Comparison of AUC in clinical trials with follow up censoring:
Application to HIV therapeutic vaccines

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Introduction & objectives

- HIV therapeutic vaccine efficacy is typically assessed in **analytic treatment interruption** (ATI) protocols trial, in which antiretroviral treatments (ART) are interrupted over a period of time, inducing viral rebound.

- Prematurely ART resumption when viral load reach a threshold induces **missing data**, which is a **follow up censoring**. Additionally, data are left-censored by a **limit of detection** (LOD).

- We are interested in the use of **area under the curve normalized** by the time of follow up (nAUC) as primary endpoint of analysis in ATI studies. Without further adjustment/modeling, the use of nAUC with follow up censoring is biased **[Bell,2014].**

- **Objective**: We aim at developing a broad parametric statistical test to compare the nAUC in ATI trials.

[Bell,2014] Bell, M. L., King, M. T., & Fairclough, D. L. (2014). Bias in area under the curve for longitudinal clinical trials with missing patient reported outcome data: summary measures versus summary statistics. *SAGE Open*, *4*(2), 21582440145348580

Method – MEM nAUC

- We want to perform the following **t-test** between the two vaccine arms g_1 and g_2:

$$\begin{cases} \boldsymbol{H_0 : \Delta\widehat{nAUC}_{g_1-g_2} = 0} \\ \boldsymbol{H_1 : \Delta\widehat{nAUC}_{g_1-g_2} \neq 0} \end{cases}$$

- $\boldsymbol{\Delta\widehat{nAUC}_{g_1-g_2}}$, is calculated using a **2 steps approach** using modeling:

STEP 1: Mixed Effects Model to fit available data

Let Y_{ij,g_i} be the HIV RNA load measurement of the subject i, belonging to the vaccine arm g_i, at the jth time point

$$\boldsymbol{Y_{ij,g_i}} = \underbrace{\gamma_0 + \sum_{g=1}^{G} \mathbb{1}_{[g=g_i]} \times \sum_{k=1}^{K_g} \beta_k^g \phi_k^g(t_{ij,g})}_{\text{Population dynamics = Fixed effects}} + \underbrace{h_i(t_{ij,g_i})}_{\text{Random Effects}} + \boldsymbol{\varepsilon_{ij}}$$

Splines Curves, Group-specific

$$\boldsymbol{\varepsilon_{ij} \sim \mathcal{N}(0, \sigma_e^2)} \qquad \boldsymbol{B_i \sim \mathcal{N}(0, \Sigma_b^2)}$$

STEP 2: Estimation of $\Delta nAUC$ (Trapezoid method)

$$\boldsymbol{\widehat{nAUC}_g = \mathcal{F}_g(\hat{\gamma}_0, \hat{\beta}_k^g, t_g) =} \quad \frac{1}{T_g} \sum_{j=2}^{m_g} \frac{t_{j,g} - t_{j-1,g}}{2} \times \left(2\hat{\gamma}_0 + \sum_{k=1}^{K_g} \hat{\beta}_k^g \left(\phi_k^g(t_{j,g}) + \phi_k^g(t_{j-1,g}) \right) \right)$$

$$\{t_{j,g}\} = \bigcup_{i \in g} t_{ij,g} \quad ; \quad m_g = |\{t_{j,g}\}|$$

$$T_g = \max_j(\{t_{j,g}\}) - \min_j(\{t_{j,g}\})$$

$$\boldsymbol{\Delta\widehat{nAUC}_{g_1/g_2} = \widehat{nAUC}_{g_2} - \widehat{nAUC}_{g_1} = \overline{\mathcal{F}_{g_1/g_2}}(\hat{\gamma}_0, \hat{\beta}_k^{g_1}, t_{g_1}, \hat{\beta}_k^{g_2}, t_{g_2})}$$

