HTI-vaccine-induced, broad and polyfunctional CD4 and CD8 T cell responses are associated with prolonged time off ART and lower pVL at the end of ATI in the AELIX-002 therapeutic vaccine trial

Beatriz Mothe, Lucia Bailon, Anuska Llano, Yovannina Alarcon-Soto and Christian Brander on behalf of the AELIX-002 Study Group

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Co-inventor of the HTI immunogen with Christian Brander & Anuska Llano (patent application PCT/EP2013/051596), Consultant for AELIX Therapeutics SL and Speakers’ fees from Gilead, Janssen and ViiV Healthcare, outside this work
Introduction

- HTI vaccines are designed to induce HIV-specific T cell responses associated with better viral control in humans\textsuperscript{1,2}
- AELIX-002 was a FIH Phase 1/2 study to evaluate safety, immunogenicity and efficacy of HTI vaccines in early-treated people with HIV (PWH) NCT03204617\textsuperscript{3}

\begin{figure}[h]
    \centering
    \includegraphics[width=\textwidth]{figure.png}
    \caption{Acute/early HIV
    \begin{itemize}
        \item ARV > 1y
        \item n = 45
        \item (15 P + 30 V)
    \end{itemize}
    \end{figure}

\begin{itemize}
    \item DNA-HTI
    \item MVA-HTI
    \item Placebo
\end{itemize}

\begin{itemize}
    \item ARV x 24 wk
    \item ARV > 1y
\end{itemize}

\begin{itemize}
    \item ART RESUMPTION CRITERIA DURING ATI
    \item ARS / confirmed COVID-19
    \item pVL of HIV-1 RNA > 100,000 copies/mL
    \item pVL of HIV-1 RNA > 10,000 copies/mL for 8 weeks
    \item CD4 count < 350 cells/mm\textsuperscript{3} for 2 consecutive determinations
\end{itemize}

\textsuperscript{1}Mothe JTM 2011; \textsuperscript{2}Mothe JTM 2015; \textsuperscript{3}Bailon Nat Med 2022
AELIX-002 RCT

Participants Without Beneficial HLA class I alleles

N=12 Placebo

N=20 Vaccine

All participants rebounded
Similar initial pVL kinetics

How to improve this effect?

HOST / Baseline conditions
VIRUS
VACCINE-INDUCED RESPONSES
ATI endpoints

- Time to 1st pVL>50
- Time to pVL>10K
- Time to peak pVL
- pVL end of ATI
- Time off ART
Host / Baseline conditions: pVL pre-ART

- Time to 1st pVL > 50
- Time to pVL > 10K
- Time to peak pVL
- pVL end of ATI
- Time off ART

Age
Abs CD4
CD4/CD8
pVL pre-ART
Days HIV to ART
Time ART-suppressed

Rho = 0.6837
P = 0.0009

Rho = 0.6062
P = 0.0046

CHAMP; Namazi JID 2018
Virus: ~reservoir

- Time to 1st pVL>50
- Time to pVL>10K
- Time to peak pVL
- pVL end of ATI
- Time off ART

Total Study entry
Intact Study entry
Total at ATI
Intact at ATI

Rho = -0.4428
P = 0.0765

*** <0.0001
** <0.001
* <0.05

Accelevir
Anuska Llano
Marc Noguera
HTI Magnitude

10 peptide pools covering HTI sequence:
- Pol: p6 (Prot), p7 (RT), p8 (Int), Vif-Nef, Linkers

*** <0.0001
** <0.001
* <0.05

Ex-Vivo Fresh

ORF1
ORF2
ORF3

Samandhy Cedeño
Tuixent Escribà
## HTI Magnitude

<table>
<thead>
<tr>
<th>Time to 1st pVL&gt;50</th>
<th>Time to pVL&gt;10K</th>
<th>Time to peak pVL</th>
<th>pVL end of ATI</th>
<th>Time off ART</th>
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- **HTI Magn entry**
- **HTI Focus entry**
- **HTI Magn at ATI**
- **HTI Focus at ATI**

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<tr>
<th>HTI Magn entry</th>
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<tbody>
<tr>
<td>*</td>
<td>**</td>
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</table>

### HTI Magnitude

**<0.0001**  
**<0.001**  
* <0.05

### Ex-Vivo Fresh

- gag
- pol
- Env
- vif
- nef
- vpr
- vpu
- rev

### 5 peptide pools covering non-HTI sequence:
- OUT-Gag
- OUT-Pol

### 10 peptide pools covering HTI sequence:
- **Gag:** p1 (p17), p2 (p17), p3 (p24), p4 (p24), p5 (p15)  
- **Pol:** p6 (Prot), p7 (RT), p8 (Int)  
- **Vif-Nef:** p9  
- **Linkers:** p10

### 5 peptide pools covering non-HTI sequence:
- OUT-Env
- OUT-Vif-Nef
- OUT-TTVR

### ORF1 ORF2 ORF3
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<td>Time off ART</td>
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**Rho** = 0.6869  
**P** = 0.021

**Rho** = 0.6837  
**P** = 0.0009

*** <0.0001  
** <0.001  
* <0.05

---

**HTI Magnitude**

- HTI Magn at ATI
- HTI Focus at ATI
- HTI Magn entry
- HTI Focus entry

---

**DNA-HTI**  
**MVA-HTI**  
**ChAdOX1-HTI**  
**MVA-HTI**

- Placebo
- Placebo
- Placebo
- Placebo

---

**HTI Focus**

- **PPP**
- **PPP**
- **DDDMM**
- **CCM**

---

**HTI Magn**

- **Rho = 0.6837**  
  **P = 0.0009**
- **Rho = 0.6869**  
  **P = 0.021**
HTI Breadth

