rates per 100 person-years and compared using Poisson regression analysis.

Results

Of 367 patients initiating salvage regimens, 168 met the inclusion criteria, 123 received raltegravir and 45 other third line drugs (40 patients darunavir/ritonavir, 3 patients maraviroc, and 2 patients etravirine, no patient was taking enfuvirtide or dolutegravir during the analyzed period). Of them, 90 were matched with PS, 45 patients from each group (See Additional file 1: Figure S1). While in the overall study population both groups differed by PVL, CD4 cell count, and drug sensitivity, in the PS-matched subgroup groups were comparable (**Table 1**).

Table 1 Baseline characteristics of people with HIV receiving salvage regimen.

Characteristics	Eligible population *(n = 168)*			Matched subset *(n = 90)*		
	Raltegravir *(n = 123)*	Other drugs *(n = 45)*	*p* value	Raltegravir *(n = 45)*	Other drugs *(n = 45)*	*p* value
Age (years)	44.2 (9.7)	46.0 (10.6)	0.30[c]	45.5 (10.1)	46.0 (10.6)	0.82[c]
Male sex (%)	78 (63.4)	34 (75.6)	0.14[a]	31 (68.9)	34 (75.6)	0.48[a]
Black race (%)	108 (87.8)	37 (82.2)	0.35[a]	38 (84.4)	37 (82.2)	0.78[a]
Years receiving ART	10.6 (4.2)	9.7 (3.4)	0.16[c]	11.1 (4.0)	9.7 (3.4)	0.07[c]
Previous treatment failures ≥ 3 (%)	37 (30.1)	9 (20.0)	0.19[a]	9 (20.0)	9 (20.0)	1.00[a]
Alcohol use (%)	58 (47.2)	16 (35.6)	0.18[a]	18 (40.0)	16 (35.6)	0.66[a]
Cigarette smoking (%)	41 (33.3)	13 (28.9)	0.59[a]	16 (35.6)	13 (28.9)	0.50[a]
Illicit drug use (%)	15 (12.2)	4 (8.9)	0.55[a]	4 (8.9)	4 (8.9)	1.00[b]
PVL (log10 copies/mL)	4.5 (0.8)	4.2 (0.6)	0.01[c]	4.2 (0.6)	4.2 (0.6)	0.57[c]
CD4 count (cells/mL)	230.7 (210.3)	342.7 (232.3)	0.00[c]	286.8 (178.3)	342.7 (232.3)	0.20[c]
Hemoglobin < 9 g/dL (%)	8 (6.5)	0 (0.0)	0.11[b]	1 (2.2)	0 (0.0)	1.00[b]
Body mass index < 18.5 kg/m^2 (%)	15 (12.2)	2 (4.4)	0.25[b]	2 (4.4)	2 (4.4)	1.00[b]
Existing comorbidities (%)	58 (47.2)	23 (51.1)	0.65[a]	27 (60.0)	23 (51.1)	0.40[a]
Diabetes mellitus (%)	10 (8.1)	3 (6.7)	0.75[b]	8 (17.8)	3 (6.7)	0.11[a]
Blood hypertension (%)	20 (16.3)	13 (28.9)	0.07[a]	13 (28.9)	13 (28.9)	1.00[b]
Hyperlipidemia (%)	21 (17.1)	11 (24.4)	0.28[a]	9 (20.0)	11 (24.4)	0.61[a]
Past coinfections (%)	69 (56.1)	27 (60.0)	0.65[a]	20 (44.4)	27 (60.0)	0.14[a]
Pulmonary TB (%)	27 (22.0)	10 (22.2)	0.97[a]	7 (15.6)	10	0.42[a]

						(22.2)	
(%)	CNS toxoplasmosis	26 (21.1)	5 (11.1)	0.14[a]	7 (15.6)	5 (11.1)	0.54[a]
	Syphilis (%)	12 (9.8)	5 (11.1)	0.78[b]	4 (8.9)	5 (11.1)	1.00[b]
Genotypic Sensitivity Score< 3 (%)		62 (50.4)	31 (68.9)	0.03[a]	30 (66.7)	31 (68.9)	0.82[a]

Data was presented as mean (SD) or n (%)

PVL HIV-1 RNA plasma viral load, *SD* standard deviation.

[a] Pearson χ^2 test, [b] Fisher's exact test, [c] Student´s t-test; were used to compare groups.

