Analysis of raltegravir **plasma concentrations** and the impact of raltegravir **therapeutic drug monitoring** during pregnancy: impacts on the viral control of women living with HIV

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Background

- Pregnancy is related to many physiological changes that can have a significant impact on antiretroviral (ARV) pharmacokinetics (1).
- Despite raltegravir (RAL) being a first line ARV treatment for HIV in pregnancy, limited data about the impact of these changes on RAL plasma concentrations is presently available.
- Furthermore, the relevance of therapeutic drug monitoring (TDM) for pregnant women is not demonstrated.
- This project aims to study :
  - the effect of pregnancy on RAL plasma concentration,
  - the association between RAL plasma concentration during pregnancy with its efficacy, and
  - the impact of TDM on viral load control and management during pregnancy.

Methodology

- We analyzed the data from the CHU Sainte-Justine Mother and Child Infectious Diseases Center Cohort (CIME, Montreal, Quebec, Canada).
- Inclusions criteria : Pregnant HIV+ women who used RAL at any time during their pregnancy, between January 1st, 2011 and August 1st, 2020.
- Exclusion criteria : No consent or an abortion in the first trimester.
- Undetectable viral load was set to <50 HIV RNA copies/mL.
- The predetermined RAL target minimum concentration* (C_{min}) was 0.02 mg/L (2).
- RAL C_{min} were assessed by liquid chromatography / tandem mass spectrometry

Did you know ?

C_{min} is the lowest concentration measured in the dosing interval and it is the most commonly used parameter to determine if the concentration is therapeutic in patients with virus harbouring no mutations conferring resistance to the antiretroviral analyzed.

Results TDM

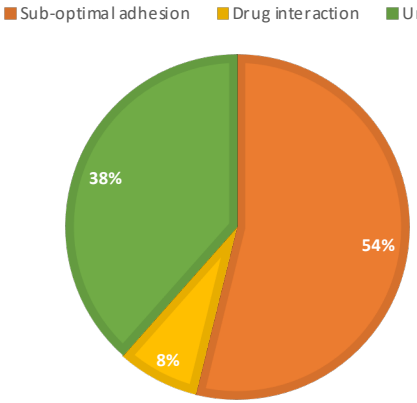
Table 1 : Women characteristics

	Total (n =76)	TDM (n=47)	No TDM (n=29)	P-value [b]
Age at delivery (years)	33 (5)	33 (5)	32 (6)	0.456
Weight at delivery (kg) [c]	85.8 (19.1)	84 (21.2)	85 (15.1)	0.730
CD4 + lymphocyte count at delivery (cells / mL) [d]	579 (299)	468 (322)	549 (253)	0.829
CD8 lymphocyte count at delivery (cells / mL) [e]	771(390)	728(305)	824 (531)	0.920
Gestational age at delivery(weeks)	39 (1)	39 (2)	39 (1)	0.349
Geographic origin				
Africa	38 (50 %)	23 (49 %)	15 (52 %)	1
Caribbean	24 (32 %)	13 (28 %)	11 (38 %)	0.447
Other	14 (18 %)	11 (23 %)	3 (10 %)	0.225
ART naive at conception	36/74 (49 %)	22/47 (47%)	14/27 (52%)	0.810
Substance use during pregnancy				
Recreational drugs (other than marijuana)	1 (1 %)	1 (2 %)	-	1
Cigarettes	9 (12 %)	4 (9 %)	5 (17 %)	1
Marijuana	4 (5 %)	3 (6 %)	1 (3 %)	0.633
Alcohol	7 (9 %)	5 (11 %)	2 (7 %)	0.702
Co-morbidities %				
Diabetes	15 (20 %)	7 (15 %)	8 (28 %)	0.556
Chronic hepatitis B	1 (1 %)	1 (2 %)	-	1
Hyperemesis gravidarum	1 (1 %)	1 (2 %)	-	1
Non-HIV meds during pregnancy				
PPI	6 (8 %)	4 (9 %)	2 (7 %)	1
H_2 receptors blockers	23 (30 %)	12 (26 %)	11 (38 %)	0.308
Vitamins and minerals	62/72 (86 %)	41/47 (87%)	21/25 (84%)	0.730
Undetectable viral load at delivery	56/59 (95 %)	36/37 (97%)	20/22 (91%)	0.549
Infant received a triple ART	15 (20 %)	9 (19 %)	6 (21 %)	1

