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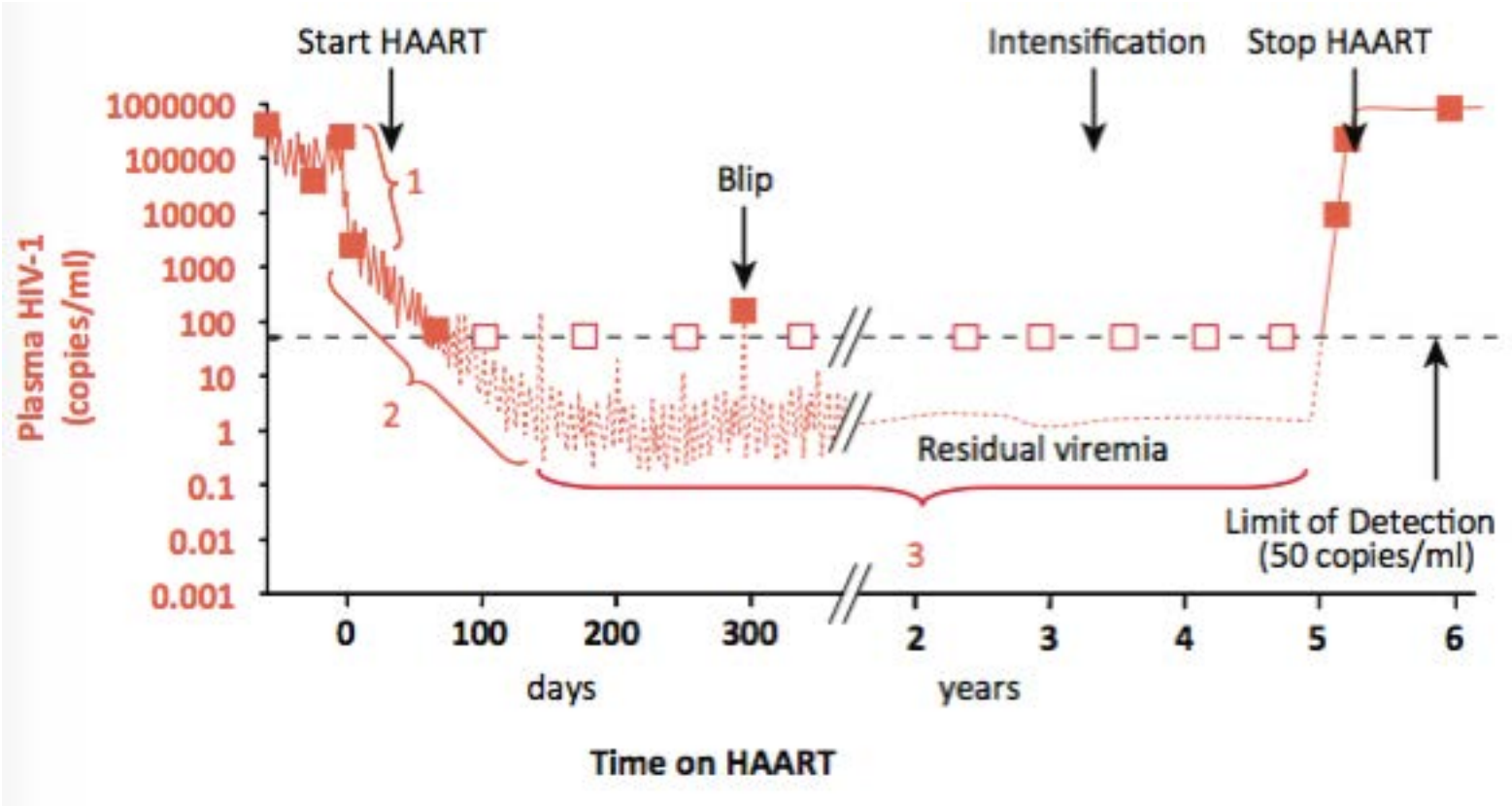
Anti-proliferative therapy for HIV Cure

Joshua T Schiffer, MD, MSc

Overview

- Mechanisms of HIV reservoir persistence despite ART
- Anti-proliferative strategy for decreasing the HIV reservoir
- Clinical trial of MMF to reduce the HIV reservoir

HIV dynamics during ART



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Durand, Trends Immunol 2012.

The HIV reservoir

- The body:
  - 1-10 million latently infected cells
  - One cell per 10^6 resting memory CD4+ T-cells
  - Cells disseminated throughout the body

- The infected cell:
  - HIV is integrated into human chromosomal DNA
  - One HIV DNA molecule per infected cell
  - Low protein expression & low immunogenicity

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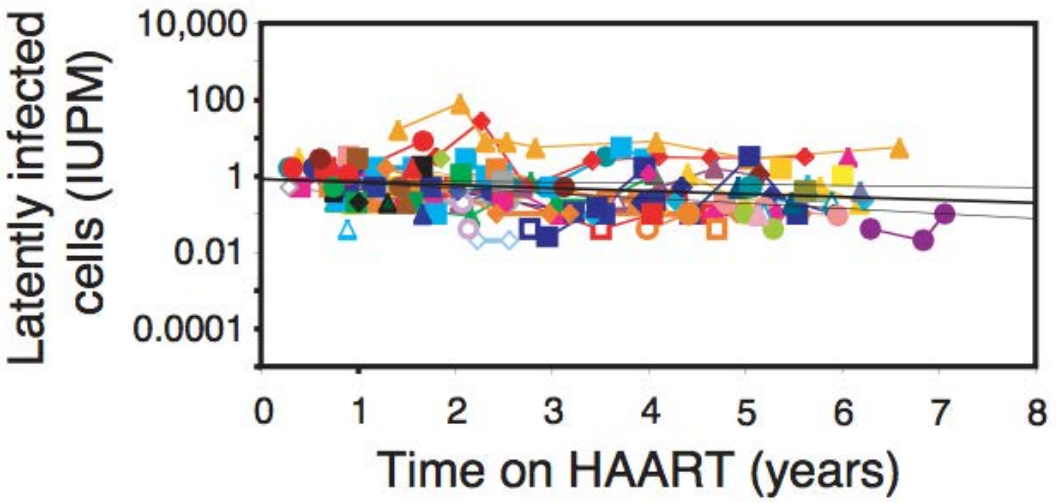
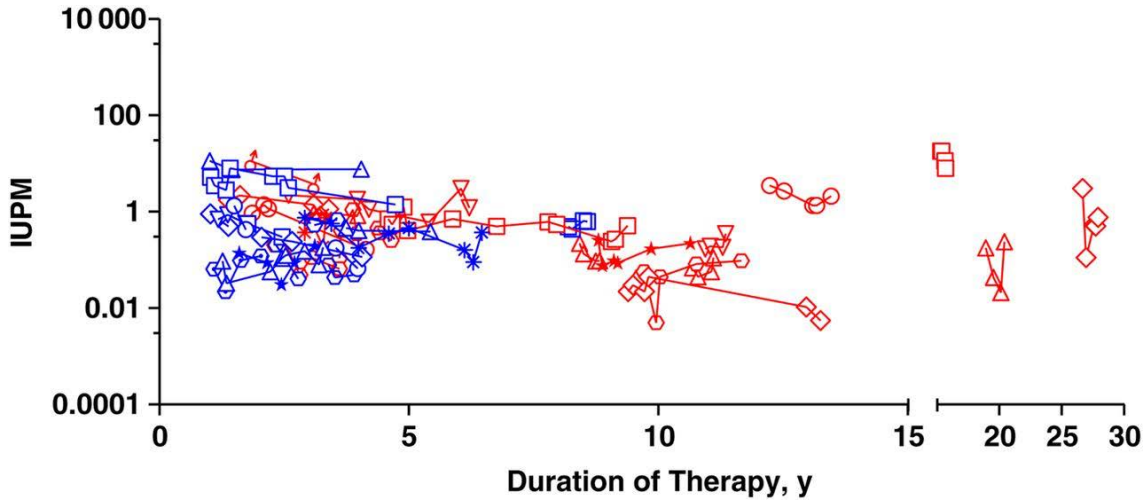
Joseffson L, PlOS Path, 2013

The HIV reservoir is remarkably stable



Siliciano, Nat Med, 2003



Crooks, JID, 2015

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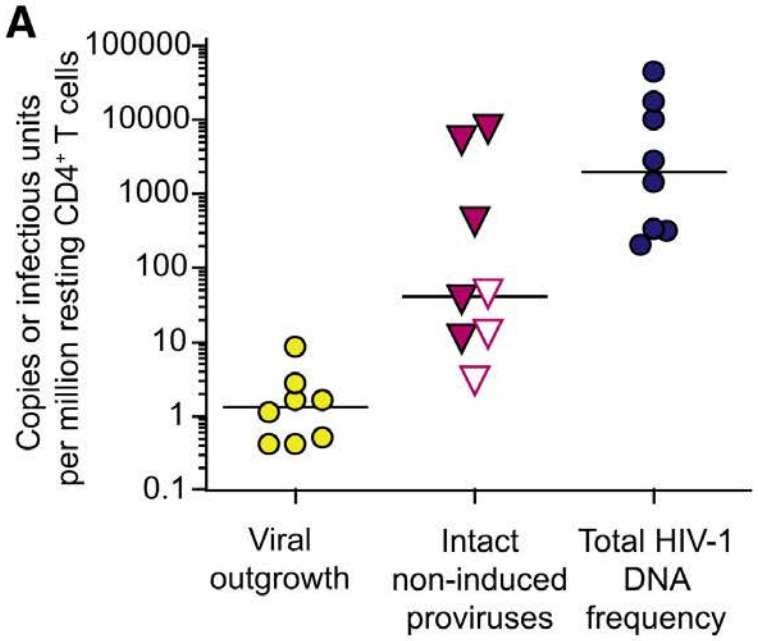
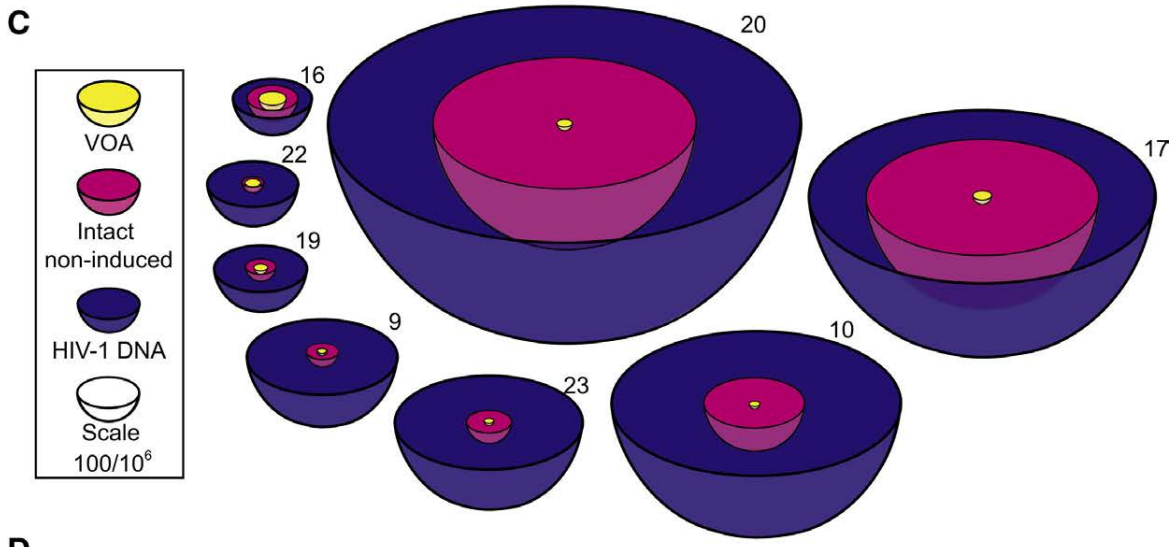
The HIV reservoir is challenging to measure





