Slow burn

CLINID conference
Hunter Ratliff
02/12/2025

Ages, dates, and other identifying information may have been changed
I have no conflict of interest in relation to this presentation

Shortcuts

Case 1: Start | Summary slide

Discussion 1: Objectives

- **Defining LTNP & EC** | Natural history | compare & contrast
- **Mechanisms** | viral factors | cell mediated | humoral immunity | location of integration
- **Inflamm-aging** | CD4:CD8 ratio | monocytes | telomeres | consequences
- **Should you start ART?**

Case #1

Case 1: HPI

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- Diagnosed **7 years ago**; RF unprofessional tattoos
- Had followed at CAMC in the past (records not available for review)
    - Has **not seen CAMC in over a year**
    - Currently **not on ART**

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- **Currently asymptomatic** (ROS negative)
  - No known history of OIs

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  - Has **not seen CAMC in over a year**
  - Currently **not on ART**
- **Currently asymptomatic** (ROS negative)
  - No known history of OIs
- MFM notes indicate patient believes "**she feels fine & doesn't need ART**"
- States her two living kids and partner **are HIV negative**

Case 1: Labs

A **37 y/o F** with PMH including beta thalassemia minor, **HIV** (Dx 7 years ago, **not on ART**) who presents at **32 weeks gestation** for HIV management. Lost to follow up and not on ART because "she feels fine & doesn't need ART".

CBC	Result
WBC	7.5
Hgb	9.5
Platelets	267

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Lymph abs (%)	2320 (31%)

CD4/CD8	Result
CD8 abs (%)	???
CD4 abs (%)	???
CD4:CD8	???

HIV PCR	Result
Viral load	???
Log VL	???

Time to guess the CD4!

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CD4 abs (%)	**738** (37%)
CD4:CD8	0.8

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Viral load	**283**
Log VL	2.45

Case 1: Summary

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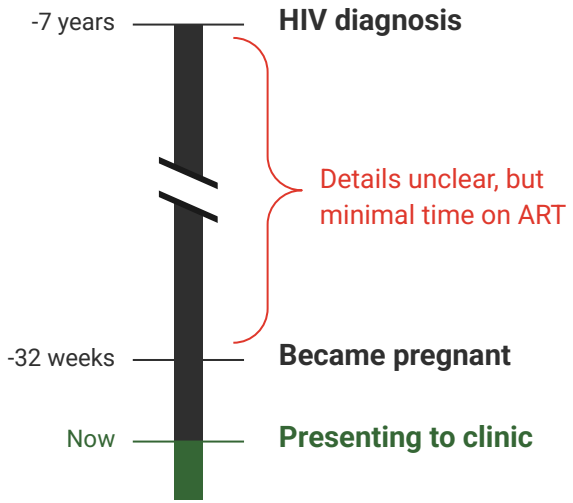
She has had **difficulty with keeping appointments** and has **not been on ART for awhile** (details unclear) because "**she feels fine** & doesn't need ART"



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Is she right?

Does she need treatment for HIV?

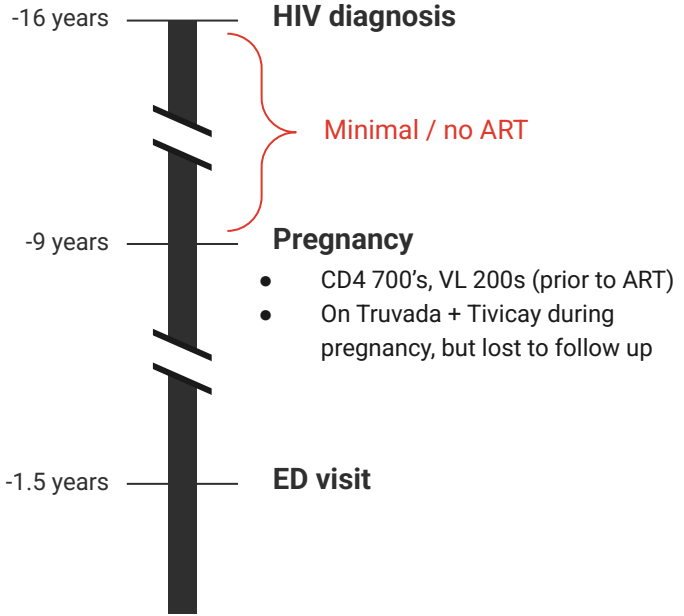
- During pregnancy?
- After pregnancy?
- Even if she doesn’t want to?

