Short Communication:
Use of Raltegravir in Late-Presenting HIV-Infected Pregnant Women

Isabella Nóbrega,[1] Ana Gabriela Travassos,[1] Tatiana Haguihara,[1] Fábio Amorim,[2] and Carlos Brites[3]

Abstract

The risk of HIV-1 mother-to-child transmission (MTCT) is clearly correlated with the maternal HIV cell-free viral load (VL) at delivery. Preventing MTCT in late-presenting (after 28 weeks) HIV-infected pregnant women remains a clinical challenge, and ensuring a rapid decrease of maternal VL is an important preventive strategy. Raltegravir (RGV) has a higher first and second phase viral decay rate, has a high placental transfer, with a potential preloading effect for neonate, and demonstrates effective accumulation in cervicovaginal secretions. We report 14 cases in which RGV was used late in pregnancy for HIV-1 MTCT prophylaxis. All women were RGV naive and the prophylaxis regimens included RGV plus at least two other antiretroviral agents. At RGV initiation, the median gestational age was 36 weeks (range 34–38) and the median maternal plasma HIV-1 RNA viral load was 35,364 copies/ml (range 636–391,535). At delivery, the median gestational age was 38 weeks (range 37–40). The median exposure time to RGV was 17 days (range 7–32), with a mean maternal VL decay of 2.6 log. At delivery, seven women had undetectable (<50 copies/ml) VL, four had between 64 and 457 copies/ml, and in three VL was not available. All but one infant's HIV-RNA tests were negative at 1 and 3 months (one case of *in utero* MTCT). Raltegravir-containing antiretroviral regimens induced a rapid HIV-RNA decline in maternal VL at delivery, and were safe and effective in preventing MTCT for late-presenting, HIV-infected women.

T HE RISK OF HIV-1 MOTHER-TO-CHILD transmission (MTCT) is greater in the third trimester of pregnancy than in earlier gestational ages.[1] It is associated with maternal immune status, as well as with HIV-1 RNA plasma viral load at delivery.[2–4] As a consequence, reaching maximal suppression of the HIV-1 RNA viral load (VL) in plasma and the maternal genital tract before delivery is the main goal of anti-HIV treatment in pregnancy.[5] A recent multicenter cohort study in the United Kingdom concluded that in pregnant women with VL greater than 10,000 copies/ml (and especially greater than 100,000 copies/ml) at presentation, the probability of achieving a VL less than 50 or 1,000 copies/ml at delivery was compromised by initiation of antiretroviral (ARV) therapy later than 20 weeks of gestational age.[6]

In Brazil, a combination of at least three ARV agents is recommended for use in pregnancy. It usually consists of two nucleoside analogue reverse transcriptase inhibitors (NRTIs) with good placental passage, associated with a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted protease inhibitor (PI), and must take in account the previous

ARV history and comorbidities.[7] In addition, it is recommended that HIV-1 genotypic testing be performed before initiation of therapy (the standard test in Brazilian public laboratories is the TRUGENE HIV-1 Genotyping Assay, Siemens Healthcare).[8] However, due to a lack of time available for intervention in late-presenting pregnant women, a PI-based regimen is usually commenced, regardless of the availability of a resistance testing result.

Cases of vertical transmission represent approximately 90% of reported AIDS cases in individuals younger than 13 years in Brazil. Between 1980 and 2012, 17,539 cases were identified in children younger than 5 years in the country, representing 2.6% of all cases.[9] Recent studies reported a prevalence rate of vertical HIV transmission in Brazil that ranges from 2.5% to 8.6%.[10,11] Although there are only a few publications on late-presenting pregnant women, the available information suggests that poor access to prenatal care and HIV late diagnosis during pregnancy remain major problems in Bahia, Brazil.[10–12] Twenty percent of HIV pregnant women present beyond 28 weeks of pregnancy at the

[1]Centro Estadual Especializado em Diagnóstico, Assistência e Pesquisa, Salvador, BA, Brazil.
[2]Maternidade de Referência Professor José Maria de Magalhães Neto, Salvador, BA, Brazil.
[3]Laboratório de Pesquisas em Infectologia, Universidade Federal da Bahia, Salvador, BA, Brazil.

major HIV reference center in Bahia, which is also the main antenatal care service for HIV-infected women in the state. The majority of women have a VL at presentation higher than 10,000 copies/ml. In this population, reducing the plasma HIV-1 RNA VL to undetectable levels before delivery is a major challenge.

