A Review of the Efficacy, Safety, and Pharmacokinetics of Raltegravir in Pregnancy

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6th International Workshop on HIV & Women, February 21-22, 2015, Seattle, WA
Abstract No. P_30

Abstract

- Recent pregnancy guidelines recommend raltegravir as a preferred integrase treatment option.
- Data from published articles and preliminary meeting reports between 2001 and July 2015 are reviewed.
- The **standard raltegravir dose** appears **safe** and **effective** in **preventing mother to child transmission** (MTCT) in late pregnancy presenters with unknown or unsuppressed viral load, or in multi-drug resistance.
- Raltegravir was well tolerated. No infant adverse effect was consistently reported.

Introduction

- Early and sustained virological control is associated with a lower risk of MTCT. Integrase inhibitor-based regimens are observed to suppress viral load rapidly.
- The DHHS guidelines have recently recommended raltegravir as a preferred option for initial therapy in pregnancy. This review was undertaken to collate available data on raltegravir use in pregnancy, including first trimester use, late pregnancy presenters, uncontrolled viremia, or multi-drug resistance.

Methods

- A search was performed on March and June 2015 in EMBASE, Google Scholar, MEDLINE, PubMed, and Web of Science
- Key words: (*raltegravir* OR *RAL* OR *Isentress* OR *MK-0518*), (*pregnan**) AND (*HIV* OR *HIV-1* OR *human immunodeficiency virus*)
- Results of all languages, published after 2001, were included.

Results and Discussion

- A total of 278 maternal-infant pairs (69% from retrospective case reports/series, 31% from 3 prospective clinical studies, ~50% peer-reviewed data) were reviewed.
- 87% were from resource-rich settings. Maternal ARV history: 9.3% naïve, 33% experienced, 58% not reported. 83% (122/147 cases) received ZDV infusion at delivery and 79% (143/182 cases) underwent Caesarean section.
- **Maternal outcomes were not frequently reported**. The only consistently reported effect was a reversible and transient increase in liver transaminase.
- **Most infants were born without adverse outcomes**; of the reported events, there was no consistency among type or severity.
- **There were 2 cases where the infant tested positive after birth**: one was likely an in utero transmission before initiation of raltegravir, while details on maternal viral load at delivery, drug resistance and adherence were lacking in the second case.

Pharmacokinetic Properties of Raltegravir

- Physiologic changes in pregnancy lowers maternal raltegravir exposures, often with subtherapeutic trough plasma concentrations, but **MTCT was not observed**.
- Rapid and **high transplacental passage**, **prolonged neonate elimination**, and **high cervicovaginal fluid:blood plasma ratios** contribute to the potential use of raltegravir for infant preexposure prophylaxis.
- Adherence may be a factor in the rate of viral decay.

Limitations and Areas for Further study

- The quality and type of reports available (Table 1) varied significantly, and maternal and infant characteristics failed to be reported in a consistent manner.
- The **number of cases** reviewed is too **small** to rule out uncommon toxicities or potential increases in birth defect prevalence in pregnancy, or to generalize findings to the use of alternative integrase inhibitor.

Conclusions

- Due to the inherent **pharmacokinetic variability** of raltegravir, the highly variable but overall reduced maternal plasma raltegravir levels do **not appear to affect viral suppression**.
- The **viral decay** associated with raltegravir treatment is reliably **rapid** and most women delivered at undetectable viral levels.
- Raltegravir is **highly transferred across placenta** and has **prolonged elimination in the neonate**. These two properties support its efficacy in preventing MTCT.
- There is evidence for **maternal safety** with the exception of transient increase in maternal transaminases. However, the relation to raltegravir is unclear.
- **No infant adverse effect** was consistently reported.
- **Raltegravir 400 mg twice daily** appears **efficacious** and **safe** for both ARV-naïve and ARV-experienced **pregnant women**.

Acknowledgements

- Sandra Shan Jiang prepared the presentation poster.

Declaration of Interest

- AM declares no conflict of interest.
- SW has served on advisory boards and spoken at CME events for AbbVie, Bristol-Myers Squibb, Gilead, Merck and ViiV.
- AT has served on advisory boards and spoken at CME events for Gilead, Janssen and Merck.