Case 1: Interim history

- Started on **Truvada + Tivicay**
  - This encounter was before Descovy was FDA approved
- Pregnancy is uneventful
- **Lost to follow up** with ID

Case 1: Interim history

- **8 years after pregnancy**, has ED visit (outside hospital)
  - CC: **Earaches** + **dry cough**
  - Duration: **few months**
  - Labs: **absolute lymphocytes were 930**
- Still not on ART



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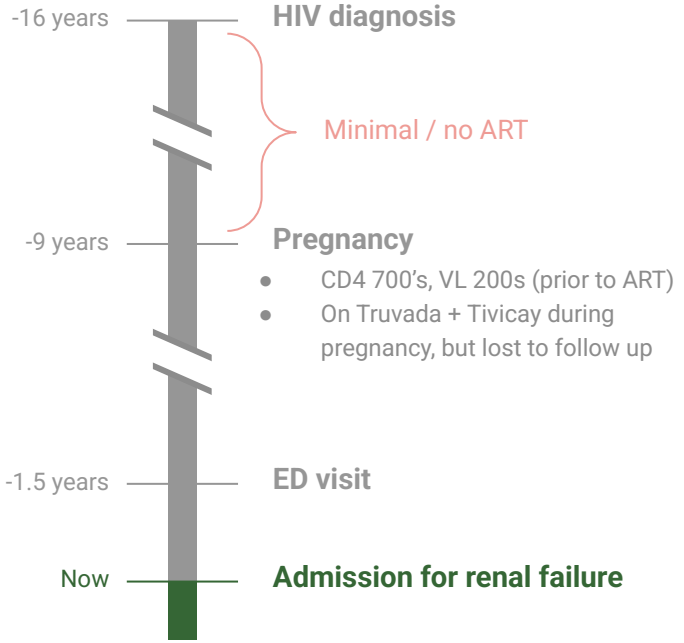
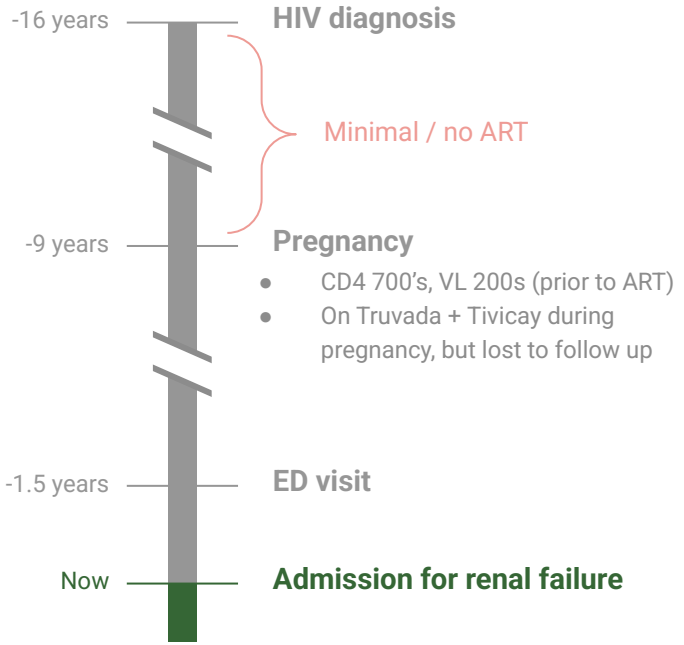
Fast forward to present day

16 years after her diagnosis of HIV, she is admitted to OSH **with AMS** & **renal failure**



