HIV Elite Controllers and What We've Learned from Them

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Disclosures:

None

Learning Objectives

- Be aware of data on antiretroviral therapy in people with HIV (PWH) who are elite controllers
- Understand how HIV elite control may inform new cure strategies
- Know recent information on HIV reservoir decay in PWH who are receiving antiretroviral therapy

Outline

- How do we identify HIV elite controllers? How do they maintain HIV control?
- Are elite controllers a good model for HIV functional cure?
- Should elite controllers be treated with ART?
- Lessons from elite controllers for HIV cure research

How do we identify HIV elite controllers? How do they maintain HIV control?

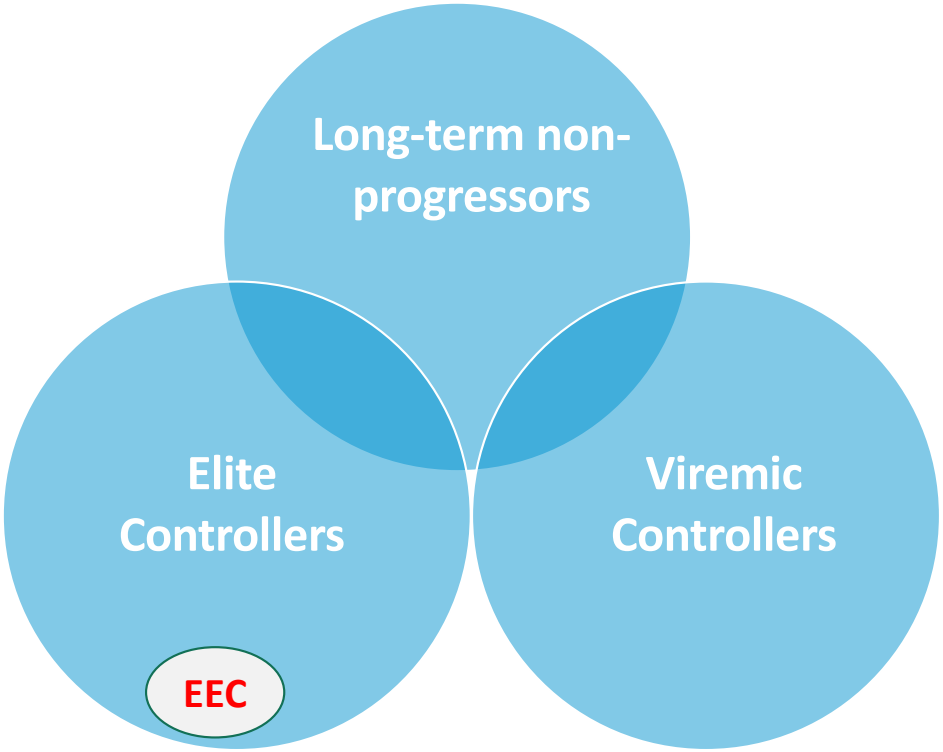
Are elite controllers a good model for HIV functional cure?

Should elite controllers be treated with ART?

Lessons from elite controllers for HIV cure research

Definitions

- **Long-term non-progressors (LTNP)**
  - Disease free, normal CD4 counts for >10 y
  - Heterogeneous viral loads
  - Prevalence: ~2-15%
- **Viremic controllers (VC)**
  - HIV RNA 50-2,000 without ART
  - Prevalence: unknown, >EC
- **Elite controllers (EC)**
  - Undetectable HIV RNAs without ART
  - Prevalence: ~0.3-0.5%
- **Exceptional elite controllers (EEC)**
  - EC characteristics for decades
  - No intact proviruses. N=2



Modified from slide from Dr. Sam Schnittman

Characteristics of HIV Elite Controllers

- Demographics
  - More frequent in women, those of African descent
- Clinical features
  - Lower HIV RNA, higher CD4 count during acute HIV than progressors
- Despite initial viral control, HIV controllers may have:
  - CD4 cell declines
  - Loss of virologic control
  - AIDS-defining events

Mastrangelo A et al, Curr Opin HIV AIDS 2022
Goujard C et al, CID, 2009
Slide from Dr. Sam Schnittman

Diagnosing EC in the Era of Early ART Initiation

- US Department of Health and Human Services ART Guidelines discourage clinicians from waiting to start ART to assess for elite control because of importance of early ART initiation
- In French ANRS PRIMO cohort, people who became controllers (n=8) had a lower initial HIV RNA (median 1000) than people who were non-controllers (n=204; median HIV RNA 50,000)
- Patient with newly acquired HIV who has an HIV RNA <1000 may end up being a controller, although close monitoring needed

https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/initiation-antiretroviral-therapy?view=full; Goujard C et al, CID, 2009

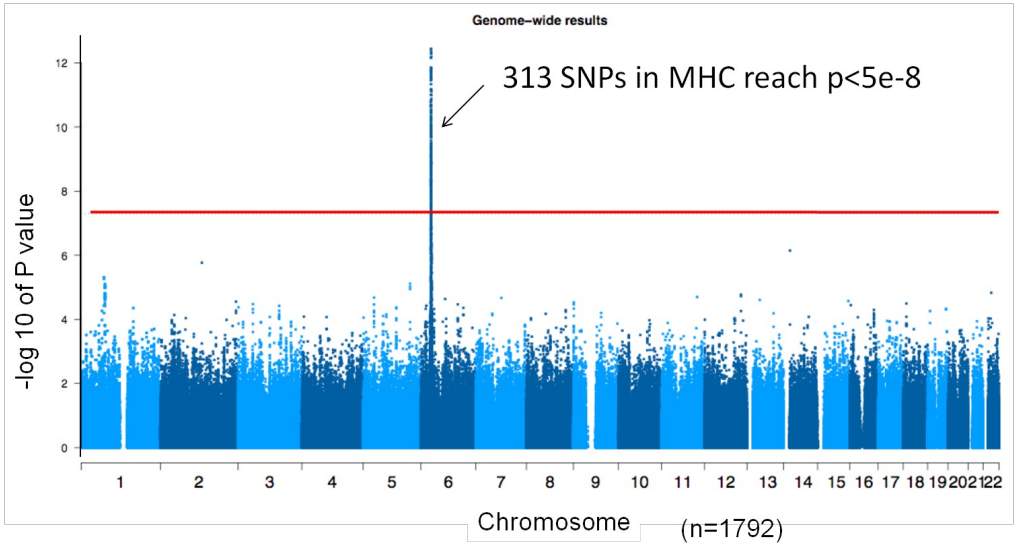
Mechanisms of EC

- Genetics
- Immunologic
- Virus: Decreased replication capacity
- Integration of virus into quiescent parts of the genome

Genetic factors: International HIV Controllers Study

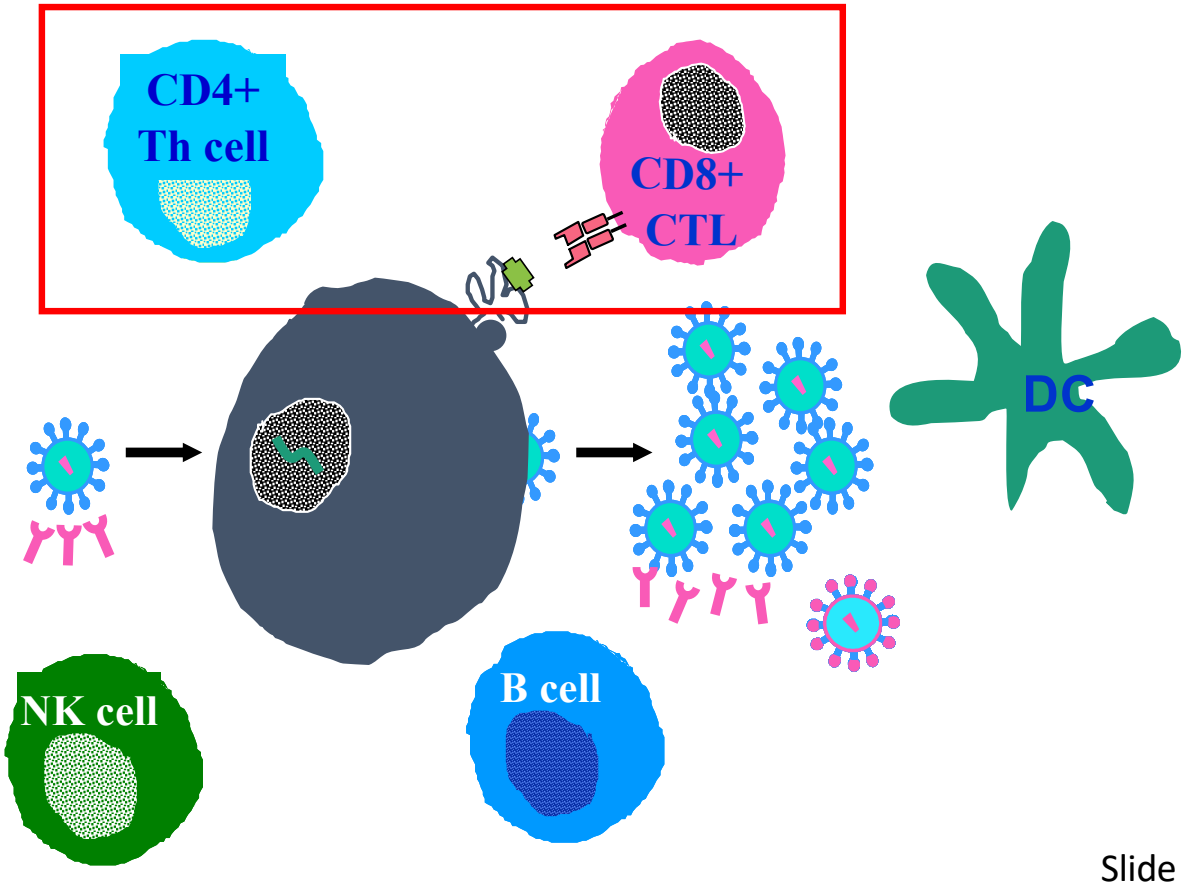
- Genome-wide association scan
- Protective HLA alleles: B57, B27, B14/Cw08.
- Risk alleles: B35, Cw07
- Recent study: long term control linked to similar genetic factors
- Implication: HLA-viral peptide interaction is major genetic factor modulating HIV control