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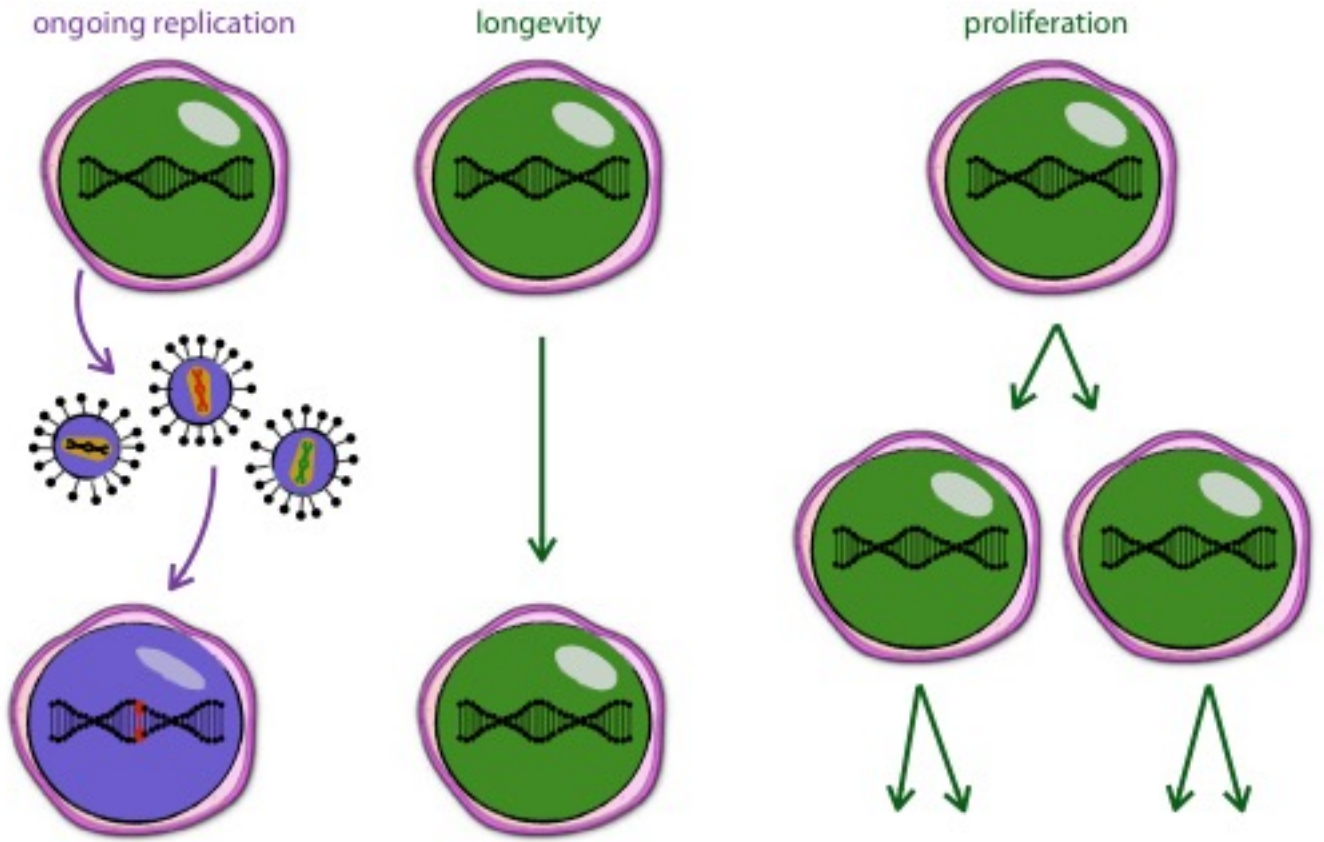
Ho YC, Cell, 2013.

Possible mechanisms of HIV persistence during ART



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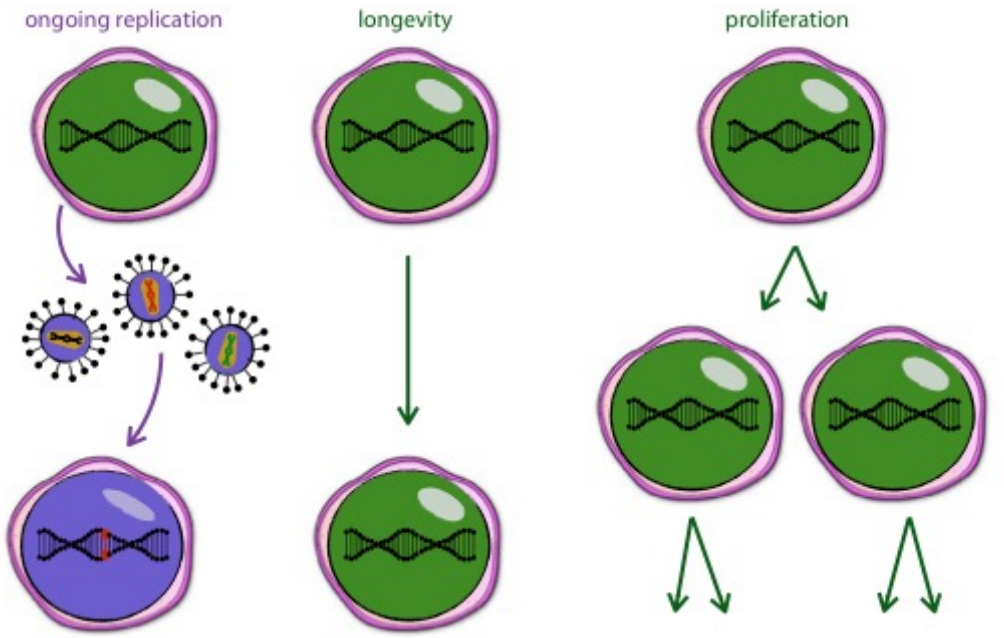
Therapeutic implications



	Mechanism	Therapeutic solution
HIV replication	• Micro-anatomic ART sanctuary	• Improved delivery of ART to micro-anatomic sanctuaries (nanoparticles, new agents)
Infected cell longevity	• Lack of HIV epitope expression • Lack of HIV replication	• HIV latency reactivating agents • Vaccines / CAR T cells / antibody infusions / stem cell transplant with CCR5 deleted cells
Infected cell proliferation	• Homeostatic proliferation • Antigen driven proliferation	• Lymphocyte anti-proliferation therapies (MMF, azathioprine)

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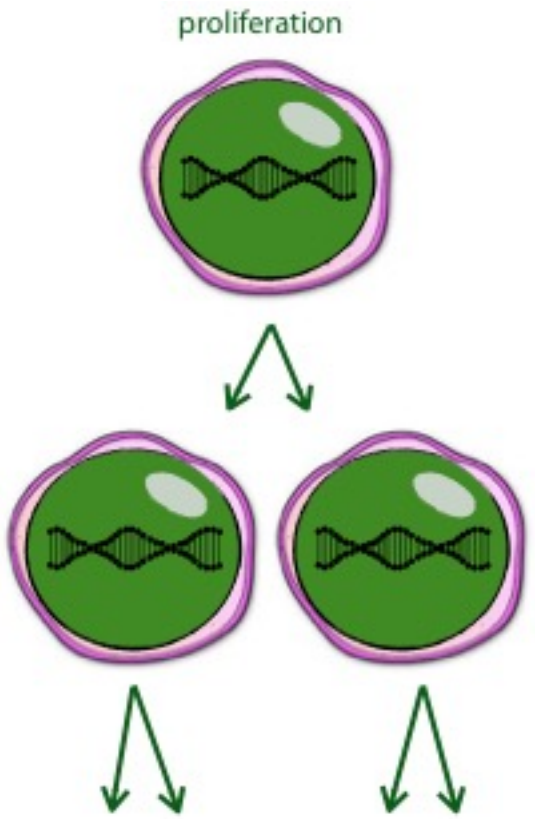
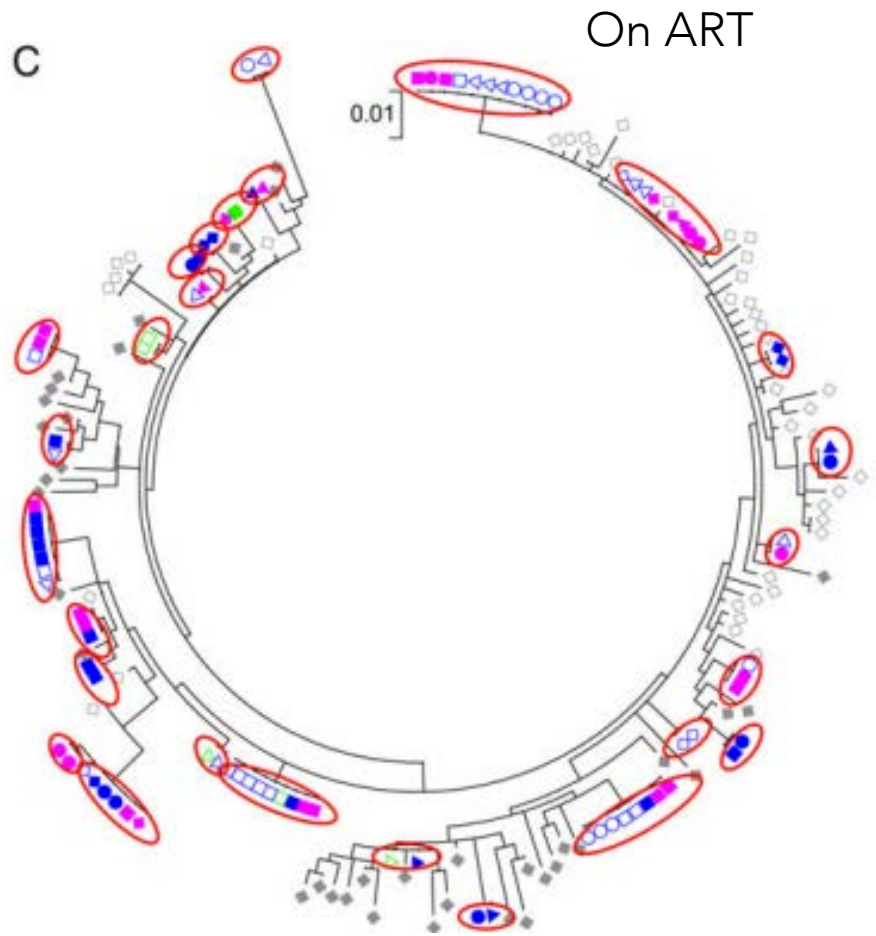
Evidence for cellular proliferation during ART





