Immune Profile During ATI in AELIX-002 HTI Vaccine Trial and Its Role in Post-Intervention Control

00506

Cristina Peligero-Cruz[1], Lucía Bailón[2], Samandhy Cedeño[1], Tuixent Escribà[1], Yovaninna Alarcón-Soto[3], Nalia Lopez[3], Edwards Pradenas[1], Anna Pons-Grífols[1], Anuska Llano[4], Devi SenGupta[5], Ian McGowan[6], Jose Molto[2], Christian Brander[1] and **Beatriz Mothe**[1], for AELIX-002 study team

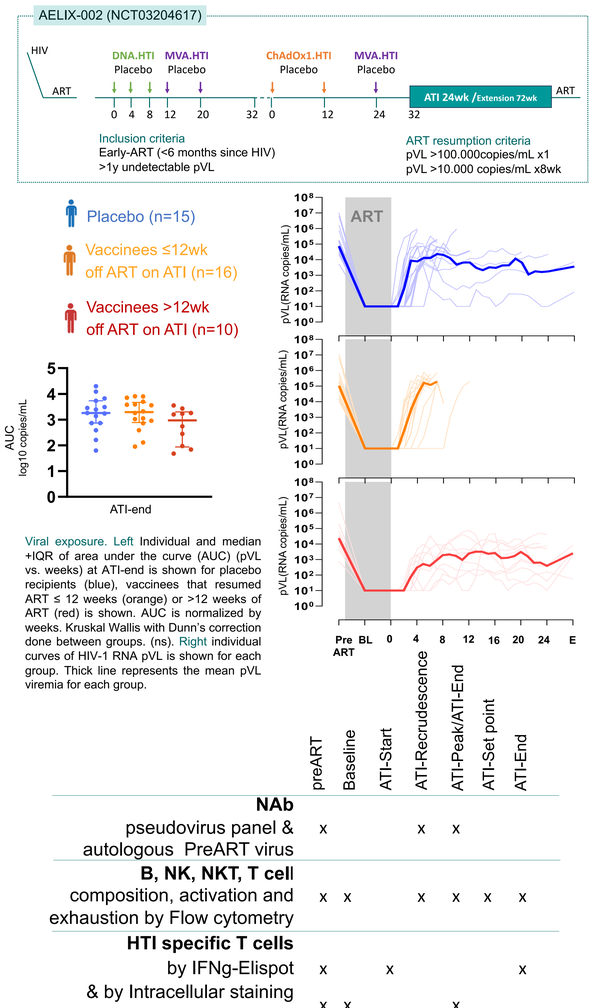
[1]IrsiCaixa Institute for AIDS Research, Badalona, Spain, [2]Hospital Germans Trias i Pujol, Badalona, Spain, [3]Lluita contra les Infeccions Foundation, Hospital Germans Trias i Pujol, Badalona, Spain, [4]Parc Taulí Hospital Universitari, Sabadell, Spain,[5]Gilead Sciences, Inc, Foster City, CA, USA, [6]AELIX Therapeutics SL, Barcelona, Spain

Background

In AELIX-002[1] (NCT03204617), a randomized controlled clinical trial testing HTI T-cell vaccines in early-treated PWH, all participants experienced detectable viral rebound during an analytical treatment interruption (ATI), but lower viremia and longer ART-free periods (>12 weeks) were observed in vaccine recipients in whom vaccination induced robust cytotoxic HTI responses pre-ATI.

Here, we explored humoral and cellular responses during ATI to:
(1) Assess the dynamics of the immune response in the ATI
(2) Investigate the relation between the immune response in the ATI and the early HIV response (pre ART)
(3) Understand the immune determinants of ATI outcomes

Methods



Viral exposure. Left Individual and median +IQR of area under the curve (AUC) (pVL vs. weeks) at ATI-end is shown for placebo recipients (blue), vaccinees that resumed ART ≤ 12 weeks (orange) or >12 weeks of ART (red) is shown. AUC is normalized by weeks. Kruskal Wallis with Dunn's correction done between groups. (ns). Right individual curves of HIV-1 RNA pVL is shown for each group. Thick line represents the mean pVL viremia for each group.