Case 1: Interim history - renal failure

Admitted for **lethargy / AMS**



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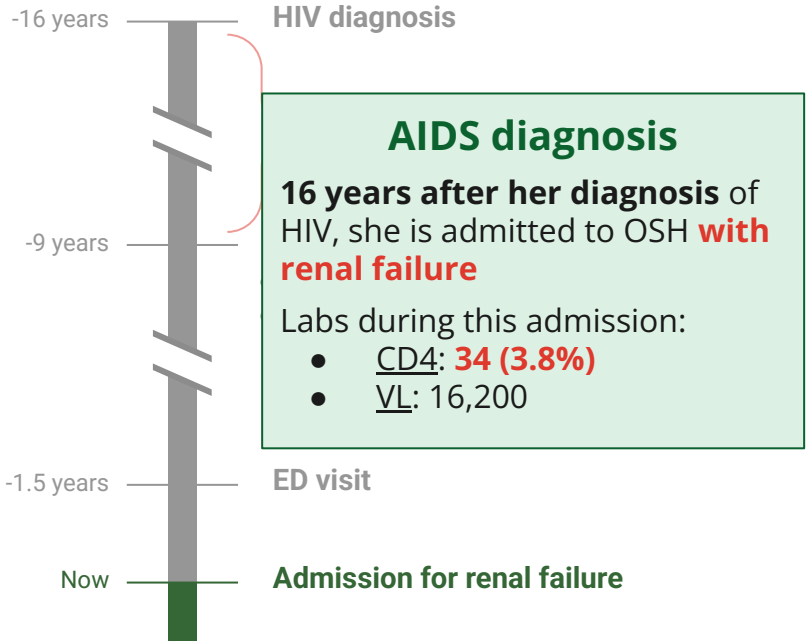

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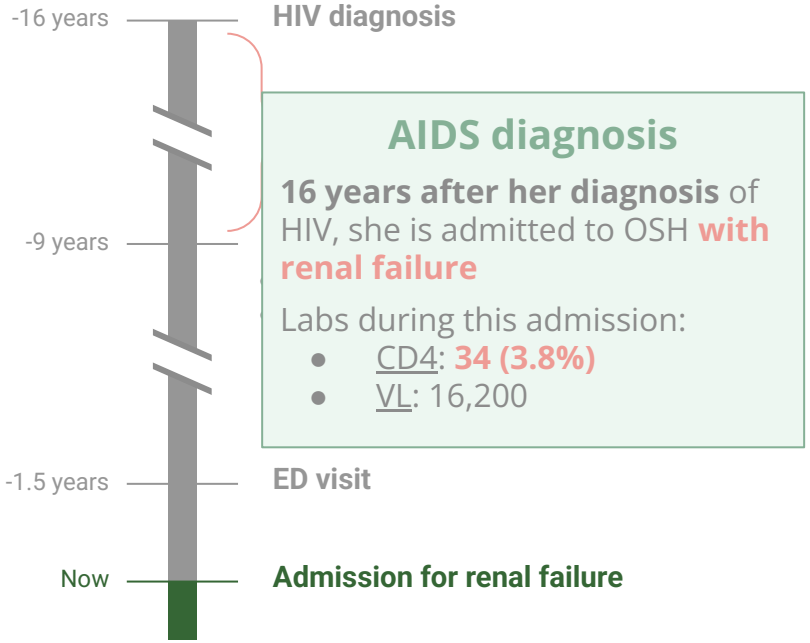
 # Renal failure / ESRD

- Found to be in renal failure
  - **Nephrotic range** proteinuria (>14g)
  - Started on iHD