ART time 1

ART time 2

Lymph node

Blood

Galt

= clonal sequence

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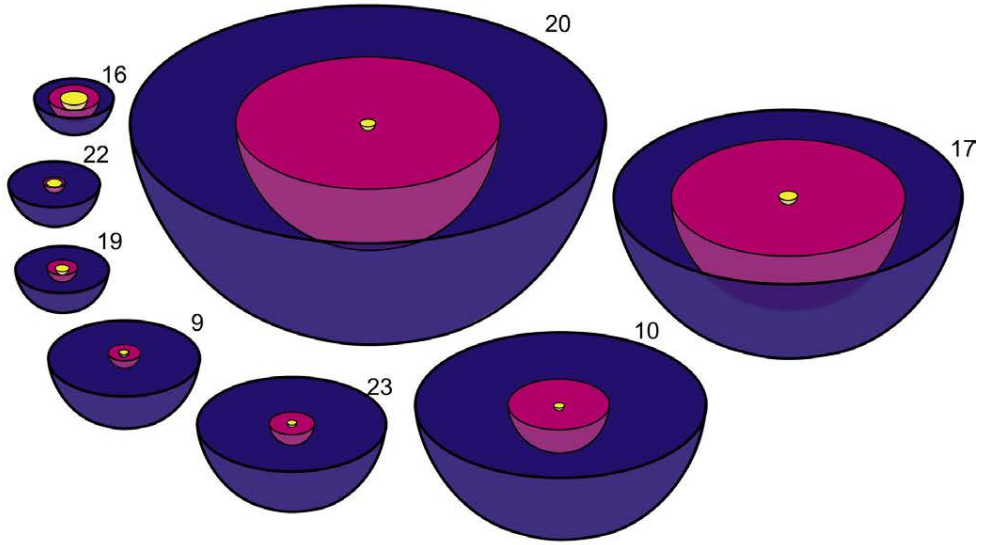
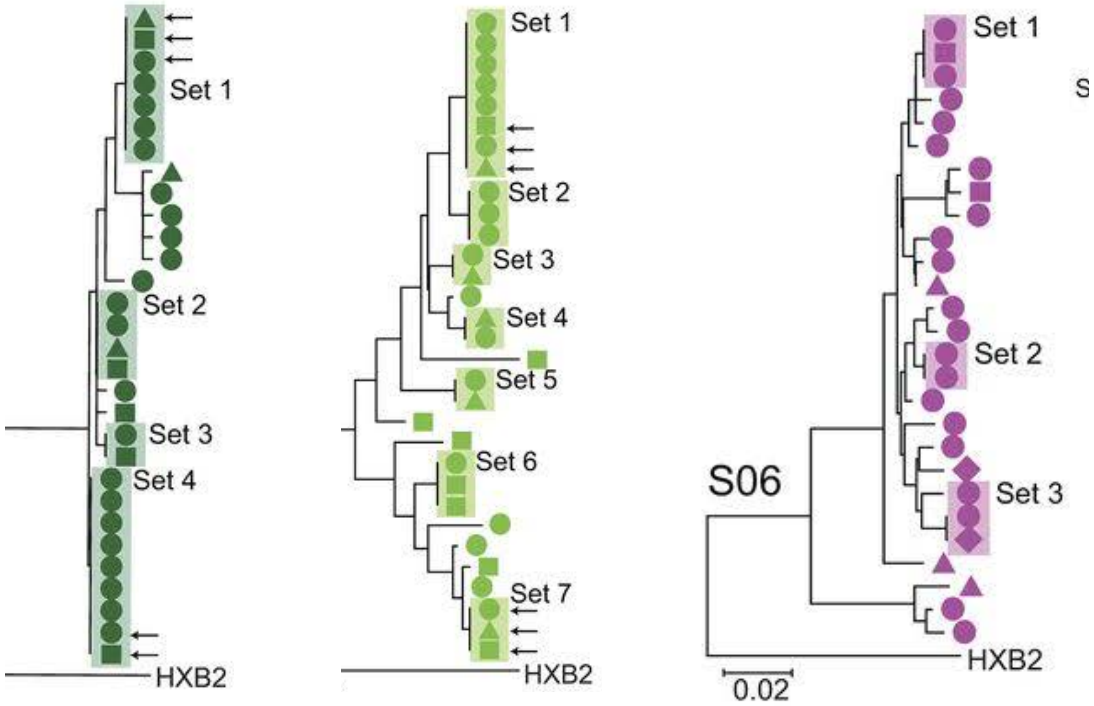
Von Stockenstrom, JID, 2015.

Replication competent sequences exhibit clonal proliferation





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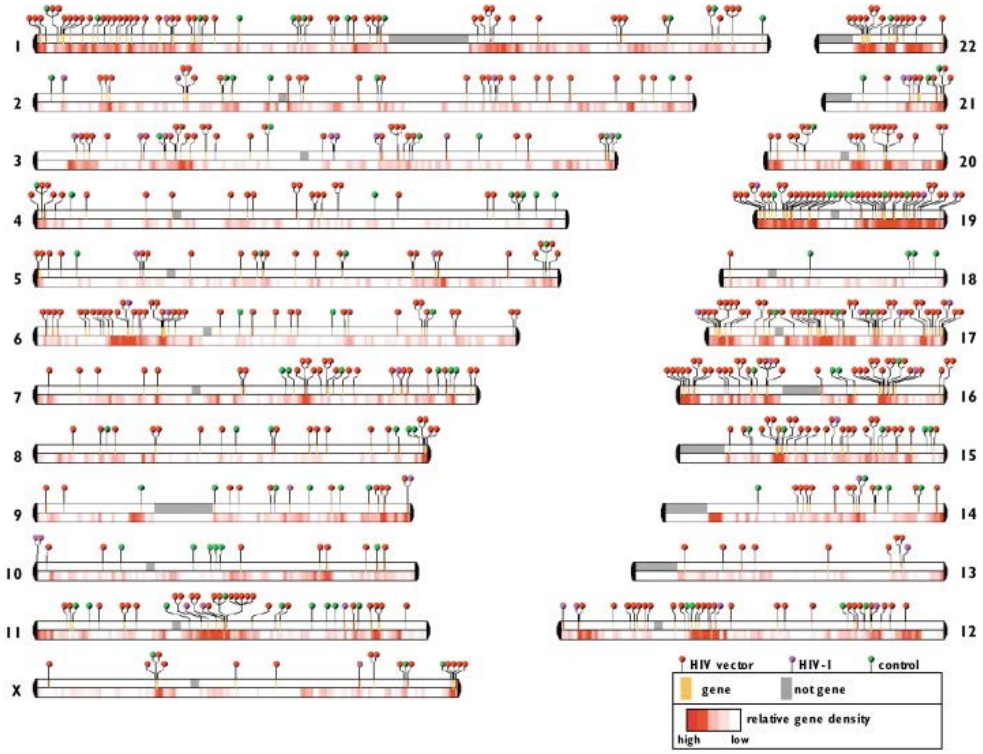
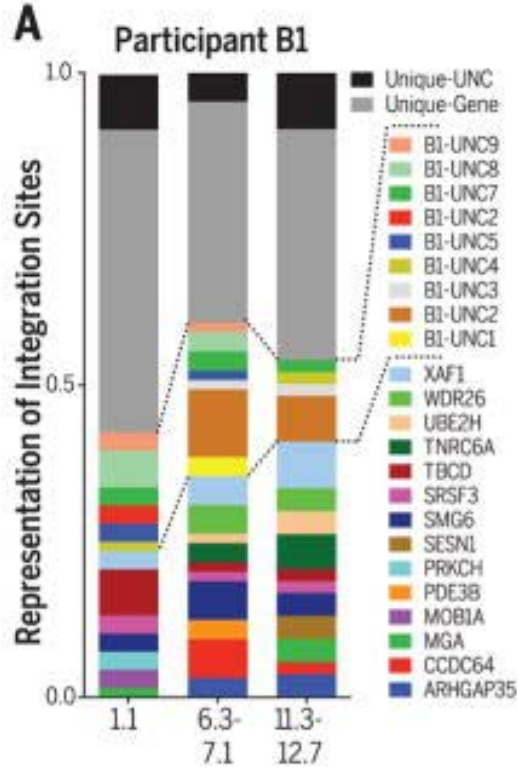
Hosmane N, JEM, 2017.

Clonal proliferation is confirmed by human chromosomal integration site data



Schroder, Cell, 2002.



Wagner T, Science, 2014.

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Mathematical modeling

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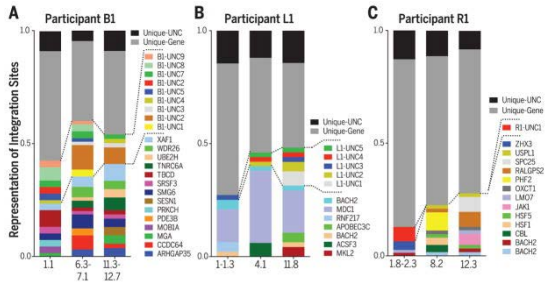
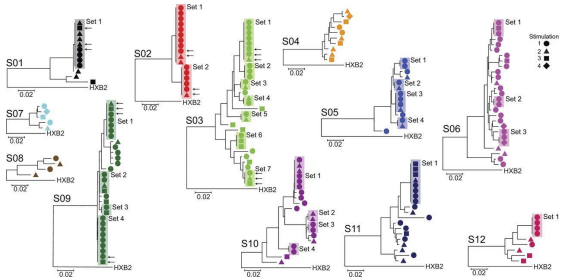
NIAID

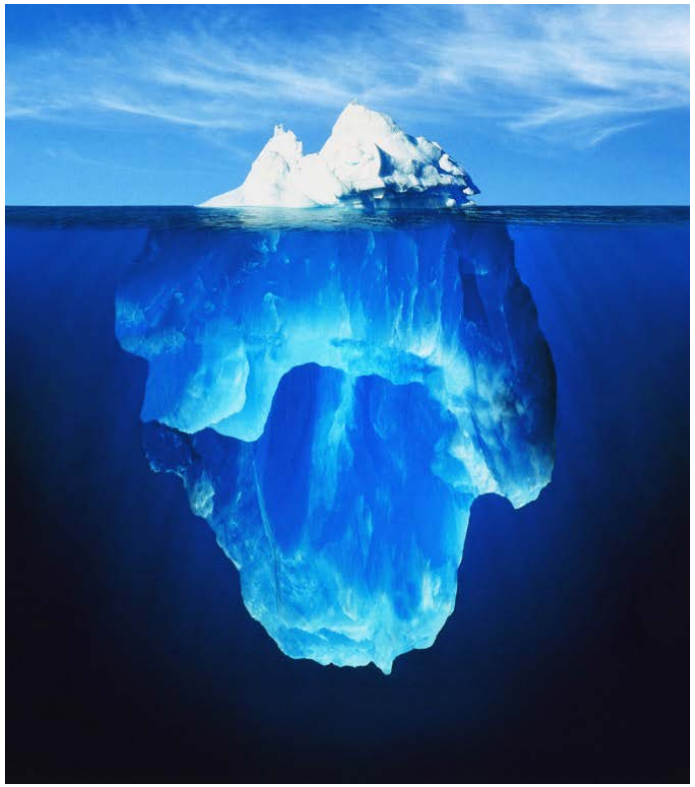
What is the true percentage of HIV reservoir cells generated via cellular proliferation?

