

# Raltegravir Concentrations in the Cervico-Vaginal Compartment in HIV-1 infected Women treated with Raltegravir: DIVA 01 study

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## Abstract

**Background:** There is concern about the penetration of new drugs including integrase inhibitors into the female genital tract, which may impact sexual and vertical transmission as well as antiretroviral drug resistance.

**Methods:** HIV-1 infected women over 18 years old receiving a stable RAL (400 mg bid)-containing antiretroviral therapy with good adherence and a plasma HIV-RNA <40 copies/mL for at least 3 months were enrolled with informed consent. Paired samples of blood plasma (BP) and cervico-vaginal fluids (CVF) were collected. Intervals between last drug intake and sampling were recorded. CVF sampling using blotting papers was performed in the absence of menstruation, sexual intercourse or intra-vaginal treatment within the last 2 days. Screening for genital tract infections was performed at time of sampling. HIV-RNA was determined (Roche Taqman) in BP and CVF with limits of detection of 40 and 200 c/mL, respectively. RAL BP and CVF concentrations were measured at steady-state using UPLC-MS/MS method (Acquity UPLC® - Acquity TQD®) after sample pretreatment (LOQ ~ 1ng/ml). Results are presented as median (IQR25%-75%).

**Results:** Fourteen women were enrolled. All were non-pregnant, aged of 43 years (33-64) with a median CD4 lymphocyte count of 463 per microl. (122-1325). The duration of RAL treatment was 347 days (49-756). RAL was associated with a median of 3 other antiretroviral drugs (1-6), including darunavir/r in 7, etravirine in 5, maraviroc in 4 cases and 10/14 regimens contained NRTI. At the time of sampling, all patients had undetectable CVF HIV-RNA despite evidence of genital infection for 3 of them and a low HIV replication detected in BP in 2 others (88 c/mL and 169 c/mL). RAL concentrations, determined 13.6 hours (13.0-14.5) after the last drug intake, were 93 ng/mL (48-167) in BP and 235 ng/mL (135-775) in CVF. Inter-patient variability of RAL concentrations were 127% in BP and 176% in CVF. RAL concentrations in CVF were about 2.3 fold those in BP. **Conclusion:** The penetration of RAL into the genital tract was good in HIV-infected women, confirming a previous report in 7 HIV-negative females. The median RAL CVF concentration was approximately 16-fold higher than the IC95 on wild type HIV-1 in this study, likely contributing to virological control in the compartment.

## Background

- Penetration of antiretrovirals (ARVs) in the Genital Tract (GT) is a key issue in the control of HIV replication in this compartment. With an expected impact on:
  - Prevention of mother to child and sexual transmission
  - Prevention of the emergence of viral resistance in GT and its recirculation in blood plasma or transmission

- Raltegravir (RAL) is the first approved in class integrase strand transfer inhibitor. Little is known about its penetration in GT<sup>1</sup> in HIV-infected women.

- DIVA is a multicentre study assessing the penetration of different ARVs into the cervicovaginal fluids (CVF) of HIV-1 women. **DIVA 01** is addressing the issue of **raltegravir**.

## Objectives

- To determine the penetration of raltegravir (RAL) into the genital tract of HIV-1 women
- To determine the concurrent intragenital and plasma HIV-1 viral load
- To describe factors potentially associated with RAL CVF concentration

## Patients and Methods

### Patients population

- Women ≥ 18 years old, infected with HIV-1, non pregnant
- Plasma HIV-RNA <40 cp/mL for at least 3 months
- On stable RAL (400 mg bid)-containing ARV regimen for more than 2 months
- Absence of menstruation, sexual intercourse or intra-vaginal treatment within the last 2 days

### Samples collection

- A single determination of RAL concentrations and HIV viral load was performed in both Blood Plasma (BP) and CVF within less than 1 hour.
- Collection of samples in CVF was done just after pelvic examination and tests for genital tract infection were performed by:
  - Blotting paper used for pharmacological tests.
  - Cervico vaginal lavage for virologic tests.
- RAL BP and CVF concentrations were measured at steady-state using UPLC-MS/MS method (Acquity UPLC® - Acquity TQD®) after sample pretreatment (LOQ ~ 1ng/ml).
- Viral load was quantified using the Cobas TaqMan Roche assay with a threshold of 40 copies for BP and 200 copies for CVF.

