Raltegravir plasma concentrations on HIV-1 infected pregnant women

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INTRODUCTION

In France, around 1 500 HIV-infected women give birth each year. With the combination antiretroviral (ARV) therapy, the rate of mother-to-child transmission (MTCT) of HIV-1 is reduced from 25-30% to 0.5%[1]

Objectives for ARV use are:

- prevention of mother-to-child transmission (PMTCT) to decrease and to maintain plasma viral load (pVL) < 400 copies/mL during all pregnancy until the delivery
- to treat maternal HIV infection
- to limit emergence of HIV-resistance in mother

Raltegravir (RAL) is classified in FDA pregnancy Category C[2]

RAL is used in association with other ARV[1]:

- before pregnancy
- in case of early pregnancy for PMTCT or intensification in late presenters or low level viremia

RAL permit a rapid decrease of pVL to allow pVL < 400 copies/mL at delivery[3]

OBJECTIVES

•Primary objective: assessment of RAL plasma concentration 12 hours post-dose (C12h) at different trimesters of pregnancy

•Secondary objectives:

- Evaluation of virological efficacy and safety in mothers
- Evaluation of virological efficacy and safety in neonates
- Assessment of other ARV plasma concentrations

METHODS

•Design: single center, observational, descriptive study

•Inclusion criteria:

- HIV-1 pregnant women receiving RAL 400 mg BID containing regimen
- Initiation of RAL at least 2 weeks before delivery
- Maternal data available: demographic, immuno-virological and therapeutic

•ARV maternal plasma and cord blood concentrations

-Therapeutic drug monitoring
-Performed using UPLC-MS/MS after liquid-liquid extraction[4]
-Limit of quantification < 5 ng/mL

•Plasma HIV-1 RNA

- Performed as routine test
- Limit of quantification < 50 copies/mL

•Statistical analysis

- All results are expressed as median (IQR25-75%)
- Mann-Whitney test was used for continuous variables

RESULTS 1: Patient characteristics (n = 23)

Age (years)	31 (27 - 38)
Ethnicity	
-Caucasian	2 (9%)
-African	21 (91%)
Co-infections	
-None	20 (87%)
-HVB	2 (9%)
-HVC	1 (4%)
History of HIV infection	
-Time since diagnosis (years)	8.3 (4.0 - 12.1)
-pVL before ARV (copies/mL)	32,365 (3,792 - 200,500)
-pVL before RAL (copies/mL)	1,055 (137 - 16,407)
-CD_4 count Nadir (cells/mm^3)	224 (42 - 352)
Gyneco-obstetrical history	
-Number of previous pregnancy	3 (2 - 4)
-Parity	1 (0 - 2)

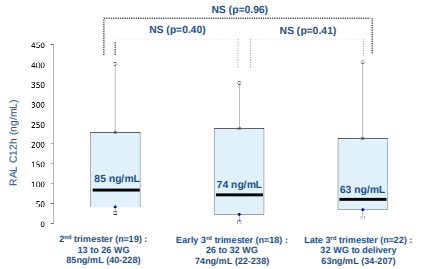
RESULTS 2: Historic and ongoing ARV therapy (n = 23)

Previous ARV combination before RAL	
Duration (years)	7.1 (1.1 – 11.7)
Number	3 (4 – 8)
Duration of RAL containing regimen (months)	8.1 (2.6 – 67.1)
Indication for RAL initiation	
-Before pregnancy	9 (39%)
-PMTCT	3 (13%)
-intensification	11 (48%)
ARV backbone in RAL containing regimen	
-PI/r	
• DRV/r 600/100mg BID	16 (70%)
• DRV/r 800/100mg QD	1 (4%)
• LPV/r 400/100mg BID	4 (17%)
• SQV/r 1000/100mg BID	1 (4%)
-NRTIs	
• FTC/TDF 200/300mg QD	8 (35%)
• ABC/3TC 600/300mg QD	5 (22%)
• ZDV/3TC 300/150mg BID	2 (8%)
• ABC 600mg QD	3 (13%)
• TDF 300mg QD	5 (22%)

SUMMARY of RAL PK/PD CHARACTERISTICS[3]

Formula	$C_{20}H_{21}FKN_4O_5$
Molecular weight	482.51 g/mol
Oral absorption	• Tmax ~ 3 hours • Increased by high-fat meal • Increased by alkalinisation of digestive pH
Distribution	• Protein bound ~ 83 %
Metabolism	• UGT1A1 • Inactive metabolite: raltegravir-glucuronide (G-RAL)
Elimination	• $T_{1/2}$ = 9 hours • 51 % feces • 32 % urine (9 % unchanged form, 23 % G-RAL)
Plasma pharmacokinetic after 400mg BID	• $AUC_{0\text{-}12h}$ = 6900 ng.h/mL • C_{12h} = 69 ng/mL • Intra-patient variability ~ 122% • Inter-patient variability ~ 212%
Pharmacodynamic	• EC_{95} = 14 ± 10 ng/mL (*In vitro*, wild type HIV-1) • IC_{50} = 22 ng/mL (*In vivo*, supposed activity)

RESULTS 3: Median RAL maternal plasma C12h



WG: weeks of gestation)

