HIV-1 superinfected individuals exhibit low-titer autologous neutralizing antibody responses prior to intrasubtype C superinfection

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Emory University
7th International Workshop on HIV Transmission
HIV-1 Transmission in Unlinked Couples
from the Zambia-Emory HIV Research Project Cohort (Lusaka, Zambia)

ZEHRP cohort presents a unique opportunity to analyze superinfection in cohabiting heterosexual couples over a longitudinal time course.
Confirmation of Intrasubtype Superinfection

- Neighbor-joining Phylogenetic Tree
  - Full-length env single genome amplification
  - Superinfected individuals colored
  - Longitudinal sampling

- 3/22 (13.6%) acutely-infected individuals superinfected
- All during the first year of infection
- All Subtype C superinfections
- SI virus from non-spousal donor
- 19/22 not superinfected over next 3 years of follow-up
Lack of Env sequence evolution in superinfected individuals
HYPOTHESIS

Based on the relative lack of env diversification in longitudinal viral sequences prior to superinfection, we hypothesize that lower titers of protective antibodies (as reflected by autologous NAb to the initial infection) exist in superinfected individuals in the ZEHRP cohort.

Such low titer responses could predispose individuals to superinfection.
EXPERIMENTAL METHODS

SGA of full-length env of founder/early virus

TOPO-clone founder env

pSG3Δenv

293T cells

pcDNA3.1 env

Founder Env-pseudotyped virions

pSG3Δenv = env-deficient HIV-1 provirus

pcDNA3.1 env = CMV promoter-driven exp. plasmid containing patient-derived env

Nab Assay

Autologous longitudinal plasma
Superinfected individuals mount delayed and low autologous NAb to founder virus prior to superinfection.

* Time of Superinfection Detection

$p = 0.039$
No cross-neutralization of superinfecting virus by autologous plasma prior to SI

<table>
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<tr>
<th>Superinfecting Env Pseudovirus</th>
<th>1\textsuperscript{st} plasma time point</th>
<th>2\textsuperscript{nd} plasma time point</th>
<th>3\textsuperscript{rd} plasma time point</th>
<th>4\textsuperscript{th} plasma time point</th>
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<td>&lt;100</td>
<td>&lt;100 (SI)</td>
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IC50 Titers

- **Strong**: 10,000+
- **1000-10,000**
- **100-1000**
- **Weak**: <100
Non-superinfected individuals exhibit highest heterologous Nab breadth and potency to subtype C panel

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IC50 Value key: 20 - 20-50 - 51-100 - 100+

*Breadth score was calculated by adding the total number of envelopes neutralized at an IC50 greater than or equal to 20
*Potency score was calculated by dividing individual plasma-env IC50 by median IC50 per envelope against all plasma and then adding the sum of these scores (rounded to the nearest integer) for each plasma.
*Auto indicates that a plasma sample was tested against an autologous envelope in the panel. IC50 values were not counted in breadth and potency scores.
Plasma binding antibody levels to purified subtype C gp120 protein is reduced in superinfected individuals

$p=0.115$
Plasma binding antibody levels to subtype C V1V2 protein is absent in superinfected individuals prior to superinfection.

* Time of superinfection detection
Conclusions

• Despite small numbers, the correlation between autologous NAb titers and superinfection outcome and lack of additional superinfection after 1 year, suggests poor early immune responses may predispose to superinfection

• High levels of antibodies (as reflected by autologous NAb to the initial infection and binding Abs in early infection) could result in protection from superinfection OR could be an indirect surrogate for another protective immune factor

Big Picture:

- If confirmed in a larger ongoing study of 70 acutely infected partners, these results would support the feasibility of inducing a primary protective immune response via a vaccine.

- This would be hopeful from an HIV-1 vaccine perspective at least in the context of intra-clade C protection
Thanks!!

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