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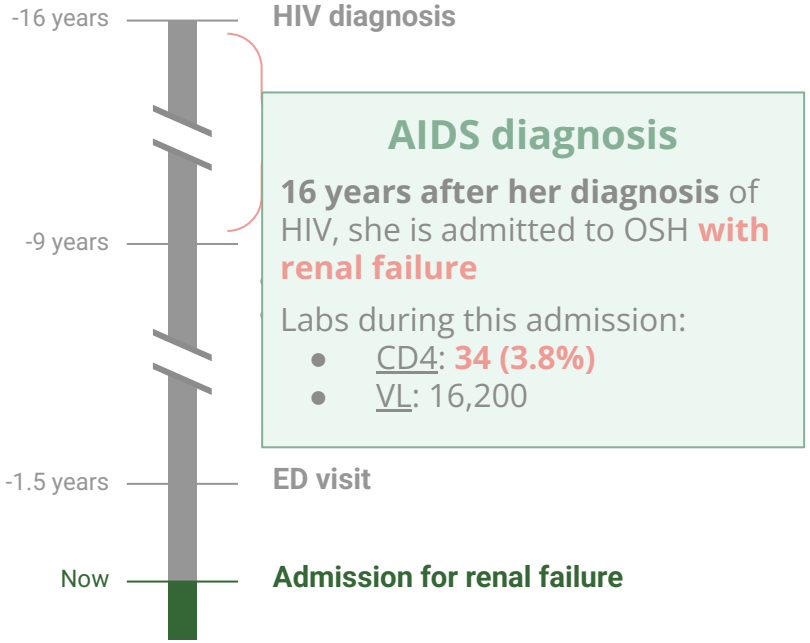
 # Anemia, thrombocytopenia (severe)

- Seen by hematology, unclear etiology
- **Had BMBx**, results not available



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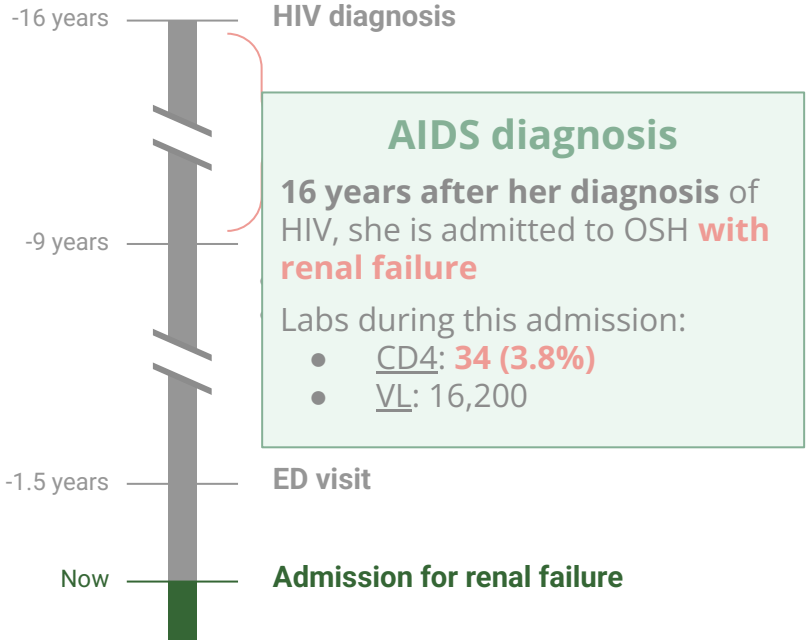

