OBJECTIVE: To describe the impact of initiating raltegravir (RAL)-containing combination antiretroviral therapy (cART) regimens on HIV viral load (VL) in pregnant women who have high or suboptimal VL suppression late in pregnancy. 

METHODS: HIV-infected pregnant women who started RAL-containing cART after 28 weeks' gestation from 2007 to 2013 were identified in two university hospital centres.

RESULTS AND DISCUSSION: Eleven HIV-infected women started RAL at a median gestational age of 35.7 weeks (range 31.1 to 38.0 weeks). Indications for RAL initiation were late presentation in pregnancy (n=4) and suboptimal VL suppression secondary to poor adherence or viral resistance (n=7). Mean VL at the time of RAL initiation was 73,939 copies/mL (range <40 to 523,975 copies/mL). Patients received RAL for a median of 20 days (range one to 71 days). The mean decline in VL from the time of RAL initiation to delivery was 1.93 log, excluding one patient who received only one RAL dose and one patient with undetectable VL at the time of RAL initiation. After eight days on RAL, 50% of the women achieved a VL <1000 copies/mL (the threshold for recommended Caesarean section to reduce the risk for perinatal transmission). There were no cases of perinatal HIV transmission.

CONCLUSION: The present study provides preliminary data to support the use of RAL-containing cART to expedite HIV-1 VL reduction in women who have a high VL or suboptimal VL suppression late in pregnancy, and to decrease the risk of HIV perinatal transmission while avoiding Caesarean section. Further assessment of RAL safety during pregnancy is warranted.

Key Words: HIV-1; Integrase inhibitor; Pregnancy; Raltegravir; Viral load.

More than one-half of the cases occurring during the late antenatal period and delivery (3). The risk of perinatal transmission is proportional to maternal plasma VL at delivery (4). Therefore, reaching maximal viral suppression before delivery is the main goal of antiretroviral treatment in pregnancy. To further reduce the risk of transmission, North American guidelines recommend elective Caesarean.
delivery at 38 weeks' gestation for women when the last measured VL is >1000 copies/mL (4,5).

Late presentation of pregnant women with HIV, either due to limited or absent prenatal care or acquisition of HIV in late pregnancy, continues to occur and hinders the timely initiation of HIV perinatal transmission preventive measures (6). An Italian cohort study reported that 16% of new HIV-infection diagnoses during pregnancy occurred in the third trimester (7), and 20% of HIV-infected pregnant women presented beyond 28 weeks of pregnancy at the major HIV reference centre in Bahia, Brazil (8). Canadian data reported by the Perinatal HIV Surveillance Program found that between 1997 and 2011, 13% of the HIV-infected pregnant women received no antiretroviral therapy and 17% received <4 weeks of antiretrovirals (9). In 2011 in Canada, 10% of HIV-infected pregnant women had received none or <4 weeks of antiretrovirals. Because women continue to present in late pregnancy with suboptimal VL suppression despite the availability of cART, new therapeutic modalities are required to achieve a prompt decline of HIV VL to decrease the risk of perinatal transmission, potentially also obviating the need for an HIV-indicated Caesarean section.

Raltegravir (RAL) is an HIV-1 integrase strand transfer inhibitor that leads to potent viral suppression while maintaining a favourable adverse effect profile and minimal drug interactions (10). Its effectiveness to rapidly control HIV VL has been demonstrated in patients with drug resistance as well as in the antiretroviral-naïve population (11-14). Although there are limited data regarding the use of RAL in pregnancy, there is increasing anecdotal evidence of its efficacy to rapidly reduce maternal VL when used as a part of cART regimens late in pregnancy, with few maternal side effects and no detrimental effects on the fetus (8,15-26).

The objective of our case series was to describe the impact of initiating RAL-containing cART regimens on HIV VL in pregnant women who have high or suboptimal VL suppression late in pregnancy.

METHODS
A retrospective review of two Canadian HIV perinatal databases (those of the Oak Tree Clinic at BC Women's Hospital, Vancouver, British Columbia, and of the Grossesse Avec Maladie Infectieuse clinic at Sainte-Justine Hospital, Montreal, Quebec) was conducted to identify HIV-infected pregnant women who initiated treatment with RAL (400 mg twice per day orally) after 28 weeks’ gestation. Data collected between 2007, the year when RAL became available, and December 2013 were reviewed. Each patient's chart was then retrospectively abstracted for data including RAL indication, tolerability, and exposure and timing of use.