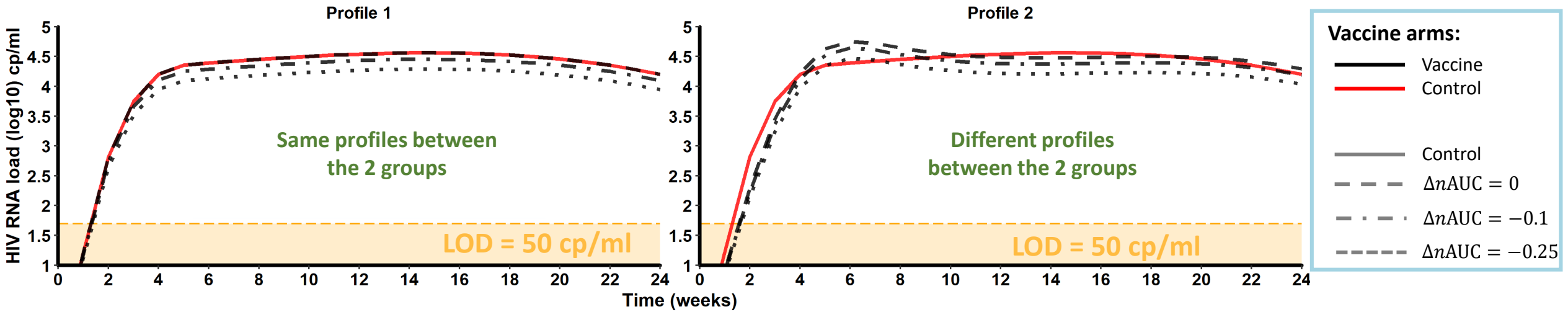
Simulations

- We simulated trials of **2** vaccine arms with **20**, **50** or **100** patients by group
- Protocol defining ATI:
  - 24 weeks of ART interruption
  - 1 measure every week
- 3 values of $\Delta n\mathrm{AUC}$ tested:

$\Delta n\mathrm{AUC} \in \{0, -0.1, -0.25\}\ \log_{10}\mathrm{cp/ml}$

  - ART resumption above α^* (+ 1 confirmed measure)
    1. $\alpha = 100\,000$ cp/ml ⇒ 5-40 % of censored follow up
    2. $\alpha = 50\,000$ cp/ml ⇒ 30-80 % of censored follow up
    3. $\alpha = 10\,000$ cp/ml ⇒ 95-100 % of censored follow up

↳ **Unbalanced missing data**



*α: Threshold of lost of follow up ; $Y_{ij,g} \in \left\{Y_{ij,g} \middle| \exists j' \leq j\,, \{Y_{ij',g} \geq \alpha\} \cap \{Y_{ij'-1,g} \geq \alpha\}\right\}$ is missing

N= 50 patients/group

Results

Missing data pattern	Methods	Profile 1			Profile 2		
		Type-I Error	Power ($\Delta nAUC$)		Type-I Error	Power ($\Delta nAUC$)	
			-0.1	-0.25		-0.1	-0.25
No censoring	Raw data*	0,060	0,95	1,00	0,046	0,94	1,00
	MEM nAUC	0,058	0,96	1,00	0,049	0,95	1,00
LOD	Raw data	0,056	0,96	1,00	0,047	0,94	1,00
	MEM nAUC	0,060	0,95	1,00	0,047	0,94	1,00
LOD & $\alpha = 100\,000$	Raw data	0,060	0,49	1,00	0,540	0,92	1,00
	LOCF	0,052	0,84	1,00	0,281	0,31	1,00
	Mean Imput.	0,059	0,51	1,00	0,529	0,83	1,00
	MEM nAUC	0,063	0,94	1,00	0,053	0,92	1,00
LOD & $\alpha = 50\,000$	Raw data	0,050	0,05	0,13	0,946	0,20	0,70
	LOCF	0,046	0,77	1,00	0,483	0,11	1,00
	Mean Imput.	0,051	0,05	0,14	0,940	0,81	0,70
	MEM nAUC	0,063	0,84	1,00	0,045	0,77	1,00
LOD & $\alpha = 10\,000$	Raw data	0,041	0,04	0,12	0,894	0,91	0,85
	LOCF	0,058	0,20	0,81	0,555	0,18	0,13
	Mean Imput.	0,039	0,04	1,00	0,746	0,83	0,80
	MEM nAUC	0,330	0,32	0,30	0,624	0,58	0,37

- **Valid results**
- **Too high Type-I Error or too weak power**
- **Weak power**
- **Meaningless with wrong Type-I Error**

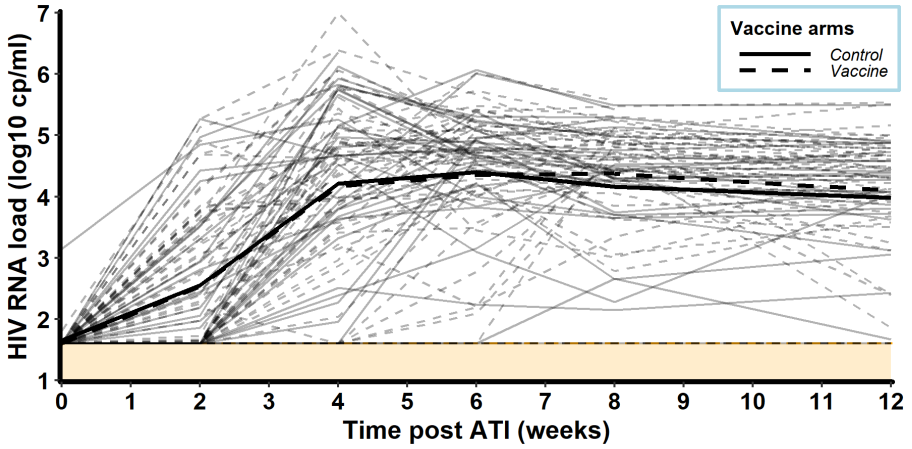
- **No censoring & LOD :**
  - ✓ All methods are valid
- **LOD & α=100 000 and 50 000:**
  - ✓ MEM nAUC method valid for all profiles
  - ✓ Indiviual methods failed at least for profile 2
- **LOD & α=10 000:**
  - χ All methods failed for at least one profile

