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Acute HIV Infection and HIV Cure: Where are we now and where are we going?

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WRAIR Walter Reed Army Institute of Research Soldier Health • World Health

MHRP U.S. MILITARY HIV RESEARCH PROGRAM

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Disclosures

- Jintanat Ananworanich has received honoraria for participating in advisory meetings from Gilead, Roche, AbbVie, Merck and ViiV Healthcare

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Outline

- HIV remission and eradication
  - Acute HIV and relevance to HIV remission
    - RV254 study and its remission trials
    - Perspectives of participants
- Where are we now?
- Where are we going?

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Question 1

1. Is it true that many people have been cured of HIV (No HIV left in the body)?

A) Yes

B) No

From Treatment to HIV Eradication

Living with HIV
36 million

HIV remission
~ 100+ cases, early treated
(0.0000002%)

- VL suppressed
- No therapy
- Need VL monitoring
- Transmission risk?

HIV eradication
1 case, the Berlin pt
(0.000000002%)

- No HIV replication
- No therapy
- No VL monitoring
- No transmission risk

Impact on stigma and discrimination?

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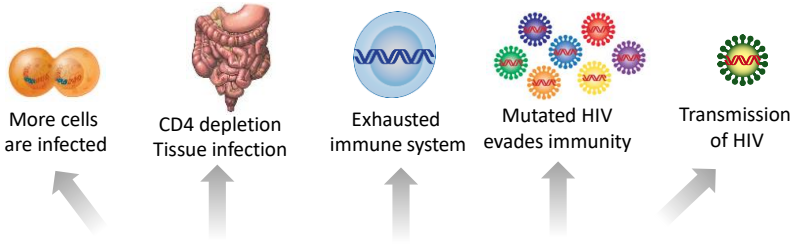
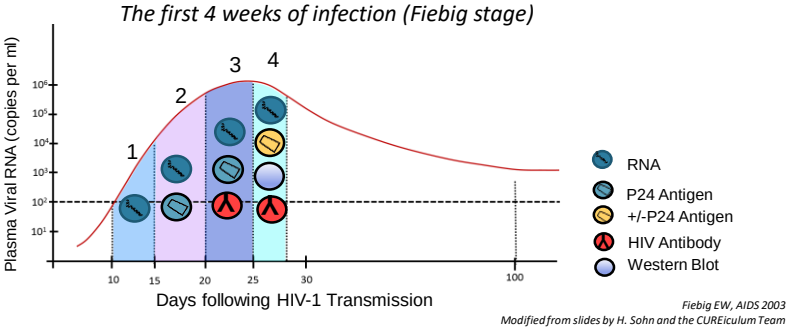
Why is Acute HIV Infection Important?



The first 4 weeks of infection (Fiebig stage)



Fiebig EW, AIDS 2003
Modified from slides by H. Sohn and the CUREiculum Team

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SEARCH clinic, Bangkok

RV254/SEARCH010

Acute infection cohort with early ART

Real-time screening of **299,004** samples in Thailand

Acute HIV infection **(n=564 enrolled/ 703 identified)**

Immediate ART

95% male, 91% MSM
26 years old, 81% CRF01_AE
19 days of infection
80 Fiebig I
130 Fiebig II
252 Fiebig III
70 Fiebig IV
32 Fiebig V

Data as of 17 August 2018

What do people say about acute HIV infection treatment?

R01AI27024 (Henderson and Peay)

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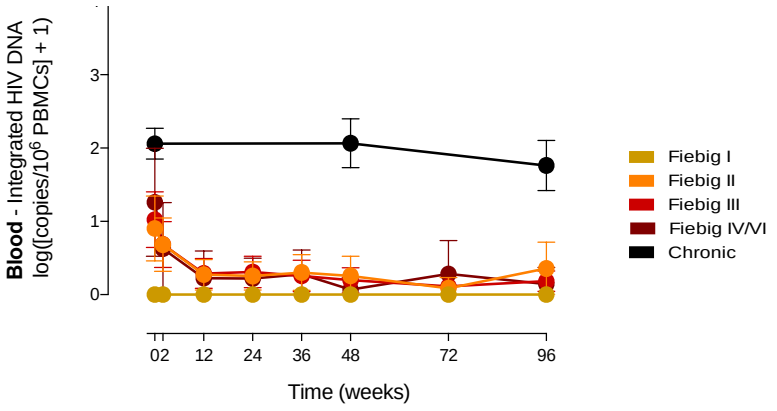
Small HIV Reservoir Size with Early ART