In addition to CCR5, single nucleotide polymorphisms (SNP) in MHC class I (HLA) are strong determinants of HIV control



Pereyra F et al Science, 2010; Real LM, iScience, 2023

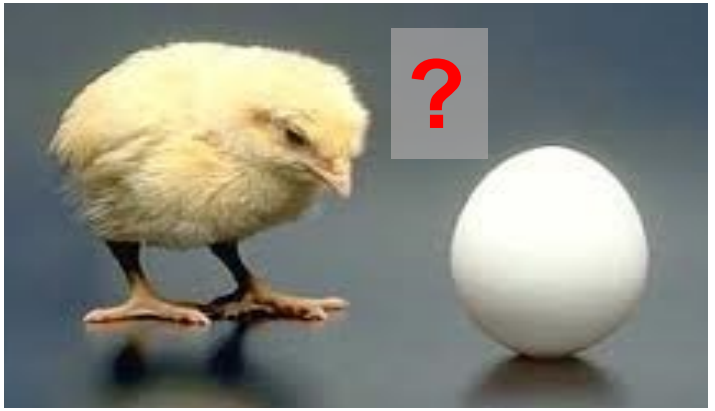
Mechanisms of immune control in EC



Slide from Bruce Walker, MD

HIV-specific T cell Responses

- Polyfunctional CD4 and CD8 cells (IFN-gamma/IL-2; degranulation markers; proliferation markers) higher in EC than progressors



- In EC, cytolytic HIV-specific T cells localize to lymph node germinal centers where HIV is replicating

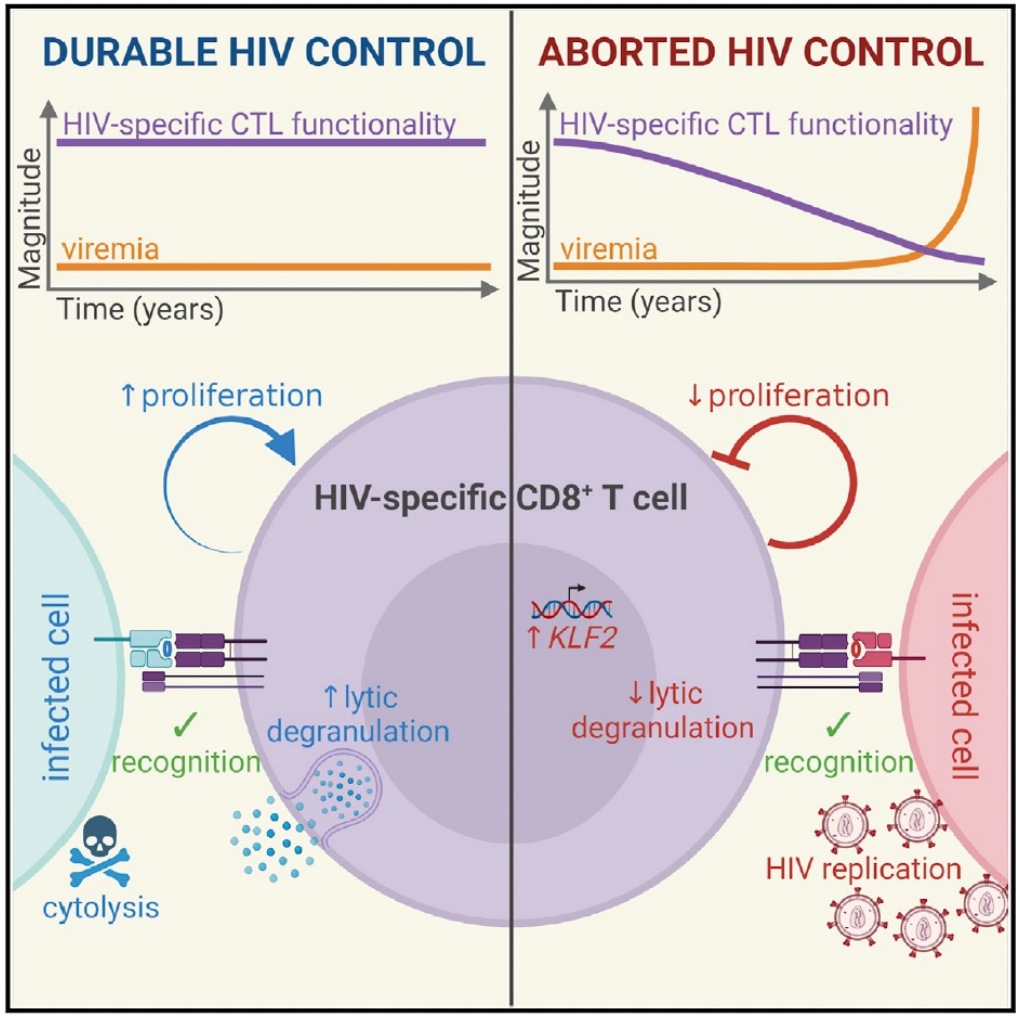
Are strong and localized HIV-specific immune responses the cause or consequence of virologic control?

Pereyra F et al, JID, 2008; Rutishauser R and Trautmann L, Curr Op HIV/AIDS, 2022; Collins DR, Science Immunology, 2023

New Data Suggesting How T Cells Might Control HIV

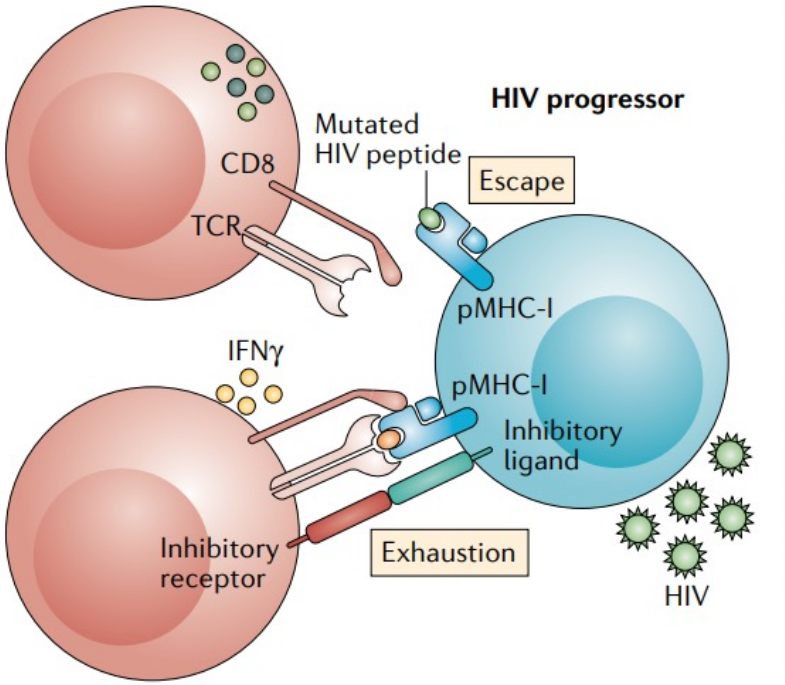
Impairment of HIV-specific CD8 T cells precedes loss of control of viremia