The standard of care in both clinics included treatment of HIV-infected pregnant women with cART regardless of baseline CD4 cell count and HIV-1 VL, as well as assessment of the women's clinical, virological and immunological status every four weeks. Toxicity due to the antiretrovirals was monitored at these times. Infants were evaluated at least at birth, two weeks of age, one month of age and then every three to four months until 18 months of age. HIV-negative status in infants was defined presumptively by at least two negative HIV RNA polymerase chain reaction test results before four months of age, and confirmed by the absence of HIV-1 antibody at 18 months of age.

Maternal and neonatal adverse reactions were systematically addressed according to WHO criteria (27), with specific attention devoted to hematological and hepatic complications.

HIV-1 VL was measured either using the Ultrasensitive Amplicor HIV-1 Monitor Test or COBAS TaqMan HIV-1 Test, v1.0 (Roche Molecular Systems Inc, USA) for cases in Vancouver, and the Abbott RealTime HIV-1 assay (Abbott Molecular Inc, USA) for cases in Montreal.

The study was approved by the institutional review board of each centre.

Statistics
A descriptive analysis of population characteristics was performed. Because of the non-normal distribution, median and range are reported.

RESULTS
A total of 11 women who initiated RAL during the third trimester of their pregnancies were identified. Their clinical and laboratory characteristics are summarized in Table 1. The median age was 31 years (range 21 to 39 years). Five were antiretroviral-naïve before pregnancy. Three women (cases 3, 5 and 7) had a new diagnosis of HIV during the current pregnancy. The median gestational age at their first clinic visit was 24 weeks (range seven to 35 weeks). The median duration of consistent cART received was 42 days (range seven to 202 days). The women had any previous exposure to RAL. Indications for RAL were late presentation in pregnancy (n=4) and suboptimal VL reduction secondary to poor adherence or viral resistance (n=7). All patients received RAL in combination with at least two other active antiretroviral agents, started at a median gestational age of 35.7 weeks (range 31.1 to 38.0 weeks). Exposure duration was a median of 20 days (range one to 71 days). Five women received <2 weeks of RAL.

The median gestational age at delivery was 38.7 weeks; one patient (case 9) delivered at 35 weeks in a context of spontaneous preterm labor. At the time of delivery, nine women had a HIV VL <1000 copies/mL, of which seven were <50 copies/mL. Figure 1 summarizes the typical VL evolution after RAL initiation.

Among the 11 women, three had a vaginal delivery, three had a Caesarean section for obstetrical indications and five had a Caesarean section to further decrease the risk of HIV perinatal transmission. Three of these Caesarean sections could have been avoided (ie, the VL was below threshold of 1000 copies/mL) if the HIV VL had been known at the time of the delivery.

Maternal RAL was discontinued after delivery in all 11 cases. There were no cases of HIV perinatal transmission observed in the in utero-exposed infants. One infant was believed to be breastfed (case 2). One infant (case 11) presented a transient symptomatic cardiac arrhythmia at birth, as well as unilateral hydronephrosis and skin abnormalities (necresis, four nipples), which were not prenatally diagnosed.

The following two cases were excluded from subsequent analysis:

- One woman (case 3) had an undetectable VL at RAL initiation. She was initially started with a combination regimen with zidovudine, lamivudine and ritonavir-boosted lopinavir at 28 weeks and four days. However, she had adherence issues in a context of a newly diagnosed HIV infection in pregnancy with hepatitis C coinfection and substance use. The woman was admitted for directly observed therapy and RAL was started at 33 weeks to rapidly suppress her VL. At the time of RAL initiation, the last available VL result (measured two weeks previously) was 1762 copies/mL, and the woman reported poor adherence to her cART regimen during this time period. Retrospectively, it was determined that at the time of RAL initiation, her VL was undetectable; however, because of concerns surrounding adherence and risk of resistance rise, RAL was pursued. The woman discharged herself from hospital for three days at approximately 35 weeks' gestation but returned with a positive urine cocaine screen. She had a vaginal delivery at 38 weeks and five days' gestation with a confirmed undetectable VL.

- One woman (case 10) received only one dose of RAL. Her pregnancy had been complicated by poor adherence and intolerance to cART. At 37 weeks' gestation, she was admitted for supervised cART and her VL was found to be 232,245 copies/mL. As soon as this result was known, RAL was added to her regimen to attempt a rapid and maximal suppression of the HIV VL before delivery. However, 3 h after receiving the first dose of RAL the woman experienced spontaneous rupture of membranes and went into active labour.