- Low levels of total HIV DNA with ART in acute vs. chronic
- Total HIV DNA is barely detected in Fiebig I treated participants

RV254/SEARCH010 data
Louise Leyre, Amelie Pagliuzza, Nicolas Chomont (University of Montreal)

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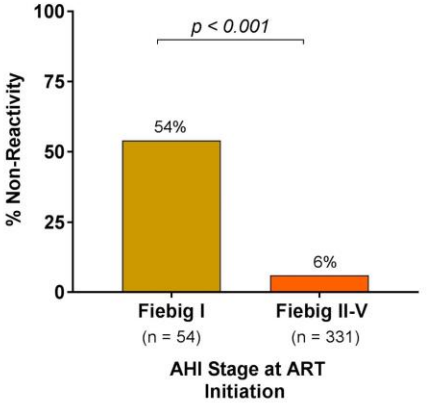
High Seronegativity in Very Early Treated Thais

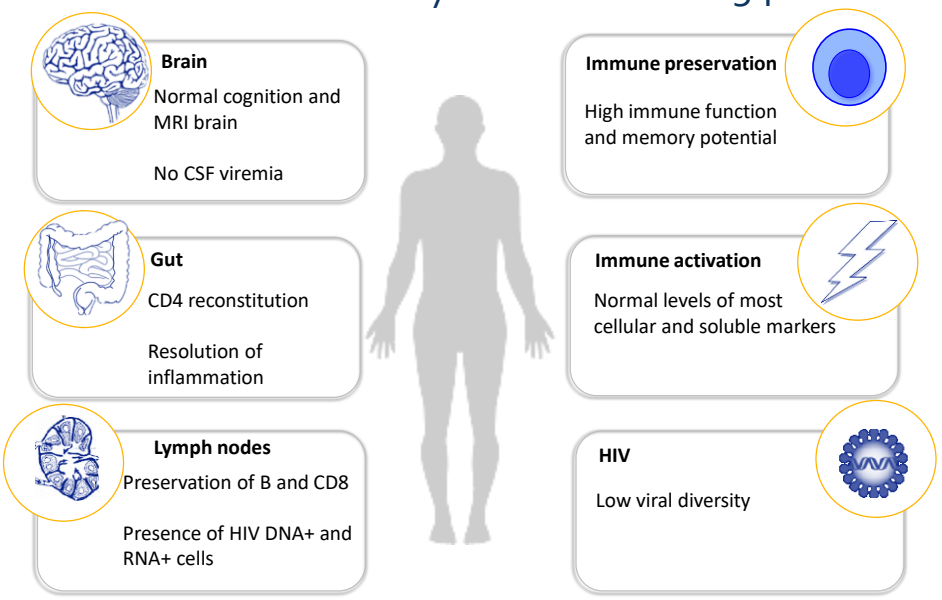
4th generation antigen-antibody combo immunoassay after ART



- Very early treated individuals can remain HIV antibody negative more than 6 months from onset of infection

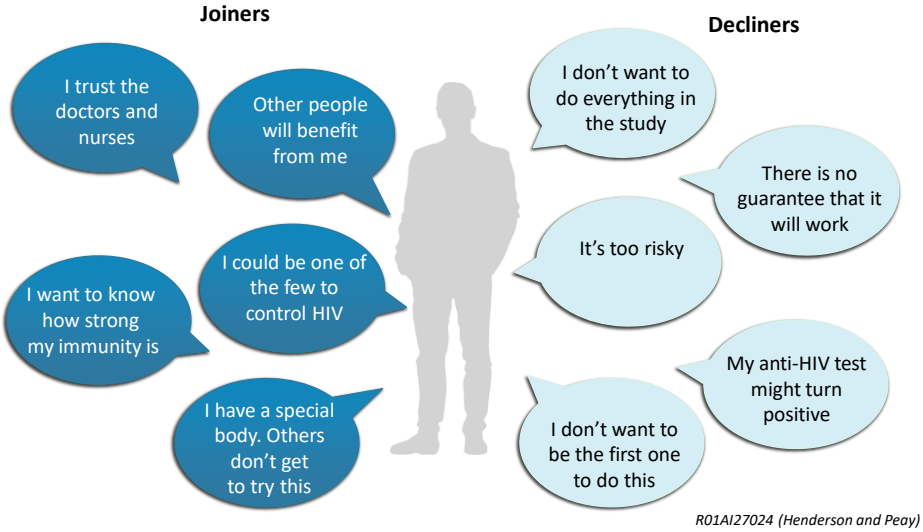
Updated from de Souza, Ananworanich, Clin Infect Dis 2016