- Longitudinal evaluation of 34 PWH: 17 maintained control; 17 had loss of control (increased viremia)
- HIV specific proliferative and cytolytic T cell function became impaired prior to loss of control

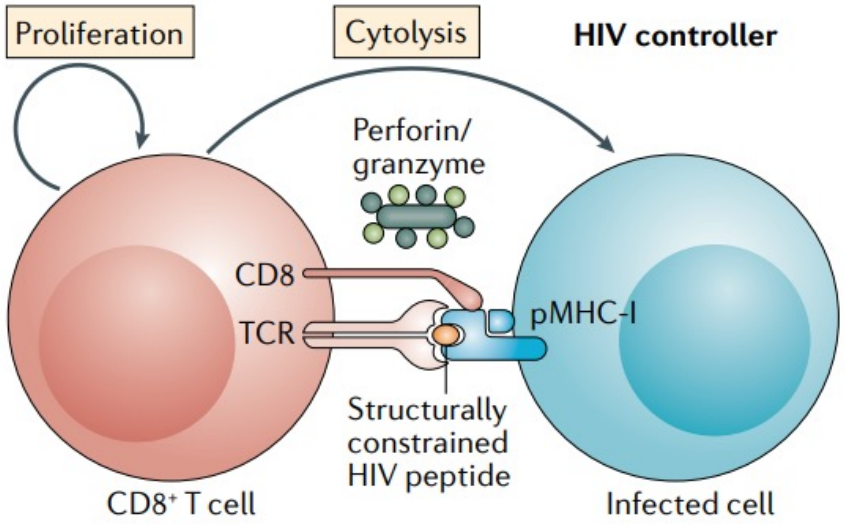


Collins D, Immunity, 2021

HIV progressor: ineffective or exhausted T cells that target mutated HIV peptides



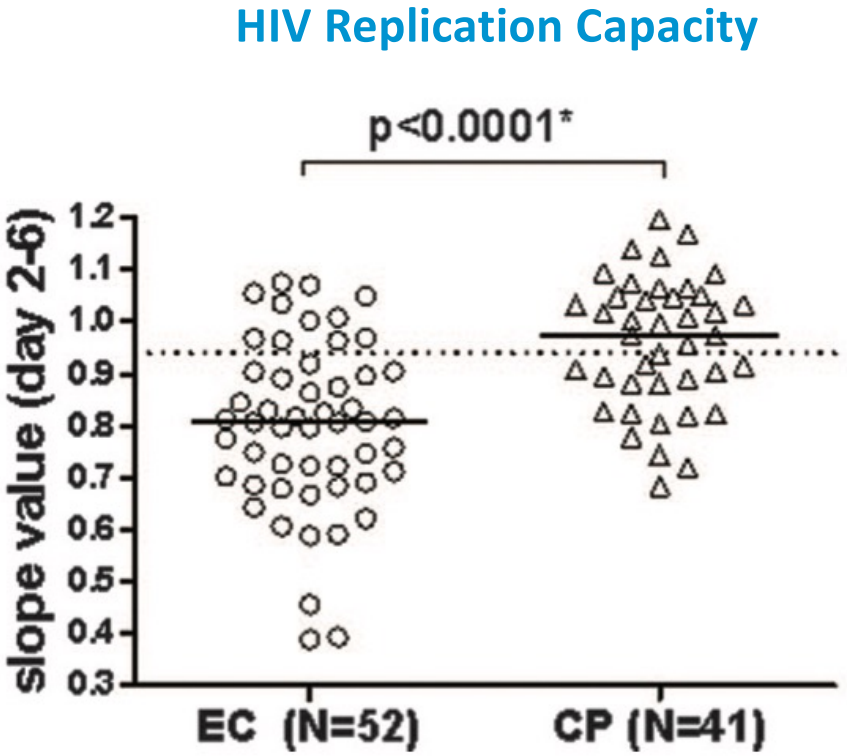
HIV controller: effective T cell responses against HIV peptides that don't tolerate mutations



Gaiha G et al, Science, 2019
Collins D et al, Nature Reviews Immunology, 2020

Virologic Mechanisms of EC: Reduced HIV Replication Capacity

- Replication capacity (RC) compared between EC and PWH who have progressive infection (chronic progressors, CP)
- ECs had HIV with reduced replication capacity
- Immune-induced mutations may reduce viral RC in EC



Miura T et al, J Virol, 2009

Lesson #1 from HIV Elite Controllers

Identifying ECs: Low HIV RNA during acute infection may be a clue. Genetic, immunologic and viral mechanisms

Are elite controllers a good model for HIV functional cure?

Should elite controllers be treated with ART?

Lessons from elite controllers for HIV cure research

Outline

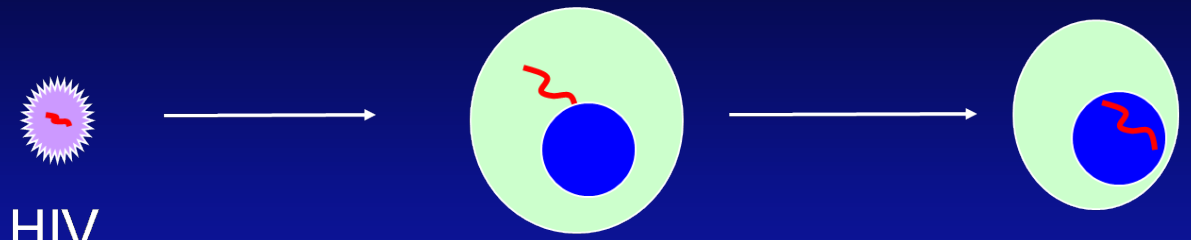
How do some PWH achieve HIV control? Genetic, immunologic and viral mechanisms

Are elite controllers a good model for HIV functional cure?

Should elite controllers be treated with ART?

Lessons from elite controllers for HIV cure research

Why does ART Not Cure HIV?



HIV

Infection of activated CD4 cell and integration of virus into the genome

Reversion of activated T cell to a resting, memory CD4 cell

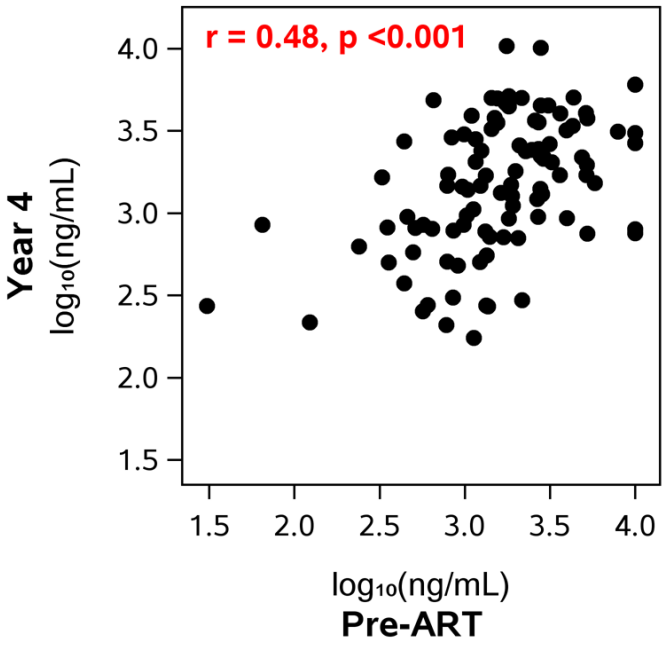
Latently-infected resting memory CD4 cell

1. **Long-lived**
2. **No expression of viral gene products**
3. **Not seen by the immune system**
4. **Established during acute infection**

Despite ART, PWH Have Elevated Levels of Inflammation

- PWH (not elite controllers) on ART with undetectable HIV RNA for >10 years (n=101)
- High levels of inflammation before ART correlate with high levels while on ART ("immune dysregulation legacy effect")
- Persistent immune dysregulation may drive CVD disease, non-AIDS complications

High pre-ART CRP levels correlated with high on-ART levels



Gandhi RT et al, PLoS Pathogens, 2017

Sterilizing vs. Functional Cure

- Sterilizing Cure: absence of any replication competent HIV
- Functional cure: long-term control of HIV replication in absence of ART
- Are EC a good model for a functional cure?
  - Yes… and no
  - EC have undetectable plasma HIV RNA but some have elevated levels of immune activation and inflammation