RESULTS 4: Other Median ARV plasma concentrations

(ng/mL)	2nd trimester	Early 3rd trimester	Late 3rd trimester
DRV C12h	966 (548-2009) N=12	1476 (1199-1956) N=14	1817 (1412-2383) N=13
DRV C24h	524	998 (953-1958) N=4	909 and 1115
LPV C12h	4967 and 3345	NA	4583 (2986-9555) N=5
SQV C12h	4940	NA	1639 and 4715
TDF C24h	47 (42-51) N=5	45 (39-72) N=12	61 (53-72) N=11
FTC C24h	85 (67-183) N=3	180 (152-183) N=7	86 (73-305) N=7
ABC C24h	29 (20-67) N=3	47 and 186	30 (21-69) N=7
3TC C24h	113 (91-142) N=3	53 (46-92) N =3	38 and 212
ZDV C12h	<5 (<5-<5) N=6	NA	<5 (<5-<5) N=8
3TC C12h	NA	NA	54 (<10-380) N=4

NA: Non Available

➔ All RAL C12h < 15 ng/mL (IC_{95}= 33 nM in 50% human serum) determined at several times during pregnancy were related with detectable pVL

➔ After initiation of RAL during pregnancy, a ΔpVL of -4.2 log_{10} copies/mL (-2.3;-4.6 log_{10}) was observed 2-3 weeks later in 11 patients

RESULTS 5: virological efficacy & Safety in mothers

•Virological data:

- **Before pregnancy:** pVL≈184 copies/mL (<50 – 17,650): 4/9 women receiving RAL containing regimen before pregnancy had pVL < 50 copies/mL
- **At delivery,** 17 (74%) patients had pVL < 50 copies/mL
- **At delivery,** among the 6 women with detectable pVL:
  - 2 were non adherent: pV= 54 and 246 copies/mL
  - 4 were late presenters: pVL = 76, 113, 500 & 109 copies/mL

•Immunological:

- **Before pregnancy,** CD_4 ≈ 434/mm^3 (280 – 529)
- **At delivery,** CD_4 ≈ 440/mm^3 (327 – 567)

•Safety data:

-1 patient stopped her treatment (DRV/r 600/100 mg BID + TDF + RAL) at 30 weeks of gestation because of severe increase of ASAT/ALAT with adequate median C12h (DRV = 2,385 ng/mL and RAL = 47 ng/mL) before the event
-No other adverse event had been reported

•Delivery :

-7 vaginal delivery
-16 caesarian sections
-18 ZDV infusion during labor

RESULTS 7: virological efficacy & safety in neonates

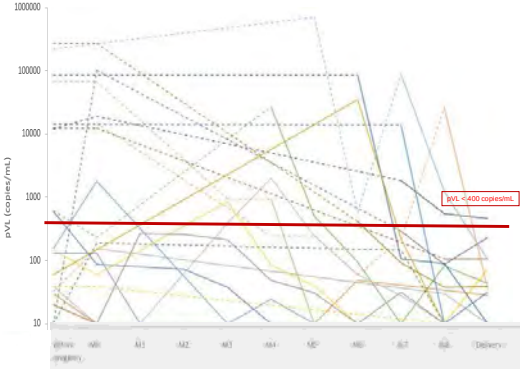
•Pharmacokinetic: Cord blood/maternal plasma RAL concentration ratio ($R_{CB/MP}$) = 3.56 (2.27 – 4.69) (n=4)

•Efficacy: No neonate was HIV-infected

•Safety:

-Gestational age at birth: 38+4 weeks+days (37+4 – 39+4); 4 premature births (≤ 37 weeks of gestation)
-Weight at birth : 2920 g (2750 – 3370)
-Hemoglobinemia : 15.9 g/dL (14.6 – 17.5) (n=22)
-Bilirubinemia : 27 µmol/L (23 – 35) (n=20)
-Neither congenital abnormalities nor other adverse event were reported

RESULTS 6: individual pVL during pregnancy : before RAL regimen (dash line) and after RAL initiation (full line)



SUMMARY

• Despite a large inter-patient variability, RAL plasma concentrations were not significantly modified during pregnancy and are similar to historical data in non pregnant population ➔ 400mg BID seems to be an appropriate daily dosage in pregnant women

• All pregnant women except one late presenter (pVL = 500 copies/mL) reached pVL < 400 copies/mL and 74% < 50 copies/mL at delivery

• RAL containing regimen seems to be effective and safe for mothers and children

• Favorable placental transfer ($R_{CB/MP}$ >1.0) and accumulation in Amniotic Fluid[5] ($R_{AF/CB}$ = 1.05) because an immaturity of fetal UGT1A1

($R_{AF/CB}$ = Amniotic Fluid/Cord blood RAL concentration ratio)

REFERENCES

1 - Prise en charge médicale des personnes vivant avec le VIH, recommandations du groupe d'experts, rapport 2013 sous la direction du Pr Phillipe Morlat et sous l'égide du CNS et de l'ANRS.http://www.cns.sante.fr/IMG/pdf/dias_experts2013_synthese.pdf (last consultation 02/12/14)

2 - AIDS info. 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. http://aidsinfo.nih.gov/contentfiles/lvguidelines/peri_recommendations.pdf (Last consultation : 02/12/14)

3- Summary of Product Characteristics : Isentress®(Raltegravir). MSD. Last update 07/2009. http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022145s004lbl.pdf (last consultation 02/12/14)

4- Jung BH, Rezk NL, Bridges AS *et al*. Simultaneous determination of 17 antiretroviral drugs in human plasma for quantitative analysis with liquid chromatography-tandem mass spectrometry. *Biomed Chromatogr* 2007; **21**:1095-1104.

5-Belissa E, Mandelbrot L, Damond F et coll. Accumulation of antiretroviral drugs in amniotic fluid in HIV-infected pregnant women. Abstract P44. 15th International Workshop on Clinical Pharmacology of HIV Therapy. Washington DC, Co, USA. 2014