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Raltegravir in the Treatment of HIV-2 Infection: A Report of Eight Cases

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Background: Although endemic in West Africa, HIV-2 infection dissemination is limited to about 1.2 million people worldwide. However, the prevalence of HIV-2 infection is in Portugal disproportionately high, similarly to other countries with strong socioeconomic ties with West African former colonies. Due to HIV-2 intrinsic resistance to non-nucleoside reverse transcriptase inhibitors (non-NRTIs) and enfuvirtide, along with reduced susceptibility to several of the protease inhibitors (PI), antiretroviral therapy (ART) relies on a regimen containing two NRTIs and a selected boosted PI. The integrase inhibitor raltegravir (RAL) showed, *in vitro*, activity against HIV-2 infection, and small case series published report RAL efficacy in the treatment of HIV-2 infection.
Methods: We report eight HIV-2 ART-experienced patients treated with a RAL-containing regimen.
Results: In this small series of eight patients, medium time of known HIV-2 infection before RAL introduction was 9.4 years; all had previous exposition to ART, some with more than 3 past therapeutic regimens. The majority had low CD4+T cell count. Despite these clinical aspects, the majority showed undetectable viral load (75%) and improvement or stability of the CD4+ T cell count (63%).
Conclusion: Despite limitations inherent to this small case series, RAL proved to be useful in the

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treatment of HIV-2 infected patients, with beneficial effect in virus control and CD4+T cell preservation. In the presence of extensive resistance to other antiretrovirals, the benefit of RAL seems to be decreased. Accordingly to other emergent data, RAL may represent a novel therapeutic possibility for HIV-2 infected patients.

Keywords: HIV-2 infection; raltegravir; RAL.

1. INTRODUCTION

HIV-2 infection is endemic in West Africa, but unlike HIV-1infection, its worldwide spread was limited to about 1-2 million people. In Portugal the prevalence of HIV-2 infection is disproportionately high, due to ongoing socioeconomic ties with West African former colonies. Although HIV-2 infected individuals present a much longer asymptomatic stage of infection, show slower decrease in CD4+T cell counts and lower plasma viral loads (VL), once advanced immunosuppression has occurred, disease progression and mortality rates appear similar to those seen in HIV1-infection, demonstrating the need to treat these patients.

Nowadays, antiretroviral therapy (ART) of HIV-2 infection relies on a regimen containing two nucleoside reverse transcriptase inhibitors (NRTIs) and a boosted protease inhibitor (PI), since HIV-2 is intrinsically resistant to non-NRTIs and fusion inhibitors, along with reduced susceptibility to several of the PI's. HIV-2 isolates showed, *in vitro,* susceptibility to the integrase inhibitor (INSTI) raltegravir (RAL) similar to HIV-1 isolates; despite 40% heterogeneity between the HIV-1 and HIV-2 integrase genes, the HIV-2 phenotypic susceptibility of clinical HIV-2 isolates to INSTI was similar to that of HIV-1.

2. OBJECTIVES

To characterize the clinical, virological and immunologic course of HIV-2 infected patients treated with RAL-containing regimens**,** and to evaluate differences in RAL-treated patients due to past exposure of previous ART regimens.

3. PATIENT AND METHODS

Eight patients treated with a RAL-containing regimen were retrospectively analyzed from a total of eighty-nine confirmed HIV-2 infected patients. All patients had HIV-2 infection confirmed by immunoblot and patients with dual infection by HIV-1 and 2 were not included in this case series. Plasma HIV-2 viral load quantification was determined by an in-house quantitative real-time polymerase chain reaction (RT-PCR) assay (limit of detection of 40 copies/mL) based on the European 2009 ACHIEV2E Quality Control Study [1] and adapted to the Rotor-Gen 3000 or 6000 platform. The standards where obtained from Human Immunodeficiency Virus Type 2 (HIV-2) Purified Virus, strain NIH-Z, propagated in a Hut 78 cell line with a virus particle count of 7.2×10^{10}vp/ml. Genotypic resistance assays were performed using in-house RT-PCR and sequencing as previously described by the Portuguese HIV-2 Resistance Study Group [2]. The authors analyzed data regarding VL, CD4+T cell count, clinical outcome**,** and resistance testing, when available.