Raltegravir (RGV)-based regimens cause a significantly faster reduction in HIV-1 viral load (~2 log by week 2) in comparison to a conventional ARV combination.[13] Raltegravir is effectively transferred across the placenta barrier, causing a potential preloading effect for the neonate, and is considered a potential protective factor against *in utero* HIV transmission.[14,15] In addition, it also demonstrated a rapid and effective accumulation in cervicovaginal secretions.[16] These are desirable drug properties for prevention of HIV-1 MTCT, particularly among women who are going to have a vaginal delivery, when the infant is potentially exposed to genital tract virus during passage through the birth canal. These characteristics make RGV a potential pharmacologic candidate to prevent HIV-1 MTCT and treat late-presenting pregnant women.

We reviewed the medical records of 14 HIV-infected, late-presenting pregnant women in which RGV-based regimens were used to rapidly reduce maternal HIV-1 viral load. All women were attended in the period of 2010–2012. RGV was prescribed in the standard dose of 400 mg q12h for women presenting with gestational age higher than 34 weeks and detectable plasma viral load at first antenatal evaluation. The study was approved by the institutional review board.

All women were RGV naive, nine were ARV naive, but five had conceived on HAART and were previously exposed to a protease inhibitor. The prophylaxis regimens included RGV plus at least two other ARV agents. In some patients, RGV was added to the standard ARV regimen already on board. The ARV combination included zidovudine + lamivudine + lopinavir/r + raltegravir (6), zidovudine + lamivudine + raltegravir (5), zidovudine + lamivudine + darunavir/r + raltegravir (1), zido-vudine + lamivudine + tenofovir + darunavir/r + raltegravir (1), and zidovudine + lamivudine + atazanavir/r + raltegravir (1).

The median maternal age was 29.5 years (range 17–37). The median time since HIV infection diagnosis was 2.9 years (range 0–14), but 64% of the women were diagnosed during the current pregnancy. The median of previous gestations was 1.8 (range 0–7) and the median gestational age was 36 weeks (range 34–38). The mean CD4 cell count was 338 cells/ml (median 239 cells/ml, range 65–1.203 cells/ml) and the median maternal VL was 35,364 copies/ml (range 959–391,535). Five women had VL < 10,000 copies/ml, six had VL within the range of 10,000 to 100,000, while three women had VL > 100,000 copies/ml at RGV initiation.

At delivery, the median gestational age was 38 weeks (range 37–40). The median exposure time to RGV was 17 days (range 7–32), with a median maternal VL decay of 2.6 log. Seven women reached undetectable plasma VL at delivery (< 50 copies/ml), four had less than 500 copies/ml (range 64–457 copies/ml), and three did not have a VL measurement at the time of delivery (these women had VL results only a few days after childbirth). In these cases, one women had an undetectable plasma VL result 2 weeks after delivery (case 6), while in the remaining two, we detected 266 copies/ml for the first mother (case 1) after 3 weeks, while the second had 89 copies/ml (case 13) 1 week after delivery.

No maternal adverse events or obstetrical complications were reported. The mode of delivery was elective C-section in 10 women, emergency C-section in three, and vaginal in one woman. All women received zidovudine (ZDV) intravenous prophylaxis during labor and delivery, and all newborns received postexposure prophylaxis with ZDV for 6 weeks. The median infant birth weight was 2,950 g (range 2,055–3,380). The median APGAR score was 9 (range 6–10) and 10 (range 8–10) for evaluations at 1 and at 5 min, respectively. For infants, no adverse event or laboratory abnormality was reported during a postnatal observation period of at least 6 months.

TABLE 1. SUMMARY CHARACTERISTICS OF 14 HIV-INFECTED PREGNANT WOMEN WHO USED RALTEGRAVIR LATE IN PREGNANCY FOR HIV-1 PREVENTION OF MOTHER-TO-CHILD TRANSMISSION IN BAHIA, BRAZIL

Case	Gestational age at RGV initiation (weeks)	VL at RGV initiation (copies/ml)	ARV drugs during current pregnancy	Gestational age at delivery (weeks)	Exposure to RGV (days)	VL at delivery (copies/ml)	Decline of VL (log) from RGV initiation to delivery
1	35	61.505	ZDV + 3TC + LPV/r + RGV	37	7	Unknown	—
2	36	27.026	ZDV + 3TC + TDF + DRV/r + RGV	38	20	< 50	2.74
3	37	114.059	ZDV + 3TC + RGV	40	18	< 50	3.36
4	35	68.891	ZDV + 3TC + DRV/r + RGV	38	22	< 50	3.14
5	38	959	ZDV + 3TC + LPV/r + RGV	39	7	139	0.84
6	35	129.842	ZDV + 3TC + LPV/r + RGV	37	9	Unknown	—
7	36	391.535	ZDV + 3TC + LPV/r + RGV	39	32	< 50	3.90
8	37	7.361	ZDV + 3TC + RGV	39	15	64	3.06
9	35	15.957	ZDV + 3TC + LPV/r + RGV	38	18	< 50	2.51
10	36	95.734	ZDV + 3TC + ATV/r + RGV	39	17	457	2.33
11	36	43.703	ZDV + 3TC + RGV	38	17	194	2.36
12	34	5.408	ZDV + 3TC + RGV	37	7	< 50	2.04
13	37	6.168	ZDV + 3TC + LPV/r + RGV	39	14	Unknown	—
14	35	4.665	ZDV + 3TC + RGV	38	25	< 50	1.97