Total HIV DNA



Replication competent HIV DNA





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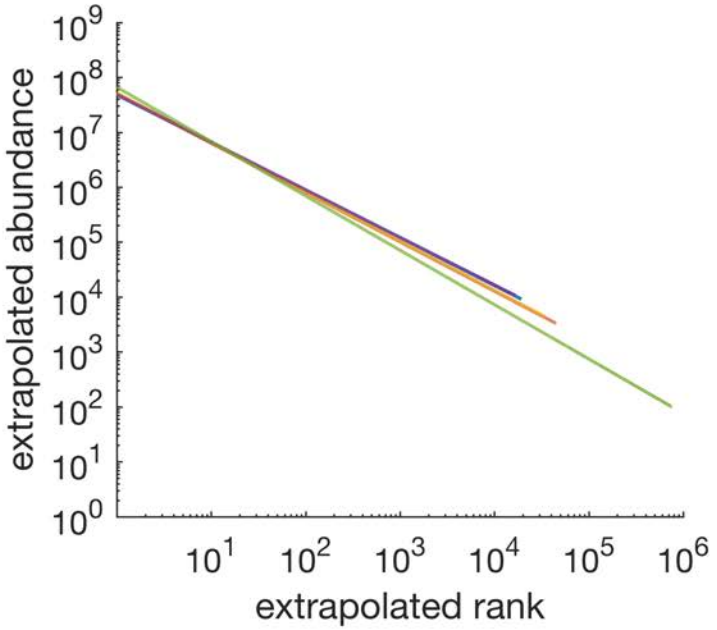
Wagner, Science, 2014.
Hosmane N, JEM, 2017.

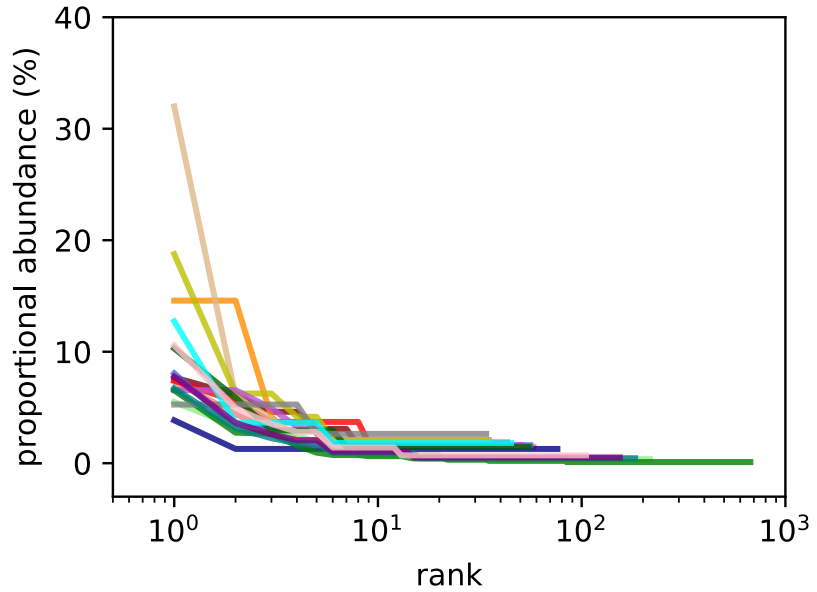
The experiment is the equivalent of randomly sampling 100 Americans & assigning clonality according to city of residence

Reality
n~10^9 people or sequences



New York Tacoma Hood River, OR Bow, WA
Seattle Bellingham, WA Twisp, WA

Experiment
n=50-100 people or sequences



New York Seattle Tacoma Bellingham, WA
Hood River, OR
Twisp, WA
Bow, WA

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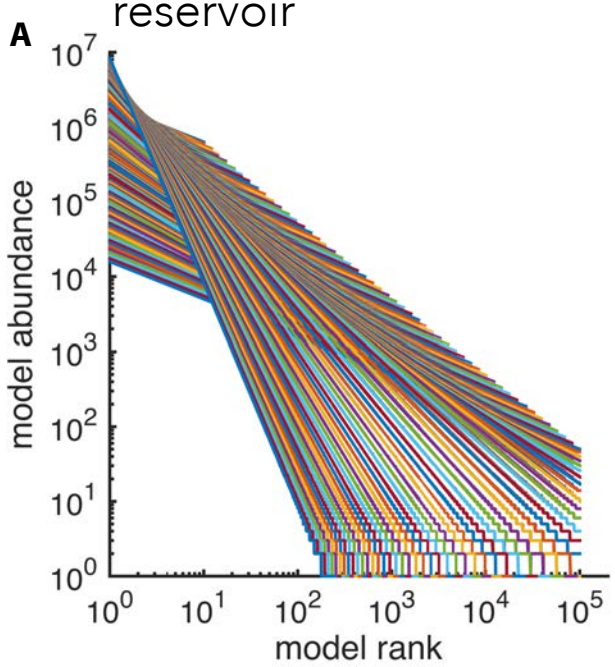
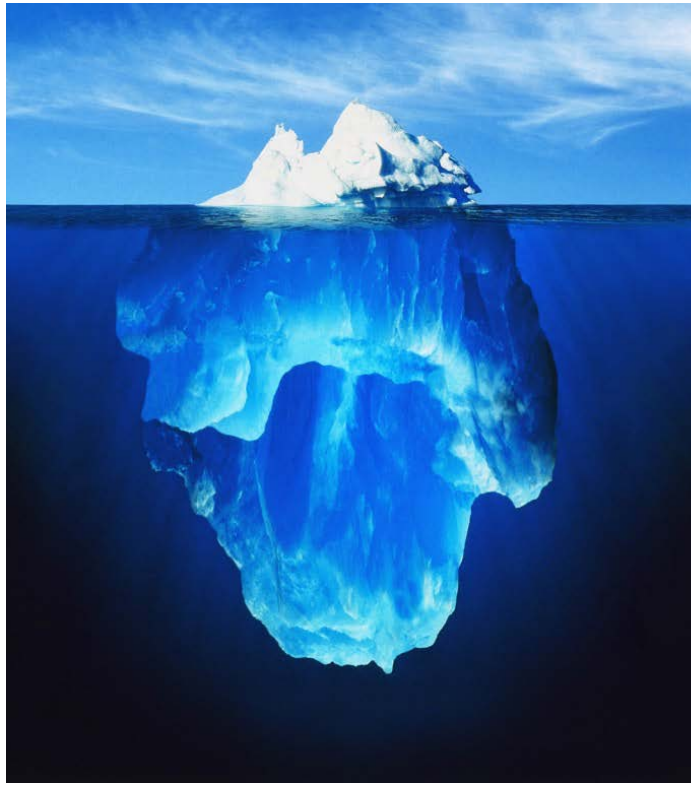
Computationally recreate the entire iceberg

Generate 1000s of theoretical clonal distributions of all HIV infected cells in the reservoir



- 10^9 total HIV DNA sequences
- 10^7 replication competent HIV sequences

- Free parameter: Power law slope
- Free parameter: Sequence richness



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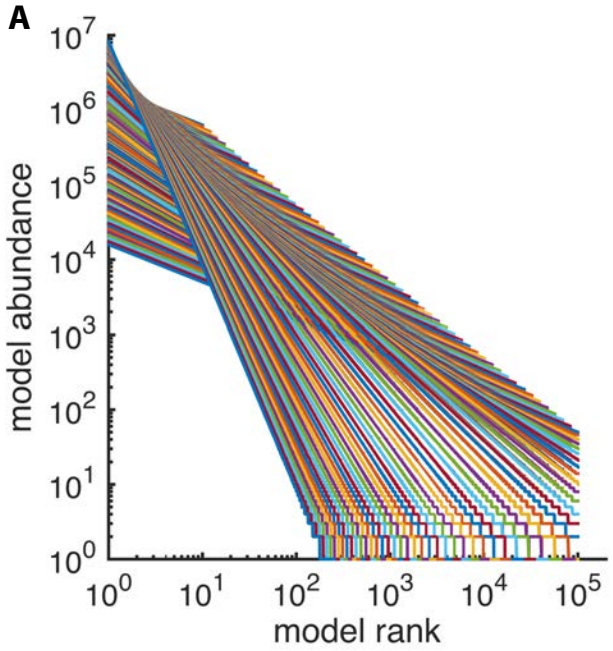
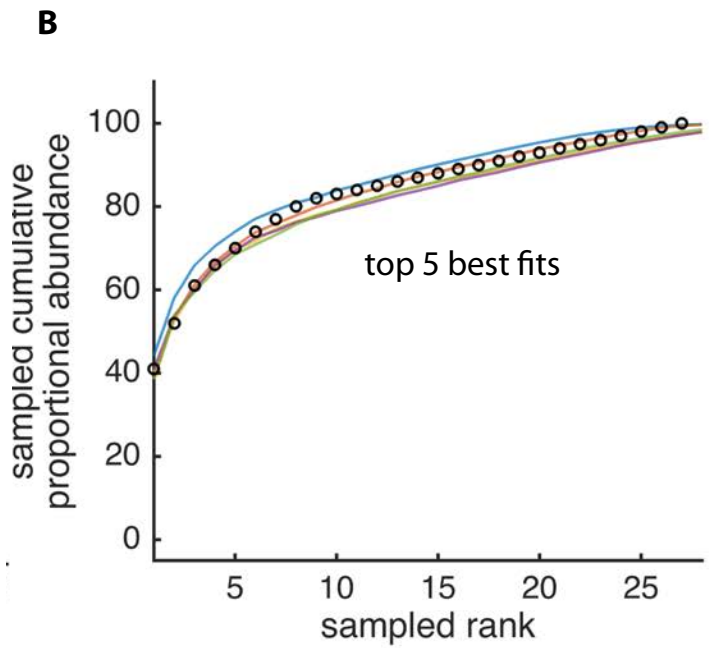
Reeves DB et al, Nature Communications, 2018.

