Which endpoint to choose during antiretroviral treatment interruption ?

0382

Rodolphe Thiébaut[1,*], Marie Alexandre[1], Mélanie Prague[1], Yves Lévy[2,3]

[1]Bordeaux University, Department of Public Health, INSERM UMR 1219, Bordeaux Population Health Research Center, Inria SISTM, Bordeaux, France
[2]Vaccine Research Institute, Créteil, France ; [3]Hôpital Universitaire Henri-Mondor, Créteil, France
*rodolphe.thiebaut@u-bordeaux.fr

CROI Conference on Retroviruses and Opportunistic Infections

Background

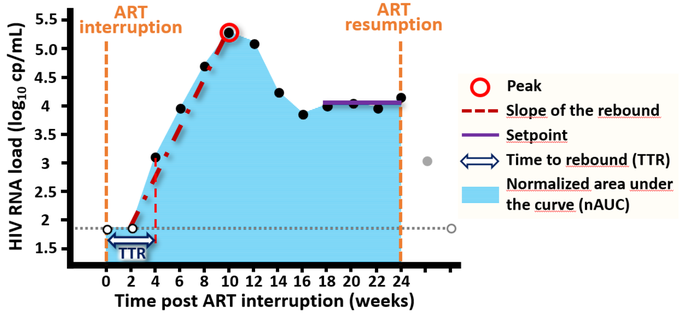
- The development of HIV therapeutic vaccine aiming at maintaining viral control in the absence of antiretroviral treatment (ART) is ongoing.
- In absence of relevant surrogate marker, the evaluation of their efficacy typically requires analytical treatment interruption (ATI) to measure their effect on viral load dynamics.
- The stable level reached after the viral rebound (setpoint) is the major viral endpoint used in ATI as primary endpoint [1]. However, this latter can not always be observed.

Objectives

1. To evaluate potential viral endpoints during ATI and identify the optimal surrogate to the setpoint.
2. To study the impact of the trial design and an early study dropout.

Viral endpoints of interest during ATI

- Various HIV RNA endpoints were defined to analyze viral rebounds induced by ATI in each trial.



Methods

Viral endpoints estimated on observed data

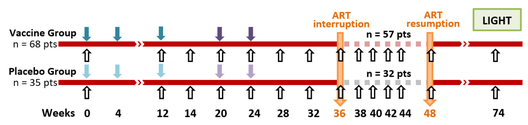
- Descriptive analysis of HIV RNA endpoints across arms.
- Spearman correlation analysis between viral endpoints within each of the 5 groups of treatment

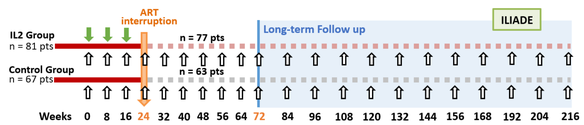
Impact of virological ART resumption criteria

- Simulation of an early ART resumption (i.e, study dropout) when HIV RNA load rebound above a threshold, for 1) at least one or 2) two consecutive measures.
- Consideration of virological threshold ranging from 2 to 6 log_{10} cp/mL.
- Estimation of Spearman correlations between the nAUC calculated on censored follow-up and the observed setpoint.

Three HIV therapeutic vaccine trials

- **VRI02 ANRS 149 LIGHT** (NCT01492985) [2]
  - Phase II randomized, placebo-controlled trial
  - Heterologous prime-boost vaccine strategy
- **ANRS 118 ILIADE** (NCT0001890) [3]
  - Phase II/III randomized, open-label trial
  - IL-2 immunotherapy
- **ANRS/VRI DALIA** (NCT00796770) [4]
  - Phase I single arm trial
  - Dendritic cell vaccine







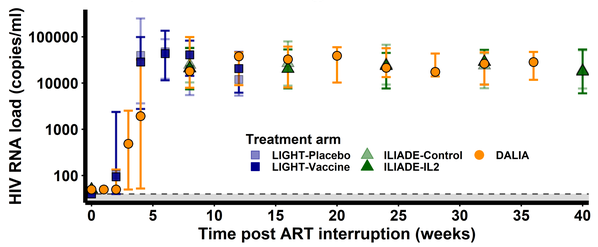
	Groups	Sample size	ATI duration	Timepoints during ATI
LIGHT	Vaccine + Placebo	57 + 32	12 Weeks: W36 → W48	6, every 2 weeks
ILIADE	IL-2 + Control	77 + 63	⩾ 48 Weeks: W24 → ⩾ W72	7, every 8 weeks & 11, every 12 weeks
DALIA	DC vaccine	19	⩾ 24 Weeks: W24 → ⩾ W48	5, every week & 8, every 4 weeks



Results

To evaluate viral control in the absence of ART, we recommend a minimum of 12 weeks of ATI with the AUC as criteria endpoint and a virological ART resumption criteria of at least 100,000 cp/mL with one confirmation measure.