Benefits of Early Treatment: RV254



Colby, Nat Med 2018; Ananworanich, JIAS 2017, Ebiomedicine 2016; Peluso, AIDS 2017; Takata, Sci Transl Med 2017
Muir, Plos Pathog 2016; Deleage, JCI Insight 2016; Valcour, Plos One 2015; Schuetz, Plos Pathogens 2014

Decision Making in HIV Remission Trials:
Interviews of Thais who Joined and Declined Trials with ART Interruption+/-Experimental Agents



R01AI27024 (Henderson and Peay)

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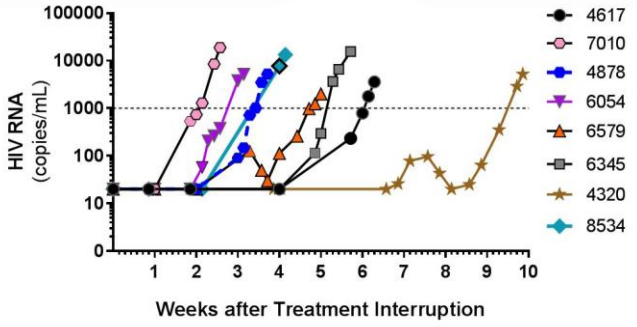
Time to Viral Rebound in Fiebig I Treated Thais: RV411

7 men and 1 woman
median age 29 yrs
ART in Fiebig I for median of 2.8 yrs
VL < 20, no blips
Median CD4 577 cells/mm^3

Interruption for up to 24 weeks
(VL q 3-7 days)

ART resumed with VL > 1000



Median time to viral load rebound >20 copies/ml: 26 days (range 13 to 48 days)

Colby, Ananworanich, Nature Medicine 2018

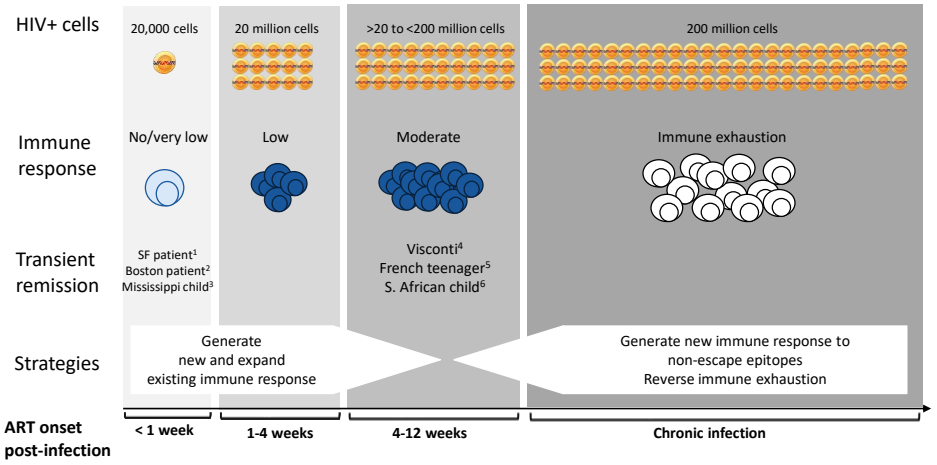
Decisional Conflict Scores from RV411 Fiebig I Interruption Trial

Scoring is 0 (no conflict) to 100 (extremely high)

	First interview (Before interruption)	**Second interview (VL rebound)**	**Third interview (After ART)**
Participants:	12.6/100	14.6/100	12.6/100
	Not everyone gets to do this. Close monitoring lowers the risk. I can restart ART if it fails.	I almost forgot I had HIV when I was off ART. I am disappointed how fast the virus came back.	I made the right decision. Others should think about risks and benefits in the long run.
Decliners:	28.0/100		19.1/100
	ART takes away my worry. I feel selfish for not joining. I want to join but I'm not ready		I made the right decision. People who joined need moral support

R01AI27024 (Henderson and Peay)

Concepts of Reservoir, Immune Response and Remission



[1]Henrich, Plos Med 2017; [2]Henrich, Ann Int Med 2014; [3]Persaud, NEJM 2013, 2014
[4]Saez-Cirion, Plos Pathog 2013; [5]Frange P, Lancet HIV 2016; [6]Violari A, 2017 IAS

