Towards a Cure Symposium

Addressing HIV Persistence: Challenges and Opportunities

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July 16, 2016
Two Main Remaining Scientific Challenges for HIV Research

- Development of a safe and effective preventive HIV vaccine

- Addressing HIV persistence
Two Main Remaining Scientific Challenges for HIV Research

- Development of a safe and effective preventive HIV vaccine

- Addressing HIV persistence
Addressing HIV Persistence

- Eradicate the reservoir – classic “cure”

- Control viral rebound – sustained virologic remission
Addressing HIV Persistence

- Eradicate the reservoir – classic “cure”

- Control viral rebound – sustained virologic remission
Potential Strategies to Eradicate HIV from an HIV-infected Individual

- Latency-reversing agents to deplete HIV reservoirs
- Immunotoxic therapy directed at reservoir
- Stem cell transplantation
- Gene editing
Potential Strategies to Eradicate HIV from an HIV-infected Individual

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Examples of Latency-Reversing Agents

- Interleukin-2
- Anti-CD3 (OKT3) antibody
- Valproic acid
- Vorinostat
- Panobinostat
- Romidepsin
- Disulfiram
- Toll-like receptor 7 agonist
"Purging" with IL-2 Does Not Eradicate the HIV Latent Reservoir in Patients Receiving HAART

Re-Emergence of HIV After Stopping Therapy
T-W Chun, RT Davey Jr, D Engel, HC Lane & AS Fauci
Potential Strategies to Eradicate HIV from an HIV-infected Individual

- Latency-reversing agents to deplete HIV reservoirs

- Immunotoxic therapy directed at reservoir

- Stem cell transplantation

- Gene editing
Selective Killing of HIV-infected Cells by Recombinant Human CD4-\textit{Pseudomonas} Exotoxin Hybrid Protein

VK Chaudhary, EA Berger et al.
Bi-functional Antibodies (e.g. Bind HIV and CD3/CD8)

Antibody platforms exist and entered clinical trials (for cancer)

For HIV-1: *In vitro* proof-of-concept

Courtesy of John Mascola
Bifunctional: DARTs and BITEs (in vitro proof-of-concept)

Dual-Affinity Re-Targeting Proteins Direct T Cell-Mediated Cytolysis of Latently HIV-Infected Cells

Activation and Lysis of Human CD4 Cells Latently Infected with HIV-1
A. Pegu, PD Kwong, JR Mascola, GJ Nabel, et al.

Targeting HIV Reservoir in Infected CD4 T Cells by Dual-Affinity Re-targeting Molecules (DARTs) that Bind HIV Envelope and Recruit Cytotoxic T Cells
DD Sloan, T Cihlar, S Koenig, et al.

Little or no in vivo data yet
Potential Strategies to Eradicate HIV from an HIV-infected Individual

- Latency-reversing agents to deplete HIV reservoirs
- Immunotoxic therapy directed at reservoir
- Stem cell transplantation
- Gene editing
Long-Term Control of HIV by CCR5 Delta32/Delta32 Stem-Cell Transplantation
G Hütter, E Thiel et al.

- Stem cell transplant from donor homozygous for CCR5 delta32 into patient w/acute myeloid leukemia and HIV
- No viral rebound 20 mos after transplant and discontinuation of ARVs
- Stem cell transplant as possible cure

Timothy Brown, a.k.a. “the Berlin patient”

Image source: New York Times
Potential Strategies to Eradicate HIV from an HIV-infected Individual

- Latency-reversing agents to deplete HIV reservoirs
- Immunotoxictic therapy directed at reservoir
- Stem cell transplantation
- Gene editing
Gene Editing of CCR5 in Autologous CD4 T Cells of Person Infected with HIV

P Tebas, CH June, et al.
The Promise of CRISPR

Making the cut
CRISPR genome-editing technology shows its power

by John Travis
Excising HIV Provirus with CRISPR/Cas9 Technology

Elimination of HIV-1 Genomes from Human T-lymphoid Cells by CRISPR/Cas9 Gene Editing
R Kaminski, K Khalili et al.