All authors hereby declare that privacy of all patients described in this case series has been protected and that no patient opposed to his/her clinical data being used in this case series report.

4. RESULTS

As shown in Table 1, of the eight patients treated with a RAL-containing regimen, five were female, and the mean age was 48 years (31-60 years). Six patients were from West African countries and the medium time of known HIV-2 infection before the beginning of RAL was 9.4 years (4-12 years). None of the patients had history of INSTI treatment in the past, but all had previous exposition to ART, some with more than 3 past therapeutic regimens (Table 2). The mean duration of ART prior to RAL introduction was 49.4 months.

The majority had low CD4+T cell count when RAL was included in ART (mean baseline CD4+T cell count of 152 cells/μL; 42-324 cells/μL).

In four patients, RAL was used as part of a salvage regimen; one of them had detectable HIV-2 VL prior to RAL introduction.

In the other remaining four patients, RAL was started for other reasons than salvage therapy. In this group, the CD4+T cell count remained stable (Fig. 1).

Table 1. Demographic and clinical characteristics of 8 HIV-2 infected patients

Patient	Sex	Age (years)	Origin	HIV-2 infection diagnosis	
				CD4+ T cells/mm3	CDC class
1	female	39	Guinea-Bissau	65	C3
2	female	42	Cape Verde	145	C3
3	female	31	Guinea-Bissau	182	C3
4	male	49	Guinea-Bissau	220	C3
5	male	60	Portugal	330	B2
6	male	59	Portugal	85	C2
7	female	59	Guinea-Bissau	248	B2
8	female	50	Guinea-Bissau	198	B3

Table 2. Virological characteristics and outcome of 8 HIV-2 infected patients

Patient	Prior ART exposure and mutations	RAL-containing regimen	Follow-up (weeks)	Outcome
1	AZT/3TC+IDV–4y d4T+ddI+NFV– 2y TDF+ABC+LPV/r–4y Genotyping: RT - K65R, V111I, Q151M and M184V PR - I54M, I82F, V71I and L90M	TDF/FTC+DRV/r+RAL – 1y AZT/3TC+DRV/r+ +MVC+RAL – 2y	136	Death due to sepsis and severe inflammatory bowel disease
2	AZT/3TC+IDV	ABC+ddI+DRV/r+RAL	180	Increase in CD4+ T cells from 49 to 354 cells/μL, detectable HIV-2 VL after a period undetectability for 172 weeks
3	3TC+d4T+ NFV– 2y 3TC+d4T+FPV/r – 2y ABC/3TC+FPV/r - 2y	ABC/3TC+RAL	120	Increase in CD4+ cell count from 131 to 220 cells/μL, undetectable HIV-2 VL
4	AZT/3TC+LPV/r - 1y ABC/3TC+SQV/r -1y ABC/3TC+LPV/r - 1 y Genotyping: High grade resistance to 3TC and FTC. Possible resistance to ABC and ddI. Apparent susceptibility to other NRTI's. High-grade resistance to LPV, probable susceptibility to SQV and DRV.	TDF/FTC+RAL+SQV/r	12	Persistent immunologic failure despite decrease of HIV-2 VL from 13256 copies/mL to undetectability
5	TDF/FTC+SQV/r	TDF/FTC+RAL 6 months, then ABC/3TC+RAL	100	CD4+ T cell count stable and undetectable HIV-2 VL
6	AZT+3TC+IDV – 8y TDF/FTC+SQV/r – 2y Genotyping: Failure to perform	TDF/FTC+RAL+DRV/r	112	Failure to increase CD4+T cell count; persistent detectable HIV-2 VL
7	ABC/3TC+SQV/r - 4m	ABC/3TC+RAL	68	CD4+ T cell count stable and undetectable HIV-2 VL
8	TDF/FTC+SQV/r	TDF/FTC+RAL	92	Increase in CD4+ cell count from 198 to 409 cells/μL, undetectable HIV 2 VL

Key to abbreviations: 3TC = lamivudine; ABC = abacavir; AZT = zidovudine; d4T = stavudine; ddI = didanosine; DRV= darunavir; FPV = fosamprenavir; FTC = emtricitabine; IDV = indinavir; LPV = lopinavir; m = months; MVC = maraviroc; NFV = nelfinavir; PR = protease; TDF = tenofovir; y = years; r = ritonavir; RT = reverse transcriptase; SQV = saquinavir

The overall follow-up period was during a mean of 21 months.

