HIV cure: current status and implications for the future

Carolyn Williamson, PhD
Head of Medical Virology, Faculty Health Sciences, University of Cape Town
CAPRISA Research Associate, Centre of Excellence in HIV Prevention

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Defining a Cure

“The optimal outcome would be the complete eradication within an individual of all replication-competent HIV. Such a sterilizing cure will be challenging to achieve and impossible to prove with current technologies. A more feasible outcome will be the achievement of long-term remission...”

Deeks et al., 2016 Nature Med
Outline

• Why is it difficult to cure HIV?
• Why do we think it is possible?
• Interventions:
  – Therapeutic Vaccination
  – Passive Immunization
Why is it hard to cure HIV?

CD4 T-cell

REPLICATION

CTLs  Ab

✓  ✓

ART and LATENCY

✗  ✗  ✗  ✗
Slow decay:
>70 years to eliminate HIV infection

Infect Dis. 2015 Nov 1; 212(9): 1361–1365.
Precise Quantitation of the Latent HIV-1 Reservoir: Implications for Eradication Strategies.
Amanda M. et al
Mechanisms of reservoir persistence

**Long lived CD4 memory T cells**

- No / limited replication

**Homeostatic proliferation** (insertion site / stimuli) =
Generate viral clones

Cohn et al., 2015
Composition of viral reservoir

Only 7-12% of the reservoir viruses on intact

Bruner et al., Nature Med Mar 2017
Ho et al., Cell Oct 2013
The viral reservoir: major hurdle

Memory CD4 T-cells
The viral reservoir: major hurdle

Memory CD4 T-cells

Lymph node, brain, breast, liver, spleen, colon, lung etc
Does reservoir size matter?

- Generally thought that eliminating a ‘small’ reservoir will be easier.

- Individual who start therapy in acute infection will have smaller reservoirs.

- A number of factors may increase reservoir size: non-adherence, immune activation, concurrent chronic infections etc.

- There is evidence of expression from defective proviruses that may result in increased inflammatory state (Imamichi et al., 2016).

...still unknowns......
Ugandans had lower reservoir size compared to Americans

Δ = 0.43 Log10 IUPM; P < 0.001
Adjusted Δ = 0.55 Log10 IUPM; P = 0.04

*Preliminary results from SA suggest that the reservoir is higher in a cohort of women (Swanstrom/Williamson/Garret)

Clinical Infectious Diseases 2017: 65
(15 Oct) Prodger
Outline

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• Interventions:
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Out of 70 million HIV cases ..........one cured

Eradication

Timothy Ray Brown
“Mississippi baby”: off ART, no virus for 28 mths; SA child infected at birth, short treated, no evidence of virus replication 10 years later……..Remission

A. Violari, M. Cotton, L. Kuhn et al; IAS 2017
~5-10% adults control virus after early ART, no drugs (Remission) (Visconti cohort)
What happens in most people

Rebound as early as 2-3 weeks post ART cessation

What can we do to prevent rebound?
Outline

• Why is it difficult to cure HIV?
• Why do we think it is possible?
• Interventions:
  – Latency reversing agents
  – Gene-editing therapy
  – Antibodies
  – Therapeutic vaccines
Approach to therapeutic vaccination

• Person on treatment
• Vaccination to boost immune responses
• Has be done in combination with latency reversing agents.
• Withdraw treatment
• Measure time to VL rebound to determine how effective the vaccine responses were at controlling virus
Therapeutic vaccines

• > 40 clinical trials completed to date
  – DNA-based vaccines
  – Viral vectors: MVA, VSV
  – Peptide-based vaccines,
  – Lentiviral vector-based vaccines
  – Dendritic cell - based vaccines
  – RNA-based vaccines

• Vaccines are safe, immunogenic but largely ineffective (time to rebound, VL setpoint, reservoir)
Virus in the reservoir was laid down late in infection when many of viruses have escaped immune pressure.

Deep sequencing of virus over duration of infection.

Time from infection

M. Abrahams, S.B. Joseph, Williamson, Swanstrom
CTL escape emerges in a few weeks to months and gets deposited in “reservoir”

>98% of provirus in patients treated in chronic infection harbored escape mutations in dominant epitopes

Need strategies that augment CD8+ T cell responses to non-escaped epitopes
Broad CTL response is required to clear latent HIV-1 due to dominance of escape mutations

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Need strategies that augment CD8+ T cell responses to non-escaped epitopes

Need to design vaccines that can elicit responses against ‘escaped’ viruses.
Established and cleared mediated by prophylactic administration of strain RhCMV/SIV vectors

Controlling and actively clearing, or vaccine arrests spread and reservoir is cleared spontaneously?
Broadly neutralizing antibodies in prevention and treatment

Yesterday you heard from Nyaradzo Mgodi that VRC01 is in Phase 2b clinical trial to determine if it can prevent infection.

Can they be used in Cure?

Haynes et al., Cell 2016
Evidence that broadly neutralizing Abs can impact viral reservoirs

- Mice: bNAbs and ART treatment during acute infection - no viral rebound after ART interruption (Horwitz et al., 2013)
- Mice: bNAbs and LRA reduced reservoir size and cleared infection by FcR interaction (Halper-Stromberg et al., 2014)

- Monkeys: Long-term control after PGT121 and reduced proviral DNA (Barouch et al., 2013)
- Infant Monkeys: Early treatment prevents establishment of reservoir (Hessell et al., 2016)
- Monkeys: Systemic clearance of virus (PGT121) (Liu et al., 2016)

- Humans: bNAbs reduce time to viral rebound (Schied et al., 2016)
Long-lasting elite controller status can be conferred by administering combination bNAbs very early during the acute SHIV-AD8 macaque infection

(Nishimura et al. Nature. 2017 Mar)
Broadly neutralizing antibodies confer long term control

Depletion of CTLs resulted in increase viral load.
• CAPRISA 256 is a 27 year-old primary school teacher
• Became infected in 2005, accessed ART in 2009;
• Lynn Morris and team, in collaboration with John Mascola and team, discovered this bnAb in 2007;
• Found to be very potent;
• Protect Monkeys in an SHIV challenge.
nAb activity (virus)  ADCC activity (virus infected cells)

Developed for prevention but has potential for cure research

Simone Richardson, Lynn Morris (NICD)
Conclusions

• For remission, it will be important to augment immune responses e.g through vaccination and/or passive immunization and/or in combination with latency reversing agents.

• We need to define the reservoir in African populations:
  – most studies done in USA/Europe and there is limited information on characteristics of the viral reservoir in Africans who may differ in timing of ART initiation, drug regimes, environmental factors, gender etc.

• Most people have initiated ARTs during chronic infection and thus have larger and more diverse reservoirs and more immune dysfunction: harder to get remission/cure?

• Cure research is still in the discovery phase, and there are many hurdles to overcome before it becomes a reality.
Thank you / Merci / Enkosi