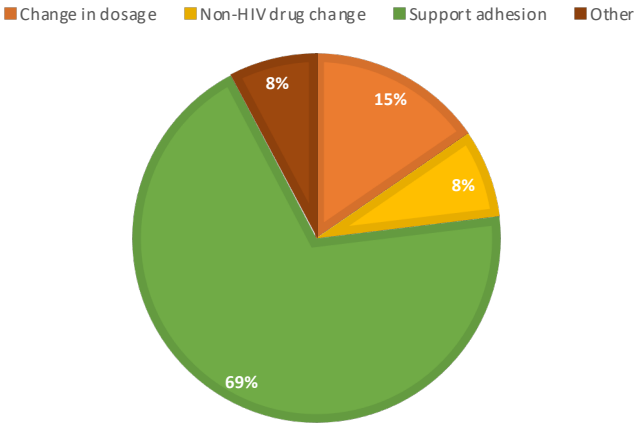
[a] Mean (SD) or number (%)
[b] Chi Square test of proportions or Mann-Whitney U Test
[c] n 'Total' = 75, n 'TDM' = 47, n 'No TDM' =28
[d] n 'Total' = 62, n 'TDM' = 41, n 'No TDM' =21
[e] n 'Total' = 61, n 'TDM' = 41, n 'No TDM' =20

Abbreviations: ART: Antiretroviral therapy, PPI, proton pump inhibitor; TDM: Therapeutic drug monitoring

POSSIBLE CAUSES OF A SUBTHERAPEUTIC TDM RESULT



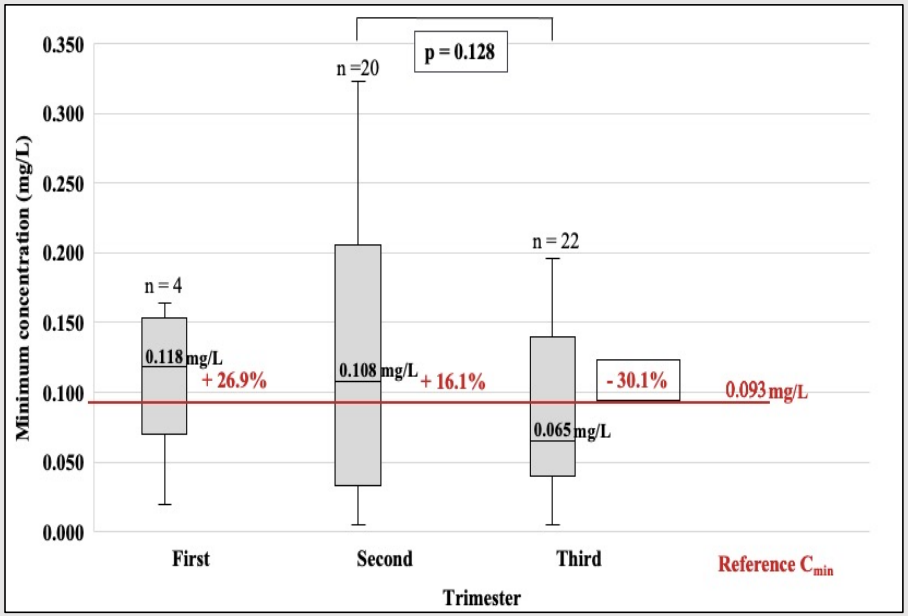
THERAPEUTIC DECISIONS MADE AFTER A SUBTHERAPEUTIC TDM RESULT



- A total of 82 interpretable TDM results were analysed.
- TDM were further divided into 3 groups according to RAL posology:
  - RAL 400 mg twice daily (n = 76, 92.7%),
  - RAL HD 1200 mg once daily (n = 1, 1.2%),
  - RAL other (n = 5, 6.1%).
- 13 TDM results were subtherapeutic (C_{min}< 0.02mg/L)
- No statistical association was found between TDM and viral load control during pregnancy nor with TDM and prescription of a triple therapy to the neonate