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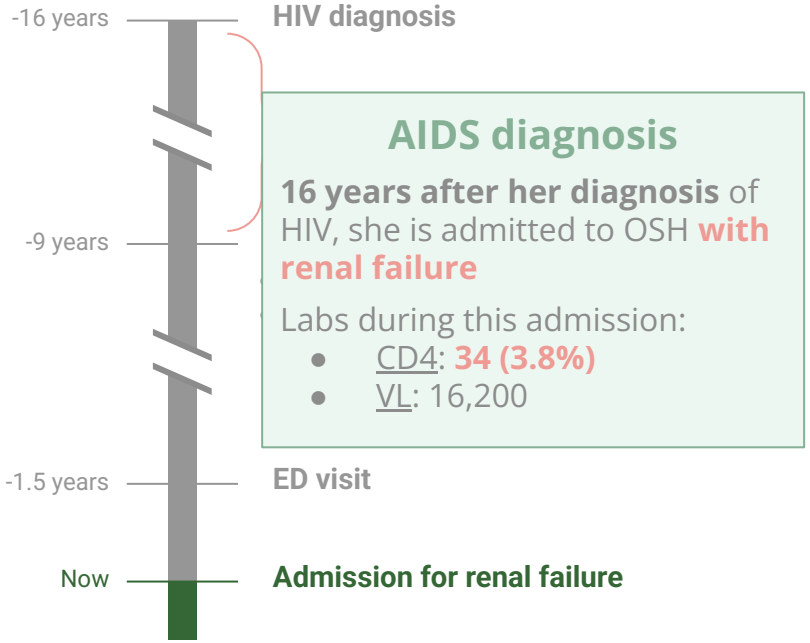
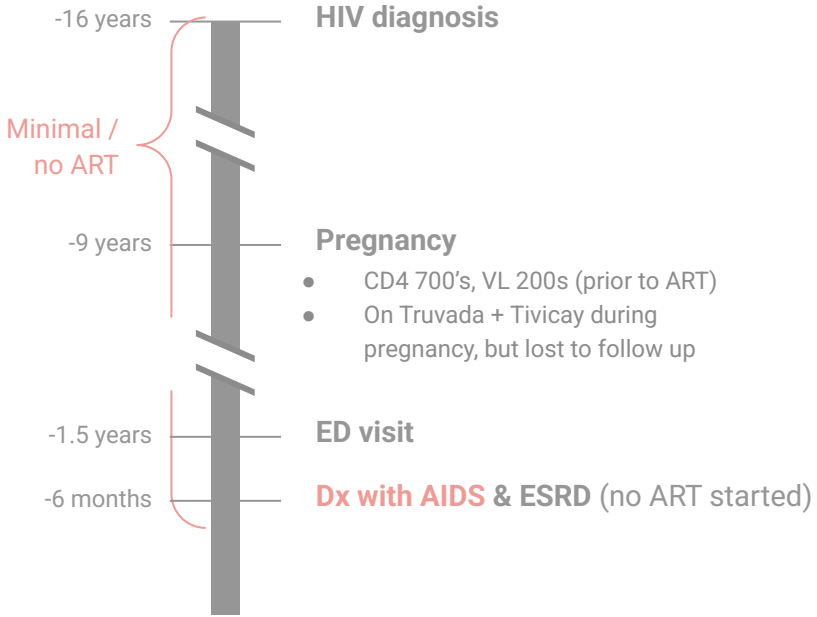
- Seen by tele-ID, said to ~~**start Biktarvy**~~
  - **Not started inpatient** (non-formulary)
- Unclear if able to get it outpatient



Case 1: Interim history

- After leaving OSH, seems like she **still has not been in care**
  - No outpatient Rx for ART



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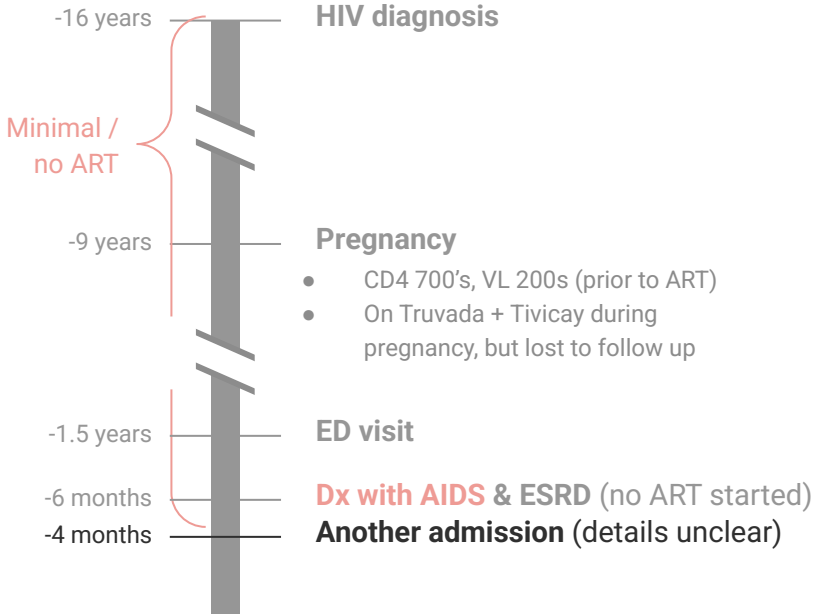
- Has **another admission for AMS** (two months after ESRD Dx)
  - Limited EMR records indicate ID saw her during this admission
  - Gets **started on Biktarvy** (for real)