Why EC May Not Be a Good Model for Functional Cure

1. Heterogeneity of HIV levels

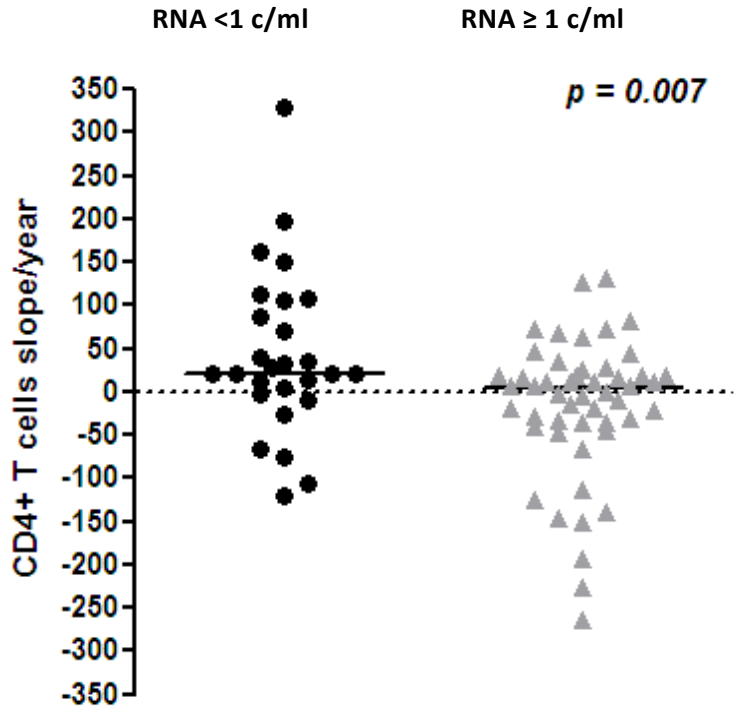
2. Loss of elite control in some instances

3. Increased immune activation and inflammation

4. Accelerated atherosclerosis

Residual Viremia in EC

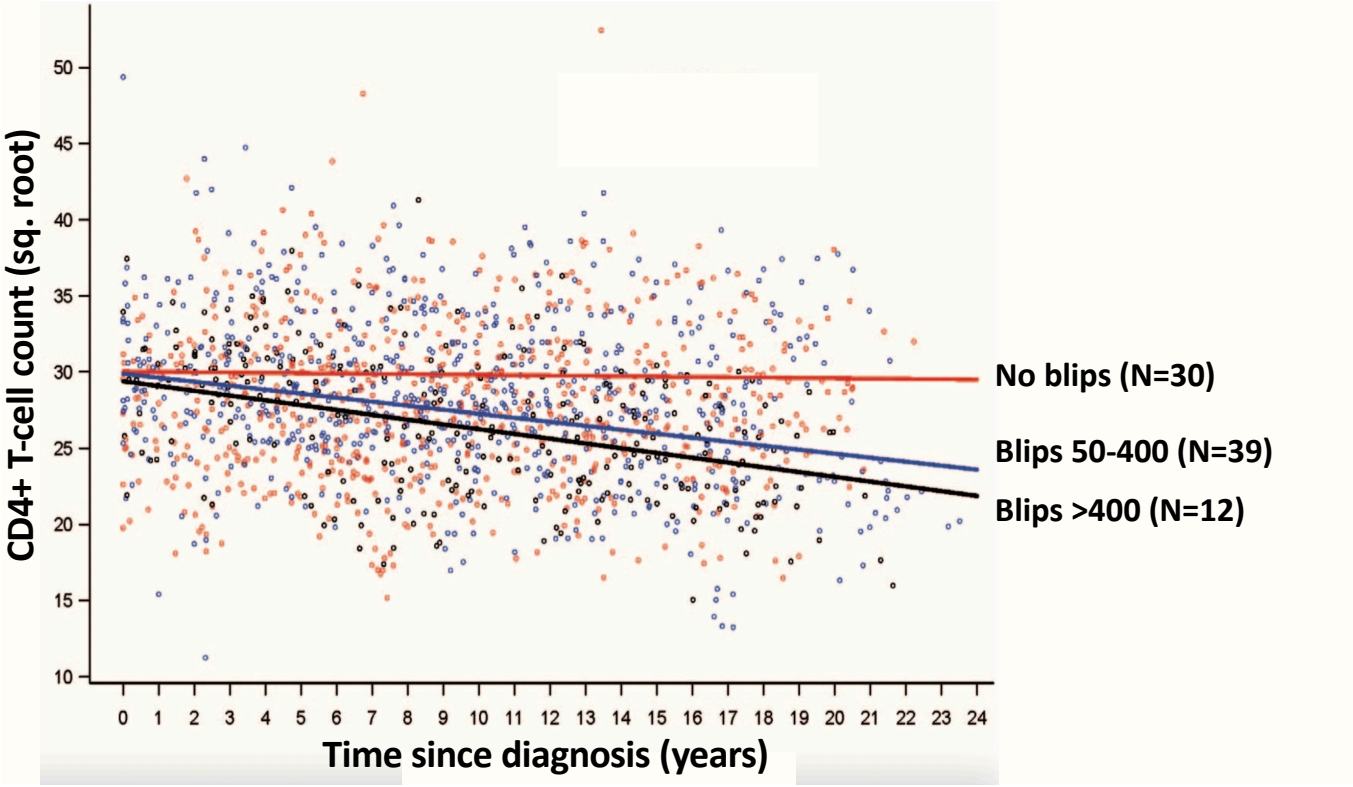
- Residual viremia found in most EC
- HIV RNA levels higher in EC than in ART-suppressed pts
- CD4 cell decrease more common in EC with HIV RNA ≥1 c/mL



Hatano J Virol 2009; Pereyra JID 2009

Fluctuating HIV RNA Levels May Lead to CD4 Cell Decline

- 81 French HIV controllers
- Controllers with transient viremia ("blips) had more rapid CD4 cell count declines than those who had no detectable viremia

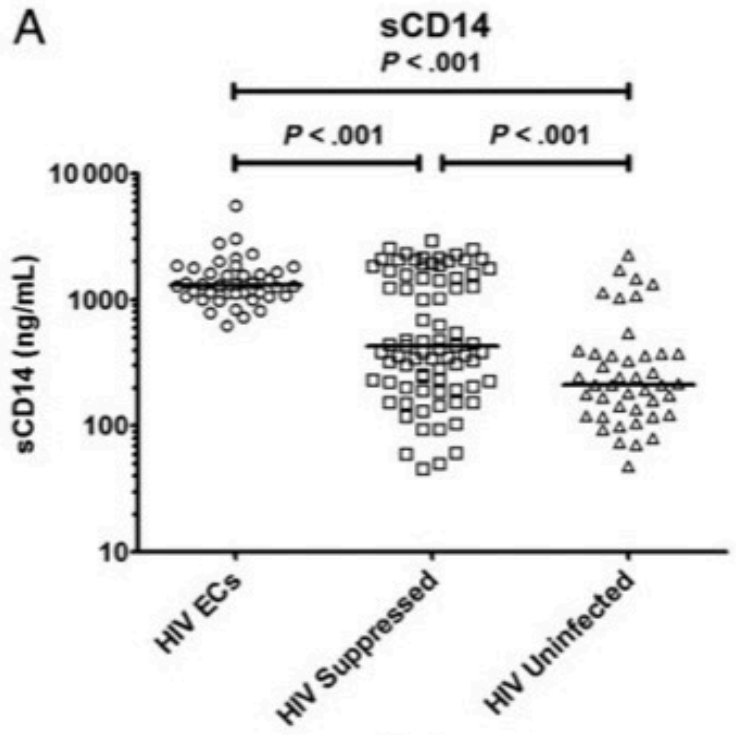


Boufassa F, PLoS One, 2011

EC have elevated levels of immune activation and inflammation

- EC have higher CD4 and CD8 T cell activation than people without HIV and higher CD8 T cell activation than ART-suppressed PWH
- EC have higher levels of inflammatory markers (sCD163, sCD14), than HIV suppressed and uninfected
- sCD14 levels associated with atherosclerosis