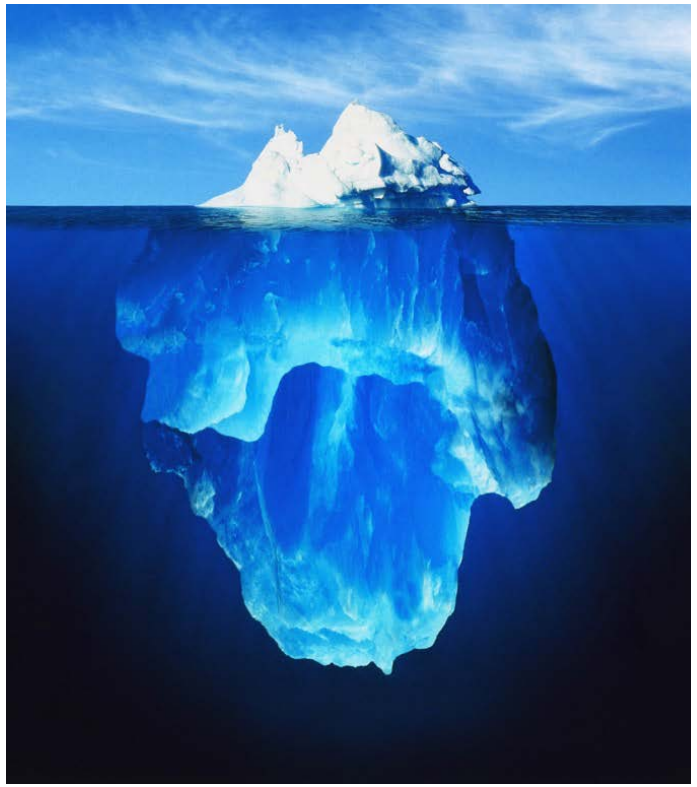
Model fit to data

Generate 1000s of theoretical clonal distributions of all HIV infected cells



Randomly sample 100 sequences from each distribution & fit to proportional abundance curves from actual data





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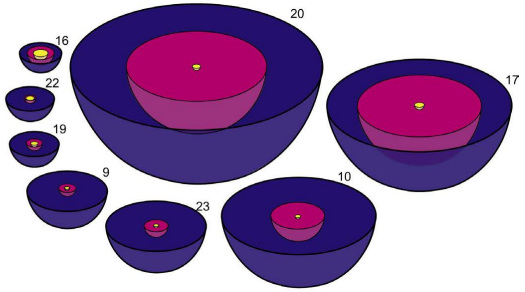
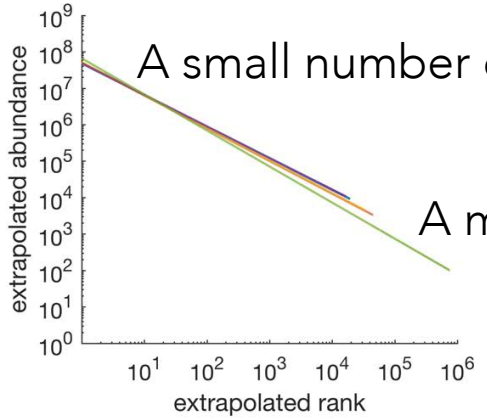
Reeves DB et al, Nature Communications, 2018.

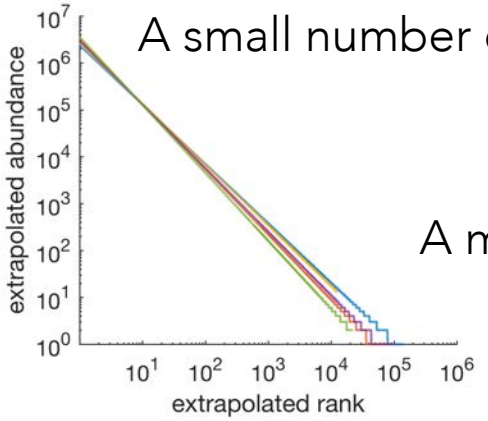
Model prediction: a highly organized clonal structure of the HIV reservoir



Total HIV DNA



Replication competent HIV DNA



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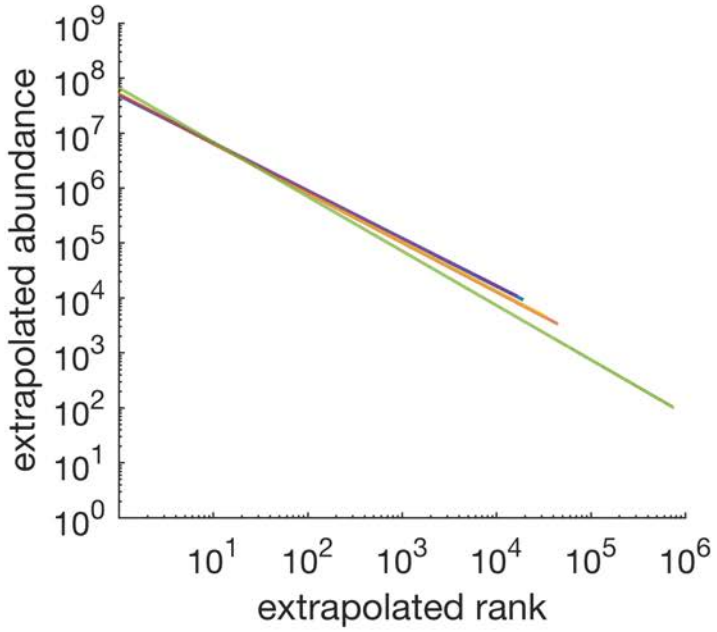
Reeves DB et al, Nature Communications, 2018.

HIV DNA in the reservoir has a remarkable similarity to the distribution size of towns & cities in the USA



New York Tacoma Hood River, OR Bow, WA

Seattle Bellingham, WA Twisp, WA

Reality:

- 10^9 total HIV DNA sequences
- 2.25×10^8 Americans

- 10^4-10^5 unique HIV DNA sequence clones
- 19354 American towns / cities

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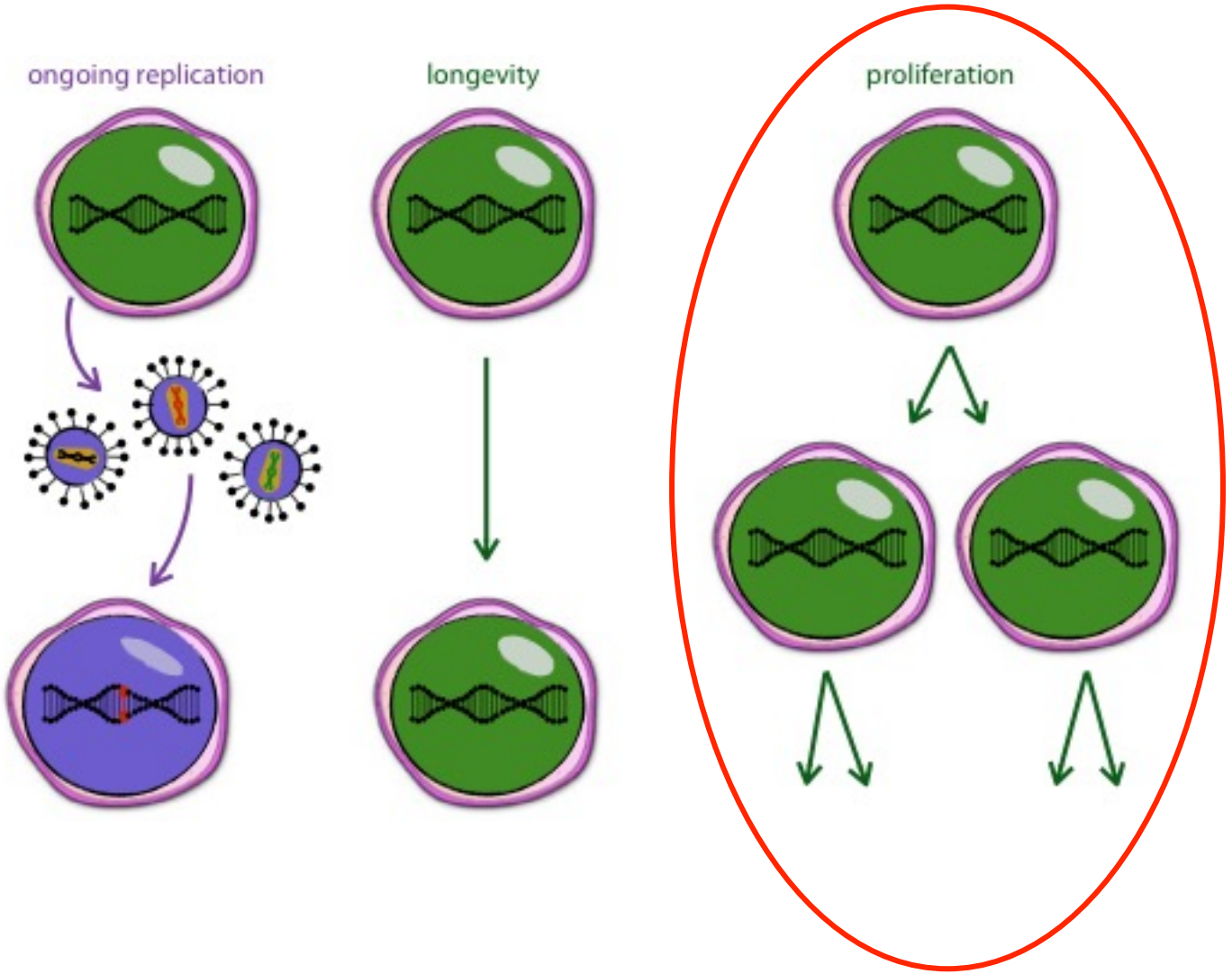
Conclusion: HIV persistence during ART is primarily due to cellular proliferation

- >99% of cells with HIV DNA were generated via cellular proliferation
- >98% of cells with replication competent HIV DNA were generated via cellular proliferation



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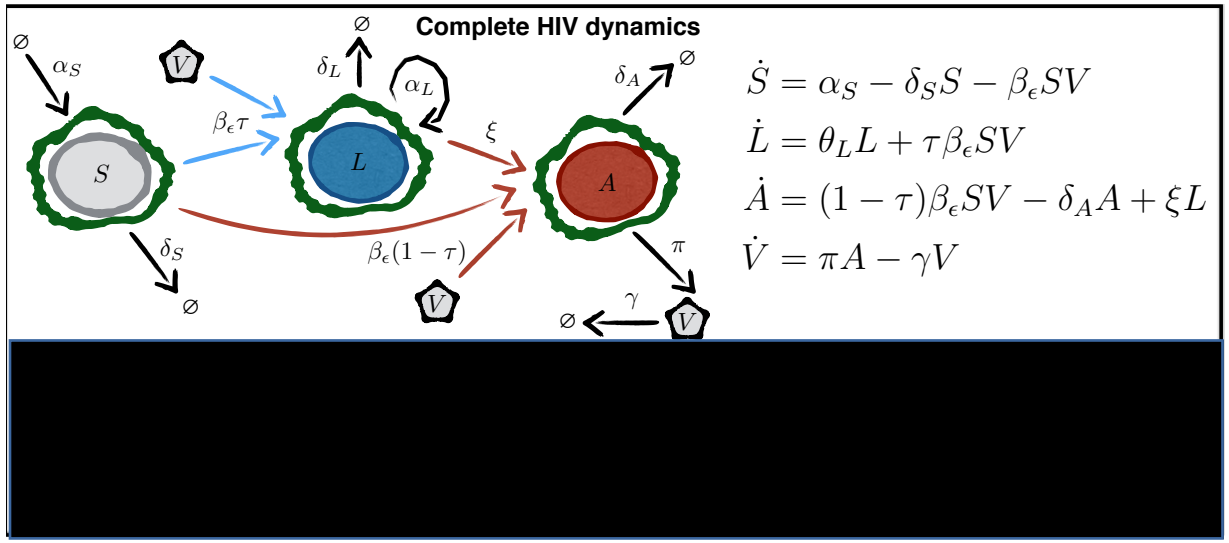
Anti-proliferative therapy to reduce the HIV reservoir



