ULTRASTOP: Is remission achievable in chronically HIV-1 infected patients with low HIV DNA reservoir?

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BACKGROUND: Viral remission is observed in elite controllers and post early-treatment controllers (PTCs). All share a good immune status and extremely low blood total cell-associated HIV-DNA levels. ULTRASTOP investigates whether HIV remission after ART discontinuation can be achieved in long-term HIV chronically-infected patients with good immunological status and low-level DNA.

METHODS: This proof-of-concept study was designed to involve 3 cohorts of 5 patients (pts) with pVL<50 copies (cp)/mL for>2 years on ART, CD4>500/mm3, CD4/CD8>0.9, CD4 nadir>300/mm3 and HIV-DNA<100 cp/106 PBMCs, selected for treatment interruption. Ultrasensitive pVL, CD4, triplicate HIV-DNA were measured at D0, W2, W4, and every 4 weeks off-ART until W48 and at W4, W12 and W24 after ART resumption (RxR). Treatment was resumed in case of pVL rebound>400 cp/mL or CD4<400 cells or HIV-related clinical event. The primary endpoint was the percentage of patients who did not reach RxR criteria at W24. Enrolment in cohort 2 started, when 1/5 pts remained in success at W8. Cohort 3 did not start.

RESULTS: Ten patients were enrolled in cohort 1, then 2, with median (min-max) duration of ART of 5.3 years (3.0-15.5), viral suppression 4.9 years (2.9-8.3), CD4 nadir 495/mm3 (330-739), baseline CD4 1118/mm3 (608-1494), CD4/CD8 2.1 (1.4-2.6), HIV-DNA 66 cp/106 PBMC (<66-80). One patient remained off-ART at W40. Viral rebound occurred in 9/10 pts: W2 (2pts), W4 (6pts) and W12 (1pt) with CD4 counts of 745/mm3 (578-1438). pVL was resuppressed on cART (<50 cp/ml) at W4 (8pts) and W12 (1pt) with a median of 835 CD4/mm3 (705-1326), CD4/CD8 ratio of 1.3 (1.1-2.1). In all patients from cohort 1 (cohort 2 on-going), HIV-DNA after increasing at time of rebound, returned to baseline values within 12 weeks following RxR.

CONCLUSIONS: Despite excellent immuno-virological characteristics apparently close to those of PTCs treated at primary infection, chronically-infected patients had viral rebound in a short delay. Extensive analyses of the viral and cellular dynamics are on-going. Importantly, rapid kinetics of HIV-DNA levels after ART discontinuation and RxR with return of each patient to their baseline status, suggests that the intervention with this study design has not been deleterious.

Background

- Recent reports provide evidence that functional cure may be attainable in certain groups of patients like
  - Elite controllers (ECs) who "naturally" control viral replication
  - Post-treatment controllers (PTCs) from the Visconti cohort,
  - Infants early treated

  => All these patients share in common a good immune status and an extremely low blood cell-associated HIV DNA levels .
- **Research question:** What would be the dynamics and potential for HAART-free remission after analytical treatment interruption (ATI) in a highly selected chronically infected HIV patient-population defined by an excellent immune status and ultralow cell-associated DNA?

Objectives

❑ Primary objectives

To evaluate the proportion of patients with HIV RNA <400 cp after 24-week interruption of antiretroviral therapy

Failure is defined as:

- A plasma HIV-1 RNA > 400 copies/mL confirmed by two successive tests between 2-4 weeks apart
- Or a CD4 cell count <400 cells / mm ^{3}
- Or the occurrence of HIV-related (grade B or C of the CDC classification)

❑ Secondary objectives

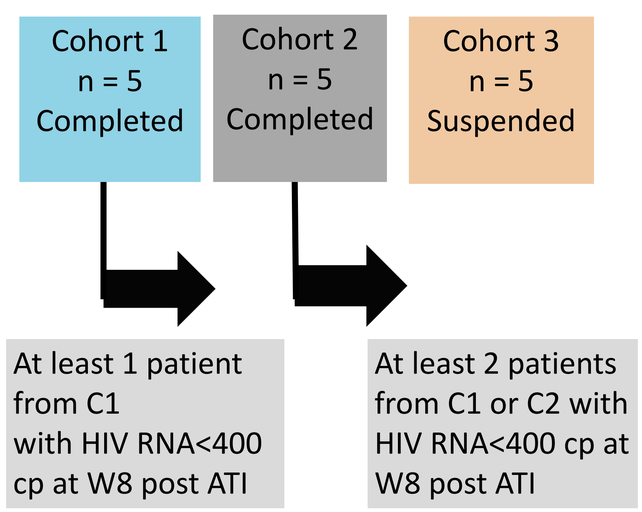
To evaluate

During ART interruption	After ART resumption
- Time to viral rebound	Time to viral suppression
- Changes in HIV DNA	CD4, CD8, CD4/CD8
- CD4, CD8 changes	
- Clinical evolution	