Monocyte/macrophage activation



Hunt P et al, JID, 2008; Li J, OFID, 2014

HIV controllers have increased atherosclerosis

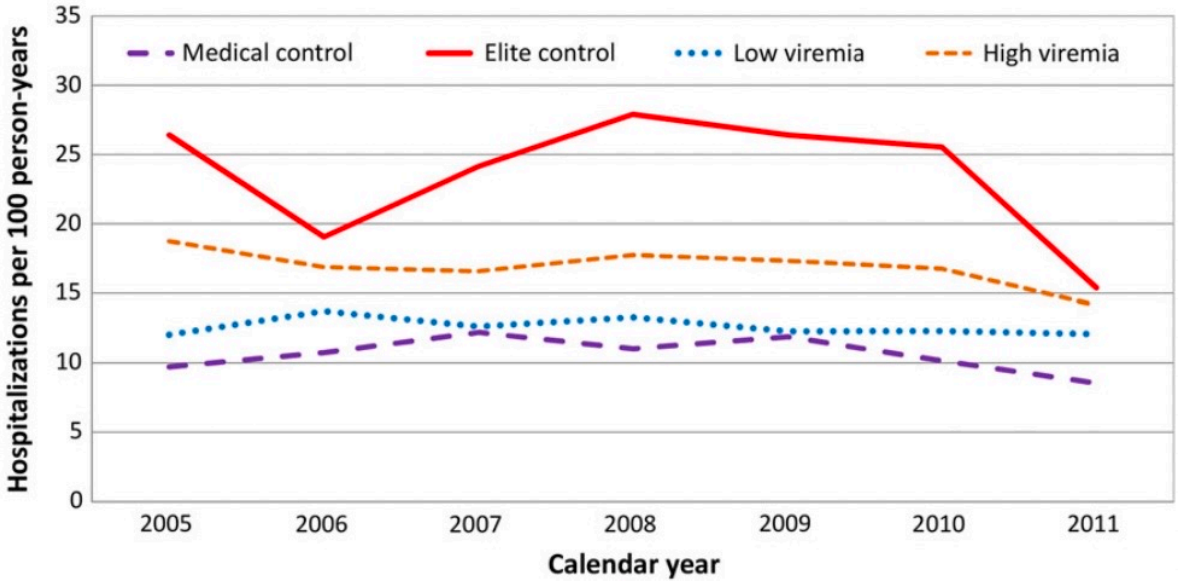
- EC more likely to have coronary plaque (on coronary CT angiography) than PWH on ART or people without HIV

	ECs N=10	HIV on ART N=103	HIV- N=49	P Value
Cor. plaque presence	78%	60%	42%	0.05
Tot. plaque segments	2.5	1	0	0.14
CAC >0	70%	41%	34%	0.11
Stenosis >50%	25%	11%	6%	0.35

Pereyra F, AIDS, 2012; Brusca R, HIV Med, 2020

HIV controllers may have higher rates of CVD hospitalization

- 149 ECs compared with PWH who have medical control with ART
- ECs hospitalized more frequently (mostly with CVD) than those with HIV who had medical control (ART)
- Other cohort studies suggest non-AIDS events mainly linked to viremic controller phenotype, CD4 nadir, age



Crowell T, JID, 2015; Noel N, Lancet HIV, 2019

Are EC a good model for a functional cure?

- Functional cure: long-term control of HIV replication in absence of ART
- However, some EC have higher levels of residual viremia, abnormal immune activation and inflammation, which may lead to CD4 decline and, possibly, clinical events
- What type of functional cure is needed? Long-term control of HIV replication in absence of ART with normal levels of immune activation and inflammation and maintenance of health

Lesson #2 from Elite Controllers

How do some PWH achieve HIV control? Genetic, immunologic and viral mechanisms

Are ECs a good model for HIV functional cure? Partially. Need to achieve viral control with normal inflammation

Should elite controllers be treated with ART?

Lessons from elite controllers for HIV cure research

Outline

Why do some people have undetectable HIV RNA even without being on ART?

Are elite controllers a good model for HIV functional cure?

Should elite controllers be treated with ART?

Lessons from elite controllers for HIV cure research

Case Scenario

- 45 yo M, family history of CAD
- 2004: diagnosed with HIV
- 2004-2009: CD4 >1000, VL <50
- 2009-2018:
  - Intermittent viremia (VL 50-200)
- 2019:
  - VL: 150; CD4 510
  - CD4:CD8 ratio 0.8

Would you recommend starting ART?

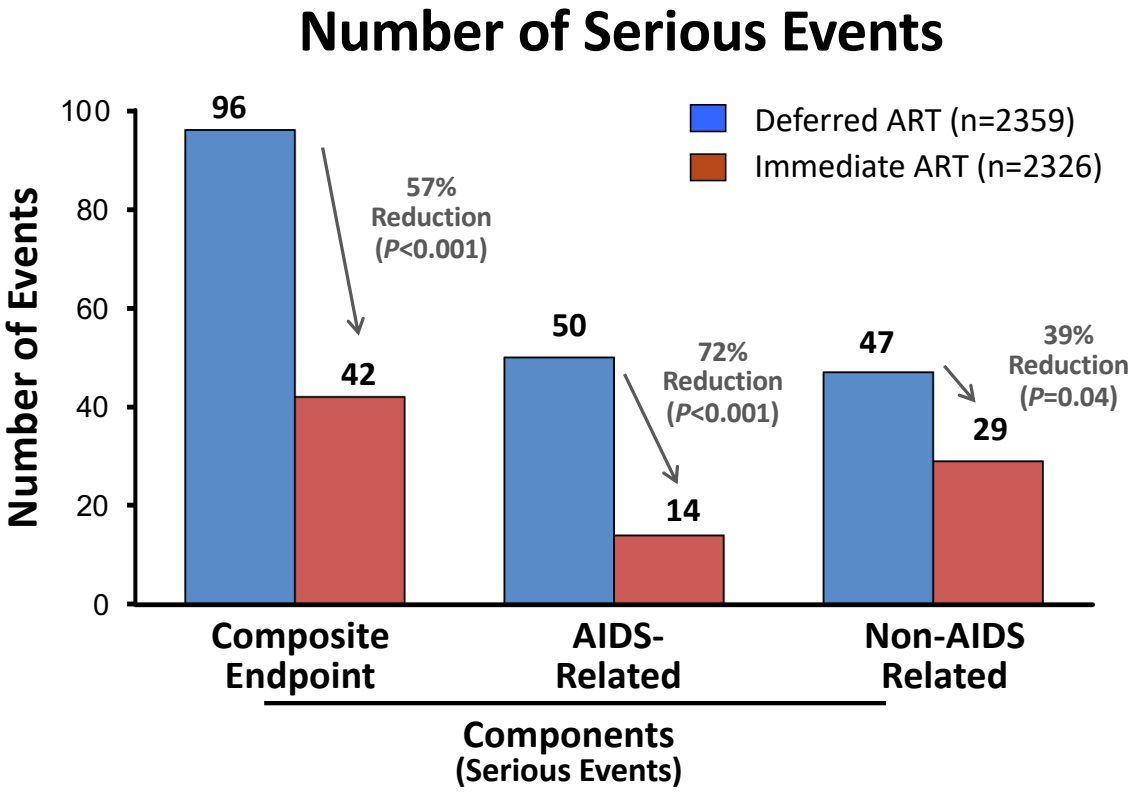
1. Yes
2. No
3. Only if CD4 < 500 or VL >200
4. Not sure

HIV Therapy Recommended Regardless of CD4: START

- PWH with CD4 >500
- Randomized to immediate or deferred ART

Who was in START?

- Median baseline CD4: 651
- Median HIV RNA: ≃13,000 (IQR ≃ 3000, 43,000)

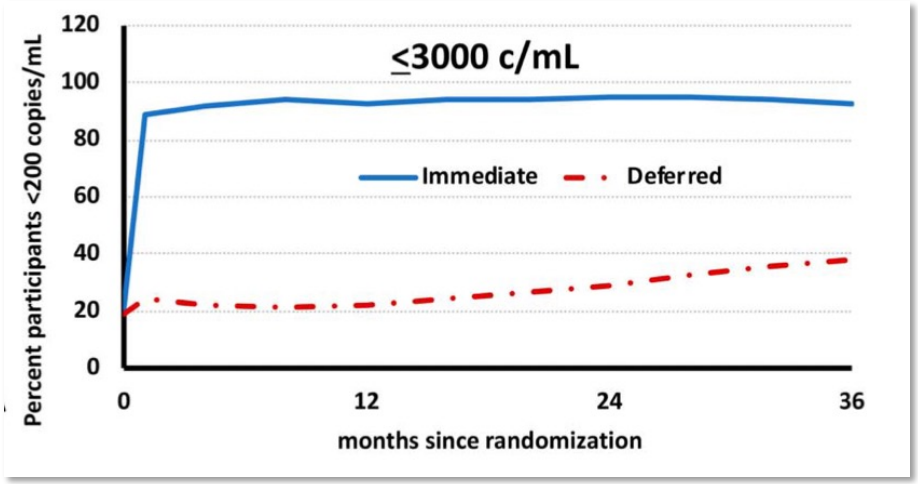


Lundgren/INSIGHT START Study Group N Engl J Med 2015; Borges CROI 2016, #160; Molina International AIDS Conference 2016, Abstract THAB0201

Do the START results apply to HIV controllers?