Results – C_{min}*

Figure 1 : Evolution of C_{min} of RAL according to trimester



* All results are from RAL 400 mg BID TDM reports due to sample size

Figure 2 : C_{min} of RAL according to viral load control

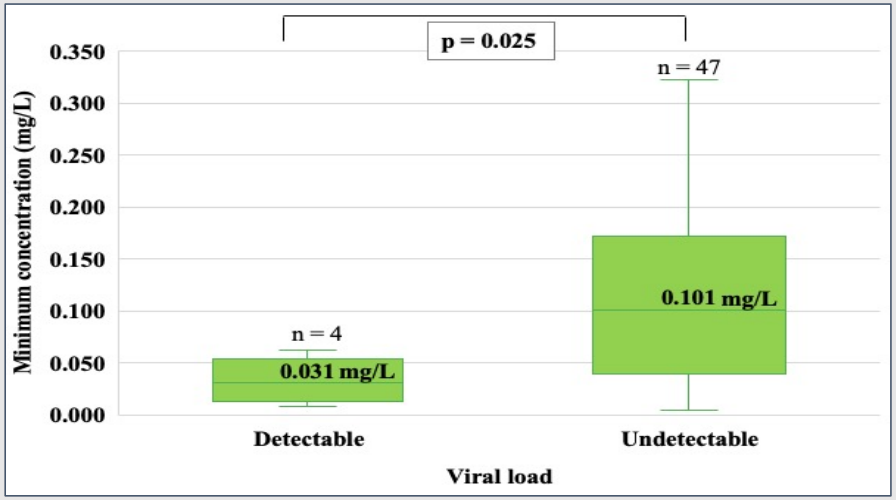
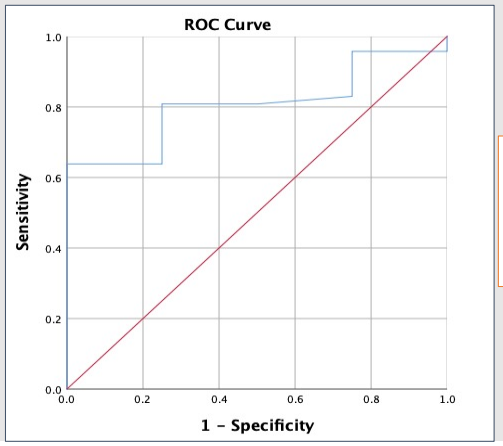


Figure 3 : ROC Curve for viral load control according to the threshold of RAL C_{min} used to define therapeutic level



ROC Curve AUC : 0.806.
p = 0.036
Discrimination threshold : 0.032 mg/L
Sensitivity (%) : 75, 95% CI : [32.6 ; 117.4]
Specificity (%) : 81, 95% CI : [69.5 ; 92.3]

Conclusions

- TDM made it possible to detect cases where **adhesion was suboptimal** and thus to **guide the clinical decision** but TDM *was not significantly associated* with **viral load control** nor enhanced **antiretroviral prophylaxis in newborns.**
- As expected, **RAL C_{min}** was **significantly higher** among women with **undetectable viral load.**
- A **nonsignificant decrease** in **RAL C_{min}** was observed in the **third trimester.**
- A new **RAL C_{min} target of 0.032 mg/L** is proposed to define therapeutic level.
- This target **should be confirmed** in other cohorts of **pregnant or non-pregnant women.**

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The authors have no conflict of interest

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