In PS-matched analysis, 77.8% (35 of 45) of patients prescribed raltegravir-based salvage regimens achieved virologic suppression, similar to the 82.2% (37 of 45) of patients on other drugs (p=0.73; Kaplan Meier analysis; Generalized Wilcoxon test) **(Figure 1).** Drug toxicity was similar between groups (IRR=0.99, 95%CI: 0.74-1.33). It was identified a grade 2 lipohypertrophy (associated with ART [tenofovir, lamivudine, and darunavir/ritonavir]) and grade 1 depression (not associated to ART) in the group receiving other salvage regimens.

Among non-matched raltegravir recipients occurred a grade 2 aminotransferases elevation and a grade 2 pancreatitis (both unrelated to raltegravir). Treatment interruptions were also similar (IRR=1.05, 95%CI: 0.78-1.41), as four episodes were identified in raltegravir recipients without a known cause. Virological failure rates were similar in both groups (IRR=0.99, 95%CI: 0.74-1.33). One patient receiving raltegravir developed resistant strains (N155H mutation), this patient had three previous treatment failures and one previous episodes of treatment interruption. Two additional cases of N155H mutation were found among the non-matched raltegravir users. Two cases of darunavir resistance were confirmed, both patients had three treatment failures, and one of them had already interrupted treatment.

Mortality rates were similar between groups (IRR=0.99, 95%CI: 0.74-1.33). Two patients died while receiving raltegravir, both with undetectable PVL and a CD4 cell count>350 cells/ml before death. Three other patients died while receiving other drugs. Two of them had undetectable PVL and CD4 cell count>350 cells/ml. All patients died from non-AIDS related infections. Another four unmatched raltegravir recipients died, none achieved an undetectable PVL, and the deaths were due to non-AIDS related infections (2), myocardial infarction (1), and non-AIDS cancers (1) **(Table 2).**

Table 2 Incidence rates of events during follow-up per 100 person-years of patients prescribed raltegravir and "other-drugs" salvage regimens

Events during follow-up	Eligible population (n = 168, 178.05 p-y)		Matched subset (n = 90, 98.06 p-y)		IRR (95%CI)[a], *p*[b]
	Raltegravir (n = 123, 129.54 p-y)	Other drugs (n = 45, 48.51 p-y)	Raltegravir (n = 45, 49.55 p-y)	Other drugs (n = 45, 48.51 p-y)	
Drug toxicity	0.77	2.06	0.00	2.06	- , 0.49
Treatment interruption	12.35	0.00	8.07	0.00	- , 0.06
Virologic failure	2.32	4.12	2.02	4.12	0.49 (0.04-5.40), 0.61
Loss of follow-up	3.86	4.12	6.05	4.12	1.47 (0.25-8.79), 0.70
Death	4.63	6.18	4.04	6.18	0.65 (0.11-3.91), 0.67

p-y person-years

[a] IRR (incidence rate ratio) and 95% CI for rates of each event by salvage regimens were calculated by Poisson regression where other drugs were considered as a comparator

[b] Wald test

Discussion

Heavily experienced people with HIV receiving raltegravir achieved and maintained high levels (77.8%) of virologic suppression after nearly two years of follow-up, similar to previous reports [28, 31, 40]. The SALIR-E study found that 73% of treatment-experienced patients on raltegravir had undetectable PVL at week 206 [31]. Similarly, BENCHMRK trials found 77% of virologic suppression in the raltegravir arm, which was maintained after five years of follow-up, this randomized clinical trial, also identified a superiority of raltegravir over placebo [28]. Nevertheless, our survival analysis showed similar virologic suppression in patients receiving raltegravir or other salvage regimens based on darunavir/ritonavir, maraviroc or etravirine. Also, Buchacz et. al. [40] found comparable virologic and clinical outcomes (76 and 63%, p=0.51) in raltegravir-based and raltegravir-sparing regimens (with etravirine, maraviroc, enfuvirtide, or elvitegravir).

Our results may be different in part because the subjects were heavily experienced patients with virologic failure and their ART rescue options were somewhat limited by resistance data. In the overall study

population, Raltegravir was preferred for sicker patients with a higher PVL, higher proportion of CD4 cell count below 100 cells/ml, and significant proportion of GSS<3 than patients receiving other salvage regimens. Other characteristics that were also higher in raltegravir recipients were the proportion of patients with three or more past treatment failures, alcohol use, cases of anemia, and malnutrition. These characteristics have been associated with an increased risk of virologic failure [41–44].