Starting ART has virologic benefits

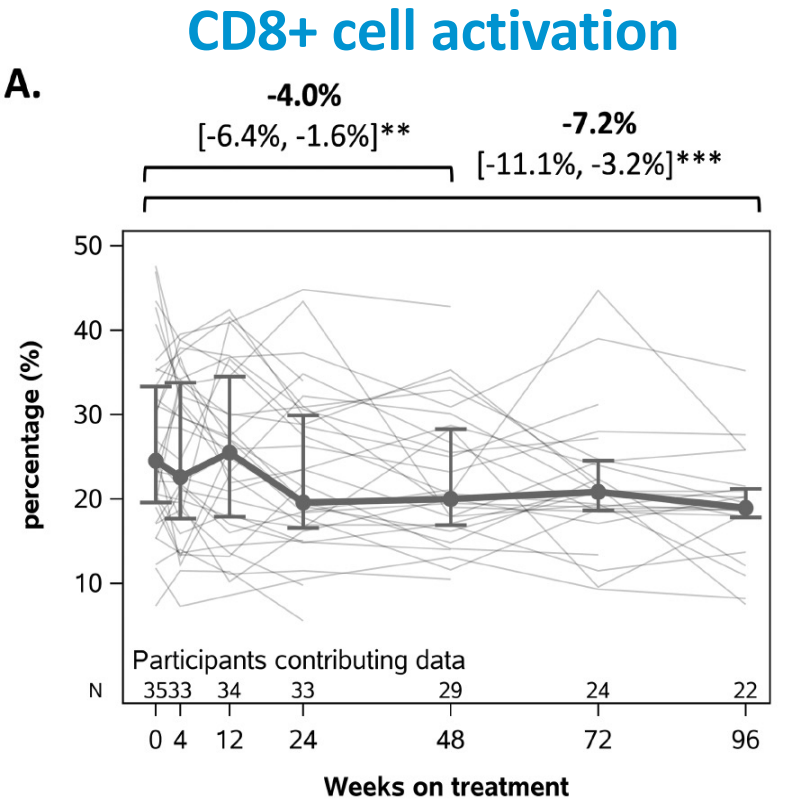
- Subset of START: participants with VL <3000 (n=1,134)
  - N=93 VL <50
- Virologic benefit: immediate group had greater time with virologic suppression (projected to decrease transmission)
- Number of participants too small to assess clinical outcomes
  - 64 events in immediate group
  - 61 events in deferred group



Sereti I, JAIDS, 2019

ACTG A5308: ART Reduces Residual Viremia and Immune Activation in HIV Controllers

- HIV controllers (n=35; 11 EC) treated with Rilpivirine/FTC/TDF
- More individuals with undetectable residual viremia after starting ART (Pre: 19%; Post: 94%)
- Significant decline in CD8+ cell activation
- Decreased markers of immune exhaustion



Li J, CID, 2020

Should we treat HIV controllers with ART?

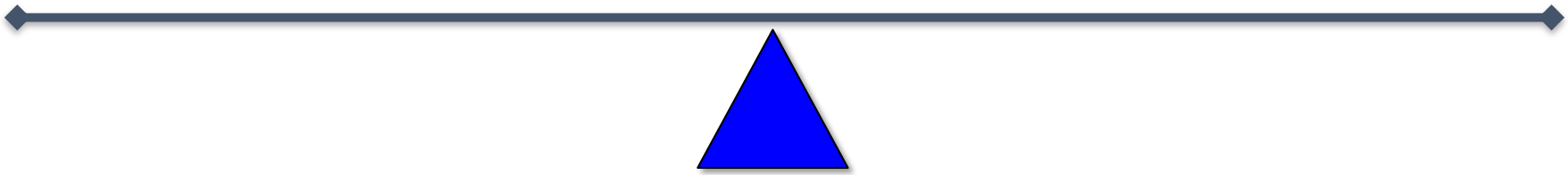
What do the guidelines say?

- US DHHS guidelines:
  - ART recommended if CD4 is declining or HIV-related complications
  - “Clear rationale for prescribing ART to elite controllers even in the absence of detectable plasma HIV RNA levels”

Should HIV Elite Controllers (EC) Receive ART?

Reasons to not start ART

- Drug toxicities
- Risk of drug resistance if patient non-adherent
- Cost of ART
- No proof that ART prevents complications



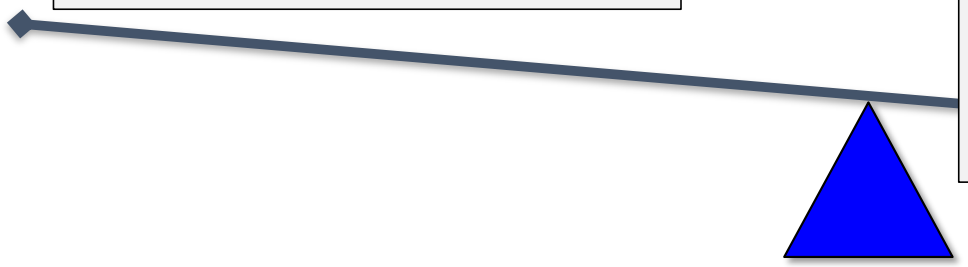
Should HIV Elite Controllers (EC) Receive ART?

Reasons to not start ART

- Drug toxicities
- Risk of drug resistance if patient non-adherent
- Cost of ART
- No proof that ART prevents complications

Reasons to start ART

- EC have higher HIV RNA levels, immune activation and inflammation than ART-treated patients – ongoing replication
- Some EC may have higher rates of atherosclerosis and hospitalization for CVD than ART-treated patients
- Some EC develop low CD4 counts, low CD4/CD8 ratio
- Treating EC decreases immune activation



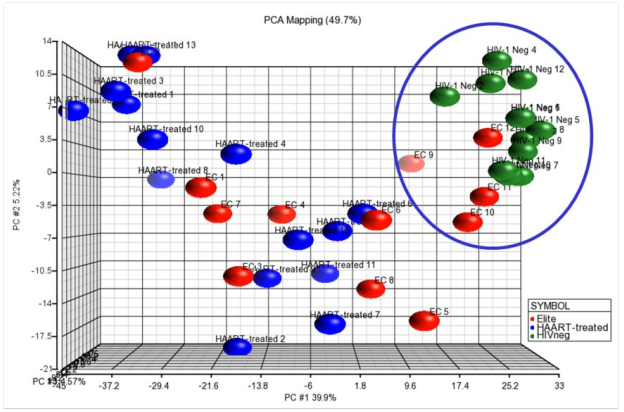
Landay AIDS 2014; Dinoso CID 2008; Chun JID 2013; Pereyra AIDS 2012; Crowell JID 2015; Hatano PLoS Pathogens 2013; Kim JAIDS 2014

Should EC be treated? My Take

- Some EC have “quiescent” phenotype
  - Higher and stable CD4 count
  - Consistently undetectable VL
  - Lower HIV RNA (ultrasensitive assays)
- Other EC have more “active” phenotype
  - Decreased CD4; elevated CD8; decreased CD4:CD8 ratio. Elevated CRP
  - Intermittently detectable VL
  - Different transcriptional profile: immune activation, cytokine genes

Canoui E, OFID, 2017

Transcriptional profiling: distinct EC subgroups



Vigneault et al, J Virol 2011

- I recommend treatment to latter group, citing theoretic rationale
- EC who are not treated must be monitored – may lose control of HIV→ declining CD4 counts, complications

Lesson #3 from Elite Controllers

Why do some people have undetectable HIV RNA even without being on ART?

Are elite controllers a good model for HIV functional cure?

Should elite controllers be treated with ART?
In most cases, yes -- after discussion

Lessons from elite controllers for HIV cure research

Outline

Why do some people have undetectable HIV RNA even without being on ART?

Are elite controllers a good model for HIV functional cure?

Should elite controllers be treated with ART?