Table 1 Maternal and infant characteristics in which raltegravir was used in pregnancy

1a Prospective clinical studies

ARV treatment history (Reference)	n	Age (years)	RAL indication	Time RAL initiated	Duration of RAL exposure (weeks)	Concomitant ARVs	Baseline HIV RNA (copies/ mL)	HIV RNA at delivery (copies/ mL)	ZDV infusion at delivery
NR (Blonk et al. Clin Infect Dis 2015.)	22	33 (29-36)	Rapid viral suppression; optimization of therapy; intolerant to other ARVs	32% before conception 9% first trimester 27% second trimester 32% third trimester	NR	68% NRTI 59% PI 9% NNRTI 9% entry inhibitor	NR	86% <50	NR
NR (Watts et al. JAIDS 2014.)	42	30 (19-43)	NR	NR	56 (2-225) weeks	49% two or more NRTI's 2% NRTI's plus NNRTI 41% NRTI plus PI 5% NRTI/NNRTI/PI	NR	92% <400 <48 (20-52066) (n=39)	NR
NR (Clarke et al. JAIDS 2014.)	22	NR	NR	At least two weeks before conception	NR	NR	NR	NR	NR

1b Peer reviewed case studies and series

ARV treatment history (Reference)	n	Age (years)	RAL indication	Time RAL initiated	Duration of RAL exposure (weeks)	Concomitant ARVs	Baseline HIV RNA (copies/ mL)	HIV RNA at delivery (copies/ mL)	ZDV infusion at delivery
Naïve (De Hoffer et al. J Chemother 2013.)	1	31	Rapid viral suppression	35 weeks	2.7	ZDV, 3TC, LPV/r	8903	20	Yes
Naïve (Hegazi. Int J STD AIDS 2013.)	1	28	Rapid viral suppression	28 weeks	10.1	TDF, FTC, SQV/r	1.74 x 10^7	208	Yes
Naïve (Renet et al. J Obstet Gynaecol Can 2013.)	1	34	Rapid viral suppression	36 weeks	1.7	ZDV, 3TC, LPV/r	523 975	376 with 2.58 logs (11 days after delivery)	Yes
Naïve (Westling et al. AIDS Pat Care STDS 2012.)	4	26.5 (16-29)	Rapid viral suppression; late presenter	35.5 (31-37) weeks	2.4 (1.1 – 7.0)	dual NRTI + PI	217 000 (65 600 – 637 000)	764 (<20 – 2700)	75% Yes
20% naïve (Taylor et al. Int J STD AIDS 2011.)	5	39 (32-39)	Rapid viral suppression; optimization of therapy; intolerance to other ARVs; late presenter	34 (33-34) weeks	3.3 (2.4 – 6.6)	40% dual NRTI 20% NRTI + PI 20% dual NRTI + PI 20% dual NRTI + PI + fusion inhibitor	4.25 (1.71 – 5.43) [log copies]	60% <1.60 log copies/mL	Yes
50% naïve (McLaughlin et al. J AIDS Clin Res 2014.)	8	32.5 (21-41)	Rapid viral suppression; intolerance to other ARVs	36 (21-39) weeks	1 (0-18)	75% dual NRTI + PI 25% dual NRTI	41 083 (201-351 321)	911 (<20 – 13 717)	NR
54% naïve (Boucoiran et al. Can J of Infect Dis & Med Micro 2015.)	11	31 (21-39)	Late presenter; multi-class resistance; suboptimal adherence	35.7 weeks (31.1-38.0)	2.9 (0.1 – 10.1)	dual NRTI + PI	73 959 (<40 – 523 975)	82% <1000 64% <50	Yes
Experienced (Adeyemo et al. Int J STD AIDS 2013.)	3	NR	Optimization of therapy	38 weeks	2	NR	23 984	2 log viral decay	NR
Experienced (Cha et al. J Int Assoc Provid AIDS Care 2013.)	1	30	Rapid viral suppression	33 weeks	5	ZDV, 3TC, LPV/r	106 110	200	Yes
Experienced (Jaworsky et al. Antiviral Ther 2010.)	1	19	Multi-class resistance	21 weeks prior to conception	61	3TC, ZDV, TDF, ETR, DRV/r	185 719	<50	NR
Experienced (Shust et al. J Pedia Infect Dis Soc 2014.)	6	21	Multi-class resistance	NR	NR	NR	NR	60% <400	Yes
NR (Nobrega et al. AIDS Res Hum Retroviruses 2013.)	14	29.5 (17-37)	Late presenter	36 (34-38) weeks	2.5 (1-4.5)	57% dual NRTI + PI 36% dual NRTI 7% 3 NRTI + PI	35 364 (959-391 535)	50% <50 29% <500 (n=11)	Yes