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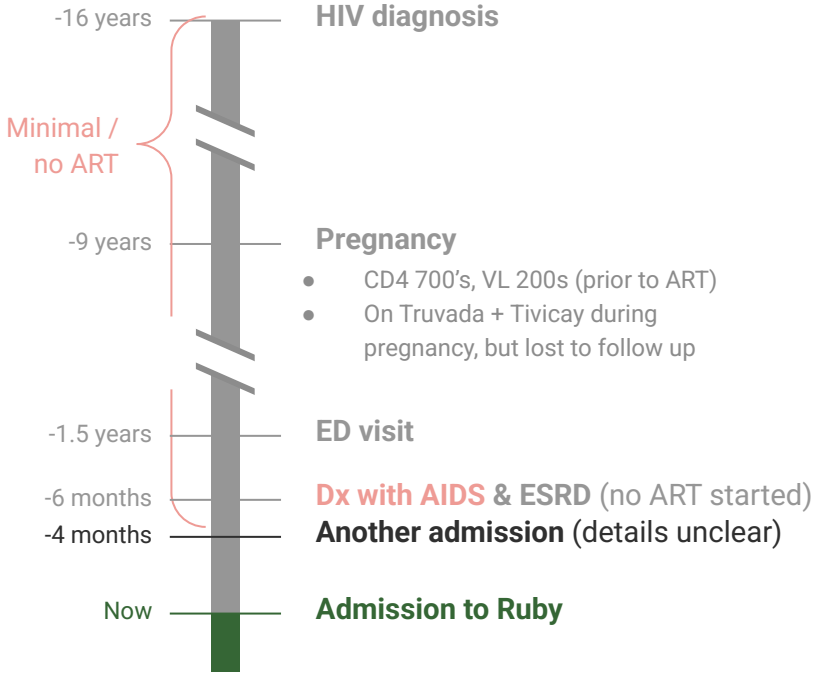
- Now admitted to Ruby ICU



Case 1: HPI

A **47 y/o F** with PMH including **ESRD**, **recently Dx AIDS** (CD4 of 34 six months ago) unclear if on ART, beta thalassemia minor who presents for **shock**, **bradycardia**, **hypothermia**, and **respiratory failure**. Intubated, so HPI is limited

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- Had missed a few sessions of HD

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- Admitted to OSH (same day) with **dyspnea** and **feeling unwell**
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At outside ED, developed

- Severe **sinus bradycardia** → **shock**
- **Hypothermia** (concern for myxedema coma initially)
- **AMS** (with mild hypoxia) → **intubated** mainly for airway protection

Case 1: Physical exam

BP	**92/63** --- **epi 0.08** (not levophed)	**Pulse**	57	**Temp**	36.1 °C (97 °F)
SpO2	100 % --- **PEEP=5, FiO2=30%**	**RR**	18	**BMI**	25 kg/m^2
General	Intubated, but **awakes to voice**				
HEENT	NCAT, no LAD				
Resp	CTAB				
CV	RRR; extremities perfused				
GI	Non-distended; no TTP				
Extremities	No clubbing, cyanosis, or edema				
Neuro/MSK	Appropriate for degree of sedation, follows commands				

Case 1: Labs

CBC	Result
WBC	8.6
Hgb	8.4
MCV	75
Platelets	**70**
Neut %	95%
Lymph %	4%
Lymph abs	**340**

Chem7	Result
Na	141
K	3.1
HCO3	23
BUN	21
Cr	**7.9**

LFTs	Result
AST	**80**
ALT	40
Alk Phos	39
Bili	**1.6**
Direct Bili	**0.9**
Albumin	1.7