Results

1. Neutralization

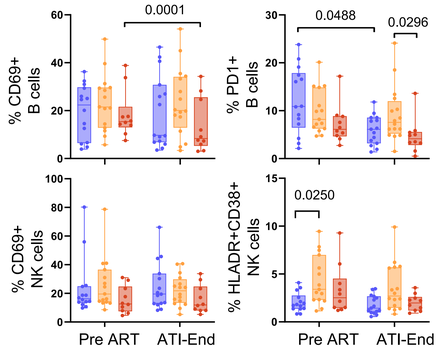
During early HIV no NAb were detected, and during ATI few participants induced NAb regardless of vaccination

	TRO.11 (CLADE B) tier 2	25710 (CLADE C) tier 2	CE1176 (CLADE C) tier 2	398F1 (CLADE A) tier 2	CNE8 (CRF01) tier 2	NL43 (CLADE B) tier 1	pre-ART Autolo-gous virus
preART							
	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)	1/15 **(6,7%)**	0/14 (0%)
	0/24 (0%)	0/24 (0%)	0/24 (0%)	0/24 (0%)	0/24 (0%)	2/25 **(8%)**	1/23 **(4,3%)**
ATI-Rc							
	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)	0/13 (0%)	2/13 **(15,4%)**
	0/23 (0%)	0/23 (0%)	0/23 (0%)	0/23 (0%)	0/23 (0%)	1/23 **(4,3%)**	1/22 **(4,5%)**
ATI-Pk							
	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)	4/15 **(26,7%)**	3/13 **(23,1%)**
	0/24 (0%)	0/24 (0%)	0/24 (0%)	0/24 (0%)	0/24 (0%)	1/24 **(4,2%)**	3/23 **(13,0%)**

Analysis of neutralizing activity of plasma samples against the indicated HIV pseudoviruses and the autologous virus isolated pre-ART. Data presented as n (neutralization detected)/N (total individuals) (%).

2. B cell & NK cell activation

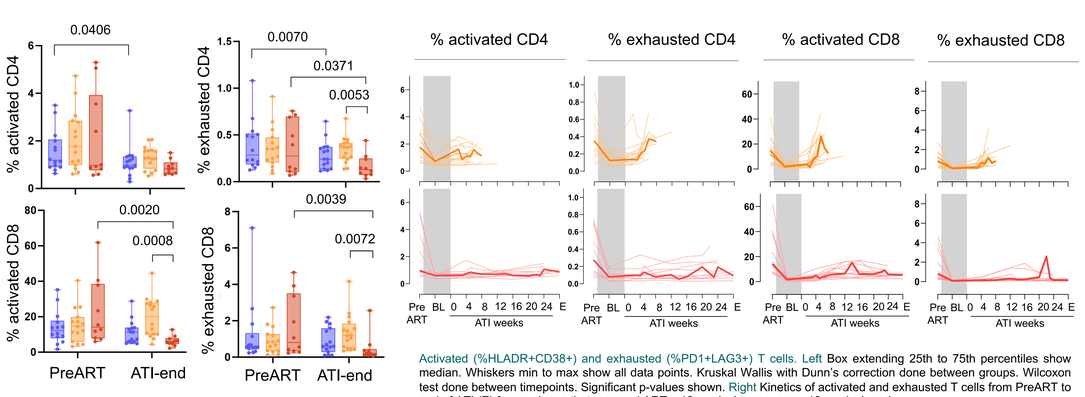
Unlike PTC, no increase in activated NK was observed in vaccinees who remained off ART for >12 weeks



Frequency of activated B and NK cells measured as %CD69+ or % PD1 expression for B cells and %CD69 and %HLADR+CD38+ expression for NK cells. Box extending 25th to 75th percentiles show median. Whiskers min to max show all data points. Kruskal Wallis with Dunn's correction done between groups. Wilcoxon test done between timepoints. Significant p-values shown.

3. T cell activation and exhaustion

Vaccinees who remained off ART >12 weeks had less activated and exhausted T cells during ATI



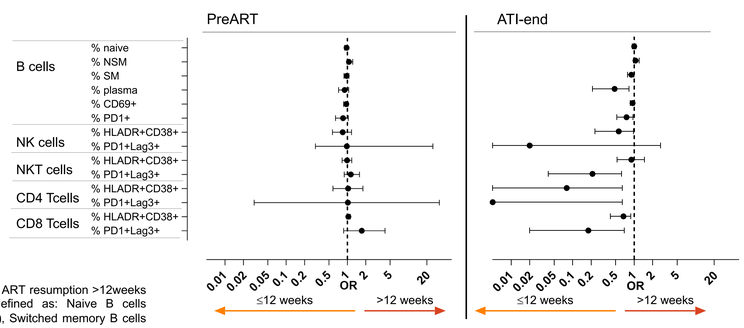
Activated (%HLADR+CD38+) and exhausted (%PD1+LAG3+) T cells. Left Box extending 25th to 75th percentiles show median. Whiskers min to max show all data points. Kruskal Wallis with Dunn's correction done between groups. Wilcoxon test done between timepoints. Significant p-values shown. Right Kinetics of activated and exhausted T cells from PreART to end of ATI (E) for vaccinees that resumed ART ≤ 12 weeks in orange or >12 weeks in red.