1c Preliminary meeting reports and letters to the editor

ARV treatment history (Reference)	n	Age (years)	RAL indication	Time RAL initiated	Duration of RAL exposure (weeks)	Concomitant ARVs	Baseline HIV RNA (copies/ mL)	HIV RNA at delivery (copies/ mL)	ZDV infusion at delivery
Naïve (Saxon et al. HIV Med 2013.)	1	35	Rapid viral suppression	39 weeks	1.9	TDF, FTC, LPV/r	3057	<40	Yes
8% naive (Rosenvinge et al. HIV Med 2012.)	59	31	High VL; intolerance to other ARVs; resistance to other ARVs; late presenter; preloading of neonate in threatened preterm birth; planned amniocentesis	31 weeks	9 weeks	Median 2 ART classes	957 (<20 – 17 400 000)	65% <50 93% <400	63% Yes
20% naïve (Cecchini et al. Enfermedades Infecciosas y Microbiologia Clinica 2014.)	10	19 (18-31)	Late presenter; optimization of therapy; part of initial HAART	NR	4.4 (1 – 6.6)	2 NRTI + PI/r	2445 (<50 – 28.100)	80% <50	Yes
Experienced (Croci et al. Eur J Clin Pharmacol 2012.)	1	22	Multi-class resistance	Since conception	39	TDF, FTC, LPV/r	<20	<20	Yes
Experienced (Lopez-Varela et al. An Pediatr (Barc) 2012.)	1	17	Rapid viral suppression	36 weeks	4	ZDV, 3TC, LPV/r	1902	Undetectable	NR
Experienced (McKeown et al. AIDS 2010.)	3	32 (26-39)	Multi-class resistance; intolerance to other ARVs; suboptimal adherence; late presenter	35 (28-39) weeks	6 (2-12)	33% dual NRTI + PI 33% dual NRTI + NNRTI 33% 3 NRTI + NNRTI	22 507 (183 – 67 100)	66% <40 100% <400	66% Yes
Experienced (Pinnetti et al. J Antimicrob Chemother 2010.)	1	NR	Rapid viral suppression	38 weeks	1.3	TDF, ZDV, 3TC, DRV/r	75 584	260	Yes
NR (Jeantils et al. 53rd Int Conf on Antib & Antib Chemo 2013.)	28	31 (18-42)	Part of initial HAART; intolerance to other ARVs; suboptimal adherence; late presenter	18% before pregnancy	11	NR	13 647 (61-114638)	80% <40	Yes
NR (Leonard et al. HIV Med 2014.)	8	NR	NR	NR	NR	NR	NR	NR	NR
NR (Tahan et al. 8th IAS 2015.)	18	NR	High VL; resistance to other ARVs, late presenter	28% pre-pregnancy 72% during pregnancy (31.9 weeks)	NR	PI-based	NR	78% undetectable	NR
NR (van Halsema et al. HIV Med 2013.)	6	NR	Optimization of therapy; intolerance to other ARVs	32 weeks	NR	NR	NR	All <40	NR

Legend: ARV = antiretroviral; 3TC = lamivudine; DRV/r = darunavir/ritonavir; ETR = etravirine; FTC = emtricitabine; LPV/r = lopinavir/ritonavir; NR = not reported; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RAL = raltegravir; SQV/r = saquinavir/ritonavir; TDF = tenofovir; ZDV = zidovudine.

Table 2 Comparison of pharmacokinetic parameters of raltegravir 400 mg BID in different female populations

	2nd trimester of pregnancy	3rd trimester of pregnancy		Postpartum		Non-pregnant population (historical data)
	Watts et al.	Watts et al.	Blonk et al.	Watts et al.	Blonk et al.	Rizk et al.
$AUC_{0\text{-}12}$ (ug*h/mL)	6.6 (2.1–18.5)	5.4 (1.4–35.6)	5.00 (3.56-7.01)	11.6 (1.6–39.9)	7.11 (4.91-10.30)	5.839
C_{max} (ug/mL)	2.250 (0.365–5.960)	1.770 (0.315–7.820)	1.43 (0.93 – 2.22)	3.035 (0.312–12.600)	1.76 (1.10—2.80)	1.502
C_{12h} (ug/mL)	0.0621 (0.0128-0.438)	0.064 (0.0114-0.607)	0.077 (0.043-0.137)	0.0797 (0.0199-1.340)	0.120 (0.074-0.193)	0.114
T_{max} (h)	4.0 (1.0-8.0)	2.0 (0-12.0)	1.98 (0-11.3)	2.0 (0-8.0)	2.03 (0-7.97)	

Legend: $AUC_{0\text{-}12}$ = area under the plasma concentration–time curve; C_{12h} = concentration 12 hours after last dose; C_{max} = maximum concentration; T_{max} = time post-dose of maximum concentration.