After matching, the outcomes of raltegravir recipients did not appear to differ from those treated with other third-line drugs, as toxicity rates, treatment interruption, virologic failure, loss of follow-up, and mortality were comparable. Raltegravir was well tolerated, confirming previous safety reports in treatment-experienced patients [21, 28–30], nevertheless adverse events were similar in both groups. Few patients developed integrase mutations at key residues, as noted elsewhere, N155H has been shown to be the primary/major pathway causing resistance to raltegravir. This may be particularly important, as it has been shown that only one mutation is sufficient to observe virologic failure in highly experienced patients [45, 46]. This substitution also reduces susceptibility to elvitegravir but does not affect dolutegravir nor bictegravir alone [47, 48]. We found no explanation for the larger, but non-significant proportion of patients with treatment interruption in the raltegravir group before and after PS matching. Possible reasons remained unknown, as this is not usually coded in medical records available to researchers. However these data raises concerns about unmeasured factors that may affect patient adherence to ART as undiagnosed depression, unreported or unrecognized illicit drug use, or other social reasons [49, 50] that increase risk of mortality or treatment failure [45, 49]. Overall mortality was very low, similar to BENCHMRK and SALIR-E studies, but our analyzes were limited by a relatively small number of participants.

In conclusion, our findings show that virological response is possible in more than 80% of heavily experienced patients who start salvage therapy. They also suggest that raltegravir-based salvage regimens are as safe and effective as those based on other ARV classes, despite the higher disease severity. These results are particularly important given the limited number of third-line drugs for salvage regimens available in Brazil.

Limitations

Some limitations include a small sample size, as a larger sample would be needed to detect a stronger association between raltegravir-containing regimens and mortality, as well as an association with immunologic or virologic history. Another limitation is a possible selection bias that motivated the use of PS to match the main covariates simultaneously and approach the design of a randomized controlled trial while using observational data from this real-life clinic population. Associated limitations lie in the trade-off between matching all patients and basing analyzes and conclusions on only a subset of ‘good’ matches.

Abbreviations

AIDS
Acquired immunodeficiency syndrome
ART
Antiretroviral therapy
ARV
antiretroviral drugs
BMI
Body mass index
CI
Confidence interval
COM-HUPES
Complexo Hospitalar Prof. Edgard Santos
GRT
genotypic antiretroviral resistance testing
GSS
Genotypic Sensitivity Score
HIV
Human immunodeficiency syndrome
IRR
Incidence rate ratio p-y:person-years
PS
Propensity score
PVL
Plasma viral load
RAL
Raltegravir
SD
Standard deviation
SICLOM
Drug Logistics Control System
SIM
National Mortality Information System
SISCEL
Laboratory Test Control System
UFBA
Federal University of Bahia.

Declarations

Ethics approval and consent to participate

This clinical research was performed in accordance to the Good Clinical Practice Guidelines, the National Regulation of Research and Helsinki Declaration. Informed consent was not obtained taking into account that our analysis looked retrospectively at outcomes for a cohort of treated patients according to Brazilian guidelines, and this procedure would be associated to distress or confusion of participants. Our study protocol was approved by the COM-HUPES Ethic Committee (Ethics Committee Resolution Nº 2340107. Salvador, October 20, 2017) before starting.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are not publicly available due to privacy, but are available from the corresponding author on reasonable request.

Competing interests

The author(s) declare that they have no competing interests.

Funding

Financial support was provided in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001.

Authors' contributions

Conception and design of study: CB, EMN, JP; analysis and/or interpretation of data: CB, EMN, JP; drafting the manuscript: CB, EMN, JP; revising the manuscript critically for important intellectual content; CB, EMN, JP have all read and approved the final manuscript for submission. All authors 1 read and approved the final manuscript.

Acknowledgements

We thank all patients included in these analyses, facilities at COM-HUPES and staff at the Infectious Disease Research Laboratory (LAPI).

Authors' information

[1]School of Medicine, Federal University of Bahia, Salvador, Bahia Brazil

[2]LAPI - Infectious Disease Research Laboratory, Complexo Hospitalar Universitário Prof. Edgard Santos, Salvador, Bahia, Brazil.