4. Correlate Analyses

Any of the studied parameters at pre-ART were associated with longer periods off ART during the ATI.

At the end of ATI, the immune profile better associated with remaining off ART >12weeks was characterized by:

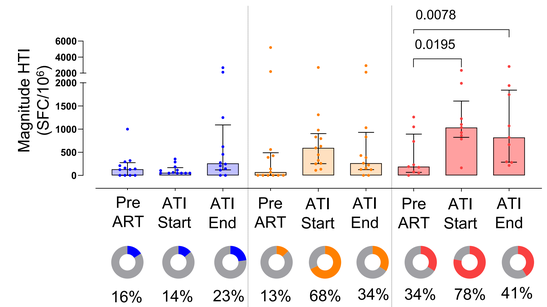
(i) lower exhaustion
(ii) lower % plasma B cells
(iii) lower B, T, NK activation



Univariate correlate analysis. Odds ratio and 95% CI of time to ART resumption >12weeks in univariate logistic regression models. B cell subsets defined as: Naive B cells (IgD+CD27), Non class switched memory (NSM) (IgD+CD27+), Switched memory B cells (SM) (IgD-CD27+CD38lo), Plasma (IgD-CD27+CD38hi).

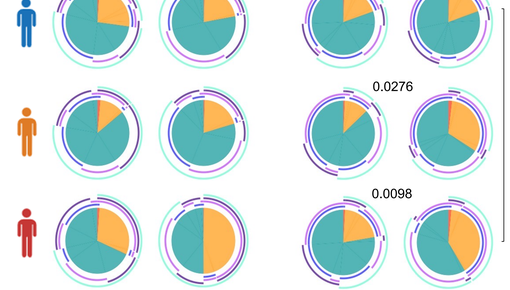
5. HTI – specific responses

Vaccinees who remained off ART >12 weeks maintain stronger and more focused HTI responses at ATI



Total HIV and HTI-specific T cells assessed by IFNγ ELISpot assay. Individual and median +IQR of magnitude of response (spot-forming cells/10^6PBMCs) shown. Significant p-values from Wilcoxon test shown. Average distribution of total HIV-1 T cells according to their specificity is shown in donuts. HTI-specific responses are shown in colour and its corresponding percentage over the total HIV response is indicated, while non-HTI HIV response are shown in grey.

Vaccinees who remained off ART >12 weeks showed higher contribution of polyfunctional CD4 and CD8 T cells during the ATI compared to the rest of participants



Polyfunctionality of HTI-specific CD4 and CD8 T cells Pie charts illustrate the relative proportion of each of the different subsets (cells producing 2, 3 or 4 functions) from cells producing at least 2 functions. Significant p-values from Spice permutation analysis shown.

Pie Legend: ++++ +++ ++

Arc Legend: Gzm b, IFNγ, IL2, TNFα

Conclusions

- Early HIV response (pre ART) does not seem to determine responses detected during ATI in vaccine recipients or impact vaccine responsiveness.
- bNAb, aNAb to preART viruses or NK cells do not play a role in preventing viral rebound in AELIX-002 study.
- Despite universal viral rebound during the ATI, vaccinees who remained off ART > 12 weeks showed (i) lower levels of plasma B cells, (ii) lower levels of activated B and CD8 T cells, (iii) less T cell exhaustion, and (iv) stronger, more focused and more polyfunctional HTI-responses during the ATI compared to the rest of participants.

HTI specific response remains the main factor contributing to an improved viral control during antiretroviral treatment interruption in AELIX-002 study.

ADDITIONAL KEY INFORMATION

1 Bailón et al. Nature Medicine, 2022

Author Contact Information: cpeligero@irsicaixa.es and bmothe@irsicaixa.es

Acknowledgements: Special thanks to all the volunteers participating in this study.
This study was co-funded by RTC-2017-6473-1, OMIT-HIV NIH P01AI178375 and ISCIII (PI20/01039) co-funded by ERDF, "A way to make Europe".

UNIÓN EUROPEA
Fondo Europeo de Desarrollo Regional
"Una manera de hacer Europa"