

Dynamic of HIV-1 RNA and DNA in plasma and cervico-vaginal secretions after Highly Active Antiretroviral Therapy initiation: ANRS EP24 GYNODYN Study

O. Launay¹, L. Belec², M. Tod¹, A. Si Mohammed², N. Matignon³, I. Tschöpe³, C. Goujard⁴, AM. Taburet⁴, O. Lortholary⁵, and V. Leroy³ for the ANRS EP24 GYNODYN Study Group

1. Hôpital Cochin, Paris, France 2. Hôpital Européen Georges Pompidou, Paris, France 3. INSERM U993 Université Victor Segalen Bordeaux2, Bordeaux, France 4. Hôpital de Bicêtre, Le Kremlin Bicêtre, France 5. Hôpital Necker-Enfants Malades, Paris, France

Odile Launay
CIC de Vaccinologie Cochin-Pasteur
Pôle de médecine interne
Cochin Hospital, Paris, France
Tel: + (33) (0) 1 43 25 38 67
odile.launay@cch.ap-hop-paris.fr

BACKGROUND

HIV shedding in cervico-vaginal secretions is a major determinant of sexual HIV transmission

A better understanding of the viral dynamics in this compartment in relation with antiretroviral treatment may improve the prevention of HIV transmission.

OBJECTIVES

We studied the dynamic of HIV-RNA and DNA levels in plasma and cervico-vaginal secretions over a period of 18-months after HAART-initiation among HAART-naïve HIV-1-infected women in France.

METHODS

Design: prospective multicentric open cohort of 23 antiretroviral (ARV)-naïve women with HIV-1 infection initiating zidovudine/lamivudine combined with lopinavir (n=17) or indinavir (n=6) boosted with low-dose ritonavir.

Laboratory method

Paired samples of plasma and cervico-vaginal secretions (obtained by cervico-vaginal lavage) were collected at baseline, then at 1, 6, 12 and 18 months to measure viral markers and antiretroviral concentrations.

Viral HIV-RNA and proviral HIV-DNA were measured using real-time PCR assay. The threshold of detection was 50 copies/ml ($1.7 \log_{10}$) for viral RNA and 10 copies/ 10^6 cells ($1.0 \log_{10}$) for proviral DNA.

Antiretroviral concentrations were measured by high performance liquid chromatography at different points in time after antiretroviral intake.

Viral HIV-RNA and antiretroviral concentration from cervico-vaginal secretions were adjusted using a gold standard solution of Lithium.

Statistical methods

Mean HIV-RNA and proviral DNA in plasma and cervico-vaginal secretions after \log_{10} transformation were described in the two compartments.

We compared mean HIV-RNA in plasma and dilution factor adjusted HIV-RNA in cervico-vaginal secretions using a Wilcoxon non parametric test, all HIV-RNA values lower than the adjusted cervico-vaginal secretions threshold being replaced by $2.7 \log_{10}$ cells.

RESULTS

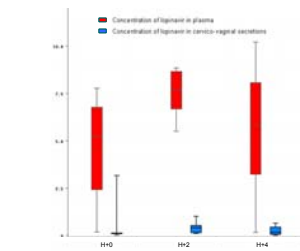
Table 1: Baseline characteristics (N=23)
ANRS EP24 Gynodyn, 2003-2006

Characteristics	n	23
Median age in years (IQR)	33	(30-35)
Transmission group, n (%)		
sexual	20	(87)
unknown	3	(13)
Body Mass Index in kg/m^2 , n (%)		
<19	1	(5)
[19-25[10	(50)
[25-30[7	(35)
≥ 30	2	(10)
Clinical stage, n (%)		
A	18	(78)
B	2	(9)
C	3	(13)
Using effective method of contraception	20	(87)
ARV treatment		
lopinavir/ritonavir	17	(74)
indinavir/ritonavir	6	(26)
Median CD4+ cells/ μl (IQR)	199	(128-310)
Median CD8+ cells/ μl (IQR)	790	(486-1055)
Mean HIV RNA in plasma in \log_{10} copies/ml (SD)	4.74	(0.96)
Mean HIV DNA in cervico-vaginal secretions in \log_{10} copies/ml (SD)	3.89	(1.01)
Mean HIV DNA in plasma in \log_{10} / 10^6 cells (SD)	3.52	(0.50)
Mean HIV DNA in cervico-vaginal secretions in \log_{10} / 10^6 cells (SD)	2.02	(0.88)

Abbreviations: IQR Interquartile range
SD Standard deviation

PHARMACOLOGICAL RESULTS

Figure 1: Concentration of lopinavir at Month 1 (N=15), ANRS EP24 Gynodyn, 2003-2006



Boxplots (median, IQR) of concentration of lopinavir in plasma and in cervico-vaginal secretions (dilution factor adjusted) at medication time (H+0), two hours after medication (H+2) and four hours after medication (H+4)