RGV, raltegravir; VL, viral load; ARV, antiretroviral; ZDV, zidovudine; 3TC, lamivudine; TDF, tenofovir; LPV/r, lopinavir/r; ATV/r, atazanavir/r; DRV/r, darunavir/r.

The HIV-1 RNA was undetectable (<50 copies/ml) at 1 month, with confirmation of the result at 3 months of age in 14 infants (one twin pregnancy), but one HIV-1 MTCT case was detected (a likely *in utero* transmission). The baby was born with a cutaneous rash, hepatosplenomegaly, anemia, thrombocytopenia, and a plasma viral load of >500,000 copies/ml after 1 week. An identical result was obtained after 4 weeks of life. In this case, maternal VL at delivery was 64 copies/ml, and the mode of delivery was a C-section. Table 1 contains the summary characteristics of the 14 patients included in this report.

In this case series we observed a rapid decay in HIV-1 RNA plasma viral load of late-presenting pregnant women treated with an RGV-containing antiretroviral regimen. The use of RGV was not associated with adverse events either for the mothers or for their babies. The only case in which we detected an HIV-1 MTCT was considered as an *in utero* transmission, and probably occurred before initiation of therapy. RGV was safe and effective in avoiding HIV-1 MTCT in women who presented to their first antenatal evaluation only after 34 weeks of gestational age.

Although there is limited information on the use of RGV in pregnancy,[17,18] this drug is well tolerated, and has a low potential for drug–drug interactions.[19] HIV-infected mothers are usually prescribed numerous medications for treatment/prophylaxis. For this population, tolerability and a potential drug–drug interaction profile are important aspects to be considered when choosing an ARV regimen.

Previous studies have shown that raltegravir-based regimens promote a very rapid decline in viral load.[13] In 2010, Pinnetti *et al.* found that adding RGV plus tenofovir to a regimen containing ZDV + lamivudine + darunavir/r resulted in a 2.4 log viral load decline in maternal VL in only 9 days.[20] The mean viral load decline of 2.6 log observed after approximately 17 days of RGV use in our report is consistent with these results. In another small case series, Westling *et al.* showed that adding RGV to four late-presenting, HIV-1-infected pregnant women induced a rapid decay of plasma VL, with no adverse event, and no MTCT.[21] Again, the speed of VL reduction was impressive, with a mean 1.12 log decline per week of use of RGV.

Our results confirm these previous findings. In our case series we treated a larger number of women than described in previous reports, and an identical viral load result was similarly obtained. One important point is the absence of MTCT in a population of late-presenting HIV-1-infected pregnant women (mean gestational age of 36 weeks). The use of RGV was quite safe for both mothers and babies, with no unexpected adverse events detected.

The recommendations of most international guidelines indicate the use of RGV in pregnant women "in special conditions" only.[5,22] However, in the 2012 Perinatal DHHS recommendations, RGV was moved from "nonrecommended drug" to "use in special situations," which should be the case with intolerance to other ARV drugs or resistance issues.[5] In this guideline, there is a clear recommendation to use optimal drug regimens, regardless of pregnancy. The specific recommendations for pregnant women include considerations of potential changes in pharmacokinetics (dosing requirements), safety issues (ability of pregnant women to adhere to a regimen), and potential short-term and long-term effects of the ARV on the fetus and newborn (which are unknown for many drugs). The scarce evidence on these points for RGV-containing regimens is still a limitation for its use, but the available information suggests it can be considered a safe and efficacious option for treating pregnant women.[19,21]

In conclusion, in this case series, RGV-containing regimens were well tolerated and were associated with an impressive, rapid viral load decay of maternal VL at delivery, suggesting that RGV is a useful and safe ARV drug to reduce HIV-1 MTCT in late-presenting, HIV-infected pregnant women.

Author Disclosure Statement

No competing financial interests exist.

