Therapeutic HIV Vaccines and Broadly Neutralizing Antibodies

Magdalena E. Sobieszczyk
Associate Professor of Medicine at CUMC
Columbia University Irving Medical Center
New York, New York

Learning Objectives

After attending this presentation, learners will be able to:
• Describe goals and challenges of therapeutic vaccine development
• Describe the status of clinical development of broadly neutralizing antibodies (bNAbs) for treatment
• Describe advances in bNAbs

Outline

• Why pursue ART-free approaches like therapeutic vaccines and antibodies to HIV-1 treatment?
• What are therapeutic vaccines
• What are broadly neutralizing antibodies - bNAbs
• Advances in bNAbs for treatment and potential for cure
Why Pursue ART-free Approaches to Treatment?

- Impossible to eradicate HIV from latent viral reservoirs with ART alone
- Important to have OPTIONS including agents with potential for less frequent dosing
- Gaps in ART delivery
- Long term side effects of ART
- Adherence and retention in care remain a challenge

Is it possible to achieve sustained HIV-1 remission/control without antiretrovirals?

Rationale for Therapeutic HIV-1 Vaccines

- Evidence from individuals whose immune system naturally control HIV-1 without ART (LTNP, elite controllers)
  - effective host mediated anti-HIV immunity is possible
- Is it possible to augment the host immune response to kill infected CD4 T cells and neutralize circulating virions?

Goals of a Therapeutic Vaccine

- At minimum
  - Make simplified ART regimens possible
  - Allow for periodic Analytic Treatment Interruption [ATI]
- Optimally
  - Eliminate need for ART either by eradicating the virus or inducing host immune response capable of controlling virus replication

In placebo-controlled studies that included interruption of ART to measure efficacy, therapeutic vaccine not successful in achieving durable suppression of HIV viremia.
A randomized controlled safety/efficacy trial of therapeutic vaccination in HIV-infected individuals who initiated antiretroviral therapy early in infection

- No effect of DNA/rVSV therapeutic vaccination on control of HIV rebound following ART interruption
- 26% of placebos sustained suppression of viremia after treatment interruption

Selected Randomized Controlled Trials of Therapeutic Vaccines

<table>
<thead>
<tr>
<th>Vaccine Name</th>
<th>Population</th>
<th>Latency/Reversal Agent</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>DC-HIV</td>
<td>ATI</td>
<td>No</td>
<td>Significant/transient decrease in VL during ATI, 3x T cell responses</td>
</tr>
<tr>
<td>ALVAC-HIV, Lipo-5T, IL-2: Canarypox vector (Env, Gag, Pol, Nef), lipopeptide vaccine (Nef, Gag, Pol, IL-2)</td>
<td>ATI</td>
<td>No</td>
<td>Induced HIV-specific CD4 and CD8 T cell responses which predicted virologic control during ATI</td>
</tr>
<tr>
<td>HIVAX: mutated HIV strain expressing range HIV proteins</td>
<td>ATI: no placebo</td>
<td>No</td>
<td>Broad responses/Reduced VL vs. pre-ART</td>
</tr>
<tr>
<td>DNA/rSV</td>
<td>ATI in pts. who started ART in early infection</td>
<td>No</td>
<td>Vx did not prevent viral rebound; 26% placebo had sustained suppression viremia after ATI</td>
</tr>
<tr>
<td>MVA-B: clade B gp120, Gag, Pol, and Nef</td>
<td>ATI</td>
<td>Yes</td>
<td>Safe &amp; immunogenic; no sig effect on VL rebound after ATI or viral reservoir with or without LRA</td>
</tr>
</tbody>
</table>

Towards a More Effective Therapeutic Vaccine: Improved Combination Approaches

**Ad26/MVA therapeutic vaccination with TLR7 stimulation in SIV-infected rhesus monkeys**

- Induced broad cellular immune responses
- No clinically significant decrease in VL setpoint after ATI

**Ad26/MVA + TLR7 agonist**

- 1.75 log reduction in VL
- 2.5-fold delay of viral rebound
- 33% monkeys maintained undetectable VL after ATI
**Therapeutic Vaccines: Take Home Points**

- No randomized controlled trials of therapeutic vaccination that induced long-term remission after analytical treatment interruption
- Need vaccines that induce broad host immune responses to recognize diverse escape viral variants after viral rebound
- Therapeutic vaccine may need to be paired with potent latency reversal agent (e.g., vorinostat) or immune modulators (TLR7 agonist) to induce long-lasting remission

Stephenson, Curr Opin HIV AIDS 2018
Graziani & Angel, JIAS, 2015
Seddiki & Levy, Curr Opin HIV AIDS 2018