RNA HIV RESULTS

Table 2: Evolution of HIV RNA in plasma and in cervico-vaginal secretions ANRS EP24 Gynodyn, 2003-2006

	Day0	Month1	Month6	Month12	Month18
Number of available samples (%)					
plasma	22 (96)	18 (78)	14 (61)	9 (39)	8 (35)
cervico-vaginal secretions	22 (96)	18 (78)	14 (61)	10 (43)	9 (39)
Number of undetectable values (%)					
plasma (< $1.7 \log_{10}$ copies/ml)	1 (5)	3 (17)	10 (71)	6 (67)	6 (75)
plasma (= 1.7 and < $2.7 \log_{10}$ copies/ml) (censored)	0	4 (22)	4 (29)	0	0
cervico-vaginal secretions (< $2.7 \log_{10}$ copies/ml)	3 (14)	14 (78)	13 (93)	9 (100)	8 (100)
Mean HIV-1 RNA in \log_{10} copies/ml (SD)					
plasma*	4.79 (0.82)	3.15 (0.75)	2.70 (0.00)	3.04 (0.52)	3.30 (1.11)
cervico-vaginal secretions*	3.95 (0.92)	2.90 (0.64)	2.81 (0.37)	2.81 (0.19)	2.94 (0.34)
p-value ^c	0.0008	0.0077	0.5000	0.8125	1.0000

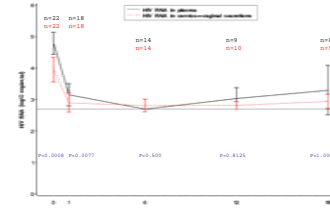
Abbreviations: SD Standard deviation

a) all HIV-RNA values lower than the adjusted cervico-vaginal secretions threshold were replaced by $2.7 \log_{10}$

b) dilution factor adjusted

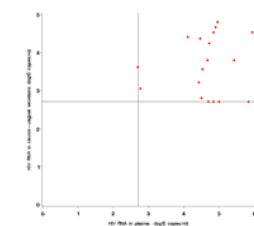
c) adjusted Student T or Wilcoxon test of plasma versus cervico-vaginal HIV-1 RNA

Figure 2: Evolution of mean HIV RNA in plasma and in cervico-vaginal secretions, ANRS EP24 Gynodyn, 2003-2006



Vertical bars represent 95% confidence intervals, the horizontal line the detection limit ($2.7 \log_{10}$). P values are results of paired T tests or paired Wilcoxon signed rank sum tests.

Figure 3: Correlation between HIV RNA in cervico-vaginal secretions and in plasma at baseline, ANRS EP24 Gynodyn, 2003-2006



Vertical and horizontal lines represent detection limits ($2.7 \log_{10}$). Pearson's correlation coefficient between HIV-1 RNA in cervico-vaginal secretions and in plasma $p=3409$ $p=0.1205$.

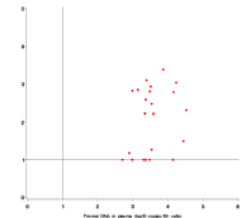
DNA HIV RESULTS

Table 3: Evolution of HIV DNA in plasma and in cervico-vaginal secretions, ANRS EP24 Gynodyn, 2003-2006

	Day0	Month1	Month6	Month12	Month18
Number of available samples (%)					
plasma	23 (100)	17 (74)	11 (48)	10 (43)	6 (26)
cervico-vaginal secretions	23 (100)	18 (78)	15 (65)	10 (43)	9 (39)
Number of undetectable values (%)					
plasma (< $1 \log_{10}$ cp/ 10^6 cells)	0	0	0	0	0
cervico-vaginal secretions (< $1 \log_{10}$ cp/ 10^6 cells)	7 (30)	11 (61)	8 (53)	7 (70)	5 (56)
Mean HIV-1 DNA in \log_{10} copies/10^6 cells (SD)					
plasma	3.52 (0.50)	3.29 (0.63)	2.77 (0.59)	2.83 (0.47)	2.80 (0.30)
cervico-vaginal secretions	2.02 (0.88)	1.47 (0.67)	1.58 (0.83)	1.33 (0.55)	1.30 (0.52)

Abbreviations: SD Standard deviation

Figure 4: Correlation between HIV DNA in cervico-vaginal secretions and in plasma at baseline, ANRS EP24 Gynodyn, 2003-2006



Vertical and horizontal lines represent detection limits ($1 \log_{10}$). Pearson's correlation coefficient between HIV DNA in cervico-vaginal secretions and in plasma $p=0.2778$ $p=0.1994$.

DISCUSSION - CONCLUSION

• Baseline viral markers were significantly lower in cervico-vaginal secretions than in plasma and were not correlated with each other

• HIV-RNA decreased significantly in both body compartments after HAART initiation reaching durable undetectable values from one-month up to 18 months.

• By contrast, HIV-DNA levels remained detectable in all plasma samples and most cervico-vaginal secretions samples over time.

• Concentration of lopinavir in cervico-vaginal secretions was lower than in plasma.