How Do We Manage Elite Controllers?

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Case Scenario

- 61 yo male with no significant PMH presenting to establish care for HIV
- No acute complaints
- Four months ago he presented to his PCP for penile pain
- HIV 4th generation was positive
- Risk factors included MSM, anal receptive intercourse with multiple partners
  - Unknown HIV statuses

Physical Examination

- General: Obese, pleasant
- HEENT: no oral thrush or lymphadenopathy
- Cardio: No murmurs, rubs or gallops
- Respiratory: Clear breath sounds bilaterally
- Abdomen: Soft, non distended
- Extremities: Peripheral pulses present
- Skin: No rashes

HIV Diagnosis at Time of Initial Encounter

- HIV 1: reactive
- HIV 1 VL: <20 copies
- No CD4 available at this time

Any Questions So far?

What Do We Do In These Situations?

Introduction

- In the last decade, the strategy for timing of initiation of ART for the treatment of HIV has shifted from a cutoff CD4 T cell count to immediate initiation
  - Result of better tolerated ART options and multiple clinical trials
  - Leads to diminished HIV transmission in sero-discordant couples

- Beneficial course for “Elite Controllers” is less clear

Promer K, Karris MY. Current Treatment Options for HIV Elite Controllers: a Review. Curr Treat Options Infect Dis. 2018;10(2):302–309. doi:10.1007/s40506-018-0158-8

Elite Controllers

- Maintain undetectable viral load and CD4 T cell counts above 200 in routine assays in the absence of ART
  - Undetectable VLs for at least 6-12 months or undetectable VLs on at least 90% of measurements over 10 years
  - Estimated prevalence ranges from 0.15 to 1.5% of all PLWH
- “Viremic controllers” – maintain RNA cutoff of 2000 copies/mL
- “Long-term non-progressors” – refers to immunological control with a CD4 T cell count of at least 500 cells over more than 8 years
- Somehow managed to naturally control HIV in the absence of medications