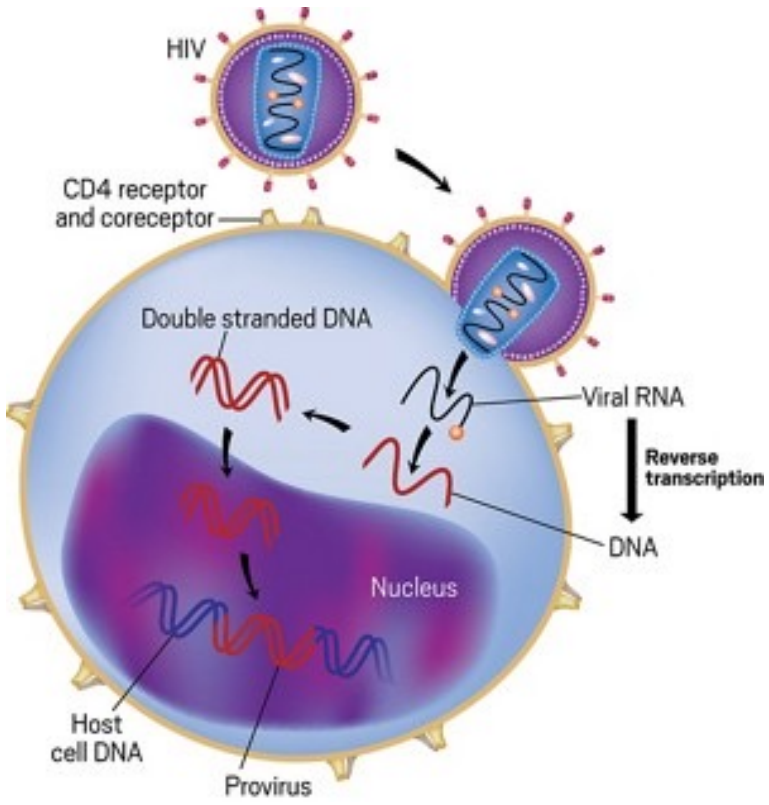
Lessons from elite controllers for HIV cure research

What will it take to cure HIV?

- How do we accurately measure the HIV reservoir?
- How do we prevent rebound from the HIV reservoir when ART is stopped?
  - ART-free remission

What is Best Method to Measure the HIV Reservoir?

- HIV proviruses: HIV integrated into human DNA
- HIV proviruses persist even when the plasma HIV RNA (viral load) is undetectable during ART
- Two types of proviruses distinguished by intact proviral DNA assay (IPDA)
  - Intact: potentially replication competent, able to lead to rebound when ART stopped
  - Defective proviruses: not replication competent, do not lead to viral rebound



https://cen.acs.org/biological-chemistry/infectious-disease/new-test-helps-researchers-track/97/i5

Intact Proviruses decline over time on ART, whereas defective proviruses do not

JCI insight

Differential decay of intact and defective proviral DNA in HIV-1–infected individuals on suppressive antiretroviral therapy

Michael J. Peluso, … , Gregory M. Laird, Steven G. Deeks

JCI The Journal of Clinical Investigation

Longitudinal study reveals HIV-1–infected CD4+ T cell dynamics during long-term antiretroviral therapy

Annukka A.R. Antar, … , Ya-Chi Ho, Robert F. Siliciano

The Journal of Infectious Diseases

MAJOR ARTICLE

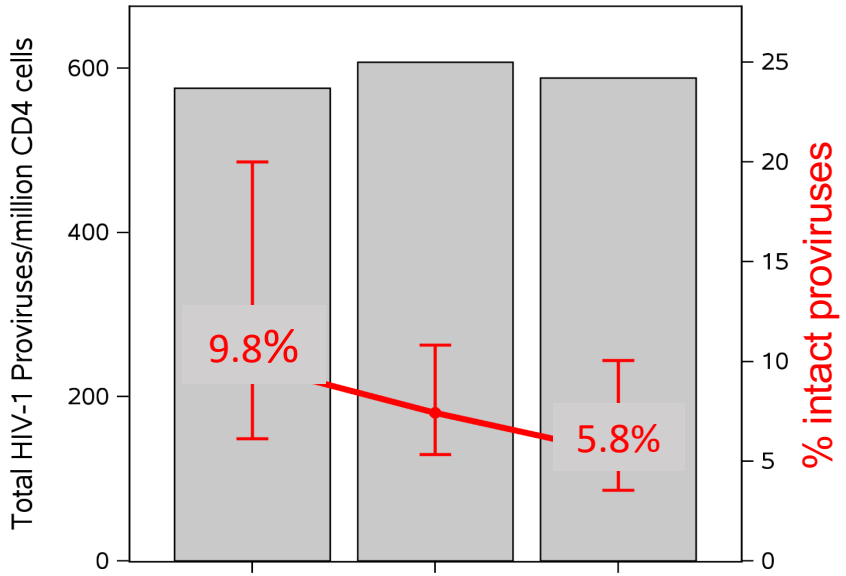
IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Selective Decay of Intact HIV-1 Proviral DNA on Antiretroviral Therapy

Rajesh T. Gandhi,[1] Joshua C. Cyktor,[2] Ronald J. Bosch,[3] Hanna Mar,[3] Gregory M. Laird,[4] Albine Martin,[4] Ann C. Collier,[5] Sharon A. Riddler,[2,6] Bernard J. Macatangay,[2,6] Charles R. Rinaldo,[6,7] Joseph J. Eron,[8] Janet D. Siliciano,[9] Deborah K. McMahon,[2,6] and John W. Mellors[2]; AIDS Clinical Trials Group A5321 Team

Peluso/Deeks JCI Insight 2020; Antar/Siliciano JCI 2020; Gandhi/Mellors JID 2021

Intact Proviruses decline over time on ART, whereas defective proviruses do not



Gandhi RT/Mellors J, JID, 2021

How Do Intact Proviruses Change in PWH Over Two Decades of ART?

The Journal of Infectious Diseases

JOURNAL ARTICLE CORRECTED PROOF

Varied Patterns of Decay of Intact Human Immunodeficiency Virus Type 1 Proviruses Over 2 Decades of Antiretroviral Therapy Get access ›

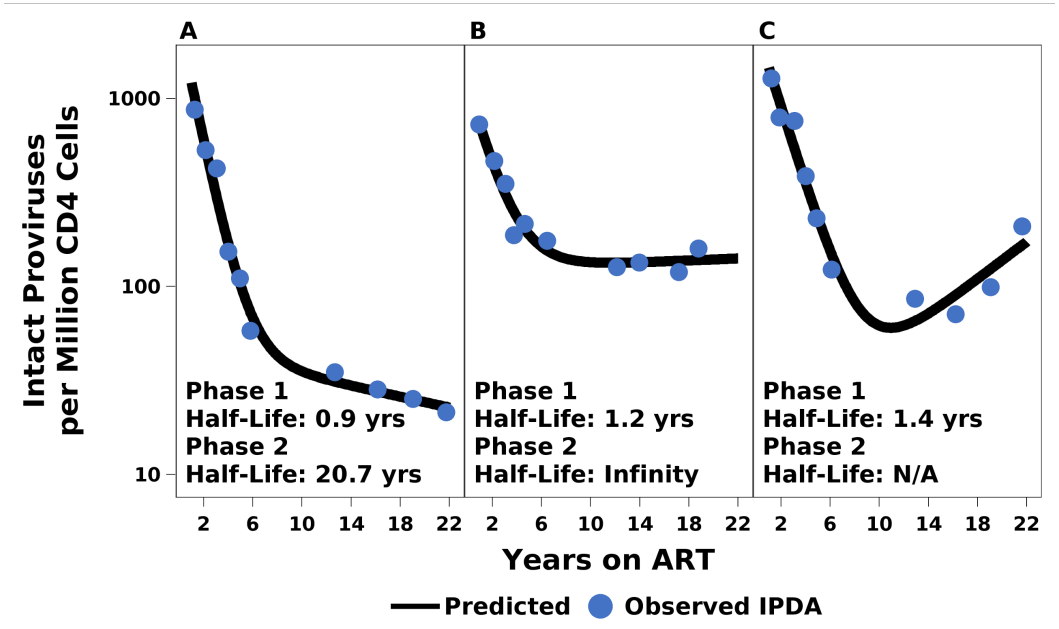
Rajesh T Gandhi ✉, Ronald J Bosch, Hanna Mar, Gregory M Laird, Elias K Halvas, Laura Hovind, Ann C Collier, Sharon A Riddler, Albine Martin, Kristen Ritter ... Show more

The Journal of Infectious Diseases, jiad039, https://doi.org/10.1093/infdis/jiad039

Published: 10 February 2023 **Article history** ▾

Over two decades of ART, rapid initial decline in intact proviruses slows and sometimes reverses

- Initial rapid decline followed by plateau (n=8 : Patterns A and B).
- Initial decline followed by late increases (n=2; both female, age >60 years) Pattern C).