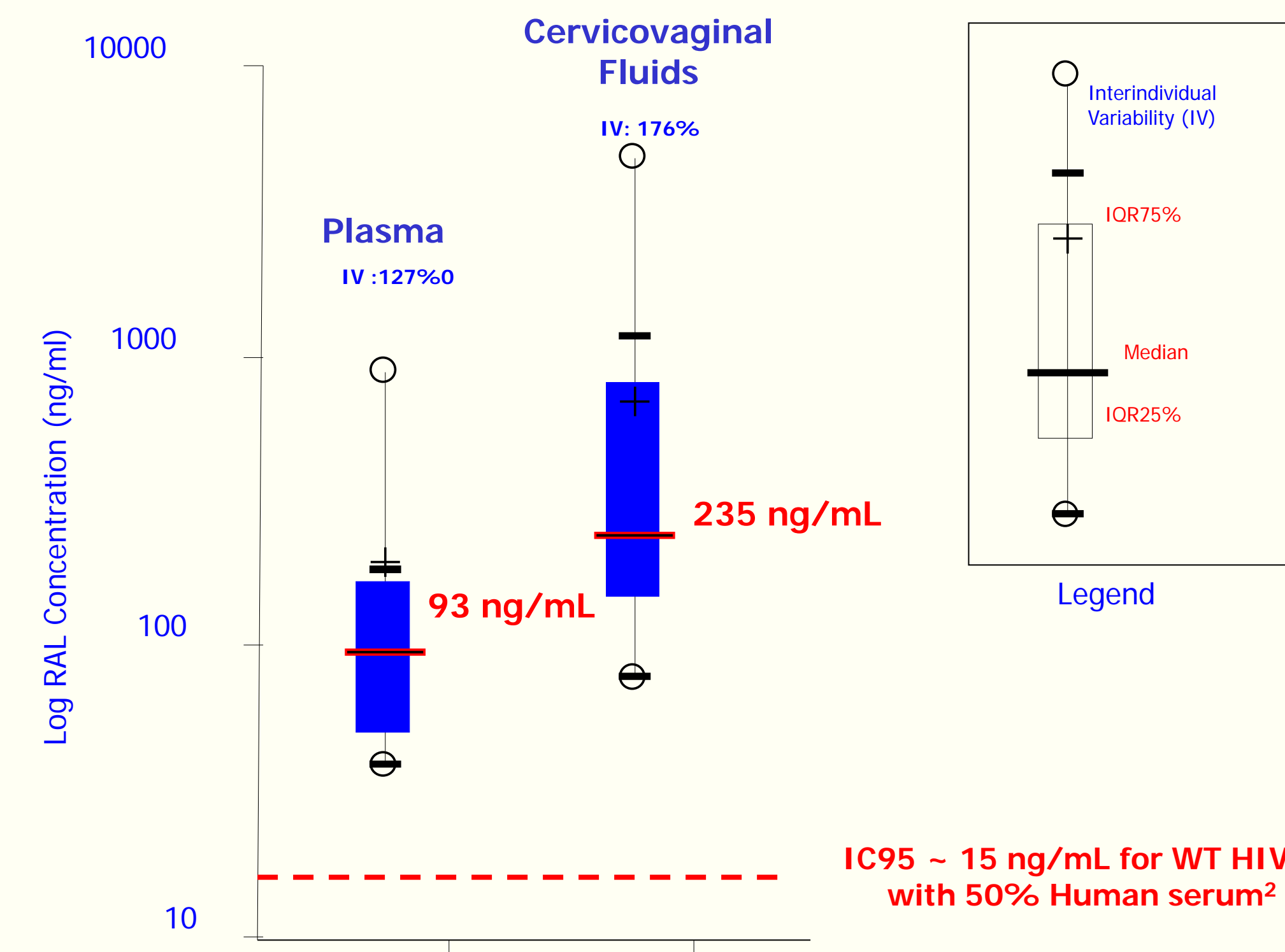
## Patients Characteristics

Pt.	Associated Regimen	Duration on RAL (months)
1	ZDV/3TC/ABC + TDF + DRV/r	16
2	ABC + MVC	9
3	MVC	2
4	TDF/FTC	8
5	ABC/3TC + TDF + DRV/r + MVC + <b>ETR</b>	14
6	TDF/FTC + DRV/r + <b>ETR</b>	7
7	TDF/FTC + DRV/r	12
8	<b>ETR</b> + omeprazole	5
9	ABC/3TC + omeprazole	2
10	TDF/FTC	5
11	ABC/3TC + MVC	8
12	TDF/FTC + DRV/r + <b>ETR</b>	3
13	DRV/r + <b>ETR</b>	25
14	DRV/r + <b>ETR</b>	7
Median [IQR25-IQR75]		7.5 [4,5-11.5]

•Age (years): 45.5 [43-52]  
•CD4(c/μl)=497 [404-712]  
•BMI (Kg/m<sup>2</sup>) =22 [20-40]

•Menopause: patients 1,3,9,14  
•No Pregnancy

## Distribution of RAL concentrations in Blood Plasma and Cervicovaginal fluids (n=14)



- Accumulation of RAL in CVF with Concentration RAL CVF/BP=2.3
- Concentrations of RAL in CVF and Blood plasma > IC95
- Interindividual variability of RAL concentration is confirmed

## Concentrations of Raltegravir and concurrent HIV viral load in blood plasma and CVF

Pt.	RAL Plasma (ng/ml)	RAL CVF (ng/ml)	Ratio RAL CVF/Plasma	Time between last drug intake and BP sample (hours)	Plasma HIV-1 RNA (cp/ml)	CVF HIV-1 RNA (cp/ml)
1	90	112	1,2	16:28	169	<200
2	46	113	2,5	Missing data	<40	<200
3	47	904	19,2	15:00	<40	<200
4*	38	77	2	13:17	<40	<200
5	96	127	1,3	12:00	88	<200
6	873	273	0,3	05:45	<40	<200
7	358	197	0,6	14:20	<40	<200
8	609	1062	1,7	12:05	<40	<200
9*	117	1154	9,9	14:00	<40	<200
10*	130	4782	36,8	12:20	<40	<200
11	73	273	3,7	14:20	<40	<200
12	179	389	2,2	12:00	<40	<200
13	51	160	3,1	13:45	<40	<200
14	46	193	4,2	14:00	<40	<200
Median	93	235	2,3	14:00		