During the follow-up period only patients 2, 4 and 6 presented detectable HIV-2 VL throughout the period of time analyzed (Fig. 2). These 3 patients had strong ART past experience, including past IP-containing regimens. Data available regarding patient 4 refer to the first 12 weeks of follow-up, which was the period of time the patient had been on RAL by the time this paper was being written.

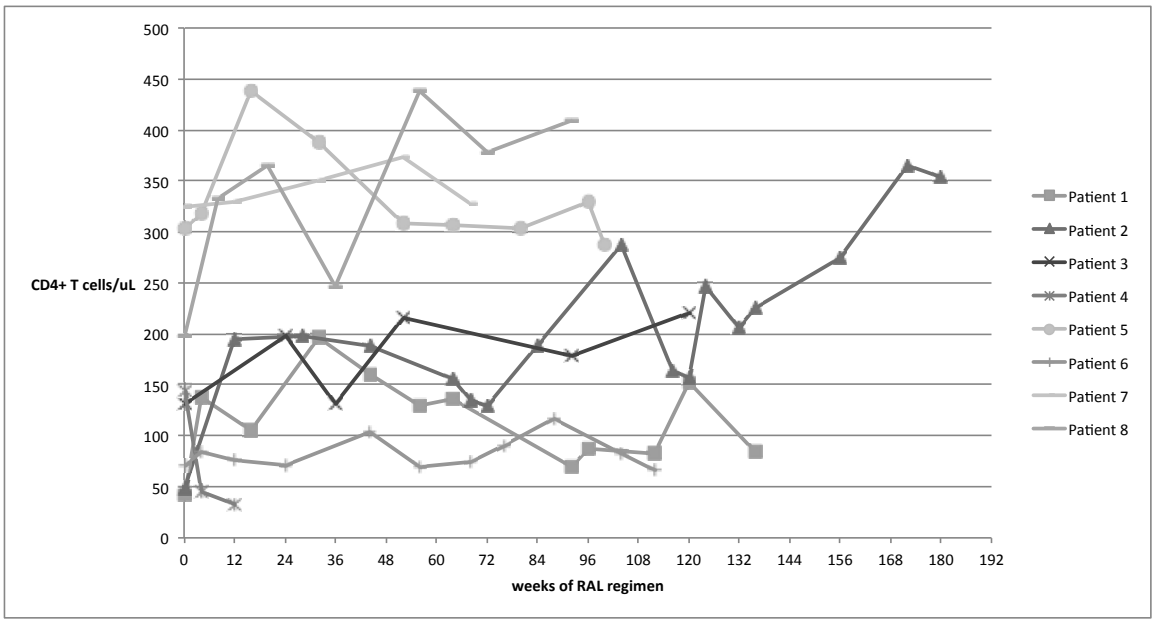

Fig. 1. CD4+ T cell count evolution on RAL-containing regimen

The CD4+ T cell count remains stable after initiation of a RAL-containing regimen in the patients in whom RAL was introduced for other than ART failure