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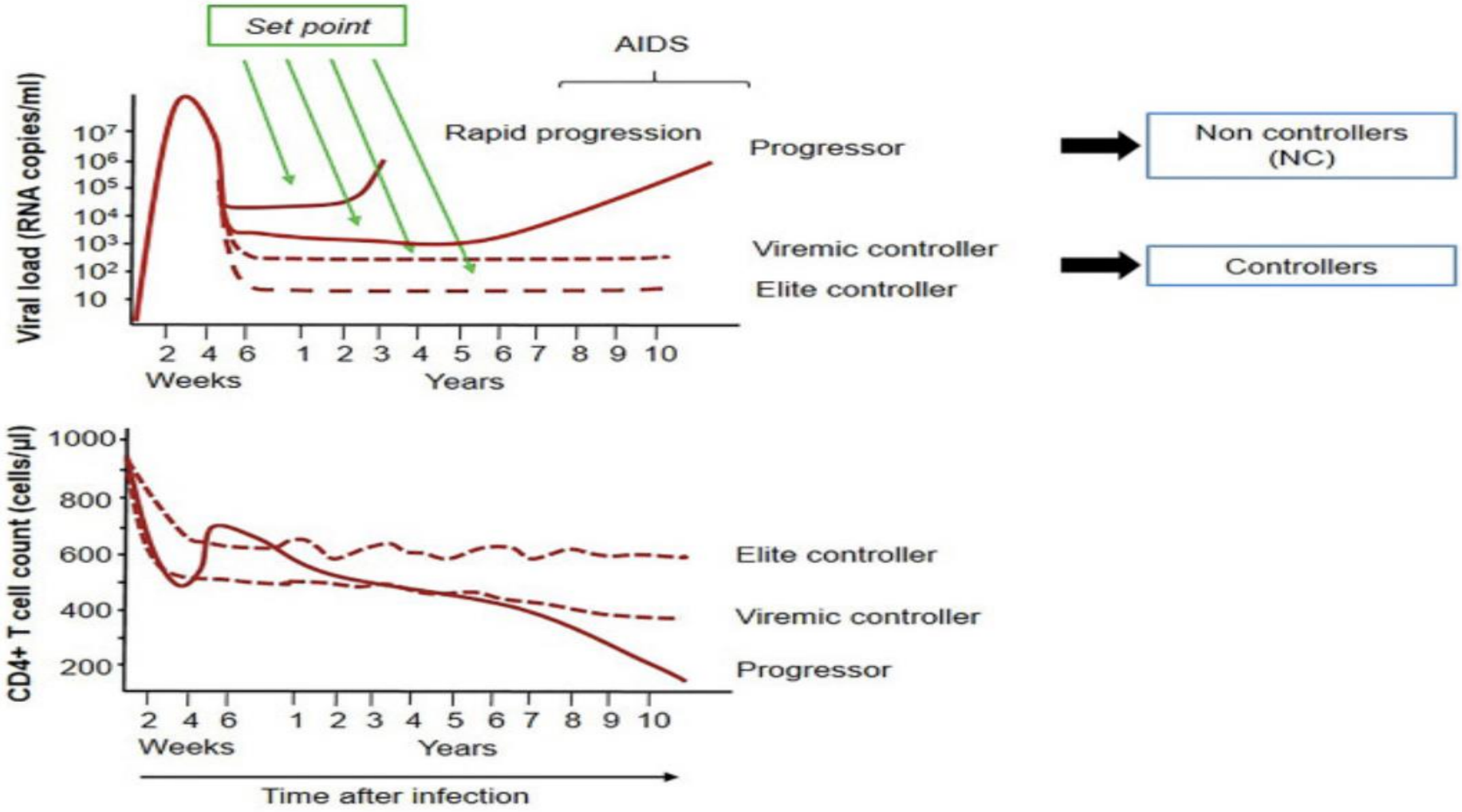
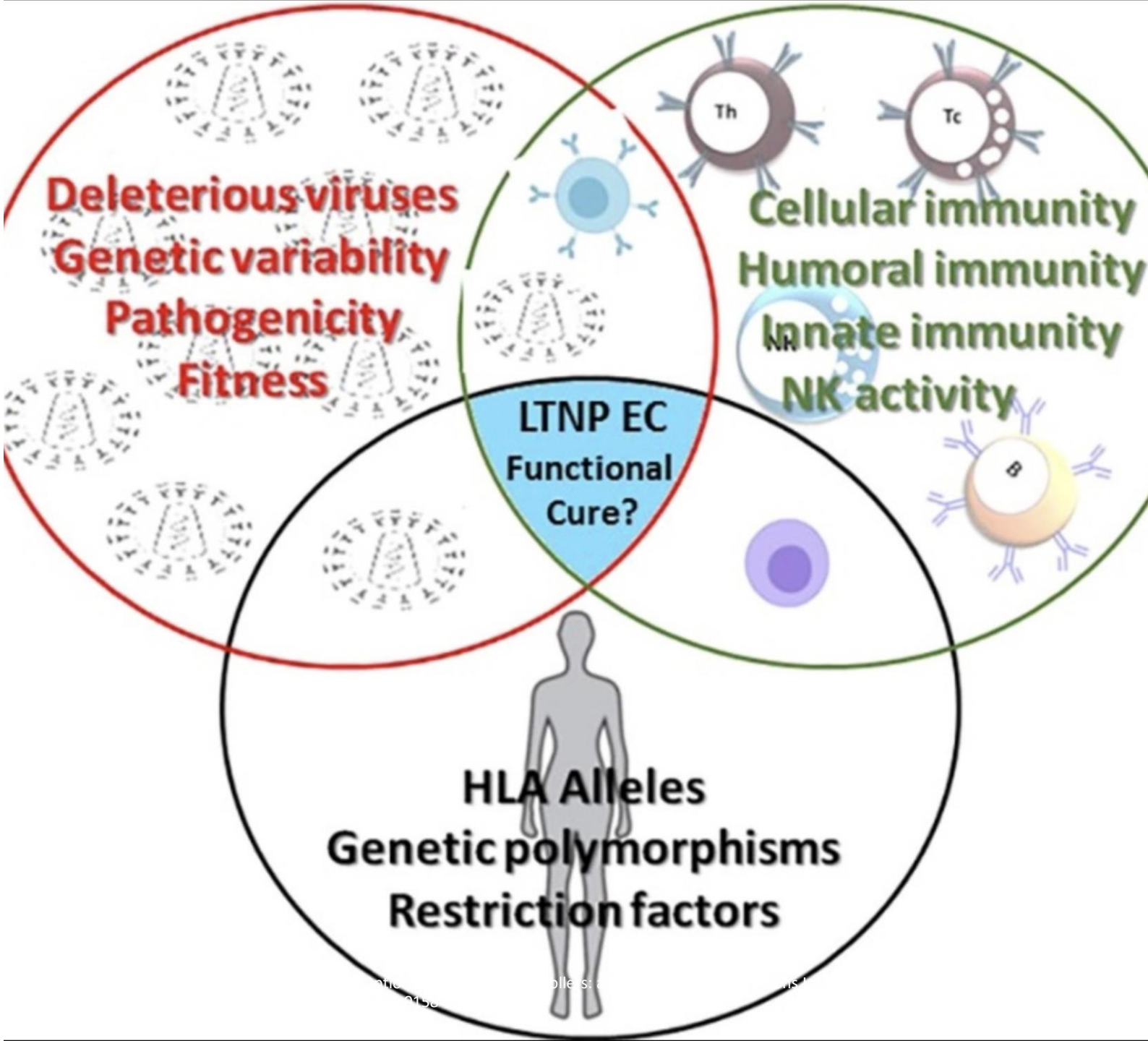
Gonzalo-Gil E, Ikediobi U, Sutton RE. Mechanisms of Virologic Control and Clinical Characteristics of HIV+ Elite/Viremic Controllers. *Yale J Biol Med*. 2017;90(2):245–259. Published 2017 Jun 23.