In the remaining nine women, median VL at RAL initiation was 88,707 copies/mL (range 246 to 523,975 copies/mL; mean 73,959 copies/mL). The mean decline of VL from time of RAL...
initiation to delivery was $1.93 \log_{10}$ copies/mL (95% CI 1.32 to 2.53 $\log_{10}$ copies/mL) (Figure 1). In the four women who received <2 weeks of RAL, the mean VL decrease was 1.82 $\log_{10}$ copies/mL. In the four women who had an initial VL > 4 $\log_{10}$ copies/mL, the mean decrease was 2.65 $\log_{10}$ copies/mL. After eight days on RAL, 50% of the women achieved a VL < 1000 copies/mL (Figure 2). Similarly, 50% of the women achieved a VL < 50 copies/mL after 26 days on RAL.

Only one maternal adverse event was observed (case 6). An asymptomatic elevation of liver enzyme levels (11- and fivefold the upper limit of normal of alanine aminotransferase and aspartate aminotransferase, respectively) was noted in a woman for whom RAL was added to a combination of zidovudine, lamivudine and ritonavir-boosted lopinavir because of late presentation. The elevation of liver enzyme levels was first observed after five days on RAL, without signs of preeclampsia or cholestasis. The status regarding hepatitis A, B and C infections was confirmed to be negative. After RAL discontinuation, liver enzyme levels immediately began to decrease significantly. This case has previously been described by the authors’ team (23).

### Table 1

| Case | Age, years | ART status | Coinfection | ART used during pregnancy (in addition to RAL) | Indications for RAL initiation | GA at RAL initiation (weeks) | CD4 at RAL initiation (cells/µL) | VL at RAL initiation (copies/mL) | VL at delivery (copies/mL) | Exposure to RAL (days) | Mode of delivery | VL decrease (log$_{10}$ copies/mL) | Peripartum prophylaxis | Infant prophylaxis | Infant HIV status |
|------|------------|------------|-------------|-----------------------------------------------|-------------------------------|-----------------------------|-------------------------------|-------------------------------|---------------------------|----------------------|---------------------|-------------------|---------------------|---------------------|------------------|------------------|
| 1    | 31         | Exp        | –           | ABC+3TC +ATZ/r                                | VL rebound despite dose adjustment | 34.1                         | 437                           | 1562                          | 40                        | 43                   | 1.59                | Urgent C-section for labour dystocia | AZT IV + 3TC        | Neg               |
| 2    | 24         | Exp        | –           | AZT+3TC +LPV/r                                | VL rebound due to resistance   | 36.4                         | 440                           | 1003                          | 41                        | 8                    | 1.39                | Elective C-section for perinatal transmission prophylaxis | AZT IV + 3TC        | Neg               |
| 3    | 39         | Naive      | HCV         | AZT+3TC +LPV/r                                | Late initiation of ART, fear of resistance due to compliance issues | 33.4                         | 308                           | <40                           | <40                       | 34                   | 0.00                | Vaginal delivery | AZT IV + 3TC        | Neg               |
| 4    | 33         | Exp        | –           | AZT+3TC +LPV/r                                | Late presentation              | 35.0                         | 54                            | 208,993                       | 154                       | 20                   | 3.13                | Elective C-section for perinatal transmission prophylaxis | AZT IV + 3TC        | Neg*              |
| 5    | 36         | Naive      | –           | AZT+3TC +LPV/r                                | VL rebound despite adequate drug levels | 35.7                         | 357                           | 246                           | <40                       | 25                   | 0.79                | Emergent C-section for nonassuring fetal heart rate and chorioamnionitis | AZT IV + 3TC        | Neg*              |
| 6    | 34         | Naive      | –           | AZT+3TC +LPV/r                                | Late presentation              | 36.3                         | 132                           | 523,975                       | 1163                      | 11                   | 2.65                | Elective C-section for perinatal transmission prophylaxis | AZT IV + 3TC        | Neg               |
| 7    | 35         | Naive      | –           | AZT+3TC +LPV/r                                | VL rebound                     | 37.6                         | 484                           | 695                           | <40                       | 13                   | 1.24                | Vaginal delivery | AZT IV + 3TC        | Neg               |
| 8    | 21         | Exp        | –           | AZT+3TC +LPV/r                                | Late presentation, multi-class genotypic resistance | 31.1                         | 168                           | 26,770                        | <40                       | 71                   | 2.83                | Emergent C-section for nonassuring fetal status and placental abruption | AZT IV + 3TC        | Neg               |
| 9    | 29         | Exp        | HCV         | ABC+3TC +DRV/r, ABC+3TC +LPV/r                | VL rebound after interruption of ART | 34.0                         | 210                           | 32,830                        | 338                       | 7                    | 1.99                | Elective C-section for perinatal transmission prophylaxis | AZT IV + NVP po + 3TC + NFV | Neg               |
| 10   | 29         | Naive      | HCV         | TDF+FTC +ATZ/r                                | VL rebound after interruption of ART | 38.0                         | 50                            | 15,153                        | 15,153                    | 1                    | NA                  | Elective C-section for perinatal transmission prophylaxis | AZT IV + NVP po + 3TC + NFV | Neg               |
| 11   | 22         | Naive      | –           | TDF+FTC +ATZ/r then ABC+3TC +ATZ/r             | VL rebound after interruption of ART | 36.0                         | 600                           | 2287                          | <40                       | 35                   | 1.76                | Vaginal delivery | AZT IV            | Neg               |