References

1. Senise JF, Palacios R, Tanno ZN, *et al.:* HIV-1 viremia during the first 28 weeks of pregnancy is not associated with mother-to-child transmission. Braz J Infect Dis 2006;10(4):259–263.
2. The European Collaborative Study: Maternal viral load and vertical transmission of HIV-1: An important factor but not the only one. AIDS 1999;13(11):1377–1385.
3. Warszawski J, Tubiana R, Le Chenadec, *et al.:* Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS French Perinatal Cohort. AIDS 2008;22(2):289–299.
4. Tubiana R, Le Chenadec J, Rouzioux C, *et al.:* Factors associated with mother-to-child transmission of HIV-1 despite a maternal viral load <500 copies/ml at delivery: A case-control study nested in the French perinatal cohort (EPF-ANRS CO1). Clin Infect Dis 2010;50(4):585–596.
5. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed 1/8/13.
6. Read PJ, Mandalia S, Khan P, *et al.:* When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? AIDS 2012;26(9):1095–1103.
7. BRASIL. Ministério da Saúde. Programa Nacional de DST e Aids. Recomendações para Profilaxia da Transmisão Vertical do HIV e Terapia Antirretroviral em Gestantes. Brasília, 2010.
8. BRASIL. Ministério da Saúde. Programa Nacional de DST e Aids. Recomendações de terapia antirretroviral para adultos vivendo com HIV/aids no Brasil 2012. Versão Preliminar. Brasília, 2012.
9. Ministério da Saúde. Secretaria de Vigilância em Saúde. Boletim Epidemiológico AIDS-DST. Ano IX no. 01. Brasília, Ministério da Saúde, 2012.
10. Lemos LM, Rocha TF, Conceição MV, *et al.:* Evaluation of preventive measures for mother-to-child transmission of HIV in Aracaju, State of Sergipe, Brazil. Rev Soc Bras Med Trop 2012;45(6):682–686.
11. da Cruz Gouveia PA, da Silva GA, and de Fatima Pessoa Militão de Albuquerque M: Factors associated with mother-to-child transmission of the human immunodeficiency virus in Pernambuco, Brazil, 2000–2009. Trop Med Int Health 2013;18(3):276–285.
12. Nóbrega I, Netto EM, and Brites C: Barriers to prevention of HIV type 1 mother-to-child-transmission in Bahia, Brazil. AIDS Res Hum Retroviruses 2012;28(3):233–234.

13. Lennox JL, DeJesus E, Lazzarin A, et al.: Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naïve patients with HIV-1 infection: A multicentre, double-blind randomised controlled trial. Lancet 2009;374(9692):796–806.

14. McKeown DA, Rosenvinge M, Donaghy S, et al.: High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women. AIDS 2010; 24(15):2416–2418.

15. Hegazi A, Mc Keown D, Doerholt K, et al.: Raltegravir in the prevention of mother-to-child transmission of HIV-1: Effective transplacental transfer and delayed plasma clearance observed in preterm neonates. AIDS 2012;26(18):2421–2423.

16. Else LJ, Taylor S, Back DJ, et al.: Pharmacokinetics of antiretroviral drugs in anatomical sanctuary sites: The male and female genital tract. Antivir Ther 2011;16(8):1149–1167.

17. Jaworsky D, Thompson C, Yudin MH, et al.: Use of newer antiretroviral agents, darunavir and etravirine with or without raltegravir, in pregnancy: A report of two cases. Antivir Ther 2010;15(4):677–680.

18. Taylor N, Touzeau V, Geit M, et al.: Raltegravir in pregnancy: A case series presentation. Int J STD AIDS 2011;22(6): 358–360.

19. Adams JL, Greener BN, and Kashuba AD: Pharmacology of HIV integrase inhibitors. Curr Opin HIV AIDS 2012;7(5):390–400.

20. Pinnetti C, Baroncelli S, Villani P, et al.: Rapid HIV-RNA decline following addition of raltegravir and tenofovir to ongoing highly active antiretroviral therapy in a woman presenting with high-level HIV viraemia at week 38 of pregnancy. J Antimicrob Chemother 2010;65(9):2050–2052.

21. Westling K, Pettersson K, Kaldma A, et al.: Rapid decline in HIV viral load when introducing raltegravir-containing antiretroviral treatment late in pregnancy. AIDS Patient Care STDS 2012;26(12):714–717.

22. European AIDS Clinical Society (EACS) guidelines for the clinical management and treatment of HIV-infected adults. Available at http:// europeanaidsclinicalsociety.org/images/ stories/EACS-Pdf/EACSGuidelines-v6.1-English-Nov2012 .pdf. Accessed 1/8/13.

Address correspondence to:
Isabella Nóbrega
Av. Prof. Sabino Silva, 862, Jd. Apipema
Salvador, BA 40155-250
Brazil

E-mail: isabellasal@gmail.com