*Methods using common t-test applied on mean nAUC estimated with individual trajectories:
1. Raw data: Data without any transformation ; 2. LOCF: Last Observation Carried Forward ; 3. Mean Imputation

Application of the method on Real data

LIGHT* – Observed data

Vaccine: 59 patients **Control**: 32 patients

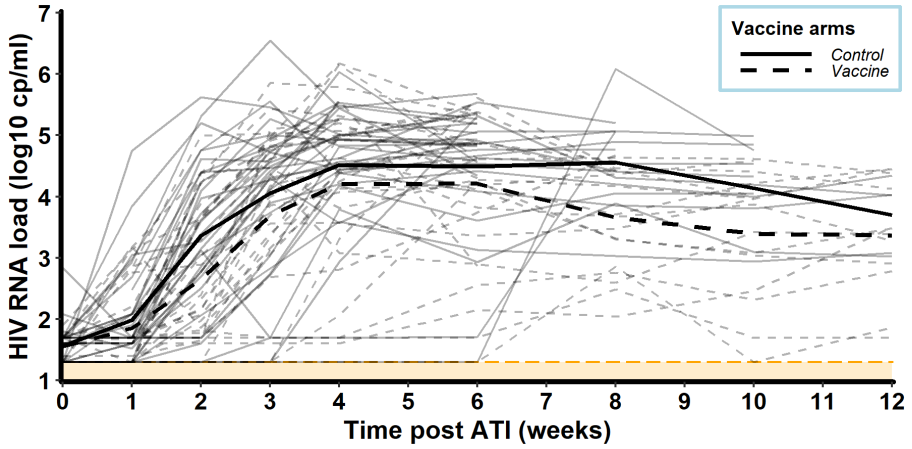


Method	Estimate (SE)	95% CI	P-value
Data	-0.030 (0.175)	[-0.312 ; 0.372]	0.864
LOCF	-0.018 (0.186)	[-0.382 ; 0.346]	0.924
Mean Imput.	0.217 (0.245)	[-0.263 ; 0.697]	0.959
MEM nAUC	0.078 (0.214)	[-0.342 ; 0.498]	0.715

No significant difference of nAUC between the 2 groups of treatment

Vac-IL2** – Observed data

Vaccine: 34 patients **Control**: 37 patients



Method	Estimate (SE)	95% CI	P-value
Data	-0.346 (0.170)	[-0.680 ; -0.013]	0.046
LOCF	-0.380 (0.198)	[-0.770 ; 0.007]	0.060
Mean Imput.	-0.345 (0.312)	[-0.957 ; 0.266]	0.276
MEM nAUC	-0.454 (0.214)	[-0.874 ; -0.034]	0.034

Significant difference of nAUC between the 2 groups of treatment

*VRI02 ANRS 149 LIGHT (NCT01492985)
Palich, R. et al (2019). Viral rebound in semen after antiretroviral treatment interruption in an HIV therapeutic vaccine double-blind trial. *Aids*, *33*(2), 279-284.

**ANRS 093 Vac-IL2 (NCT00196651)
Lévy, Y. et al (2005). Immunological and virological efficacy of a therapeutic immunization combined with interleukin-2 in chronically HIV-1 infected patients. *Aids*, *19*(3), 279-286.

Conclusion

- We developed and showed **good properties** of a parametric statistical test comparing nAUC of two vaccine arms in ATI trials using **mixed effects spline models**.
- We showed the **superiority** of this method to account for follow up censoring, especially when there is a **lag in viral rebound** between groups (Profile 2).
- **All methods fail** when there is a high percentage of follow up censoring (>90%), this is for example the case when the **threshold of ART resumption is low** ($\alpha \leq 10\,000$ copies/ml).
- The application of the method on data from HIV ATI trials allowed to show the **superiority of experimental arm of VAC-IL2 vaccine** compared to placebo, where other methods would have failed.
- Preprint and R-Code are available on request.