Excision of HIV-1 DNA by Gene Editing: a Proof-of-Concept In Vivo Study
R Kaminski, K Khalili et al.
Addressing HIV Persistence

- Eradicate the reservoir – classic “cure”

- Control viral rebound – sustained virologic remission
Post-treatment Immunological Control of HIV Infection: Sustained Virologic Remission

Early suppression of HIV viremia with ART

- Natural HIV-specific immunity
- Passive transfer of HIV-specific antibodies
- Therapeutic vaccination

Discontinuation of ART

Sustained control of HIV viremia
Post-treatment Immunological Control of HIV Infection: Sustained Virologic Remission

Early suppression of HIV viremia with ART

- Natural HIV-specific immunity
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Discontinuation of ART

Sustained control of HIV viremia
Persistence of HIV Reservoir: Virus Inevitably Rebounds Following Discontinuation of Therapy

PNAS
Proceedings of the National Academy of Sciences of the United States of America
December 21, 1999 | vol. 96 | no. 26

HIV-1 and T Cell Dynamics after Interruption of Highly Active Antiretroviral Therapy (HAART) in Patients with a History of Sustained Viral Suppression

Richard T. Davey Jr., et al.
March 14, 2013

Post-Treatment HIV-1 Controllers with a Long-Term Virological Remission after the Interruption of Early Initiated Antiretroviral Therapy -- ANRS VISCONTI Study

A Sáez-Cirió, C Rouzioux, et al.

- 14 patients treated with ART in primary HIV infection discontinued ART
- No viral rebound, very low levels of virus after 4 to 9.6 years, few HIV-infected central memory CD4⁺ T cells
- “Post-treatment controllers”
Post-treatment Immunological Control of HIV Infection: Sustained Virologic Remission

Early suppression of HIV viremia with ART

- Natural HIV-specific immunity
- Passive transfer of HIV-specific antibodies

Discontinuation of ART

Sustained control of HIV viremia

Therapeutic vaccination
Post-treatment Immunological Control of HIV Infection: Sustained Virologic Remission

Early suppression of HIV viremia with ART

- Natural HIV-specific immunity
- Passive transfer of HIV-specific antibodies
- Discontinuation of ART
- Sustained control of HIV viremia

Therapeutic vaccination
Neutralizing Monoclonal Antibodies Discovered Since 2009

**N332 Glycan Supersite:**
PGT121, PGT128, 10-1074

**CD4 Binding Site:**
VRC01, PG04, CH31, 3BNC117, 12A12, CH103, VRC07-523

**V1V2 Apex:**
PG6, PG16, CH01-04, PGT141-45, PGDM1400, CAP256-VRC26

**Trimer (gp120/41):**
8ANC195, PGT151, 35022

**gp41 MPER:**
2F5, 4E10, 10e8

Cryo-EM of viral spike by Subramaniam group. Fit with atomic level structures from Kwong and Wilson group.
Viraemia Suppressed in HIV-1-Infected Humans by Broadly Neutralizing Antibody 3BNC117

M Caskey, MC Nussenzweig et al.
Virologic Effects of Broadly Neutralizing Antibody VRC01 Administration during Chronic HIV-1 Infection

RM Lynch, JE Ledgerwood et al. for the VRC 601 Study Team
Ongoing Studies Using Broadly Neutralizing Antibodies in Analytical Treatment Interruption (ATI)

- Nussenzweig Laboratory – 3BNC117; 10-1074
- Tebas Laboratory – VRC01
- Fauci Laboratory – VRC01
An Exploratory, Open-Label Study of VRC01 in Subjects with Chronic HIV Infection Undergoing Analytical Treatment Interruption -- Collaborators

LIR, NIAID, NIH
- Tae-Wook Chun, Ph.D.
- Michael Sneller, M.D.
- Susan Moir, Ph.D.
- Katherine Clarridge, M.D.