Set point
AIDS
Viral load (RNA copies/ml)
10^7
10^6
10^5
10^4
10^3
10^2
10
Rapid progression
Progressor
Viremic controller
Elite controller
Non controllers (NC)
Controllers
2 4 6 1 2 3 4 5 6 7 8 9 10
Weeks
Years
CD4+ T cell count (cells/µl)
1000
800
600
400
200
Elite controller
Viremic controller
Progressor
2 4 6 1 2 3 4 5 6 7 8 9 10
Weeks
Years
Time after infection

Characteristics of Elite Controllers



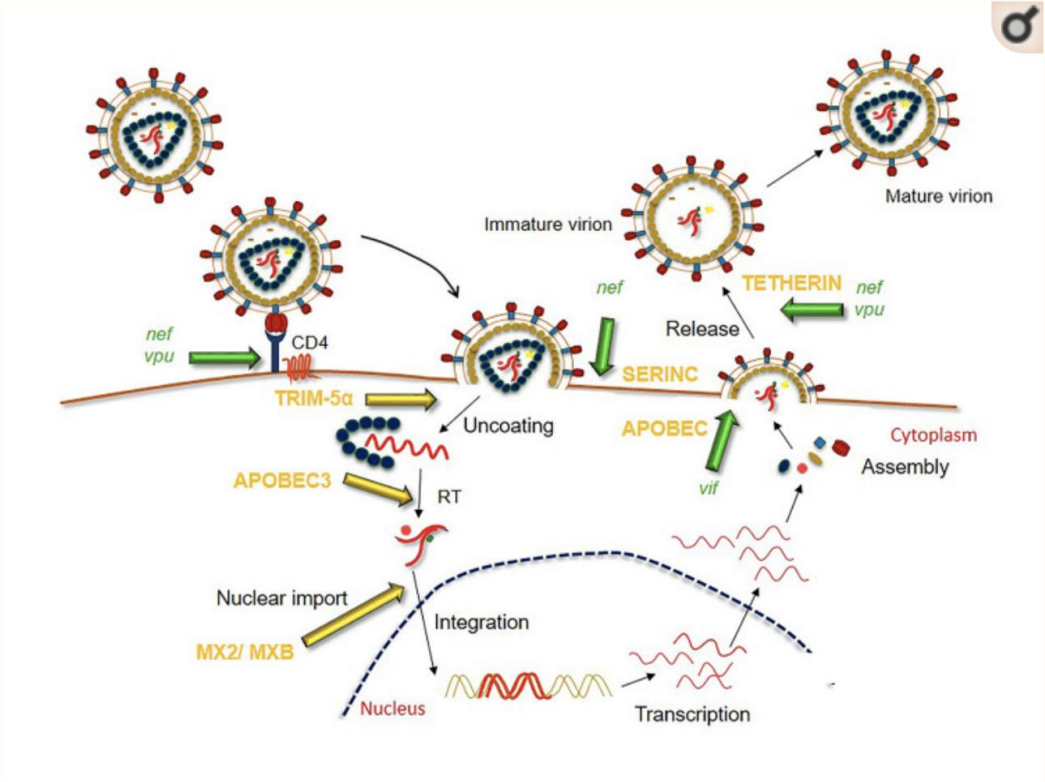


Figure 4

Host restriction factors and lentiviral proteins in HIV replication.

Table 1

Viral proteins and host restriction factors implicated in control in HIV-1 VCs/ECs.

Viral protein/ Host factor	Mechanism of action	[ref]
nef	• Downregulates surface levels of MHC-I and MHC-II	[32,138-140]
	• Modulates TCR signaling by inducing/ blocking NFAT and IL-2 production in fresh/ activated T cells, respectively	
	• Prevents incorporation of SERINC-3 and SERINC-5 into HIV-1 virions, enhancing infectivity of the virus	
vpu	• Downregulates CD4, and BST-2/tetherin	[30,141,142]
vif	• Binds to and blocks the antiviral activity of APOBEC3 proteins, in conjunction with other host factors, inducing their proteasomal degradation	[143]
TRIM-5α	• Binds to and multimerizes on the viral capsid, somehow inhibiting viral replication	[27]
	• Initiates innate immune sensing of cytosolic viral capsid	
	• Counteracted by mutations in viral capsid	
Mx2/MxB	• Delays HIV-1 DNA nuclear import and integration by targeting viral capsid, exact mechanism of action uncertain	[31,144]
	• Counteracted by mutations in viral capsid	
APOBEC3 family members	• Inhibits viral reverse transcription and integration	[28]
	• Induces lethal mutations in viral cDNA	
	• Counteracted by *vif* (see above)	
Tetherin	• Inhibits HIV-1 release by binding virus particles that bud through the cell membrane	[30,145]
	• Counteracted by *vpu* (see above)	
Serinc-3/5	• Inhibit HIV-1 particle infectivity	[32]
	• Counteracted by *nef* (see above)	

MHC: major histocompatibility complex; TCR: T Cell Receptor; NFAT: nuclear factor of activated T-cells; BST-2: bone marrow stromal antigen 2; APOBEC: apolipoprotein B mRNA editing enzyme 3 catalytic polypeptide; Mx2/McB: myxovirus resistance protein 2; BST-2: bone marrow stromal antigen 2.

Cellular Immune Responses

- Strong correlation with viral control and cellular and immune responses in humans
- Tight association between Gag-specific cytotoxic T lymphocyte responses and viral control
- HIV-1 specific CD8 T cell responses against viral structural proteins are inversely correlated to set point levels of viral RNA
- If CD4 T cells from elite controllers are intrinsically more resistant to HIV investigation remains controversial

Table 2

Genetic alleles associated with HIV control.