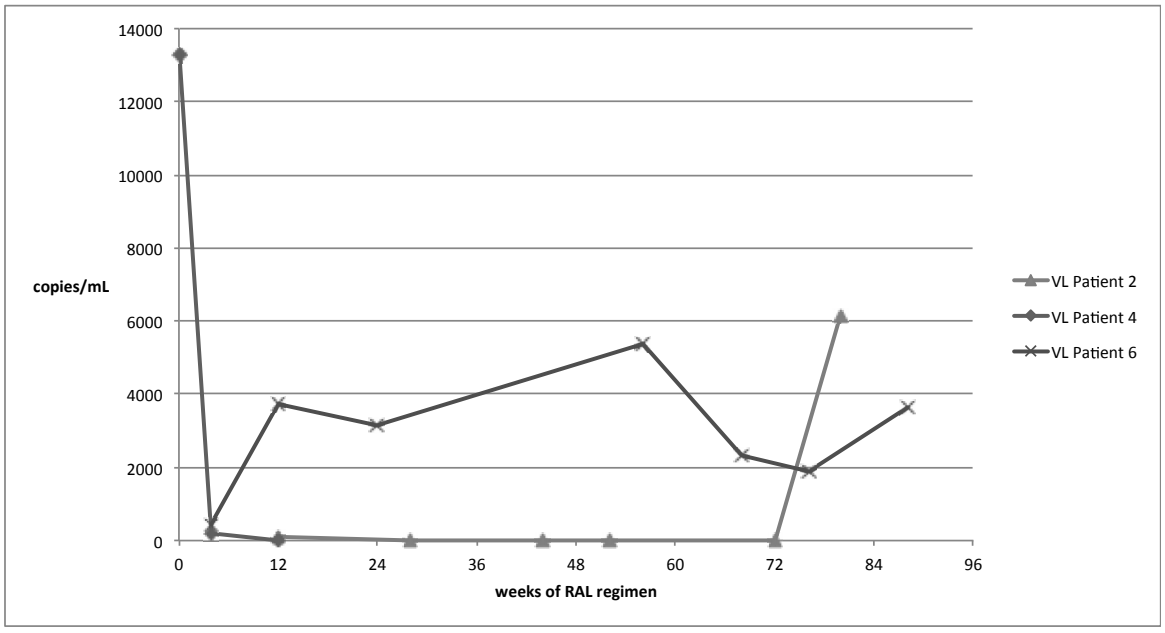

Fig. 2. HIV2 viral load evolution on RAL-containing regimen

5. DISCUSSION

HIV-1 and HIV-2 share strong similarities and both cause AIDS. HIV-2 is a *Lentivirus* from the *Retroviridae* family [3] originated from sooty mangabeys in West Africa, where the virus is endemic but has limited spread to a number of other locales worldwide. Although HIV-2 has been the predominant virus in many of these regions, prevalence in some West African countries seems to be declining along with increasingly higher prevalence of HIV-1, overtaking HIV-2 as the predominant virus [4-7]. The colonial past of numerous West African countries where HIV-2 infection prevalence was significant reflects the role these may have had in the modern era in the global dispersion of the HIV-2 infection, as is the case of Cape Verde, the place where HIV-2 was reputedly first identified in 1986 [3,8].

Similarly to other countries with strong socioeconomic ties with West Africa due to its relation with the former colonies, in Portugal the prevalence of HIV-2 infection is significant, being one of the highest among European countries [9] (527 reported infections, from 1983 until 2011, accounting for 3.1% of AIDS cases in Portugal) [10]. In our department, there are 89 cases of HIV-2 infected patients currently on follow-up.

Although HIV-1 and HIV-2 share similar routes of transmission, HIV-2 transmission appears to be less efficient than HIV-1 [11-17]. HIV-2 is characterized by lower rates of mother-to-child transmission, genital tract shedding and sexual transmission. The majority of the patients of this small subset probably acquired HIV-2 infection through sexual transmission and only one through blood transfusion. This one patient had no other link to West Africa.

Compared to HIV-1, HIV-2 exhibits a more attenuated phenotype. Most of HIV-2-infected patients behave like long-term non-progressors and only 20–25% of all HIV-2 patients progress to AIDS [18]. The patients in this small report were diagnosed after symptoms occurred and all had a CD4+T cell count inferior to 250 cells/μL, which reflects the similar disease progression and mortality rates to the ones seen in HIV1-infection once advanced immunosuppression has occurred [19]. Thereby, ART plays an important role in the management of HIV-2 infected patients. However, HIV-2 treatment is particularly challenging. Since there are no clinical trials data about the use of ART in HIV-2 infection, information comes mostly from clinical reports of small numbers of patients and observational studies. Additionally, VL measurement, fundamental in the HIV-1 treatment monitoring, is not so useful when it comes to HIV-2 infection, since VL are often lower or undetectable and many of the *in house* laboratory techniques used to quantify HIV-2 VL are not so widely available as those specific for HIV-1. The same is true for HIV-2 resistance testing.