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Question 2

2. What are strategies being studied towards a remission and cure of HIV?

A) Latency reversing and suppressing agents

B) Antibodies, vaccines and engineered T cells

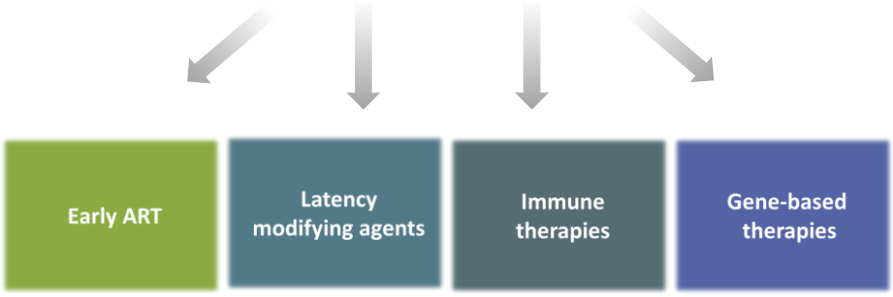
C) Gene-based therapies

D) A and B

E) All of the above

Strategies Towards HIV Remission

Reduce and control the HIV reservoirs



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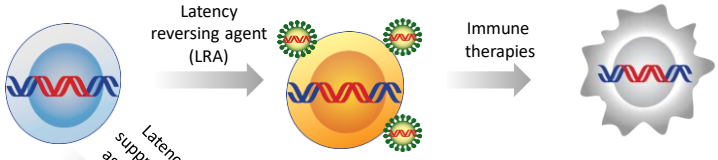
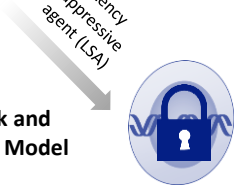
Modifying Latency

Shock and Kill Model



Current strategies

- Vorinostat in virally suppressed people (Australia)[1]
- RIVER study: vorinostat + ChAdV63.MVA vaccine (UK)[2]



Block and Lock Model

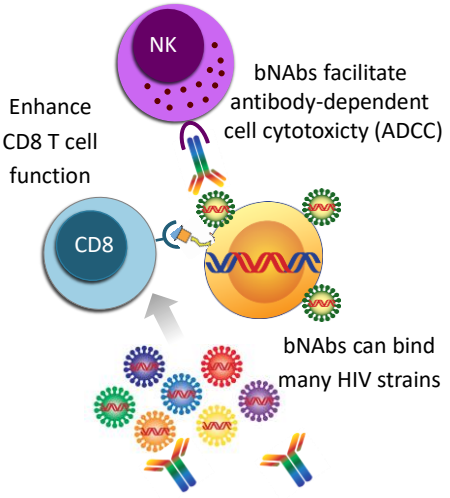
- Tat inhibitor[4]
- RNA interference[5]

Future strategies[3]

- Multiple latency reversing agents
- New classes e.g. TLR7 or 9
- Combine with more effective immune therapies

[1]Elliot and Lewin, Plos Pathog 2014; [2]Fidler, IAS 2018; [3]NCT03212980; NCT02707900; NCT02858401/NCT0306044
[4]Kessing, Cell Report 2017; [5]Ahlenstiel, Mol Ther Nucleic Acid 2015

Broadly Neutralizing Antibodies (bNAbs)

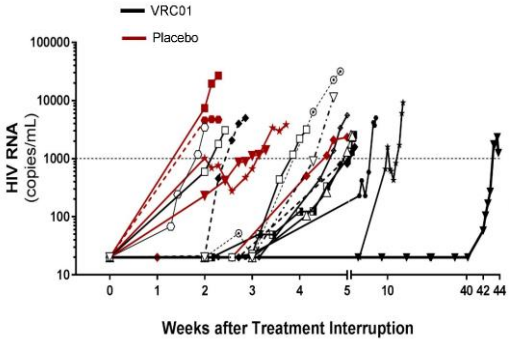


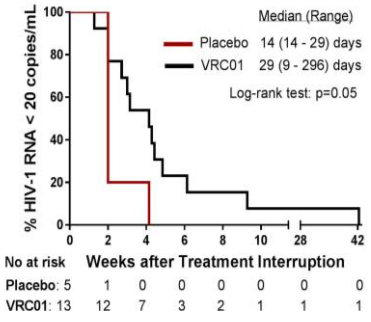
Main obstacle
- Pre-existing resistance

Strategies
- Broad and potent
- Multiple
- Tri-specific
- Long-acting
- Novel delivery platforms
- Early administration
- Combine with other agents