---

**ARS Question 1: Would any of your HIV-infected patients be interested in bNAb based therapies as an alternative to ART?**

1. None, my patients are happy taking daily ART
2. Yes but less than 25%
3. Yes, between 26-50%
4. Yes, between 51-75%
5. Yes, more than 76%

---

**Potential use of Abs for HIV-1 Treatment**

- Block HIV replication by inhibiting viral entry into cell (neutralizing activity)
- Capable of engaging the host immune system
  - Mediate killing of infected cells (ADCC)
- Potential to clear latently infected cells and enhance immune responses against HIV-1
  - Potentially target latent viral reservoir

Fig. Carillo et al, Frontiers Immunology 2018
What are Broadly Neutralizing Antibodies against HIV-1

- Minority of HIV-1 infected individuals (5-10%) develop the ability to neutralize various heterologous viruses from different subtypes within 2-3 years after infection
- Very broad and potent neutralizing antibodies have been isolated from these individuals
- Bind to relatively conserved regions of Env
- Passive transfer of bNAbs investigated for treatment, eradication/cure, prevention, and to guide preventive vaccine design

Broadly cross-neutralizing antibodies have NO impact on HIV disease progression: CAPRISA 002 Cohort

Time to CD4≥350 or ARV initiation

Broadly Neutralizing Antibody Targets on the HIV-1 Envelope Trimer

Attachment points of Abs capable of neutralizing wide range of HIV isolates

Examples of Broadly Neutralizing Abs in Clinical Development

N352 Glycan Supersite: PGT121, 10-1074
GP120 gp41 Interface
V1V2 Glycan: PGT141-45, PGDM1400, CAP256-VRC26
CD4 Binding Site: VRC01, 3BNC117, VRC07-523
Trimer (gp120/gp41): 8ANC195, PGT151
gp1 N332 Glycan Supersite: PGT121, 101074

Passive Infusion of Broadly Neutralizing Antibodies Delays the Rebound of Plasma HIV Viremia Following Interruption of ART

LETTER

HIV-1 antibody 3BNC117 suppresses viral rebound in humans during treatment interruption

- 13 ART-treated participants with 3BNC117-sensitive viruses
- Analytical treatment interruption (ATI) and 2-4 infusions
- Infusions delayed viral rebound average of 8.4 weeks vs. historical controls
- Rebound virus with low diversity and resistance to 3BNC117 in most patients

Selected Clinical Trials involving bNAbS in HIV-1 infected individuals

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Population</th>
<th>Target</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01</td>
<td>On ART and viremic</td>
<td>CD4-Ab</td>
<td>- VL decay 1.1–1.8 log_10 after single infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ATI: viral strains not selected for VRC01 sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Median delay in viral rebound of 4 and 5.6 wks after ART dis</td>
</tr>
<tr>
<td>3BNC117</td>
<td>On ART and viremic</td>
<td>CD4-Ab</td>
<td>- Average VL decay of 1.48 log_10 after single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ATI: Viral strains screened for 3BNC117 sensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Average delay in viral rebound of up to 9.9 wks after ART dis &amp; multiple doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- t_1/2 9.6 days in HIV+</td>
</tr>
<tr>
<td>10-1074</td>
<td>On ART and viremic</td>
<td>V3 loop</td>
<td>- VL decay 1.52 log_10 after single infusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Emergence of resistant viral strains in few wks (sensitive to non-V3 loop Ab)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- t_1/2 12.8 days in HIV+</td>
</tr>
<tr>
<td>PGT121</td>
<td>On ART and viremic</td>
<td>V3 loop</td>
<td>- High baseline VL: 1.7 log_10 drop with rebound resistant virus (5/9 responders)</td>
</tr>
<tr>
<td></td>
<td>CROI 2019</td>
<td></td>
<td>- Low baseline VL: 2 pts suppressed &gt;6 months</td>
</tr>
<tr>
<td>PGDM 1400</td>
<td>Viremic</td>
<td>V1/V2 loop</td>
<td>- Ongoing. Will evaluate PGDM 400 +/- PGT121</td>
</tr>
</tbody>
</table>

Optimizing bNAbS for the Treatment of HIV Infection

- More potent antibodies
- Extend half-life of antibodies
- Combinations of antibodies
- Next generation of antibodies
Potency & Breadth: In Vitro Neutralization Profiles

Potency & Breadth

Antibody Modifications Extend Half-life: Intermittent Dosing

- LS mutation: Two amino acid mutation in Fc region of the Ab
- Increased affinity for neonatal Fc receptor (FcRn): extend plasma half-lives
- Potential for less frequent administration of mAb
- Increased Ab at mucosal surface in animal studies
- Studies with LS versions are ongoing