HIV RNA load dynamics during ATI

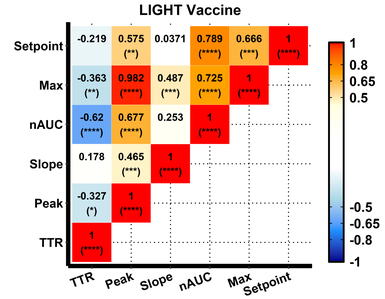


Descriptive analysis of HIV RNA endpoint

	LIGHT (n=89)		ILIADE (n=140)		DALIA (n=19)
	Placebo (n=32)	Vaccine (n=57)	Control (n=63)	IL2 (n=77)	
Time to rebound (TTR) - weeks					
Median	2.00	2.00	8.00	8.00	3.00
[IQR]	[2.00 ; 4.00]	[2.00 ; 4.00]	[8.00 ; 8.00]	[8.00 ; 8.00]	[2.00 ; 6.00]
Peak - log_{10} copies/mL					
Median	4.96	4.96	4.57	4.66	4.94
[IQR]	[4.57 ; 5.74]	[4.62 ; 5.36]	[4.21 ; 5.01]	[4.19 ; 4.99]	[4.10 ; 5.18]
Slope - log_{10} copies/mL/week					
Median	0.84	0.75	0.29	0.22	0.52
[IQR]	[0.55 ; 1.07]	[0.57 ; 1.00]	[0.15 ; 0.37]	[0.14 ; 0.35]	[0.36 ; 0.89]
Normalized AUC (nAUC) - log_{10} copies/mL					
Median	3.74	3.80	4.19	4.25	4.00
[IQR]	[3.31 ; 4.18]	[3.32 ; 4.20]	[3.74 ; 4.43]	[3.81 ; 4.50]	[3.68 ; 4.29]
Setpoint - log_{10} copies/mL					
Median	4.29	4.59	4.32	4.39	4.38
[IQR]	[3.87 ; 4.71]	[4.20 ; 4.88]	[3.82 ; 4.71]	[3.91 ; 4.70]	[4.05 ; 4.55]
Time to setpoint - weeks					
Median	8.00	8.00	16.00	16.00	12.00
[IQR]	[6.00 ; 8.00]	[6.00 ; 8.00]	[16.00 ; 24.00]	[16.00 ; 24.00]	[8.00 ; 16.00]

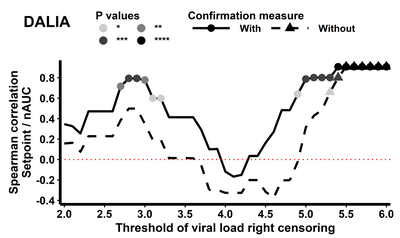
- Endpoints are sensitive to study design, in particular sampling times for the TTR and the slope, and the duration of ATI for the setpoint

Spearman correlations within each group



- Similar results for the 5 groups
- No significant correlation between the TTR/slope and the setpoint
- Highest significant **positive** correlations between the normalized AUC and the setpoint (**r>0.79**, p<1e-4)

Impact of premature ART resumption



- Retrieve significant positive correlations between the nAUC and the setpoint for a threshold higher than 5log_{10} cp/mL.
- The use of confirmation measure leads to higher correlations for a given threshold.
- A too low threshold (e.g. 4log_{10} cp/mL) can induce a wrong conclusion about vaccine efficacy (setpoint) due to lack of information.

Conclusion

- The evaluation of the **TTR** requires frequent monitoring of HIV RNA (at least once a week over 6 weeks) and is not correlated to the setpoint in the ATI trials.
- To evaluate the capacity to control viral replication, we recommend to use the **AUC** when ART are resumed if HIV RNA goes above 100,000 copies/mL.

References

[1] Julg, B., et *al.* (2019). *The Lancet HIV*
[2] Lévy, Y., et *al.* (2021). *Journal of virology*
[3] Lévy, Y., et *al.* (2012). *AIDS*
[4] Lévy, Y., et *al.* (2014). *European journal of immunology*