Genes	Author	Journal, year [ref]
HLA-DRB1*13	Malhotra, U. et al	J Clin Invest, 2001 [146]
	Chen, Y. et al	Hum Immunol, 1997 [147]
MICB, TNF, RDBP, BAT1-5, PSORSICI, HLA-C	Limou, S. et al	J Infect Dis., 2009 [148]
HLA-B57, HLA-C	Fellay, J. et al	Science, 2007 [105]
	Trachtenberg, E. et al	Genes Immun, 2009 [107]
HLA-B57, HLA-B27	Pereyra, F. et al	Science, 2010 [51]
HLA-DRB1*13 and/or HLA-DRB1*06	Ferre, AL. et al	J Virol, 2010 [149]
HCP5, HLA-C	Han, Y. et al	AIDS, 2008 [108]
HLA-B57	Tang, Y. et al	AIDS, 2010 [109]
	Migueles, SA. et al	J virol, 2003 [104]
	Gao, X. et al	Nat Med, 2005 [150]
	Kiepiela, P et al	Nature, 2004 [102]
	Bailey, J.R. et al	J Exp Med, 2006 [103]
HLA-A, HLA-B, CCR3	McLaren, P.J. et al	PNAS, 2015 [151]

But What Does This Mean Clinically?

Let’s Take a Look at a few clinical scenarios…

AIDS-Associated Clinical Outcomes

- In a retrospective study, Okulicz et al. found that individuals achieving elite controller status for ten years had more favorable time to AIDS and death
- Some viremia controllers did progress to AIDS and death
  - Loss of virological control and immune function can occur in some individuals
- A study of more than four hundred elite controllers revealed that 30% of them lost viral control, resulting in reduced CD4 counts

Rate and predictors of progression in elite and viremic HIV-1 controllers.

Leon A, Perez I, Ruiz-Mateos E, Benito JM, Leal M, Lopez-Galindez C, Rallon N, Alcami J, Lopez-Aldeguer J, Viciana P, Rodriguez C, Grau E, Iribarren J, Gatell JM, Garcia F, EC and Immune Pathogenesis Working group of the Spanish AIDS Research Network.

AIDS. 2016 May 15; 30(8):1209-20.

Clinical Outcomes - CVD

- CVD in PLWH – increased rates of myocardial infarctions and traditional CVD risk factors
- HIV: independent risk factor for the development of atherosclerosis
- SCOPE cohort: strong association between HIV sero-status and carotid intima-media thickness irrespective of VL, CD4 T cell count, ART and other confounders of arterial inflammation
- Despite viral suppression, elite controllers appears to have similar levels of coronary atherosclerosis to medical controllers
  - Unknown if ART in elite controllers impacts CVD risk

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Co-Infection with Hepatitis C

- Impacts elite controllers more significantly than medical controllers
- PLWH: 2.4% prevalence of co-infection with hepatitis C
  - Rate increases to 82.4% with associated IVDU
- Elite controllers have less associated fibrosis
- Compared to medical controllers, demonstrate differences in immune reactivation
  - Associated with lower CD4 and CD8 T cells and increased CD8 T cell apoptosis
  - Does not translate to loss in elite controller status
- Still no definite evidence that ART would benefit these patients

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Need for Immunosuppression?

- Limited information
- Case reports have revealed recovery of elite control after intense periods of immunosuppression without the use of ART
- Further studies are needed

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Future Direction

- Need more clinical trials to help determine optimal timing of therapy
- DHHS guidelines note the insufficient number of elite controllers in clinical trials prevents an adequate comparison of the risks and benefits of ART
  - ART should not be delayed in an effort to see if a patient is an elite controller
- These patients need to be regularly monitored for signs of loss of control, which would definitely justify initiation of ART

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Conclusion

- Little is known regarding the precise mechanisms that allow robust control of HIV infection, especially in elite controllers

- Further investigation into how controllers achieve such a high degree of virologic control may help facilitate efforts directed towards a “functional cure” for HIV, in which the virus is still present in latent reservoirs but never reaches high levels of replication, all in the absence of ART

Questions?

Thank You!