Kong, J Virol 2015; Barr, NEJM 2016; Scheid, Nature 2016; Caskey, Nature Med 2017; Hessell, Nature Med 2016; Liu, Science 2016; Nishimura, Nature 2017; Pardi, Nature Communications 2017; Gardner, Nature 2015; Pitman, Lancet 2018

VRC01 bNAb vs. Placebo in Treated Acutes: RV397
(First dose given at time of treatment interruption)





- Trend toward delayed virologic rebound with VRC01 in people suppressed during acute HIV infection
- Potential for improved response with better bNAbs

Crowell, Colby, Ananworanich, IAS 2017

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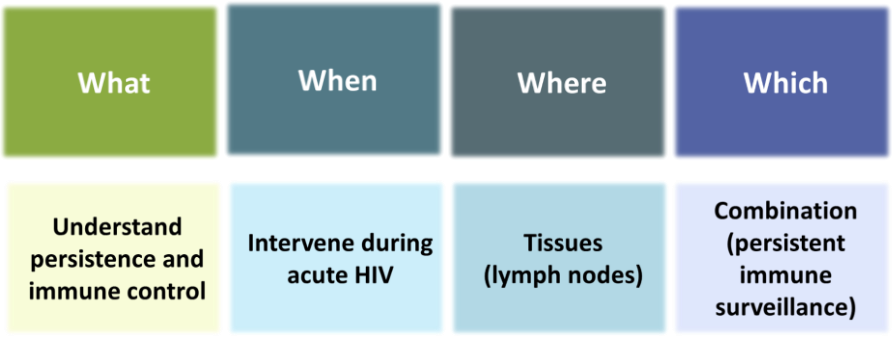
HIV Remission : Where are We?

- HIV remission is rare
- No strategies studied to date have resulted in remission
  - Acute HIV infection treatment is the only one that significantly reduces the reservoir size
  - Knowledge gained is informing future trials with more promising agents

Where Are We Going?



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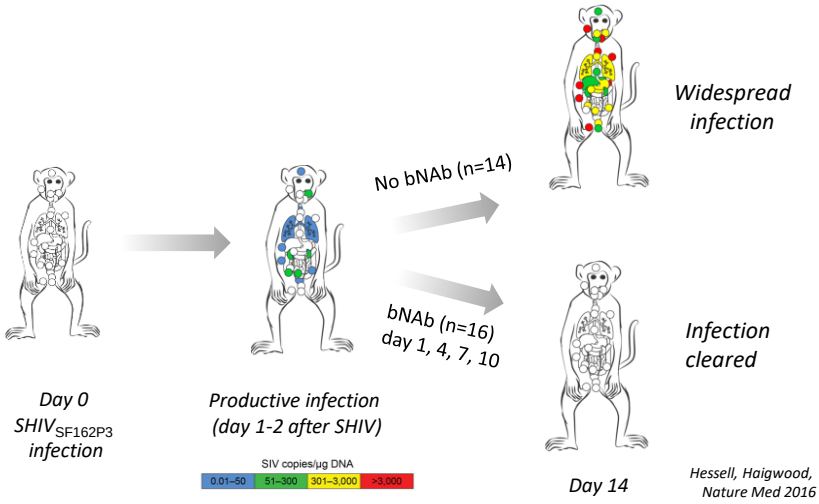
Early Administration of Combination VRC07+PGT121 bNAbs Cleared SHIV Infection in Infant Macaques



Hessell, Haigwood, Nature Med 2016

- 55% remission after PGT121 bNAb + TLR7 agonist in acutely treated monkeys

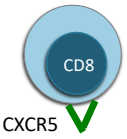
Barouch, CROI 2018

Persistent Immune Surveillance is Required

HIV-specific CD8+ cytotoxic T cells ~ 0.01-0.1%
Latently infected cells ~ 1 in 1 million cells in blood

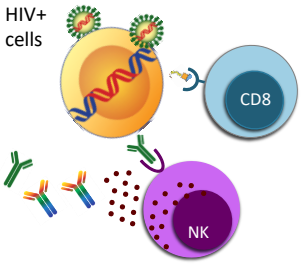
Improve CD8+ T cell killing of HIV-infected cells