Due to HIV-2 intrinsic resistance to non-NRTIs and enfuvirtide, along with reduced susceptibility to several of the PI, ART relies on a regimen containing two NRTIs and a selected boosted PI. Past studies have shown that only lopinavir, saquinavir and darunavir are efficient in HIV-2 treatment [20,21].

Despite almost 40% of genotypic heterogeneity between the HIV-1 and HIV-2 integrase genes, HIV-2 phenotypic susceptibility to INSTI appears to be similar to that of HIV-1. The INSTI RAL and elvitegravir (EVG) showed in vitro activity against HIV-2 infection [22] and small case series have been published reporting RAL efficacy in the treatment of HIV-2 infected patients, when given with other antiretrovirals (ARV) to which the virus is susceptible [23-29].

In this small report, all patients had been previously treated with several ART therapeutic regimens in the past, some with ARV drugs known today as not effective on HIV-2 treatment. Unfortunately, these past therapeutic regimens may not only have contributed to disease progression, since HIV-2 infection was not being correctly treated, but may also have favored the emergence of drug resistance.

In this small subset of patients, despite the fact that they were all treatment-experienced with advanced immunodeficiency**,** RAL proved to be useful in the treatment of HIV-2 infected patients, with benefic effect in virus control and on CD4+T cell preservation**.** In HIV-2 long-term infected patients with consequent presence of extensive resistance to other ARV, the benefit of RAL seemed to be decreased, since the presence of other fully active ARV in the regimen is needed for its efficacy.

It is today known that resistance selection in HIV-2 seems to occur faster than in HIV-1, narrowing the time window for an ARV regimen change, when viral and/or immunologic failure occurs [30].

The genetic pathways leading to RAL resistance appear to be similar to the ones known to occur in HIV-1 infection, but differences in the HIV-2 integrase region may lower the resistance barrier to INSTI comparing to HIV-1 infection [22], suggesting that RAL also has a low genetic barrier to resistance acquisition in the treatment of HIV-2 infection [28,31]. However, there seems to be evidence of presence of several naturally-occurring aminoacids in the integrase of HIV-2 *naïve* patients, associated to secondary RAL or EVG resistance replacements in HIV-1, suggesting higher levels of INSTI resistance [31]. Even though intrinsic or transmitted INSTI-resistance in HIV-2 does not seem to be frequent at the present time, it is probable that INSTI resistance may become a clinical problem in HIV-2 in the outrun [31]. This may bear more severe implications than HIV-1 treatment, since other ARV classes are not fully efficient against HIV-2 or only provide short-term efficient-treatment.

Hence, the use of INSTI such as RAL, EVG or even dolutegravir [32] in the treatment of HIV-2 infection may be considered as a part of ART in HIV-2 *naïve* patients. In Portugal, the current HIV-2 treatment guidelines recommend the use of RAL in such patients [32].

6. CONCLUSION

This small case series confirms the clinical effectiveness of RAL in HIV-2 infected patients, when part of a regimen with other drugs to which the virus is fully susceptible.

Despite emergent data regarding the possible utility of new therapeutic drug classes in the treatment of HIV-2 infection, clinical trial data are still urgently required, specially regarding more recent drugs effective against HIV-2, such as INSTI.