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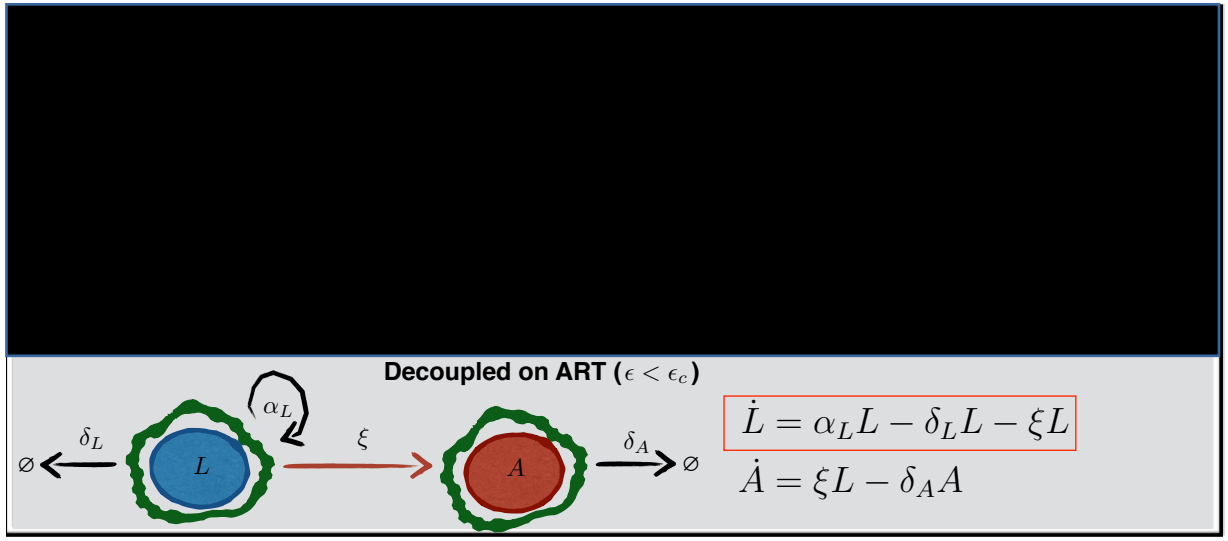
Mathematical model of the HIV reservoir



- A central memory CD4+ T cell proliferates ($\boldsymbol{\alpha}_L$) once every 45 days
- HIV reactivates ($\boldsymbol{\xi}$) from a latently infected memory CD4+ T cell once every 138 years

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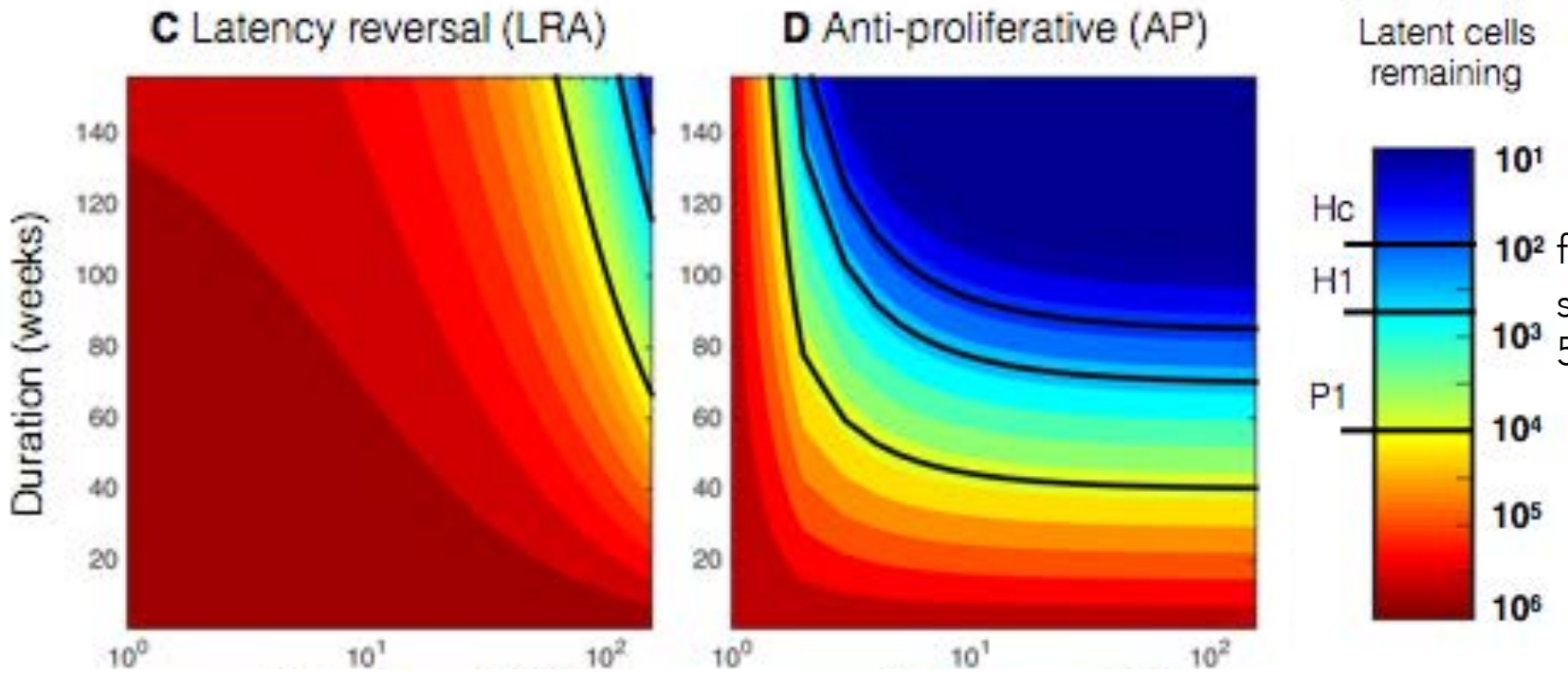
Macallan, JEM, 2004.
McCune JM, JCI, 2000.
Hill A, PNAS, 2014.

Anti-proliferative therapy requires far less potency than latency reactivating agents for therapeutic success

$$\dot{L} = \alpha_L L - \delta_L L - \xi L$$



functional cure suppression for 1 yr in 50% of patients

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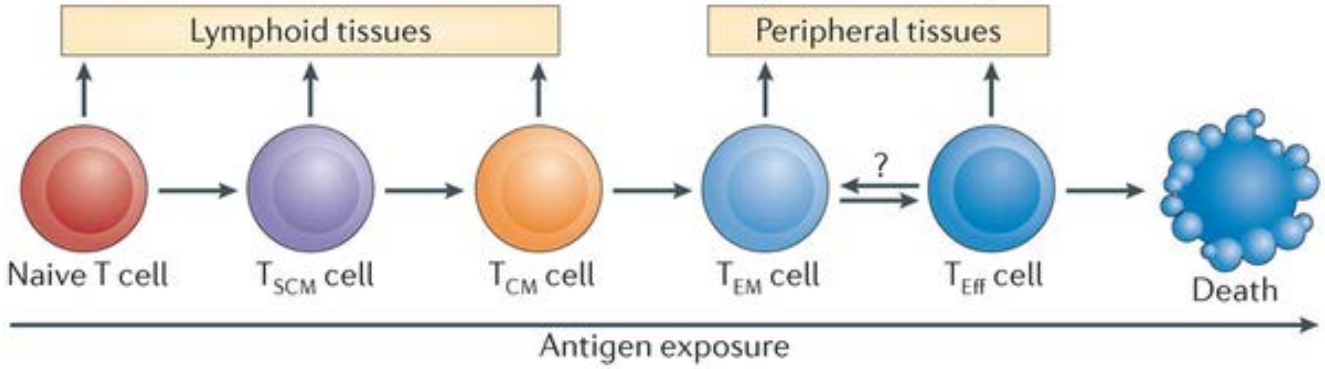
Reeves, Duke et al. Sci Reports 2017

Effect of reservoir heterogeneity on time to eradication



Less proliferation
longer lifespan
0-10% of reservoir

Moderate proliferation
moderate lifespan
40-90% of reservoir

More proliferation
shorter lifespan
10-20% of reservoir

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Chomont et al. Nat Med 2009

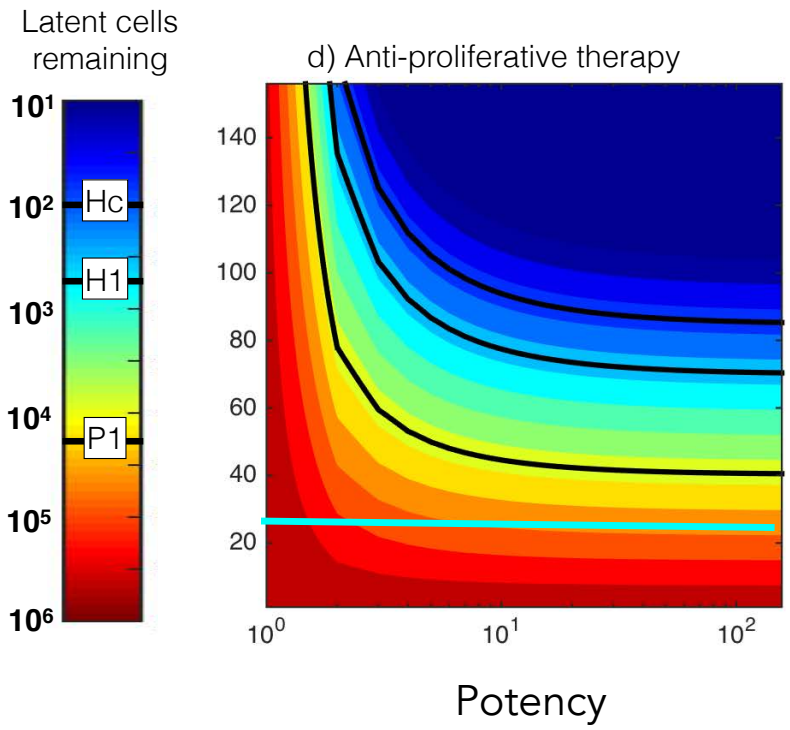
Mycophenolate mofetil (MMF)

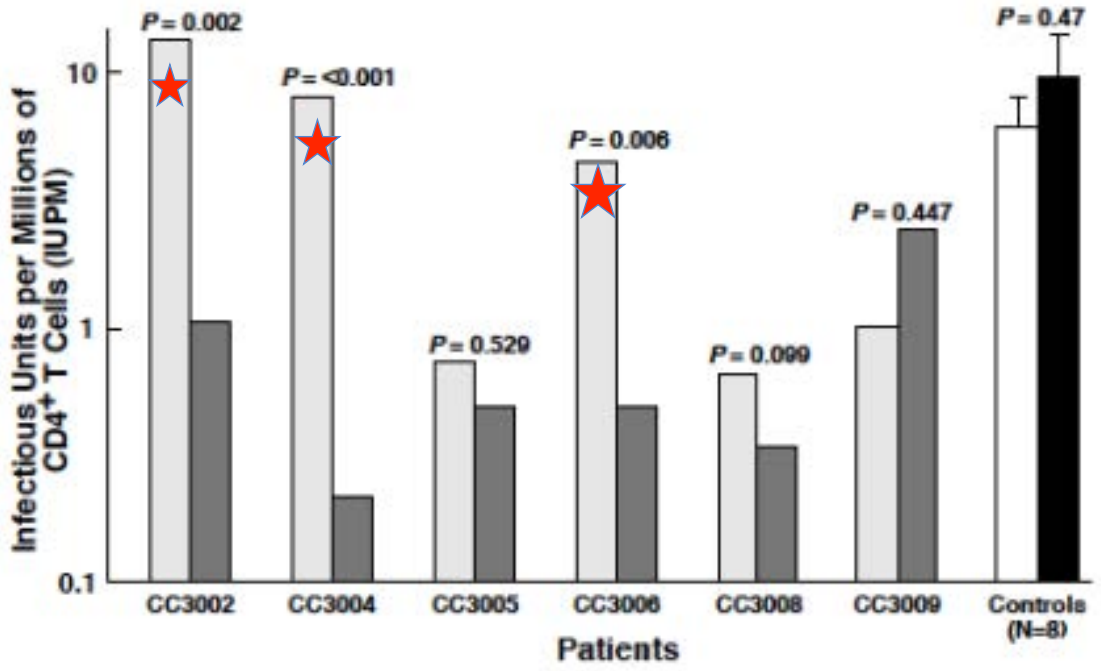
- Specifically targets proliferation of B and T lymphocytes

