Dr Jintanat Ananworanich

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Maryland, USA
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<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
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<tbody>
<tr>
<td>Dr Jintanat Ananworanich</td>
<td>acts as a speaker for a Gilead-sponsored event in October 2013. Her institution has received payment for her consultancy capacity at the ViiV Healthcare pediatric advisory meeting in May 2014 and her former institution has received an educational grant from Gilead in 2010-2012.</td>
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<tr>
<td>Date</td>
<td>October 2014</td>
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HIV Persistence and Pediatric HIV Cure: Where do we go after the Mississippi baby?

Jintanat Ananworanich, MD, PhD

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The views expressed are those of the authors and should not be construed to represent the positions of the U.S. Army or the Department of Defense.
Outline

- Goals of HIV Cure research
- Mississippi, California, Canadian and Milan babies
- Strategies to eliminate HIV persistence
- Where do we go in the future?

*Short video on patients’ perspectives on cure*
# Goals vs. Current Reality

<table>
<thead>
<tr>
<th>Eradication</th>
<th>Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>No HIV detected</td>
<td>HIV detected</td>
</tr>
<tr>
<td>Test HIV negative</td>
<td>Test HIV positive</td>
</tr>
<tr>
<td>Not HIV infectious</td>
<td>Maybe HIV infectious</td>
</tr>
<tr>
<td>No need to take ARV</td>
<td>No need to take ARV</td>
</tr>
<tr>
<td>Healthy</td>
<td>Healthy</td>
</tr>
<tr>
<td></td>
<td>Ongoing viral load monitoring</td>
</tr>
</tbody>
</table>

## Reality of Current Therapies

- Normal/near normal life span
- Propensity for co-morbidities
- Control of HIV viremia and infectiousness
  - But with strict adherence and daily medications
- Stigma and discrimination
HIV Persistence

cell death

resting state
ARVs stopped, HIV rebounds

Only one person has been “cured” of HIV.

From Cohen J, Science 2014; Courtesy of Diana Finzi (NIAID/NIH) (Hutter, NEJM 2009; Henrich, Annals Internal Medicine 2014; Persaud, NEJM 2013)
The Mississippi Baby

HIV RNA
19,812 copies/ml

HIV DNA+

ART
No ART

Loss to follow up and stop ART at age 18 months

16,750 c/ml
10,564 c/ml
9 c/ml

ART
No ART
0              10             20             30             40             50

Loss to follow up and stop ART at age 18 months

ART
No ART

19,812 copies/ml

ART
No ART

Persaud D, NEJM 2013
Cases of Early Treated Infants

**Mississippi Baby**
- ART at 30 hours
- 18 months
- Viral rebound after 27 months off ART

**California Baby**
- ART at 4 hours
- 14 months

**Canadian Babies**
- ART at <24 hours
- 2.5 years
- 3 years
- Viral rebound after 2-3 weeks off ART

**Milan baby**
- ART at 12 hours

Early-treated pediatric cases with different time to viral rebound

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mississippi(^1)</th>
<th>Canadian(^2)</th>
<th>Milan(^3)</th>
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<tbody>
<tr>
<td>Time to VL rebound</td>
<td>27 months</td>
<td>&lt; 1 month</td>
<td>&lt; 1 month</td>
</tr>
<tr>
<td>ART onset</td>
<td>30 hours</td>
<td>&lt; 24 hours</td>
<td>12 hours</td>
</tr>
<tr>
<td>Baseline VL</td>
<td>19,812</td>
<td>808</td>
<td>152,560</td>
</tr>
<tr>
<td>Time to VL &lt; 50 on ART</td>
<td>1 month</td>
<td>6 months</td>
<td>3 months</td>
</tr>
<tr>
<td>Time on ART</td>
<td>18 months</td>
<td>3 years</td>
<td>3 years</td>
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\(^1\)Persaud, NEJM 2013; \(^2\)Brophy, IAS 2014; \(^3\)Giacomet, Lancet 2014
## Early-treated pediatric cases with different time to viral rebound

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<td>Time to VL rebound</td>
<td>27 months</td>
<td>&lt; 1 month</td>
<td>&lt; 1 month</td>
</tr>
<tr>
<td>HIV DNA</td>
<td>Undetected*</td>
<td>Undetected</td>
<td>Undetected</td>
</tr>
<tr>
<td>Replication competent virus</td>
<td>Negative*</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>HIV antibody</td>
<td>Non-reactive*</td>
<td>Non-reactive</td>
<td>Non-reactive</td>
</tr>
<tr>
<td>HIV-specific T cells</td>
<td>Undetected*</td>
<td>Undetected</td>
<td>Detected</td>
</tr>
<tr>
<td>Others</td>
<td>Normal % activated T cells*</td>
<td>Detected cell-associated HIV RNA</td>
<td>High % activated T cells</td>
</tr>
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</table>