Study Design

Inclusion criteria

- HIV-1 infected patient
- CD4 ≥ 500 cells / mm^3
- CD4/CD8 ≥ 0.9
- Nadir CD4 ≥ 300 cells / mm^3
- HIV RNA-1 <50 copies / mL on ART ≥ 2 years
- HIV RNA <20 copies / mL
- HIV proviral DNA <100 copies / 10^6 PBMCs (based on triplicate value; Biocentric assay)



Baseline Patients Characteristics

	n= 10
Age, year, median (IQR)	41.5 (37.0 – 48.0)
Male sex – n (%)	7 (70.0)
Duration of suppressed HIV viremia, years, median (IQR)	4.9 (3.3 – 7.0)
Duration of antiretroviral treatment, years, median (IQR)	5.3 (3.4 – 12.8)
Nadir CD4 cells /mm^3, median (IQR)	495 (366 – 572)
Pre-HAART pVL, log_{10} copies/mL, median (IQR)	4.0 (3.6 – 4.4)
US pVL at inclusion cp/ml, median (IQR)	100% <1 (1-1)
HLA B57 and/or B27 – n (%)	5 (50%)
No AIDS history – n (%)	10 (100%)

Dynamics of HIV RNA, DNA and CD4 count following Treatment Interruption

- **1/10 patient controlled pVL (<400 cp/ml) at 48 weeks post ATI**
- **9/10 patients rebounded** with a median (min-max):
- **Time to rebound**:

  4 weeks (4-12)
- **HIV RNA pVL at rebound**:

  2125 cp/ml (496-176 548)
- **HIV DNA at rebound:**

  106 cp/10^6 PBMC (<66-424)
- **Time to re-suppression** after ART resumption:

  4 weeks (4-12)

	HIV status				US HIV pVL cp/ml			HIV DNA copies/10^6 PBMC			CD4/mm^3		
Pt	cART at BL	Duration undetectable HIV pVL (years)	Pre-HAART pVL (log_{10} cp/mL)	Nadir CD4/mm^3	BL	VR	TR+W24 Or LV	BL	VR	TR+W24 Or LV	BL	VR	TR+W24 Or LV
1	TDF+FTC+RPV	3.5	4.4	572	<1	W4 3 883	<1	<66	70	154	870	746	823
2	ETR+RAL	7.0	3.6	343	<1	W12 496	<1	<66	282	<66	582	709	705
3	TDF+FTC	7.0	4.2	366	<1	W4 176 548	<1	<66	424	104	1190	578	745
4	DRV/r	6.9	5.0	547	<1	W2 1 443	<1	<66	89	<66	1335	1389	1273
5	TDF+FTC+RAL	2.9	4.5	442	<1	W4 41 490	<1	<66	193	<66	859	690	761
6	TDF+FTC+MVC	3.3	2.3	566	<1		282 W48	<66		<66 W48	915		727 W48
7	TDF+FTC+DRV/r	3.0	4.2	330	<1	W4 544	<1	<66	106	73	792	722	641
8	TDF+FTC	8.3	3.0	377	3	W4 1 756	<1	<66	<66	<66	1429	1438	1293
9	DTG	3.8	3.6	739	<1	W4 59 780	<1	<66	202	<66	1177	744	1147
10	ABC+3TC+ATV	5.9	3.7	640	<1	W2 2 125	9	<66	<66	164	1739	1049	1452

BL: baseline; VR: viral rebound; TR: treatment resumption; LV: last visit

Conclusion

- **In this pilot study of HIV chronically infected patients with baseline ultralow HIV cell-associated reservoir and excellent immune parameters:**

- **1/10 patient controlled pVL (<400 cp/ml) at 48 weeks post ATI**
- **9/10 patients rapidly rebounded within 1 month post ATI**

⇒ **Low HIV DNA and high immune status are not sufficient for ART-free remission**

- **All patients quickly returned to baseline immune and virological parameters after prompt treatment resumption.**

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