References

1. Buchacz K, Lau B, Jing Y, Bosch R, Abraham AG, Gill MJ, et al. Incidence of AIDS-Defining Opportunistic Infections in a Multicohort Analysis of HIV-infected Persons in the United States and Canada, 2000–2010. J Infect Dis. 2016;214:862–72. doi:10.1093/infdis/jiw085.
2. Vittinghoff E, Scheer S, O'Malley P, Colfax G, Holmberg SD, Buchbinder SP. Combination antiretroviral therapy and recent declines in AIDS incidence and mortality. J Infect Dis. 1999;179 August:717–20. doi:10.1086/314623.
3. Williams G, Lima B, Gouws V. E. Modelling the Impact of Antiretroviral Therapy on the Epidemic of HIV. Curr HIV Res. 2011;9:367–82. doi:10.2174/157016211798038533.
4. Rossi SMG de, Maluf ECP, Carvalho DS, Ribeiro CEL, Battaglin CRP. Impacto da terapia antirretroviral conforme diferentes consensos de tratamento da Aids no Brasil. Rev Panam Salud Pública. 2012;32:117–23. doi:10.1590/S1020-49892012000800005.
5. McMahon JH, Elliott JH, Bertagnolio S, Kubiak R, Jordan MR. Viral suppression after 12 months of antiretroviral therapy in low- and middle-income countries: a systematic review. Bull World Health Organ. 2013;91:377–85E. doi:10.2471/BLT.12.112946.
6. Taieb F, Madec Y, Cournil A, Delaporte E. Virological success after 12 and 24 months of antiretroviral therapy in sub-Saharan Africa: Comparing results of trials, cohorts and cross-sectional studies using a systematic review and meta-analysis. PLoS One. 2017;12:e0174767. doi:10.1371/journal.pone.0174767.
7. UN Joint Programme on HIV/AIDS (UNAIDS). Global HIV & AIDS statistics — 2020 fact sheet. 2020. https://www.unaids.org/en/resources/fact-sheet. Accessed 22 May 2021.
8. Cossarini F, Spagnuolo V, Gianotti N, Carbone A, Lazzarin A, Castagna A. Management of HIV infection after triple class failure. New Microbiol. 2013;36:23–39. http://www.newmicrobiologica.org/PUB/allegati_pdf/2013/1/23.pdf.
9. Hamers RL, Rinke de Wit TF, Holmes CB. HIV drug resistance in low-income and middle-income countries. Lancet HIV. 2018;5:e588–96. doi:10.1016/S2352-3018(18)30173-5.
10. Bekolo CE, Webster J, Batenganya M, Sume GE, Kollo B. Trends in mortality and loss to follow-up in HIV care at the Nkongsamba Regional hospital, Cameroon. BMC Res Notes. 2013;6:1–16. doi:10.1186/1756-0500-6-512.
11. Hogg RS, Bangsberg DR, Lima VD, Alexander C, Bonner S, Yip B, et al. Emergence of Drug Resistance Is Associated with an Increased Risk of Death among Patients First Starting HAART. PLoS Med. 2006;3:e356. doi:10.1371/journal.pmed.0030356.
12. Ji Y, Wang Z, Shen J, Chen J, Yang J, Qi T, et al. Trends and characteristics of all-cause mortality among HIV-infected inpatients during the HAART era (2006-2015) in Shanghai, China. Biosci Trends. 2017;11:62–8. doi:10.5582/bst.2016.01195.
13. Lee SH, Kim K-H, Lee SG, Cho H, Chen DH, Chung JS, et al. Causes of Death and Risk Factors for Mortality among HIV-Infected Patients Receiving Antiretroviral Therapy in Korea. J Korean Med Sci. 2013;28:990. doi:10.3346/jkms.2013.28.7.990.

