Broadly neutralizing antibodies and the HIV reservoir
Conflict of interest disclosure

No relevant financial relationships to disclose.

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What key question was asked?
Can broadly neutralizing antibody (bNAb) therapy impact the HIV reservoir?

What was the key finding / take-home message?
Changes in the size and composition of the intact proviral reservoir after bNAb therapy.

How is this important for an HIV cure?
Goal of HIV-1 cure research is to reduce or silence the reservoir.
Reservoir Half-Life

QVOA

Latently infected cells (IUPM)

$T_{1/2} = 3.7$ years

Siliciano et al – Nature Medicine 2013

IPDA

Intact proviruses per 10^6 cells

$T_{1/2} = 4$ years (0-7 years)

$T_{1/2} = 18.7$ years (>7 years)

Peluso et al – JCI Insight 2020

Q4PCR

Intact proviruses per 10^6 CD4+s

$T_{1/2} = 4.9$ years

Cho et al – PNAS 2022
1. Broadly neutralizing antibodies mediate effector functions

2. Therapy with bNabs potentially eliminates infected CD4+ T cells and reduces HIV-1 latent reservoir in people living with HIV

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generally safe and well-tolerated. Rebound resulted in resuppression of viraemia (Supplementary Table of first antibody infusion and at rebound, respectively (Extended Data). Individuals whose regimens contained non-nucleoside reverse transcriptase inhibitors were switched to an integrase inhibitor—(Fig. three-week intervals beginning two days before treatment interruption of detection of HIV-1 RNA was 20^10−1074, blue; right y axis) in the nine bNAb-sensitive participants (left). Increased HIV-specific T cell immunity (Niessl et al – Nature Medicine 2020). IUPM reduction, not significant (Mendoza et al – Nature 2018).
bNAbs Clinical Trials

3BNC117 + 10-1074

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**bNAb Clinical Trials**

**Group 1: Late Rebound/Ongoing Viral Suppression through dosing period**

- 5104
- 5106
- 5111
- 5114
- 5115
- 5108
- 5117
- 5118
- 5120
- 5125
- 5128
- 5130

Plasma HIV-1 RNA (log$_{10}$ copies/ml)

**Group 1: Early ART restart during dosing period**

- 5122M
- 5101
- 5105
- 5112
- 5123

- Viral Load
- 3BNC117
- 10-1074
- 3BNC117
- 10-1074
- on ART

**Group 2**

- 5203
- 5210
- 5216
- 5221
- 5227
- 5231

Weeks

**Towards an HIV Cure**
Sequences recovered

**902 intact** (12.6%) proviruses

**6275 defective** (87.4%) proviruses
Reservoir Quantification

The fractions of intact and defective proviral genomes per 10^5 CD4^+ T cells are depicted by Q4PCR pre-therapy and post-therapy (26 weeks) for bNAb therapy with ART alone. Longitudinal changes in relative representation of proviral subtypes in the absence of pre-screening for sensitivity. A key challenge in the further implementation of antibody therapy is that available combinations of antibody monotherapy, close monitoring and education of participants and the parallel placebo-controlled clinical trial in individuals who have treatment interruptions are of utmost importance. Owing to the relative scarcity of intact proviruses, but, despite these current interruption studies, quantitative and qualitative testing remains suboptimal. It has been estimated that a three to four orders of magnitude dilution of intact proviruses during monotherapy is essential in this respect because of the emergence of antibody resistance.

The results of this open-label study in chronically infected individuals examined, most of whom were infected with clade B HIV-1, demonstrate that antibodies targeting non-overlapping epitopes appear to be advantageous. Sustained viral suppression among sub-populations of people living with HIV who face challenges with daily regimens of ART alone is measured by methods that can definitively distinguish between these two compartments. It has been estimated that a three to four orders of magnitude dilution of intact proviruses while receiving repeated doses of anti-HIV-1 bNAbs.

The intact proviral reservoir half-life of between four and five years is longer than intact proviruses, have a much longer half-life than defective proviruses, which are one to two orders of magnitude more abundant than intact proviruses. The degree of intact proviral decay is measured in the absence of pre-screening for sensitivity. Owing to the relative scarcity of intact proviruses, the depth of the reservoir is measured by methods that can definitively distinguish between these two compartments. The intact proviral reservoir half-life of between four and five years is longer than intact proviruses, have a much longer half-life than defective proviruses, which are one to two orders of magnitude more abundant than intact proviruses.

<table>
<thead>
<tr>
<th>Intact</th>
<th>Defective</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Baseline</td>
<td>Follow-up</td>
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</tbody>
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Relative change in proviral frequencies (indicated at the bottom of each graph) and were determined using two-tailed paired Student’s t-tests in ART alone. The graphs show the mean ± s.d. of intact and defective proviral frequencies, respectively. The x-axis range (relative change TSC) and the y-axis range (in relative change T2/T1) are shown at the top of each graph and was determined using two-tailed paired Student’s t-tests in ART alone.

Follow-up

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Reservoir Composition

- bNAb therapy associated with significant decrease in the intact proviral reservoir
- change in reservoir size was not sufficient to delay rebound

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Reservoir Group 2 (ART+bNAb)

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Conclusions

- Immunotherapy with 3BNC117 and 10-1074 was associated with significant decrease in the intact proviral reservoir without measurable effect on the defective reservoir.

Hypothesis:

**Antibody** therapies might *interfere* with *clonal expansion* and *reservoir maintenance* by *targeting* dividing *cells* that *express viral proteins directly* or by *enhancing* CD8+ *T cell immunity*.

- However, magnitude of the change in reservoir size after bNAb therapy was not sufficient to delay rebound.

Outlook:

**Longer**, and **larger studies** to determine immunological mechanisms as well as a **precise half-life** of the intact reservoir during **antibody therapy**.

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