\(^1\)Persaud, NEJM 2013; \(^2\)Brophy, IAS 2014; \(^3\)Giacomet, Lancet 2014

*Off ART
Predicting time to viral rebound: Limitation of current tools

Sharon Lewin (Doherty Institute, University of Melbourne)

Based on Hill AL, PNAS 2014
HIV Persistence and Immunity in Early Life

↓ Persistence

- Few memory CD4+ T cells
- Fewer activated CD4+ T cells

↑ Persistence

- Abundance of target cells (CD4+CCR5+ T cells in the gut)
- Immature innate and adaptive immune responses
- High viremia
- Memory-like T cells in cord blood

Strategies to Eliminate HIV Persistence

Possible interventions:
- Latency reversing agents
- Broadly neutralizing antibody
- Therapeutic vaccines
- Gene-editing therapy
VISCONTI Cohort of Post-Treatment Controllers

14 people ART in first 3 months

Control VL after stopping ART

Why are these patients able to control HIV without ART?

HIV reservoir amount and location?

✔ Low HIV DNA

✔ In shorter-lived CD4 cells

_Saez-Cirion A, Plos Pathogens 2013_

Limited infection in long-lived CD4+ T cells after treatment in acute HIV infection

_Ananworanich J, Plos One 2012, CROI 2013_
Restricted Reservoir Size in Early Treated Thai Children

HIV DNA (copies/10^6 CD4 T cells)

- Integrated HIV DNA (n=15)
- Total HIV DNA (n=12)
- 2-LTR circles (n=11)

HIV-NAT 194 study (Ananworanich J, AIDS 2014)
Low HIV DNA in Children who Achieve Viral Suppression by Age 1 Year

Persaud D et al. JAMA Peds (in press)
HIV Seronegativity in Early-treated Children: Marker for Low HIV Reservoir

% Non-reactive HIV antibody

- US\(^1\):
  - < 1 yr: 86%
  - 1-5 yrs: 19%
  - > 5 yrs: 3%

- Thai\(^2\):
  - < 1 yr: 47%

Thai children
No HIV-specific CD4/CD8 response
No immune activation

\(^1\)Persaud D, CROI 2014 and JAMA Peds 2014 (in press);\(^2\)Ananworanich J, AIDS 2014
Long-term Treated Adolescents with No Detectable HIV

ART at 15 days of life

VL < 400 by 3 months of age

VL suppression on ART for 15 years

No detectable RNA
DNA
Replication competent virus
HIV-specific immunity
Immune activation

Luzuriaga K, J Infect Dis 2014
Shock and Kill Strategy

Resting CD4 T cells

Latent HIV reservoir

HIV production

“Shock” (Reservoir activator)

Activated CD4 T cell

“Kill” (Effector mechanism)
- Therapeutic vaccine
- Neutralizing antibody
- Immune checkpoint blockade

Cell death

Barouch DH, Deeks SG, Science 2014
Broadly Neutralizing Antibody

- > 30 antibodies identified
- Human studies
  - VRC01
    - RV397/398 in acute HIV
    - ACTG in chronic HIV
    - IMPAACT in chronic HIV
  - 3BNC117, 10-1074, PGT121

Cell death

Viral clearance

PGT121
Viral load suppression in macaques (n=3)

Days after infusion

Barouch DH, Nature 2013
Examples of Strategies Currently in Human Studies

**MINIMIZE RESERVOIR**
- Limit reservoir with early treatment
- Antiretroviral therapy
- Broadly neutralizing antibodies

**SHOCK**
- Reactivating latently-infected cells
- Inhibit histone deacetylase
- Inhibit bromodomain extraterminal
- Activate toll-like receptors
- Activate protein kinase C

**KILL**
- Viral clearance by the immune system
- Broadly neutralizing antibodies
- Therapeutic HIV vaccines
- Anti programmed cell death (PD)1
- Anti PD ligand 1

**HIV RESISTANT CELLS**
- Transfusing cells without CCR5 gene
- Gene-editing therapy
- Bone marrow or cord blood transplantation

**Combination Cure**
What will it take to cure children with HIV?

**Neonates**

- Early infant diagnosis
- Immediate ART
- Triple ARV prophylaxis at birth in high-risk infants

**Older children with chronic HIV**

- Initiate ART
- Maintain viral suppression
- Assess HIV reservoirs, HIV-specific immunity, immune activation
- Immune-based therapy
- Combination cure
- Closely monitored ART pause as part of a clinical trial
Enrolling mothers at high risk of transmitting HIV
  - Informed consent during labor

Treatment interruption
  - Biomarkers for viremic control is unknown

Early phase trials
  - High risks and low/no benefits

Research in low and middle income countries
  - Cost and accessibility

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University of Melbourne
Sharon Lewin

US National Institute of Health
Diana Finzi

Johns Hopkins University
Deborah Persaud

University of Massachusetts
Katherine Luzuriaga
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What does HIV cure mean to me?

“It would be like my baby and I are born again. My baby will have a normal life and people will not stigmatize us.”

- Thai widow living with HIV