14. Temesgen Z, Cainelli F, Poeschla EM, Vlahakis SA, Vento S. Approach to salvage antiretroviral therapy in heavily antiretroviral-experienced HIV-positive adults. Lancet Infect Dis. 2006;6:496–507. doi:10.1016/S1473-3099(06)70550-3.
15. Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM. Adherence to Antiretroviral Therapy and Virologic Failure. Med (Baltim). 2016;95:e3361. doi:10.1097/MD.0000000000003361.
16. Lailulo Y, Kitenge M, Jaffer S, Aluko O, Nyasulu PS. Factors associated with antiretroviral treatment failure among people living with HIV on antiretroviral therapy in resource-poor settings: a systematic review and metaanalysis. Syst Rev. 2020;9:292. doi:10.1186/s13643-020-01524-1.
17. Parczewski M, Bander D, Urbańska A, Boroń-Kaczmarska A. HIV-1 integrase resistance among antiretroviral treatment naive and experienced patients from Northwestern Poland. BMC Infect Dis. 2012;12:368. doi:10.1186/1471-2334-12-368.
18. Lazzarin A, Clotet B, Cooper D, Reynes J, Arastéh K, Nelson M, et al. Efficacy of Enfuvirtide in Patients Infected with Drug-Resistant HIV-1 in Europe and Australia. N Engl J Med. 2003;348:2186–95. doi:10.1056/NEJMoa035211.
19. Gazzola L, Cicconi P, Ripamonti D, Di Filippo E, Gustinetti G, Di Biagio A, et al. Efficacy and Safety of Darunavir/Ritonavir Plus Etravirine Dual Regimen in Antiretroviral Therapy–Experienced Patients: A Multicenter Clinical Experience. HIV Clin Trials. 2014;15:140–50. doi:10.1310/hct1504-140.
20. Gulick RM, Lalezari J, Goodrich J, Clumeck N, DeJesus E, Horban A, et al. Maraviroc for Previously Treated Patients with R5 HIV-1 Infection. N Engl J Med. 2008;359:1429–41. doi:10.1056/NEJMoa0803152.
21. 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;359:339–54. doi:10.1056/NEJMoa0708975.
22. Pou C, Noguera-Julian M, Pérez-Álvarez S, García F, Delgado R, Dalmau D, et al. Improved Prediction of Salvage Antiretroviral Therapy Outcomes Using Ultrasensitive HIV-1 Drug Resistance Testing. Clin Infect Dis. 2014;59:578–88. doi:10.1093/cid/ciu287.
23. Hill AM, Cho M, Mrus JM. The costs of full suppression of plasma HIV RNA in highly antiretroviral-experienced patients. AIDS Rev. 2011;13:41–8. http://www.ncbi.nlm.nih.gov/pubmed/21412388.
24. Wainberg MA, Zaharatos GJ, Brenner BG. Development of Antiretroviral Drug Resistance. N Engl J Med. 2011;365:637–46. doi:10.1056/NEJMra1004180.
25. Aves T, Tambe J, Siemieniuk RAC, Mbuagbaw L. Antiretroviral resistance testing in HIV-positive people. Cochrane Database Syst Rev. 2018;2018. doi:10.1002/14651858.CD006495.pub5.
26. Brasil M, Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância Prevenção e Controle das Infecções Sexualmente Transmissíveis do HIV/Aids e das Hepatites Virais. Protocolo Clínico e Diretrizes Terapêuticas para Manejo da infecção pelo HIV em crianças e adolescentes. 2018;:412. http://www.aids.gov.br/pt-br/pub/2017/protocolo-clinico-e-diretrizes-terapeuticas-para-manejo-da-infeccao-pelo-hiv-em-criancas-e. Accessed 20 May 2021.

27. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. WHO Library. 2016; June:429. https://www.who.int/publications-detail-redirect/9789241549684. Accessed 21 May 2021.
28. 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;13:587–96. doi:10.1016/S1473-3099(13)70093-8.
29. Cooper DA, Steigbigel RT, Gatell JM, Rockstroh JK, Katlama C, Yeni P, et al. Subgroup and Resistance Analyses of Raltegravir for Resistant HIV-1 Infection. N Engl J Med. 2008;359:355–65. doi:10.1056/NEJMoa0708978.
30. 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;50:605–12. doi:10.1086/650002.
31. 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;43:189–94. doi:10.1016/j.ijantimicag.2013.10.013.
32. Blanco J-L, Varghese V, Rhee S-Y, Gatell JM, Shafer RW. HIV-1 Integrase Inhibitor Resistance and Its Clinical Implications. J Infect Dis. 2011;203:1204–14. doi:10.1093/infdis/jir025.
33. Mata-Marín JA, Smeke AEW, Rodriguez MR, Chávez-García M, Banda-Lara MI, Rios AMP, et al. Effectiveness and Risk Factors for Virological Outcome of Raltegravir-Based Therapy for Treatment-Experienced HIV-Infected Patients. Drugs R D. 2017;17:225–31. doi:10.1007/s40268-017-0174-z.
34. Gras G, Schneider M-P, Cavassini M, Lucht F, Loilier M, Verdon R, et al. Patterns of Adherence to Raltegravir-Based Regimens and the Risk of Virological Failure Among HIV-Infected Patients. JAIDS J Acquir Immune Defic Syndr. 2012;61:265–9. doi:10.1097/QAI.0b013e31826cc592.
35. Brasil M, Saúde, Secretaria de Vigilância em Saúde Departamento de Vigilância Prevenção e Controle das IST HIV/AIDS e Hepatities Virais. Protocolo Clínico e Diretrizes Terapêuticas para Manejo da Infecção pelo HIV em adultos. 2018;:416. http://www.aids.gov.br/pt-br/pub/2013/protocolo-clinico-e-diretrizes-terapeuticas-para-manejo-da-infeccao-pelo-hiv-em-adultos. Accessed 19 May 2021.
36. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abera SF, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1151–210. doi:10.1016/S0140-6736(17)32152-9.
37. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Daids. 2017; August:Version 2.1. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf. Accessed 18 May 2021.

38. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46:399–424. doi:10.1080/00273171.2011.568786.
39. Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. Comput Methods Programs Biomed. 2004;75:45–9. doi:10.1016/j.cmpb.2003.10.004.
40. Buchacz K, Wiegand R, Armon C, Chmiel JS, Wood K, Brooks JT, et al. Long-term immunologic and virologic responses on raltegravir-containing regimens among ART-experienced participants in the HIV Outpatient Study. HIV Clin Trials. 2015;16:139–46. doi:10.1179/1528433614Z.0000000019.
41. Malet I, Fourati S, Morand-Joubert L, Flandre P, Wirden M, Haim-Boukobza S, et al. Risk factors for raltegravir resistance development in clinical practice. J Antimicrob Chemother. 2012;67:2494–500. doi:10.1093/jac/dks254.
42. Rusconi S, Vitiello P, Adorni F, Bruzzone B, De Luca A, Micheli V, et al. Factors associated with virological success with raltegravir-containing regimens and prevalence of raltegravir-resistance-associated mutations at failure in the ARCA database. Clin Microbiol Infect. 2013;19:936–42. doi:10.1111/1469-0691.12100.
43. Reekie J, Mocroft A, Ledergerber B, Beniowski M, Clotet B, van Lunzen J, et al. History of viral suppression on combination antiretroviral therapy as a predictor of virological failure after a treatment change. HIV Med. 2010;11:469–78. doi:10.1111/j.1468-1293.2009.00816.x.
44. Castor D, Vlahov D, Hoover DR, Berkman A, Wu YF, Zeller B, et al. The relationship between genotypic sensitivity score and treatment outcomes in late stage HIV disease after supervised HAART. J Med Virol. 2009;81:1323–35. doi:10.1002/jmv.21500.
45. Malet I, Delelis O, Valantin M-A, Montes B, Soulie C, Wirden M, et al. Mutations Associated with Failure of Raltegravir Treatment Affect Integrase Sensitivity to the Inhibitor In Vitro. Antimicrob Agents Chemother. 2008;52:1351–8. doi:10.1128/AAC.01228-07.
46. Modica S, Rossetti B, Lombardi F, Lagi F, Maffeo M, D'Autilia R, et al. Prevalence and determinants of resistance mutations in HIV-1-infected patients exposed to integrase inhibitors in a large Italian cohort. HIV Med. 2019;20:137–46. doi:10.1111/hiv.12692.
47. Scutari R, Alteri C, Vicenti I, Di Carlo D, Zuccaro V, Incardona F, et al. Evaluation of HIV-1 integrase resistance emergence and evolution in patients treated with integrase inhibitors. J Glob Antimicrob Resist. 2020;20:163–9. doi:10.1016/j.jgar.2019.07.015.
48. Orta-Resendiz A, Rodriguez-Diaz RA, Angulo-Medina LA, Hernandez-Flores M, Soto-Ramirez LE. HIV-1 acquired drug resistance to integrase inhibitors in a cohort of antiretroviral therapy multi-experienced Mexican patients failing to raltegravir: a cross-sectional study. AIDS Res Ther. 2020;17:6. doi:10.1186/s12981-020-0262-y.
49. Palella FJ, Armon C, Buchacz K, Chmiel JS, Novak RM, D'Aquila RT, et al. Factors associated with mortality among persistently viraemic triple-antiretroviral-class-experienced patients receiving antiretroviral therapy in the HIV Outpatient Study (HOPS). J Antimicrob Chemother. 2014;69:2826–34. doi:10.1093/jac/dku190.