- Prevents organ rejection following solid organ transplantation
- Prevents graft versus host disease following hematopoietic cell transplantation
- Steroid-sparing agent for autoimmune diseases

- Well tolerated & safe in hundreds of persons with HIV
- Associated risk of opportunistic infection (when co-dosed with prednisone)
- Teratogenic

Decreased numbers of HIV infected cells following 24 weeks of mycophenolate mofetil (MMF) in 3 of 6 treated people





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Chapuis A et al. Nat Med 2000

MMF clinical trial








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UNIVERSITY OF WASHINGTON 1861

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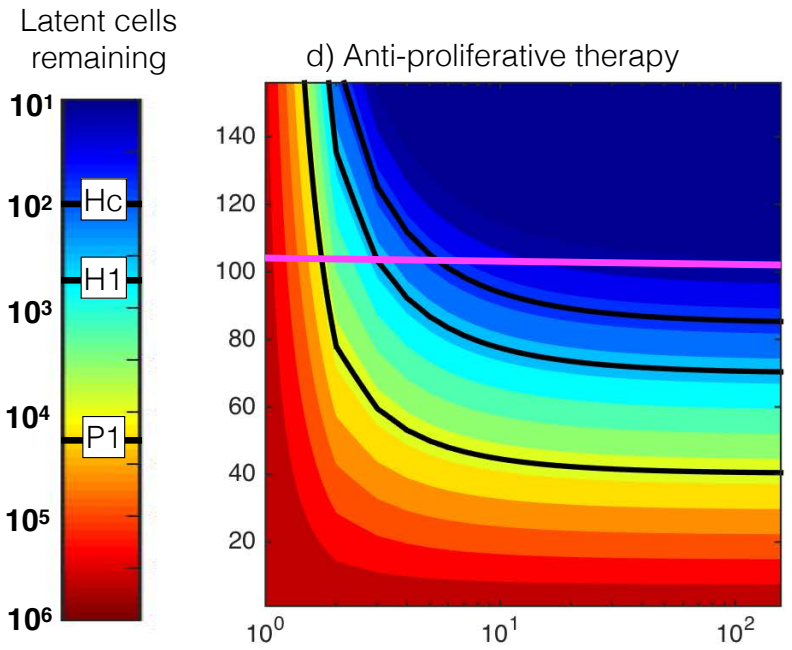
MMF clinical trial

- Hypothesis: Prolonged anti-proliferative therapy for 2 years will lower reservoir volume of HIV DNA and replication competent HIV
- 5 participants fully suppressed on ART with CD4 nadir >350/uL will receive MMF twice daily

- Historical controls
- Frequent evaluation for neutropenia, lymphopenia, infections

- Inclusion criteria include documented *in vivo* response to MMF using serum & PBMCs from participants



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MMF clinical trial

- Optional GI biopsy
- Frequent safety monitoring / blood draws early during study

- No ATI planned

- Emphasis to participants that cure is unlikely

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Study progress

- 4 enrolled
  - 6 month analysis pending
  - Drug well tolerated

- Results CROI 2020!

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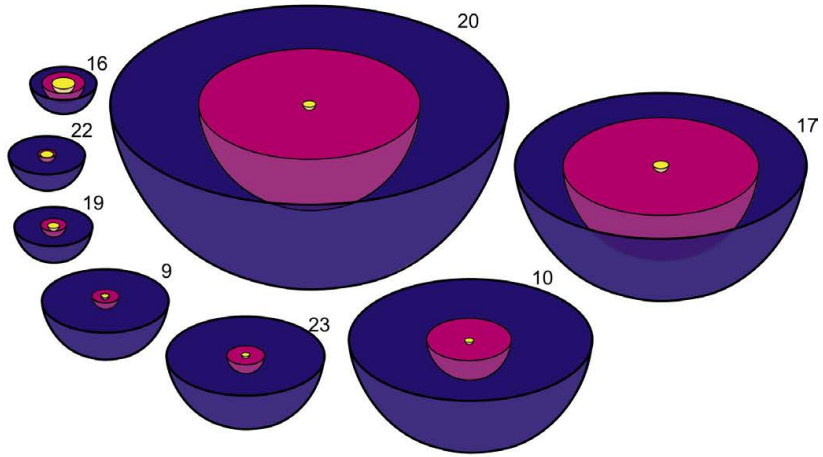
HIV DNA as a primary outcome

- Pros:
  - HIV DNA will remain positive for longer than QVOA if there is a therapeutic effect
  - The therapeutic effect could theoretically be equal for HIV DNA & QVOA
  - Less sample to sample variability
    - HIV DNA median clearance rate: -0.017 log / year (IQR: -0.061 – 0.02, range: -0.195 – 0.166)
    - QVOA: 0.4 log changes on samples separated by 3 months occur 7% of the time
- Cons:
  - Pre-treatment HIV DNA does not correlate with QVOA
  - Optimal timing of ART treatment interruption unknown



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Besson GJ, CID, 2014.
Crooks, JID, 2015

Plans for a negative result:

- A lack of reduction in reservoir volume would <u>not</u> reject the hypothesis that cellular proliferation sustains the HIV reservoir

Possible cause	Assessment	Solution
Poor drug delivery	• Drug levels	• Higher dose
MMF resistance	• Anti-proliferative assay	• Screen participants
Daughter cell death may be functionally linked to proliferation	• IL-7 levels pre & during MMF • Radiolabeling study (future)	• Limit IL-7 effects
Reduction of infected CD4+ memory cells with persistence of infected macrophages	• ??	• ??
Toxicity	• Trial	• Lower dose

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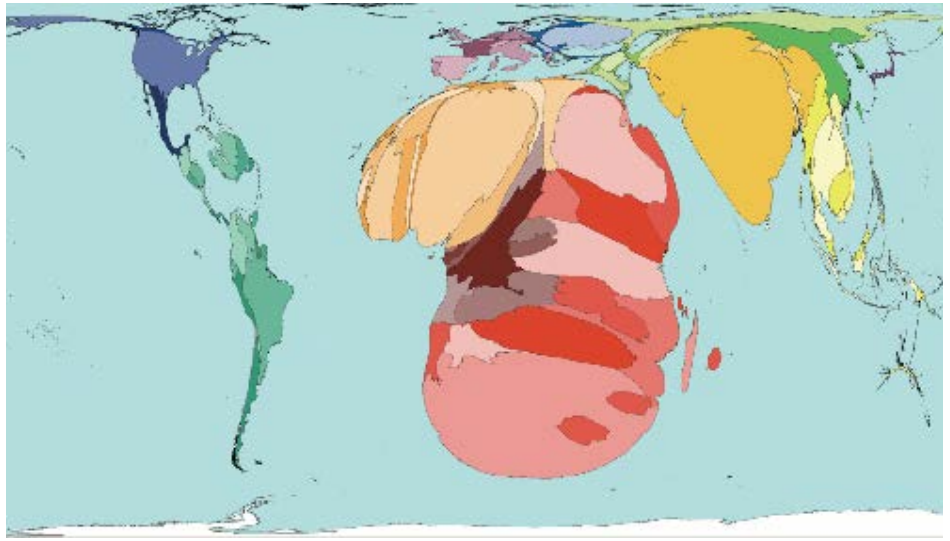
Plans for a positive result

- A meaningful reduction in reservoir volume would strongly support the hypothesis that proliferation sustains the HIV reservoir

- Further trials in Africa, Asia
- Trials in persons with primary HIV
- Combination trials
- Specific targeting to CD4 T cells



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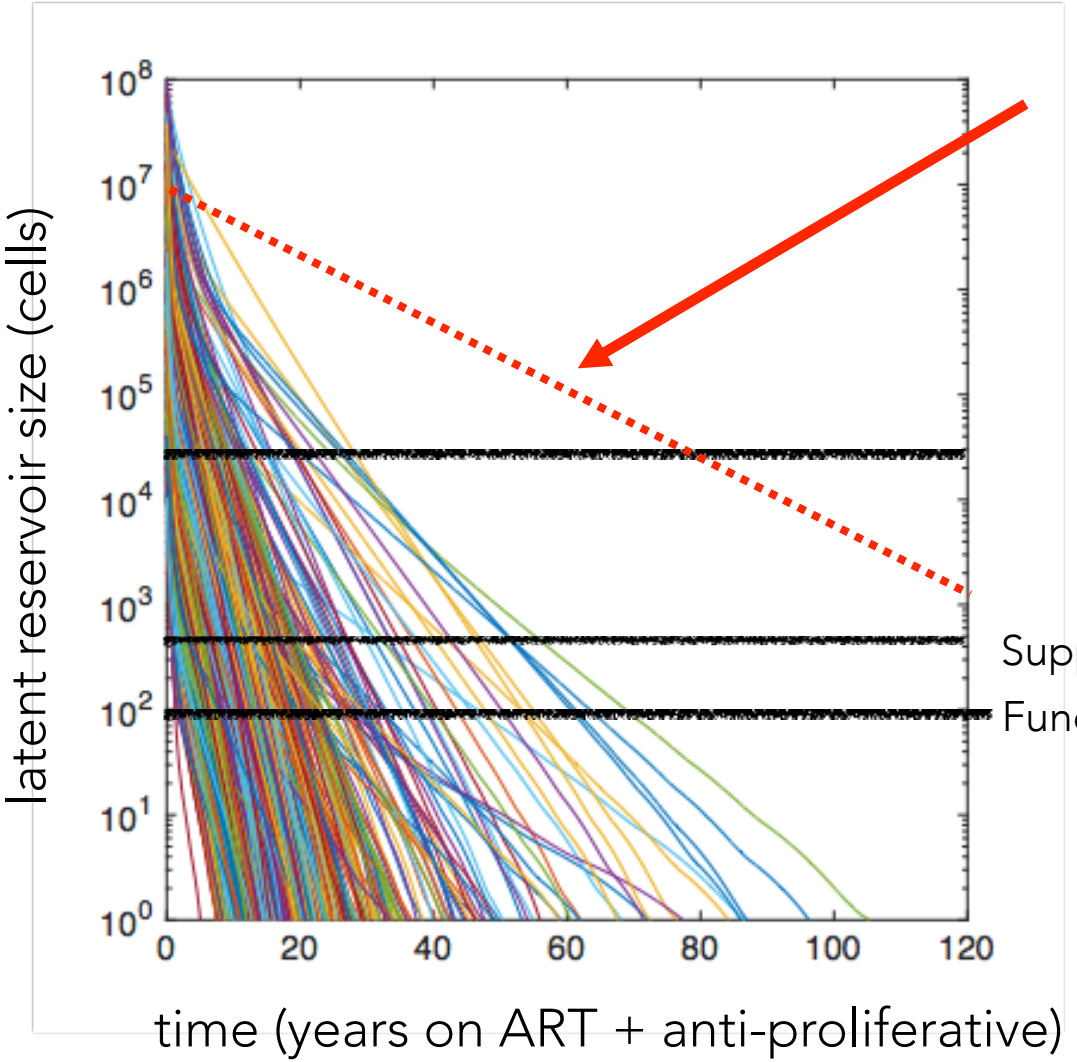
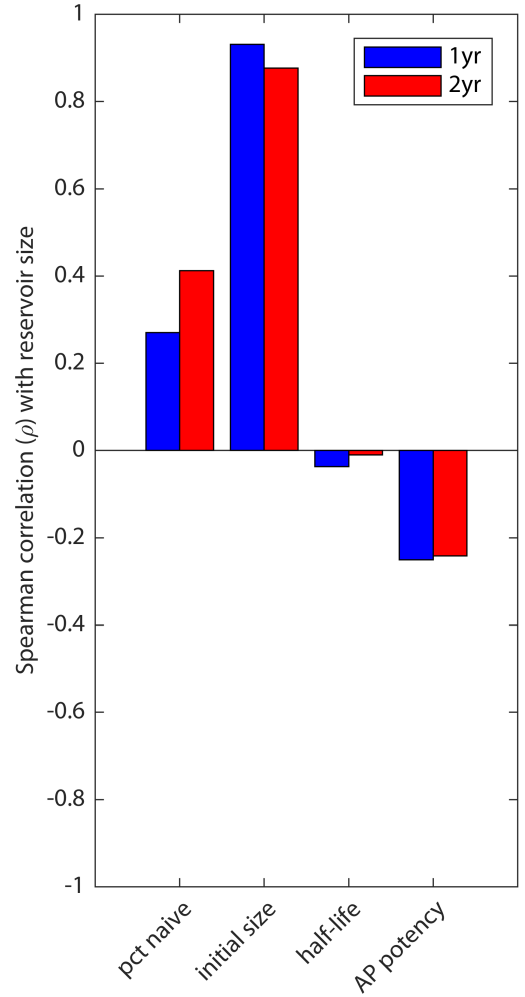
10,000 simulated trial participants