CONSENT

All authors hereby declare that privacy of all patients described in this case series has been protected and that no patient opposed to his/her clinical data being used in this case series report.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Damond F, Benard A, Balotta C, Böni J, Cotten M, Duque V, et al, ACHI(E)V(2E) Study Group. An international collaboration to standardize HIV-2 viral load assays: results from the 2009 ACHI(E)V(2E) quality control study. J Clin Microbiol. 2011;49(10):3491-7. DOI: 10.1128/JCM.02389-10. Epub 2011 Aug 3.
2. Cavaco-Silva J, Aleixo MJ, Van Laethem K, Faria D, Valadas E, Gonçalves MD, et al; on behalf of the Portuguese HIV-2 Resistance Study Group. Mutations selected in HIV-2-infected patients failing a regimen including atazanavir. J Antimicrob Chemother. 2013;68(1):190-2. DOI: 10.1093/jac/dks363. Epub 2012 Sep 13.
3. Clavel F, Mansinho K, Chamaret S, Guetard D, Favier V, Nina J, et al. Human immunodeficiency virus type 2 infection associated with AIDS in West Africa. N Engl J Med. 1987;316:1180–1185.
4. da Silva ZJ, Oliveira I, Andersen A, Dias F, Rodrigues A, Holmgren B, etal. Changes in prevalence and incidence of HIV-1, HIV-2 and dual infections in urban areas of Bissau, Guinea-Bissau: Is HIV-2 disappearing? AIDS. 2008;22:1195-202.
5. Bouckenooghe A, Shandera W. HIV trends in African blood donors. J Infect 1999;39:122–128.
6. van der Loeff MF, Awasana AA, Sarge-Njie R, Van der Sande M, Jaye A, Sabally S, et al. Sixteen years of HIV surveillance in a West African research clinic reveals divergent epidemic trends of HIV-1 and HIV-2. Int J Epidemiol. 2006;35:1322–1328.
7. Gianelli E, Riva A, Rankin Bravo FA, Da Silva Te D, Mariani E, Casazza G, Scalamogna C, Bosisio O, Adorni F, Rusconi S, Galli M. Prevalence and risk determinants of HIV-1 and HIV-2 infections in pregnant women in Bissau. J Infect. 2010;61(5):391-398.
8. De Pina-Araujo II, Guimarães ML, Bello G, Vicente AC, Morgado MG. Profile of the HIV epidemic in Cape Verde: molecular epidemiology and drug resistance mutations among HIV-1 and HIV-2 infected patients from distinct islands of the archipelago. PLoS One. 2014;24;9(4):e96201. DOI: 10.1371/journal.pone.0096201. eCollection 2014.