50. Gonzalez JS, Batchelder AW, Psaros C, Safren SA. Depression and HIV/AIDS Treatment Nonadherence: A Review and Meta-analysis. JAIDS J Acquir Immune Defic Syndr. 2011;58:181–7. doi:10.1097/QAI.0B013E31822D490A.

Figures

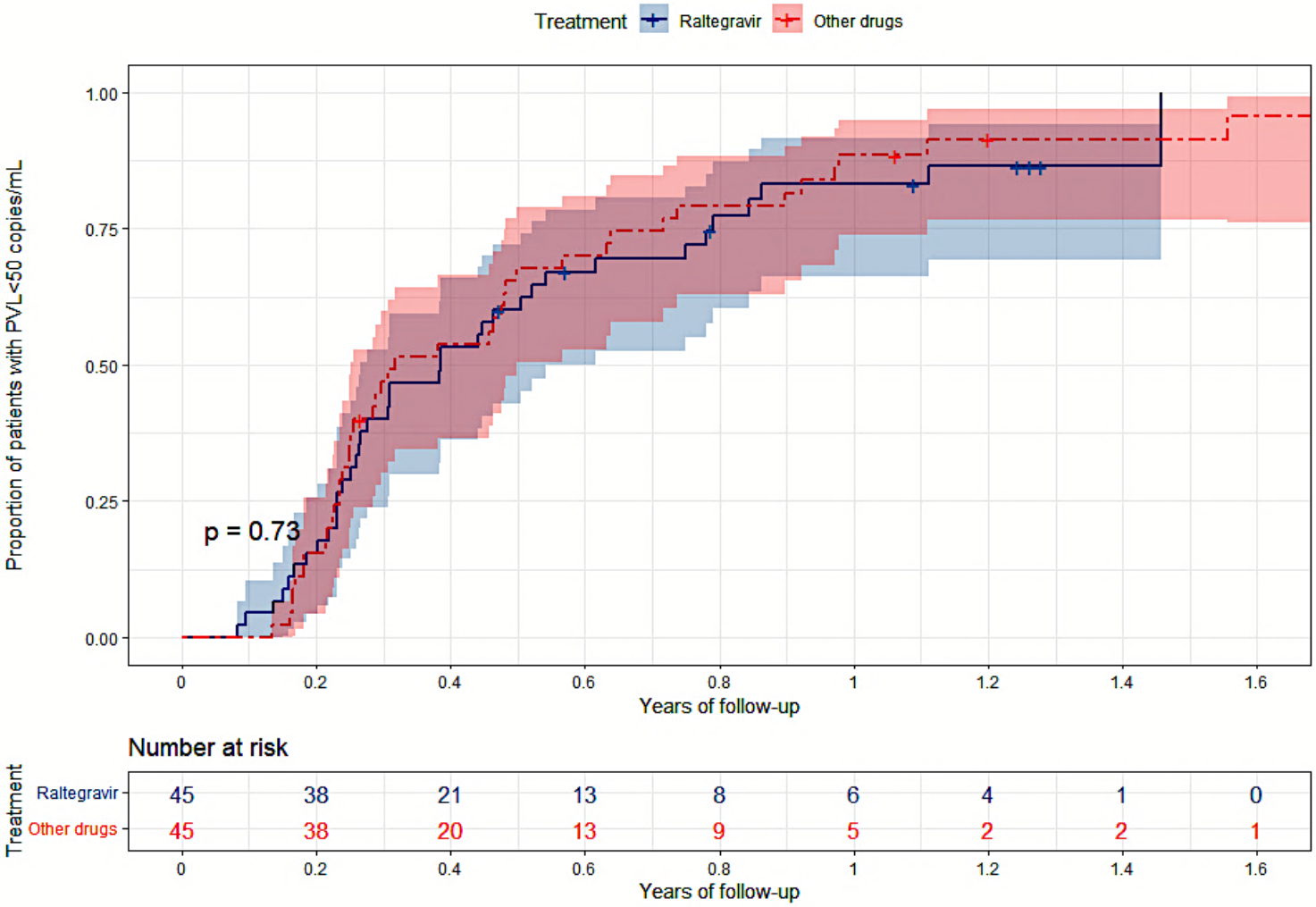

Figure 1

Kaplan-Meier survival plot of time to virologic suppression per groups. p value corresponding to Generalized Wilcoxon test.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile1Flowdiagram.pdf