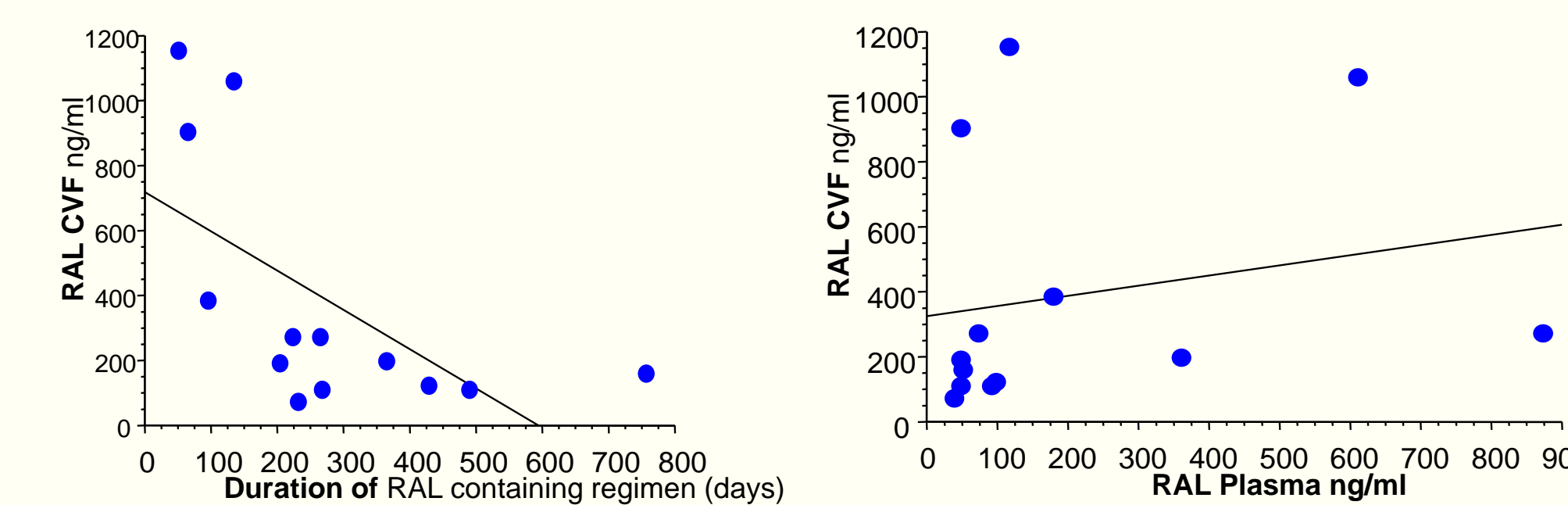
[IQR25-IQR75] [48-167] [135-775] [1.4-4.1]

Delay between BP and CVF sample (median): 35 min[22-50]

\* These patients had a vaginal infection: patient 4 and 9: corynebacterium spp; patient 10: gardnerrella vaginalis

- All patients had a HIV viral load controlled in CVF despite 3 vaginal infections.

## Relation between duration of RAL or Plasma concentration and concentration of RAL in Cervicovaginal fluids



- No relation was observed:
  - Between RAL CVF and BP concentrations
  - Between RAL CVF concentration and duration of RAL

## Discussion

- Unlike most PIs and NNRTIs of first generation, RAL penetration ratio in GT is > 1 and closed to NRTI's, especially those mainly used for PEP as FTC (3.75), TDF(1.1), ZDV(2.35) and 3TC(4)<sup>3</sup>
- Good penetration is probably related to RAL molecular weight (482.51 Da) and partial binding protein fraction in BP (83%)<sup>4</sup>; it might also be a substrate of an active transport<sup>5</sup> but data are scarce.
- Unlike previously reported<sup>6</sup>, no relevant impact of drug-drug interaction could be observed between Etravirine and RAL in BP in this study.
- Factors not found to be related with RAL concentration in CVF:
  - Duration of RAL regimen
  - Blood plasma concentration of RAL
  - Menopause
- HIV viral load controlled in all CVF even though 3 women had an asymptomatic vaginal infection with 2/3 patients displaying a high ratio CVF/BP (>10) compared to the others.
- Detectable viral load of patient 1 and 5 were blips (not shown); therefore genotypes for resistance testing were not performed.
- As complete PK study was not performed, more studies are needed to confirm and complete our data.

## Conclusion

- Good penetration of RAL in the genital tract of HIV-1 infected women with a ratio CVF/BP=2.3 and a concentration 16 fold higher than the IC95 on wild type HIV-1
- Likely contributing to virological control in the compartment
- These data also suggest a potential use of raltegravir in combination with others ARVs with known penetration in the genital tract of HIV infected women when targeting an impact on prevention of transmission and resistance.

### References

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