T-cell trafficking to lymph node

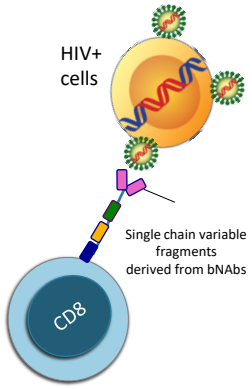


IL-15 superagonist[1]

Vaccines



- Ad26/MVA or protein[2]
- Dendritic cell+/-LRA[3]



Chimeric Antigen Receptor (CAR) T cells[4,5,6]

www.clinicaltrials.gov :[1]NCT02336074; [2]NCT02919306; [3]NCT02972450; [4]Ali, J Virol 2016; [5]Liu, J Virol 2016; [6]Hale, Mol Ther 2017

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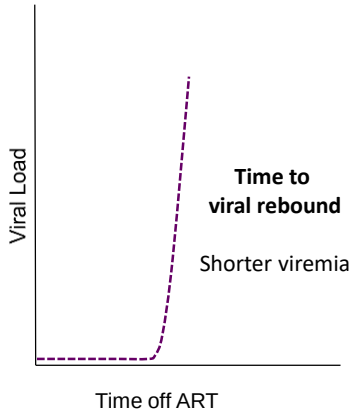
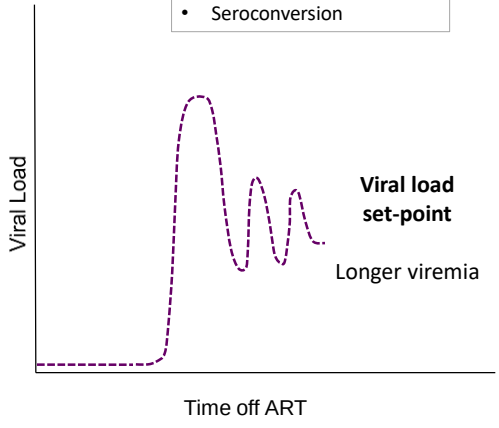
Evaluating HIV Remission Strategies:
Two Types of Treatment Interruption

- Transmission risk
- Acute retroviral syndrome
- Reservoir seeding
- CD4 decline
- Seroconversion





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HIV Cure Research and Improving Health

- Opportunity to advance therapy with cure research
  - Even the best and long-acting ART cannot significantly
    - Reduce reservoir
    - Reduce immune activation
    - Improve HIV-specific immunity

  - Cure research leads to discovery science
    - "Play the long game" towards better therapy and health
- Interventions that lower the viremia or cripple the virus can have an impact on prevention

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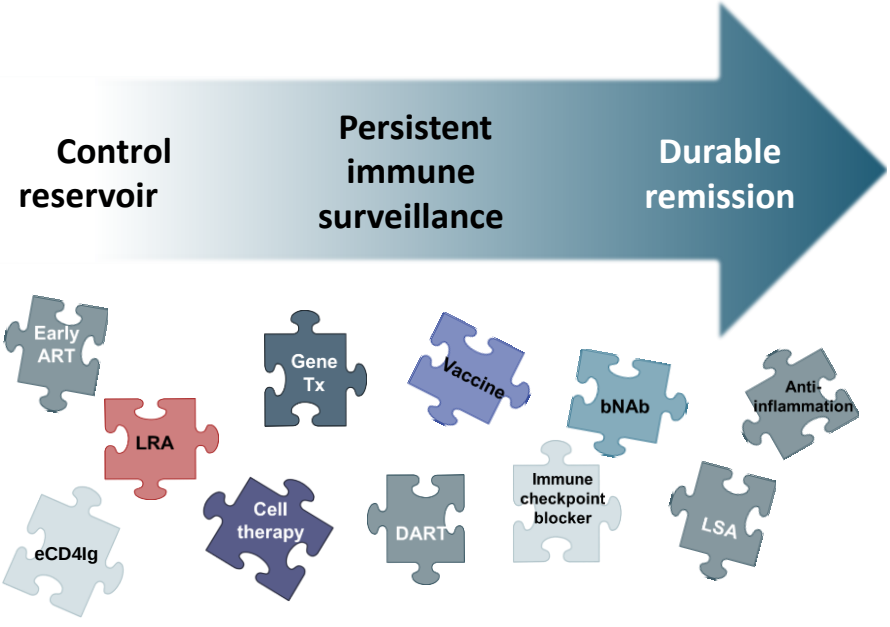
Combination Strategies Towards HIV Remission



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