Gaudinski et al., PLOSMedicine 2018
Modifications of Fc region can also Increase Effector Functions

- Fc modifications to increase antibody dependent cell-mediated cytotoxicity (ADCC) or phagocytosis
  - Potentially reduce or target the HIV reservoir

- CROI 2019: Engineered variant of PGT121 with enhanced effector function (GS-9722)
  - Enhanced killing of HIV infected CD4+ T-cells by NK cells

Thomsen et al. Abstract 356. CROI 2019

Potential of Combination bNAb Therapy for the Durable Control of HIV

- In studies to date, rebound viruses did not demonstrate increased resistance to other Ab that target different envelope epitopes
- Combinations of two or more bNAbs are likely to lead to more robust and sustained antiviral effects
  - Increase overall breadth and potency
  - Prevent emergence of resistance

Combining Abs to Improve Potency and Breadth

Rui Kong et al. J. Virol. 2015;89:2659-2671
Combination bNAbs and Treatment Interruption

- Patients virologically suppressed on ART >24 months
- Pre-screened for 3BNC117 and 10-1074 sensitivity
- 3 infusions of combination Abs during Treatment interruption (ATI)
- Median duration of suppression with Ab-sensitive virus: 21 weeks
- Median duration of suppression with Ab-resistant virus: 5 weeks

Mendoza et al. Nature 2018

Combination bNAbs and Treatment Interruption

- 2 participants maintained virologic suppression long after Ab levels waned
- 1 remains suppressed
- Important to explore if bNAbs can be a component of cure strategies

Mendoza et al. Nature 2018

Combination bNAbs

- Combinations will be necessary to increase overall breadth and potency and to prevent the emergence of resistance
- Number of bNAbs required may differ based on the indication
  - In active viremia: combination of 3 or 4 current bNAbs may be required to cover the swarm of viruses present
- Screening for bNAb sensitivity pre-therapy to potentially reduce number of bNAbs required for Rx and amplify efficacy
  - CROI 2019: Potential of PhenoSense HIV nAB Assay

Reeves et al. Abstract 305, CROI 2019
Next Generation bNAb: Bispecific and Trispecific

- Engineered Ab (single protein) that targets multiple independent epitopes on virus
- Potentially lower likelihood of escape mutations compared to single Ab or combination of 2-3 Ab
- Enhanced potency and breadth


Bispecific Antibodies Concept

Two different antibody binding arms on one IgG
- Broader, more potent, less viral escape
- Bispecific T-cell engager: CD3 and HIV-1

Mediate cell killing

Example of Bispecific Ab: 10E8.4/iMab

- One arm of IgG binds an epitope in the membrane proximal external region (MPER) of gp41
- The other arm binds either the HIV-1 CD4, or CCR5 co-receptor molecule on T-helper cell
- Phase 1, first in human, clinical study for treatment and prevention is starting 2019

Trispecific Ab

- Combines specificities of 3 Abs binding to
  - CD4 binding site & V1V2 glycan site
  - membrane-proximal external region
- **New data from CROI 2019**
  - Potent Fc effector functions in animal studies; promising for mediating ADCC and phagocytosis
  - Potent suppression of viral replication in viremic SHIV infected animals
- Phase 1 ascending dose study in HIV-infected infected starting 2019Q1

Desirable Properties of bNAbs

- Every 6 month regimen of passive transfer of **combination** of bNAbs
- SC injection
  - easier to implement
- Replaces daily antiretroviral therapy
- Safe & well tolerated
- Scalable [inexpensive]
- Manufacturing: public private partnerships

Broadly Neutralizing Antibodies: Next Steps

- A new generation of highly potent and broadly neutralizing HIV-1 antibodies has been identified
- HIV-1 exhibits genetic diversity and viral escape mechanisms.
  - Prudent to consider using a combination approach
  - Potential to screen for bNAb sensitivity prior to therapy?
- Like ART, combinations of mAbs could reduce the likelihood of viral escape, and increase neutralization breadth
- Alternative delivery systems: gene delivery viral vectors Vector-based antibody production in vivo
Summary

- bNAbs are a promising approach towards durable control of HIV rebound in absence of ART
  - also actively pursued for prevention both as passive prevention and platform for design of vaccines
- No randomized controlled trials of therapeutic vaccination that induced long-term remission after analytical treatment interruption
- Combination strategies of bNAbs, therapeutic vaccines, immunomodulators (e.g. TLR7 agonist) may be needed to diminish the reservoir

Acknowledgements

- Scott Hammer
- John Mascola
- Larry Corey
- Shelly Karuna
- Lynn Morris
- David Montefiore

Question-and-Answer