Clinical Staff, NIH
- Catherine Seamon, R.N.

Vaccine Research Center, NIAID, NIH
- Robert Bailer, Ph.D.
- Rebecca Lynch, Ph.D.
- Barney Graham, M.D., Ph.D.
- Richard Koup, M.D.
- Julie Ledgerwood, D.O.
- John Mascola, M.D.
An Exploratory, Open-Label Study of VRC01 in Subjects with Chronic HIV Infection Undergoing Analytical Treatment Interruption

Study Population

- 30 HIV-infected individuals who initiated ART during the chronic phase of HIV-infection
- Suppressed plasma viremia for >3 years
- CD4 count >450 cells/mm3 at enrollment
- 10 patients are currently enrolled
An Exploratory, Open-Label Study of VRC01 in Subjects with Chronic HIV Infection Undergoing Analytical Treatment Interruption

Criteria to Stop VRC01 and Restart ART:

- A confirmed $>30\%$ decline in baseline CD4 cell count or an absolute CD4 cell count $<350$ cells/mm$^3$

- A sustained ($\geq 4$ weeks) HIV RNA level of $>1,000$ copies/ml or incremental increases in plasma viremia $>500$ copies/ml at three consecutive visits

- Any HIV-related symptoms

- Pregnancy
An Exploratory, Open-Label Study of VRC01 in Subjects with Chronic HIV Infection Undergoing Analytical Treatment Interruption

Study Design

- All study participants received infusions of VRC01 (40mg/kg) 3 days prior to and 14 and 28 following treatment interruption, and monthly thereafter for up to 6 months.

- Plasma viremia was measured at day -7, -3, 0, 3, 7, 14, 21, and 28 and bi-weekly thereafter.
Plasma Viremia in Study Participants Following Discontinuation of ART

**Graphs showing plasma viremia levels for different groups (V01 to V10):**

- **Plasma Viremia (copies/ml):**
  - **X-axis:** Time after Cessation of ART (days)
  - **Y-axis:** Plasma Viremia (copies/ml)

- **Key Points:**
  - **ART reinitiated** with a symbol (*)
  - **VRC01 Infusion** indicated with a yellow triangle

Each graph represents a different group (V01 to V10) with varying viremia levels and time points.
Plasma Viremia in Study Participants Following Discontinuation of ART

- **Subject**
  - V01
  - V02
  - V03
  - V04
  - V05
  - V06
  - V07
  - V08
  - V09
  - V10

- **Plasma Viremia (copies/ml)**
  - Limit of detection

- **Time after Cessation of ART (weeks)**
  - 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20
Time to Plasma Viral Rebound Following Discontinuation of ART

Subject

<table>
<thead>
<tr>
<th>Subject</th>
<th>Time to Plasma Viral Rebound (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V10</td>
<td>84</td>
</tr>
<tr>
<td>V09</td>
<td>36</td>
</tr>
<tr>
<td>V08</td>
<td>40</td>
</tr>
<tr>
<td>V07</td>
<td>17</td>
</tr>
<tr>
<td>V06</td>
<td>40</td>
</tr>
<tr>
<td>V05</td>
<td>40</td>
</tr>
<tr>
<td>V04</td>
<td>53</td>
</tr>
<tr>
<td>V03</td>
<td>24</td>
</tr>
<tr>
<td>V02</td>
<td>40</td>
</tr>
<tr>
<td>V01</td>
<td>40</td>
</tr>
</tbody>
</table>

Median time to plasma viral rebound = 39 days

Historical control for time to plasma rebound = 11 to 28 days
Levels of Plasma Viremia and VRC01 in Study Participants

V01  V02  V03  V04  V05

V06  V07  V08  V09  V10

Time after Cessation of ART (days)

Plasma Viremia (copies/ml)