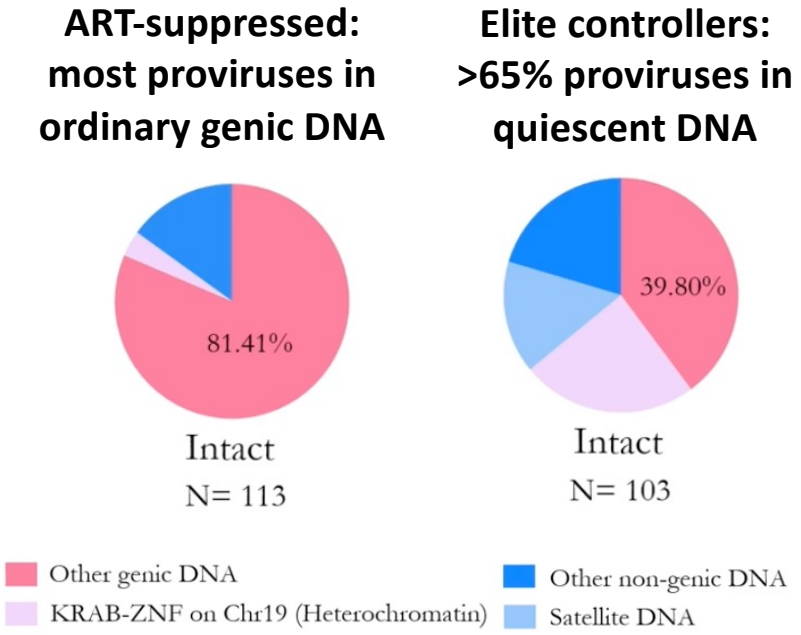
Gandhi RT et al, JID 2023

Implications for Cure Studies

- During first few years of ART, intact HIV proviral decay is rapid (half-life 1 year) and there is selective decay of intact proviruses
- During second decade of ART, decay of intact proviruses slows, perhaps because remaining infected cells harbor HIV in quiescent parts of genome
- Need interventions that accelerate decay of intact proviruses

Intact Proviruses in EC: Quality and Location Matter

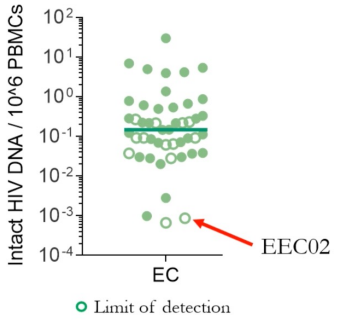
- Elite controllers more likely than ART-suppressed patients to have intact proviruses integrated into quiescent regions of genome ("gene deserts")
- Is this "blocked and locked" reservoir the basis for ART-free control in elite controllers?



Jiang C, Nature, 2020; Yu X, IAS, 2021; Cohen J, Science, 2020

Possible Sterilizing Cures: Exceptional Elite Controllers (EEC)

- California and Esperanza (Hope) patients
- No detectable intact proviruses or virus outgrowth
- Natural cures?



The Esperanza (Hope) Patient

Clinical Information

- HIV-1 infection diagnosed in 2013, treatment naive
- 8 years of recorded undetectable viremia
- 10 VL tests, none detectable

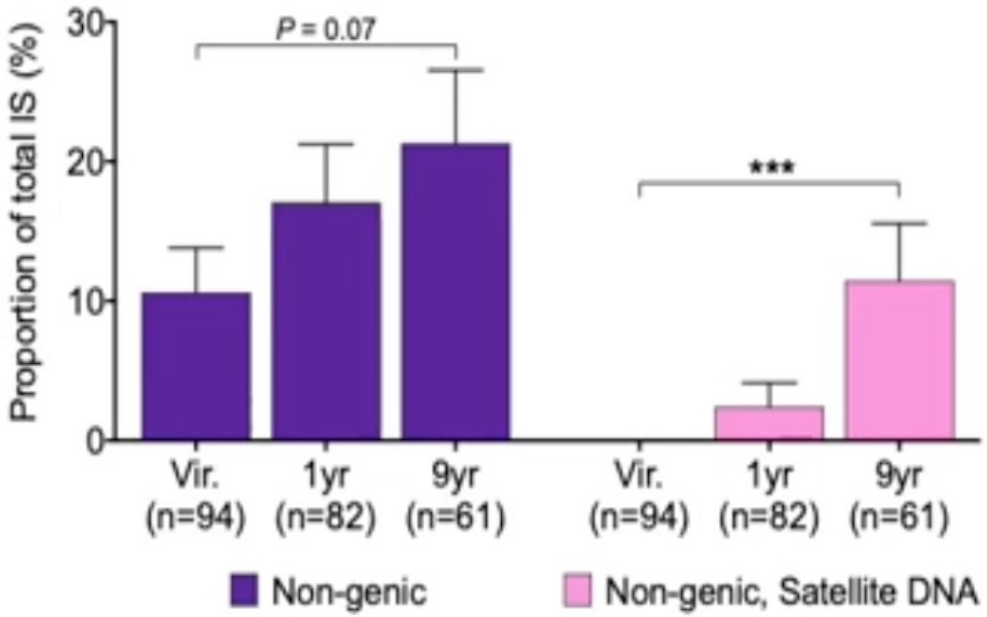
Test	Cell number	Cell type	Intact provirus	Replication competent virus
FLIP-Seq	1.19 billion	PBMC	No	
	503 million	Mononuclear cells in Placenta	No	
Viral outgrowth	150 million	Resting CD4		No

Do EEC result from loss of intact replication-competent proviruses previously present in more active regions of genome? "Autologous shock and kill"

Turk G, Ann Intern Med, 2022
Jiang C, Nature, 2020; Yu X, IAS 2021

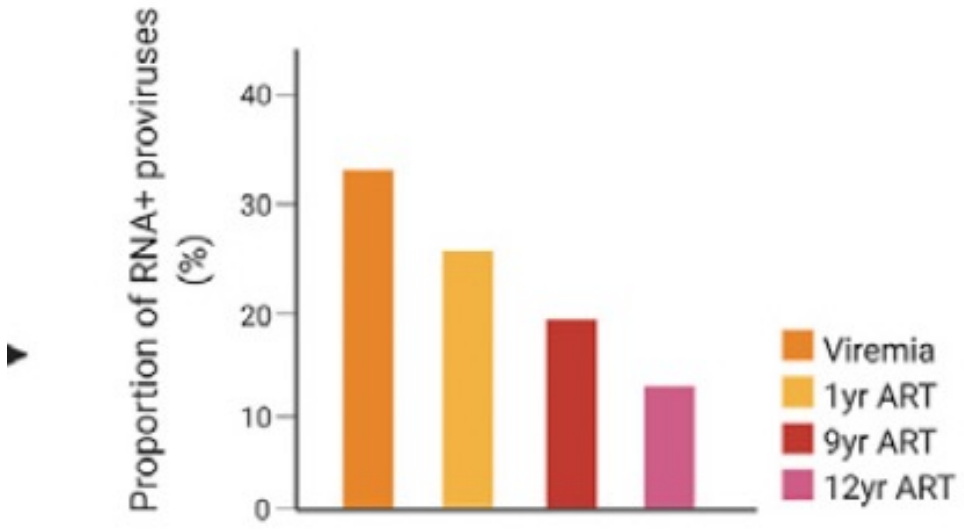
Do People on Suppressive ART Have Loss of Intact Proviruses in Transcriptionally Active Regions of the Genome?

Longitudinal enrichment of non-genic proviruses over time on ART



Einkauf K/Lichterfeld M, CROI, 2021; Coffin J, PLoS Pathogens, 2021

Transcriptionally-active proviruses are selected against during long-term ART



Can one achieve ART-free remission by inducing more quiescent reservoir by eliminating proviruses from transcriptionally active regions of genome?

Einkauf K/Lichterfeld M, Cell, 2022

Lesson #4 from Elite Controllers

Why do some people have undetectable HIV RNA even without being on ART?

Are elite controllers a good model for HIV functional cure?

Should elite controllers be treated with ART?

HIV reservoir in ECs and some ART suppressed PWH may be in quiescent parts of the genome

Conclusions

HIV control is based on genetic, immunologic and viral factors

Elite controllers control HIV replication but have elevated levels of immune activation and inflammation

ART reduces immune activation in HIV controllers and should be considered for theoretic reasons

To cure HIV, need interventions that eliminate virus or induce quiescent reservoirs. Refer HIV controllers to research studies

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Thank You for Your Attendance!
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