*Confirmatory HIV serology at 18 months is pending. 3TC Lamivudine; ABC Abacavir; ATZ/r Atazanavir/ritonavir; ART Antiretroviral therapy; AZT Zidovudine; C-section Caesarean section; DRV/r Darunavir/ritonavir; Exp Experienced; FTC Emtricitabine; GA Gestational age; HCV Hepatitis C virus; IV Intravenous; LPV/r Lopinavir/ritonavir; NA Not applicable; Neg Negative; NVP Nelfinavir; NVP Nevirapine; RAL Raltegravir; TDF Tenofovir; VL HIV RNA viral load
We observed a 1.82 log_{10} copies/mL decrease in HIV VL within two weeks of receipt of a RAL-containing cART regimen, which is faster than the mean time of approximately five weeks to suppression that is typically observed with traditional cART (33). This finding is consistent with the VL reductions (2 log_{10} copies/mL within 10 to 14 days of receipt of a RAL-based regimen) observed in randomized controlled trials using RAL-based regimens (12-14) and randomized controlled trials using RAL-based regimens (12-14)
in observational studies investigating RAL administration late in pregnancy (8,15,16,18,21).

The reported case of liver toxicity (23) is, to our knowledge, the second that has been described with RAL use in pregnancy (29). Although hepatotoxicity is one of the well-recognized side effects of antiretroviral drugs, it has not been commonly associated with RAL therapy, with increase of aspartate aminotransferase and alanine aminotransferase levels >5 times the upper limit of normal seen in only 5% of exposed individuals (31,34). Sufficient data are not yet available to conclude whether the risk of hepatotoxicity is higher in pregnancy. Close follow-up of liver enzyme levels in pregnant women treated with RAL would be prudent until more safety data are available.

RAL has not been associated with any congenital anomalies (31). The infant who was diagnosed with cardiac arrhythmia, unilateral hydrenephrosis and skin anomalies had been exposed to RAL in utero for 35 days, starting at 36 weeks’ gestation. Because of this timing, the congenital anomalies are not likely related to RAL exposure. However, safety data regarding RAL exposure in pregnancy are weak, and it remains a category C drug (31).

Considering the potential advantages of RAL noted above, it remains to be determined whether its ability to rapidly reduce VL in late pregnancy will reduce the need for Caesarean delivery and the rate of perinatal transmission for women who present near term with high VL. This would benefit HIV-infected women, particularly those with low CD4 cell counts, considering the increased risk of postpartum complications related to Caesarean delivery (35,36). An important factor to consider, however, is the availability of rapid HIV quantitative test to follow the VL and allow for a safe vaginal delivery. Indeed, in previously published cases of pregnant women treated with RAL (8,15,16,18,20-22,24-26) as well as in the three cases presented here, VL were retrospectively found to be <1000 copies/mL after Caesarean section was performed to decrease the risk of perinatal transmission. Availability of rapid HIV quantitative polymerase chain reaction would assist the clinician to better decide whether Caesarean delivery is indicated, according to their national guidelines (4,5).

CONCLUSIONS

Our findings support the consideration of the use of RAL to reduce the risk of perinatal transmission in late-presenting HIV-infected pregnant women and in women with VL rebound near term. However, long-term data are needed to assess the impact of RAL use for short-term therapy in the obstetrical setting on the resistance profile. Indeed, there is a legitimate concern about the effectiveness of future RAL-based regimens. Moreover, current Canadian (5) and United States perinatal guidelines (4) are permissive but do not advocate for RAL use in this setting due to the lack of established data. The results of two ongoing clinical trials (NCT01854762 and NCT01618305) will help to assess advantages of RAL compared with other antiretroviral drugs in pregnancy. Further research needs to be performed to understand the role of RAL in women with HIV acquisition in pregnancy, who are at even higher risk for perinatal transmission.

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