VRC01 Plasma Concentration (μg/ml)
Capacity of bNAbs to Neutralize Autologous Replication-Competent HIV Prior to and Following Infusions of VRC01

*ART reinitiated
Capacity of bNAbS to Neutralize Autologous Replication-Competent HIV Prior to and Following Infusions of VRC01

*ART reinitiated
Capacity of bNAbs to Neutralize Autologous Replication-Competent HIV Prior to Infusions of VRC01

% Suppression over Control

Study Subjects
- V01
- V03
- V04
- V05
- V06
- V08
- V09
- V10

p-values:
- p=0.008
- p=0.063
- p=0.031
- p=0.008
Capacity of bNAbs to Neutralize Autologous Replication-Competent HIV Prior to and Following Infusions of VRC01

Subject V03
\[ p = 0.048 \]

Subject V04
\[ p < 0.0001 \]

Subject V05
\[ p = 0.231 \]

Subject V06
\[ p = 0.617 \]

Subject V08
\[ p < 0.0001 \]

Subject V09
\[ p = 0.534 \]

Subject V10
\[ p = 0.011 \]

Legend:
- Pre-VRC01 Infusion
- Post-VRC01 Infusion
Capacity of bNAbs to Neutralize Autologous Replication-Competent HIV Prior to and Following Infusions of VRC01

Subject V03
\[ p = 0.048 \]

Subject V04
\[ p < 0.0001 \]

Subject V05
\[ p = 0.231 \]

Subject V06
\[ p = 0.617 \]

Subject V08
\[ p < 0.0001 \]

Subject V09
\[ p = 0.534 \]

Subject V10
\[ p = 0.011 \]
Plasma Viremia in Study Participants Following Discontinuation of ART

**V09-JF**

- Plasma Viremia (copies/ml)
  - Y-axis: 0, 1,000, 2,000, 4,000, 6,000, 8,000, 10,000
- Time after Cessation of ART (days): 0, 7, 21, 35, 49, 63
- Points:
  - 0: 0 copies/ml
  - 7: 0 copies/ml
  - 21: 0 copies/ml
  - 35: 0 copies/ml
  - 49: 0 copies/ml
  - 63: *ART reinitiated* (asterisk)

**V10-HB**

- Plasma Viremia (copies/ml)
  - Y-axis: 0, 200, 400, 600, 800, 1,000
- Time after Cessation of ART (days): 0, 7, 21, 35, 49, 63, 77, 91
- Points:
  - 0: 0 copies/ml
  - 7: 0 copies/ml
  - 21: 0 copies/ml
  - 35: 0 copies/ml
  - 49: 0 copies/ml
  - 63: 0 copies/ml
  - 77: 0 copies/ml
  - 91: 0 copies/ml

Limit of detection (yellow triangle)
Plasma Viremia in Study Participants Following Discontinuation of ART

**V09-JF**

- Plasma Viremia (copies/ml)
- Time after Cessation of ART (days)
- Limit of detection
- ART reinitiated

**V10-HB**

- Plasma Viremia (copies/ml)
- Time after Cessation of ART (days)
- ART reinitiated
Summary and Conclusions

- While multiple infusions of VRC01 were safe and well tolerated, all patients experienced plasma viral rebound despite adequate levels of plasma antibody with only a very modest prolongation of time to rebound.

- Pre-existing and/or rapid emergence of VRC01-resistant HIV likely contributed to plasma viral rebound in the study participants following discontinuation of ART.