ART alone

Suppression for 1 yr in 50% of patients

Functional cure



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MMF as a combination therapy

- May antagonize:
  - Latency reversal agents
  - CAR T cells / immunotherapies
  - Therapeutic vaccines
- May synergize:
  - “Block & lock” approaches
- May be additive:
  - Passive neutralizing antibody

Conclusions

- The HIV reservoir is sustained by clonal proliferation of infected cells
- Anti-proliferative therapy may reduce HIV reservoir volume & achieve functional cure
- Results from MMF study coming soon!

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Thank you!

- Study participants
- UW ACTU
  - Mel Padullo
  - Eric Helgeson
  - Bob Harrington
  - Katrina Puckett
- Hladik lab
  - Florian Hladik
  - Claire Levy
  - Sean Hughes
- Funders
  - amfAR
  - NIAID: Defeat HIV Collaboratory
- Schiffer group
  - Dan Reeves
  - Liz Duke
  - Florencia Tettamanti Boshier
  - Dave Swan
  - Pavi Roychoudhury
  - Fabian Cardozo Ojeda

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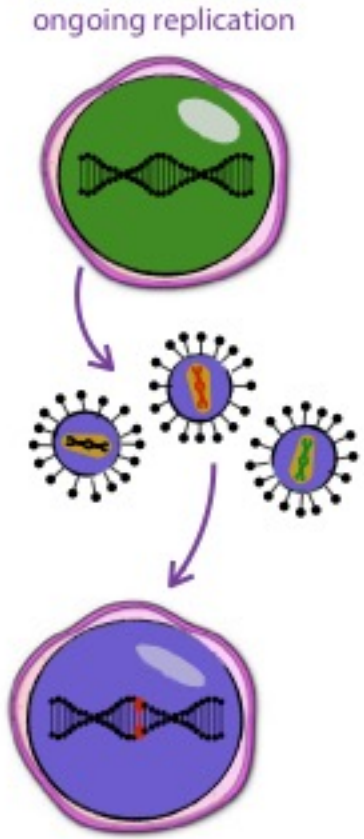
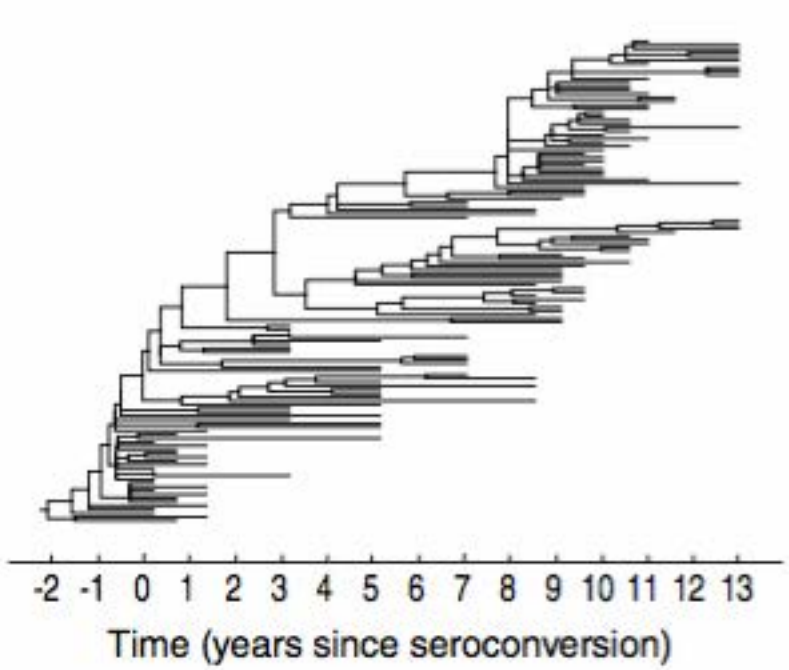
Possible evidence for ongoing HIV replication

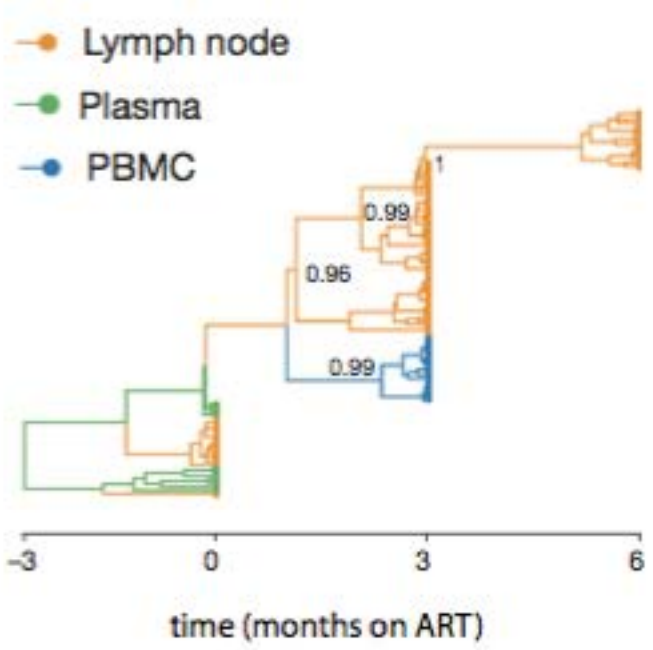


Off ART



Lemey, AIDS Rev, 2016.

On ART



Lorenzo-Redondo, Nature, 2016.

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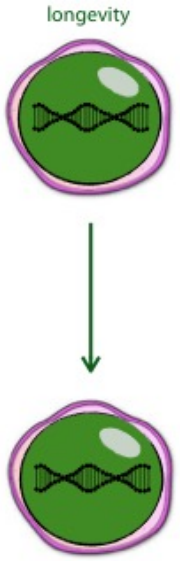
Possible evidence for longevity of infected cells



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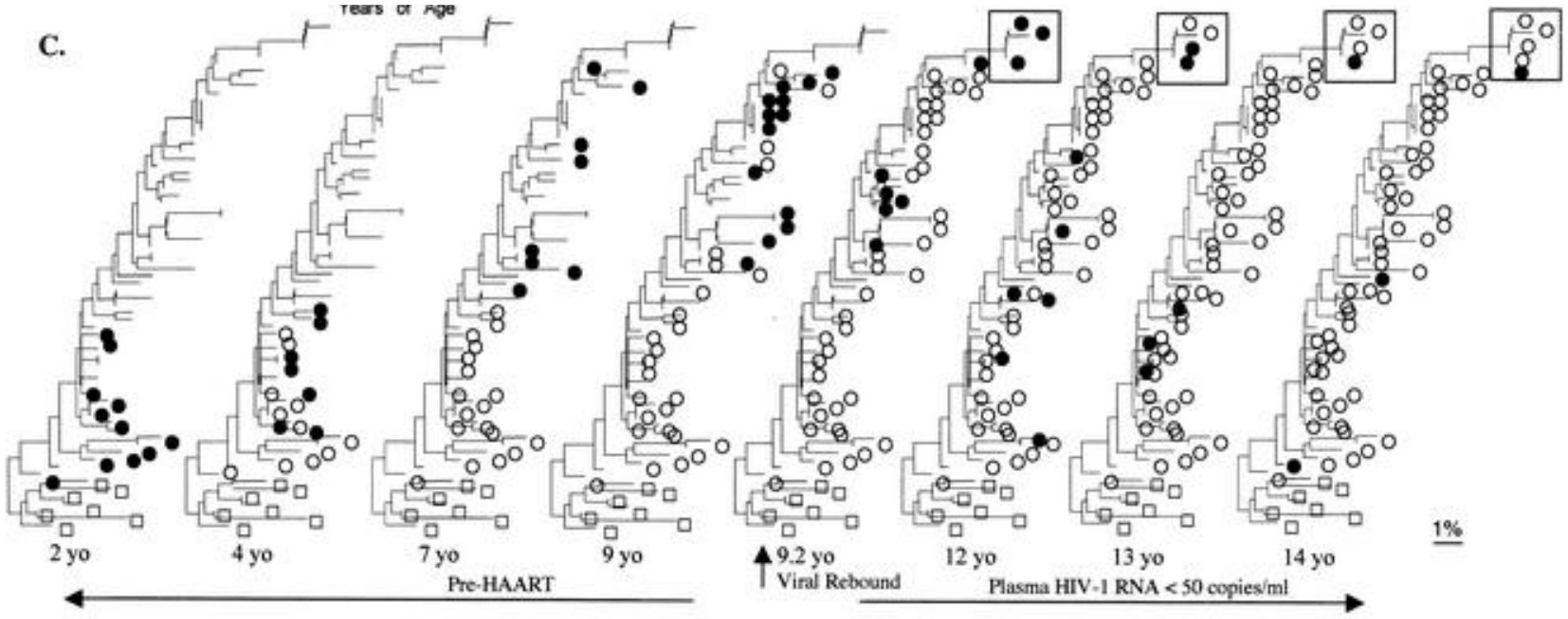

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Frenkel L, JVI, 2003.