9. Valadas E, França L, Sousa S, Antunes F. 20 Years of HIV-2 Infection in Portugal: Trends and Changes in Epidemiology. Clin Infect Dis. 2009;48:1166-1167
10. Department of Infectious Diseases. Reference Unit and Epidemiological Surveillance, Center for Laboratory Surveillance of Infectious Diseases. HIV / AIDS infection: The situation in Portugal December 31, 2011. Document 43 National Health Institute Dr. Ricardo Jorge, IP 2012.
11. Kanki PJ, Travers KU, Marlink RG, Essex ME, MBoup S, Gueye-NDiaye A, et al. Slower heterosexual spread of HIV-2 than HIV-1. Lancet. 1994;343:943-946.
12. The HIV Infection in Newborns French Collaborative Study Group. Comparison of vertical human immunodeficiency virus type 2 and human immunodeficiency virus type 1 transmission in the French prospective cohort. Pediatr Infect Dis J. 1994;13:502-506.
13. Adjorlolo-Johnson G, De Cock KM, Ekpini E, Vetter KM, Sibailly T, Brattegaard K, et al. Prospective comparison of mother-to-child transmission of HIV-1 and HIV-2 in Abidjan, Ivory Coast. JAMA. 1994;6:272:462.
14. Prazuck T, Yameogo JM, Heylinck B, Ouedraogo L, Rochreau A, Guiard-Schmid JP, et al. Mother-to-child transmission of human immunodeficiency virus type 1 and type 2 and dual infection: A cohort study in Banfora, Burkina Faso. Pediatr Infect Dis J. 1995;14:940-947.
15. Gottlieb GS, Hawes SE, Agne HD, Stern J, Critchlow C, Kiviat N, et al. Lower levels of HIV RNA in semen in HIV-2 compared with HIV-1 infection: Implications for differences in transmission. AIDS. 2006;20(6):895-900.
16. Burgard M, Jasseron C, Matheron S, Damond F, Hamrene K, Blanche S, et al. Mother-to-child transmission of HIV-2 infection from 1986 to 2007 in the ANRS French Perinatal Cohort EPF-CO1. Clin Infect Dis. 2010;51(7):833-843.
17. O'Donovan D, Ariyoshi K, Milligan P, Ota M, Yamuah L, Sarge-Njie R, et al. Maternal plasma viral RNA levels determine marked differences in mother-to-child transmission rates of HIV-1 and HIV-2 in The Gambia. MRC/Gambia Government/University College London Medical School working group on mother-child transmission of HIV. AIDS. 2000;14:441-448.
18. De Silva TI, Cotten M, Rowland-Jones SL. HIV-2: The forgotten AIDS virus. Trends Microbiol. 2008;16(12):588–595.
19. Martinez-Steele E, Awasana AA, Corrah T, Sabally S, Van der Sande M, Jaye A, et al. Is HIV-2- induced AIDS different from HIV-1-associated AIDS? Data from a West African clinic. AIDS. 2007;21:317-324.
20. Desbois D, Roquebert B, Peytavin G, Damond F, Collin G, Bénard A, et al. In vitro phenotypic susceptibility of human immunodeficiency virus type 2 clinical isolates to protease inhibitors. Antimicrob Agents Chemother. 2008;52(4):1545-1548.
21. Brower ET, Bacha UM, Kawasaki Y, Freire E. Inhibition of HIV-2 protease by HIV-1 protease inhibitors in clinical use. Chem Biol Drug Des. 2008;71:298-305.
22. Roquebert B, Damond F, Collin G, Matheron S, Peytavin G, Benard A, et al. HIV-2 integrase gene polymorphism and phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitors raltegravir and elvitegravir *in vitro*. J Antimicrob Chemother. 2008;62:914–920.
23. Peterson K, Ruelle J, Vekemans M, Siegal FP, Deayton JR, Colebunders R. The role of raltegravir in the treatment of HIV-2 infections: Evidence from a case series. Antiviral Therapy. 2012;17:1097–1100.
24. Roquebert B, Blum L, Collin G, Damond F, Peytavin G, Leleu J, et al. Selection of the Q148R integrase inhibitor resistance mutation in a failing raltegravir containing regimen. AIDS. 2008;22:2045–2046.
25. Armstrong-James D, Stebbing J, Scourfield A, Smit E, Ferns, Pillay D, et al. Clinical outcome in resistant HIV-2 infection treated with raltegravir and maraviroc. Antiviral Res. 2010;86(2):224–226.
26. Garrett N, Xu L, Smit E, Ferns B, El-Gadi S, Anderson J. Raltegravir treatment response in an HIV-2 infected patient: A case report. AIDS. 2008;22:1091–1092.
27. Damond F, Lariven S, Roquebert B, Males S, Peytavin G, Morau G, et al. Virological and immunological response to HAART regimen containing integrase inhibitors in HIV-2-infected patients. AIDS 2008;22:665-666.
28. Charpentier C, Roquebert B, Delelis O, Larrouy L, Matheron S, Tubiana R, et al. Hot spots of integrase genotypic changes leading to HIV-2 resistance to raltegravir. Antimicrob Agents Chemother. 2011;55:1293-1295.

29. Doroana M, Pinheiro C, Oliveira J, Mansinho K, Germano I, Fonseca P, et al. Comparing treatment of HIV-1 and HIV-2 patients with raltegravir plus OBT. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention. Rome, Italy. Abstract CDB 375; 2011.
30. Camacho RJ. Special Aspects of the Treatment of HIV-2 infected patients. Intervirology. 2012;55:179–183.
31. Gottlieb GS, Smith RA, Badiane NM, Ba S, Hawes SE, Toure M, et al. HIV-2 Integrase Variation in Integrase Inhibitor-Naïve Adults in Senegal, West Africa. PLoS ONE 2011;6(7):e22204.
DOI: 10.1371/journal.pone.0022204
32. Charpentier C, Larrouy L, Collin G, Damond F, Matheron S, Chêne G, et al. In-vitro phenotypic susceptibility of HIV-2 clinical isolates to the integrase inhibitor S/GSK1349572. AIDS. 2010;24:2753–2755.
33. National Programme for HIV / AIDS infection. Portuguese recommendations for the treatment of infection by HIV-1 and HIV-2; 2012. Acessed 9 November, 2013. Available: http://sida.dgs.pt/.

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