- Therapeutic strategies involving passive transfer of bNAbs may require a combination (s) of Abs and/or resistance prescreening in order to achieve sustained virologic control in HIV-infected individuals upon withdrawal of ART.
Improving Results with bNAbs to Control Viral Rebound after Analytic Treatment Interruption

- More potent antibodies
- Extend half-life of antibodies
- Vector-based antibody production in vivo
- Combinations of antibodies
Improving Results with bNAbs to Control Viral Rebound after Analytic Treatment Interruption

- More potent antibodies
- Extend half-life of antibodies
- Vector-based antibody production in vivo
- Combinations of antibodies
Antibodies with Improved Potency/Breadth

Panel of 206 Env-pseudoviruses

More Potent

IC80 Titer (Og/ml)

% Resistant

13 20 4 3 46 38 27 52 2 2

VRC01 3BNC117 VRC07-523 N6 PGT121 10-1074 PGDM 1400 CAP256-VRC26.25 10E8 10E8.4 V2

Courtesy John Mascola
Improving Results with bNAbs to Control Viral Rebound after Analytic Treatment Interruption

- More potent antibodies
- Extend half-life of antibodies
- Vector-based antibody production in vivo
- Combinations of antibodies
Extending Half-life in Humans

- Motavizumab 3 mg/kg
- Mota-YTE 3 mg/kg

- 3 amino acid mutation in Fc region protects antibody
- Maintains concentrations for ~6 months

Improving Results with bNAbs to Control Viral Rebound after Analytic Treatment Interruption

- More potent antibodies
- Extend half-life of antibodies
- Vector-based antibody production in vivo
- Combinations of antibodies
Gene Vector-Mediated Antibody Expression Provides Protection in Animal Models

AAV-expressed eCD4-Ig Provides Durable Protection from Multiple SHIV Challenges
MR Gardner, M Farzan et al.

AAV-Delivered Antibody Mediates Significant Protective Effects against SIVmac239 – Challenge in the Absence of Neutralizing Activity
SP Fuchs, RC Desrosiers et al.
Improving Results with bNAbs to Control Viral Rebound after Analytic Treatment Interruption

- More potent antibodies
- Extend half-life of antibodies
- Vector-based antibody production in vivo
- Combinations of antibodies
Combined Antibodies: Improved Potency and Breadth

Combination of 2 broadly neutralizing antibodies offers >98% coverage

Potential Analogy to the Historical Development of Combination Antiretroviral Therapy
The Efficacy of Azidothymidine (AZT) in the Treatment of Patients with AIDS and AIDS-Related Complex: A Double-Blind, Placebo-Controlled Trial

Margaret A. Fischl, et al.
HIV with Reduced Sensitivity to Zidovudine (AZT) Isolated During Prolonged Therapy

BA Larder, G Darby, and DD Richman
Antiretroviral Drugs Approved by FDA, 1987-2016

13 combination drugs have been approved, 1997-2016


NNRTIs (5)
NRTIs (8)
Fusion Inhibitor (1)
Protease Inhibitors (10)
Entry Inhibitor (1)
Integrase Inhibitors (3)
Pharmacokinetic Enhancers (2) - not shown
Evolution of Treatment Strategies for HIV Disease

1987
AZT Monotherapy

1994
Two-Drug Therapy

1996
Three-Drug Therapy

RNA Change (Log10 copies/mL)

0 8 16 24 32 40 48 56

Study Week

0 8 16 24 32 40 48 56

0 8 16 24 32 40 48 56

0 0 0 0 0 0 0 0

-3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0.0

-3.0 -2.5 -2.0 -1.5 -1.0 -0.5 0.0
Next Steps in Addressing HIV Persistence: Eradication Versus Sustained Virologic Remission

**Eradication:**
- Explore the depth and breadth of recognized as well as unrecognized viral reservoirs
- Combinations of novel latency reversing and immunotoxic regimens
- State-of-the-Art (CRISP/Cas9 and beyond) gene editing techniques to create host cellular environment incompatible with HIV replication

**Sustained Virologic Remission:**
- Passive infusion of combinations of multiple (3 or more) long-acting bNAbbs at progressively prolonged intervals
- Therapeutic vaccine regimen with induction followed by intermittent boosting
Ending the HIV–AIDS Pandemic — Follow the Science

AS Fauci & HD Marston