<table>
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<tr>
<th>HTI Magn entry</th>
<th>HTI Focus entry</th>
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<th>HTI Focus at ATI</th>
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<td>Time off ART</td>
<td></td>
<td></td>
<td></td>
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</table>

Cum Breadth at ATI
HTI Focus at ATI
HTI Magn at ATI
HTI Magn entry
HTI Focus entry

In-vitro expanded

147 individual peptide pools covering HTI sequence

*** <0.0001
** <0.001
* <0.05
Immune responses

In-vitro expanded

De-novo responses being confirmed by TCR sequencing

*** <0.0001
** <0.001
* <0.05

HTI Magn entry
HTI Focus entry
HTI Magn at ATI
HTI Focus at ATI

*** < 0.0001
** < 0.001
* < 0.05

P = 1.49 x 10^-6
Characterization of HTI-specific responses

Thaw & rest
- HTI Gag p17
- HTI Gag p24/p15
- HTI Pol Int/RT/Prot
- HTI Vif/Nef

Stimulate

Incubation 6h 37ºC

Flow stain ICS

Neg

Singlets

Lymphocytes

Live CD3+

CD8 and CD4

Anti-CD3/CD28 stimulated

CD8

IFNγ

GZMB

IL-2

TNFα

Anuska Llano
Samandhy Cedeño
Both CD4 & CD8 T cells induced
CD8⁺ GzmB⁺ (&CD4) correlates with ATI outcomes

- Rho = -0.5920, P = 0.0060
- Rho = 0.6361, P = 0.0026
- Rho = -0.5190, P = 0.0190
- Rho = 0.4246, P = 0.0620
Polifunctionality

CD4⁺ T cells
\[ P = 1.11 \times 10^{-4} \]

CD8⁺ T cells
\[ P = 0.0026 \]

IFN-γ⁺ (%)

CD8⁺ T cells (%)

P = 8.04 \times 10^{-6}

P = 7.23 \times 10^{-5}

IL-2
IFN-γ
TNF-α
GzmB

P = 0.0282
P = 0.0002
P = 0.0063
P = 0.0068

ATI x 24 wk

DNA HTI
MVA HTI
ChAdOx1 HTI
MVA HTI
Placebo
Placebo
Placebo
Placebo

ARV
Polifunctionality

CD4 T-cells

Pbo | Vax
---|---

CD8 T-cells

Pbo | Vax
---|---
Exhaustion markers

- Thaw & rest
- a-CD28/a-CD49d
- DMSO
- Stimulate
- Incubation 6h 37ºC
- Surface markers
- Flow stain

Phenotype
- CD45RA/CCR7

Exhaustion
- PD1/TIGIT

Activation
- HLADR/CD69
Conclusions

- HTI vaccines induced high frequency of broad and polyfunctional CD4 & CD8 T cell responses
- HTI magnitude, breadth and frequency of GzmB⁺ T cells at ATI correlated with time off ART and pVL at ATI end
- In the univariate and multivariate logistic regression models, reservoir levels were not associated with higher chances of remaining off ART
- In the multivariate, when accounting for pVL pre-ART and CD4/CD8 ratio, vaccination increased probability for being off ART.

<table>
<thead>
<tr>
<th></th>
<th>$\hat{\beta}$</th>
<th>s.e.($\hat{\beta}$)</th>
<th>OR</th>
<th>95% CI (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>2.9567</td>
<td>3.2682</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment (Vax)</td>
<td>2.1105</td>
<td>1.1929</td>
<td>8.25</td>
<td>1.05; 140.36</td>
</tr>
<tr>
<td>pVL at ART initiation (1 log10 copies/mL)</td>
<td>-1.5881</td>
<td>0.7807</td>
<td>0.20</td>
<td>0.03; 0.73</td>
</tr>
<tr>
<td>Ratio CD4/CD8 at AELIX-002 entry (0.2 units)</td>
<td>0.4070</td>
<td>0.8943</td>
<td>1.50</td>
<td>1.10; 65.77</td>
</tr>
</tbody>
</table>

*Vax, vaccine; pVL, plasma viral load; ART, antiretroviral treatment.*
Next steps

Participants Without Beneficial HLA class I alleles

How to improve this effect?
More individuals & better viral control!

HOST / Baseline conditions
VIRUS
VACCINE-INDUCED RESPONSES
Next steps

Improve vaccine immunogenicity
- New vectors (mRNA)
- Able to sensor latent infected cells
- Reversion of T-cell exhaustion / CTL resistance

Reduce or Silence viral reservoir
- Reverse Latency
- Target escaped variants
- Lock the reservoir

VIRUS

AELIX-003 (NCT04364035)
- ChAdOx1.HTI + MVA.HTI + Vesatolimod
- 57 early-treated
- ATI
- Unblinding (Q1 2023)

BCN03 (NCT05208125)
- ChAdOx1.HTI + MVA.HTI + SOSIP
- 30 chronics
- ATI
- Ongoing (Q4 2023)
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Jordi Naval
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M. Pierre Malice (ext)

JOSE LUIS CABERO

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P01-AI131568

Una manera de hacer Europa
• HTI vaccines were designed based on human immune data to induce better viral control
• FIH RCT in early-treated PWH show safety and immunogenicity, inducing responses with similar characteristics to those described in HIV controllers, regardless of favourable HLAs
• All participants experienced viral rebound upon ART interruption. However, vaccine responses were associated with better HIV control, despite not reaching undetectable levels.
• Next Steps:
  • Data support the use of HTI as a potential ‘T-cell backbone’ vaccine in combination trials.
  • Two RCT already ongoing (in early-treated and PWH that did not start ART in acute/recent HIV infection) with results expected in 2023-24 respectively