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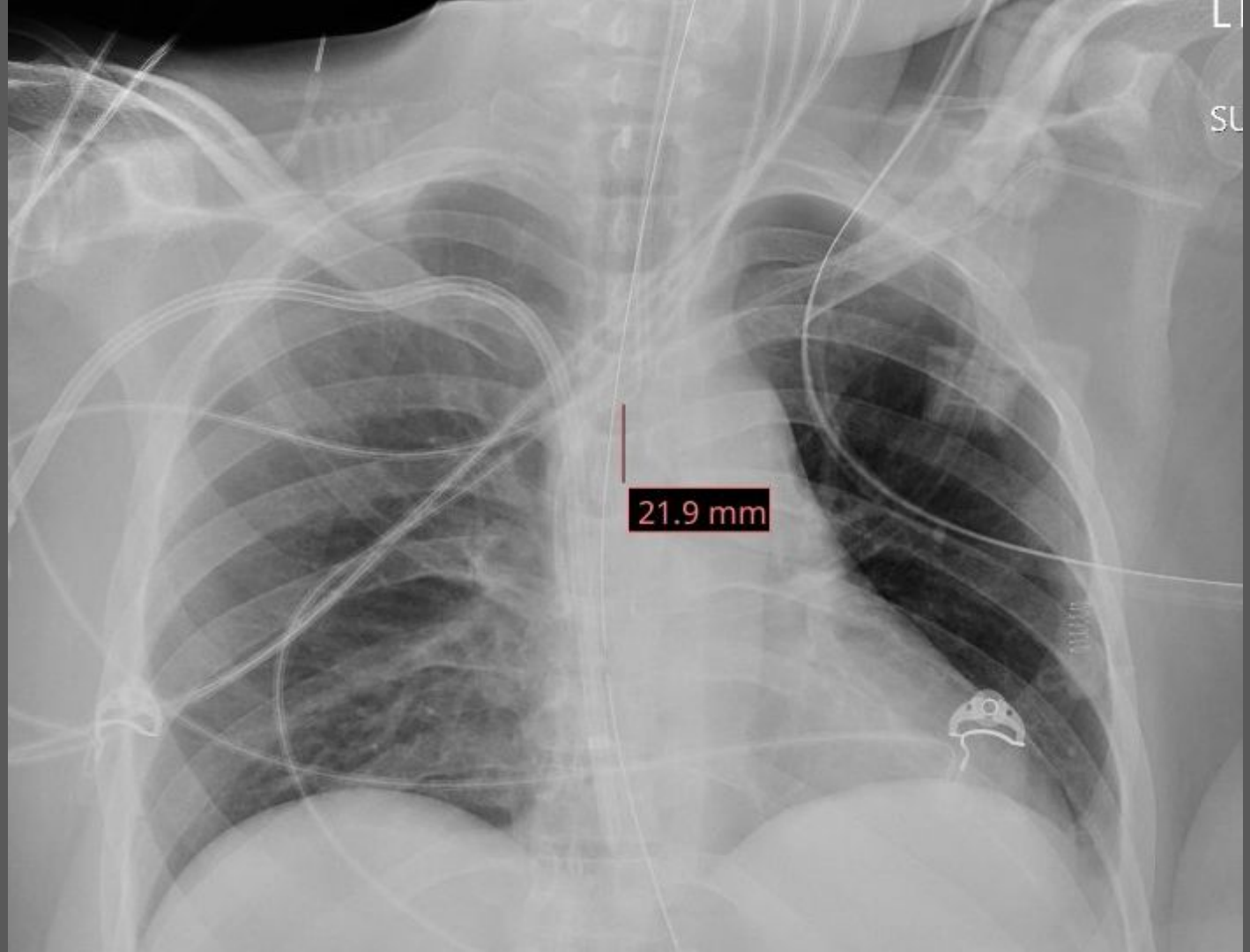
Other	Result
LDH	203
Ferritin	5900
CRP	6.6

Endo	Result
TSH	10.7
Free T4	0.99
Cortisol	wnl


21.9 mm

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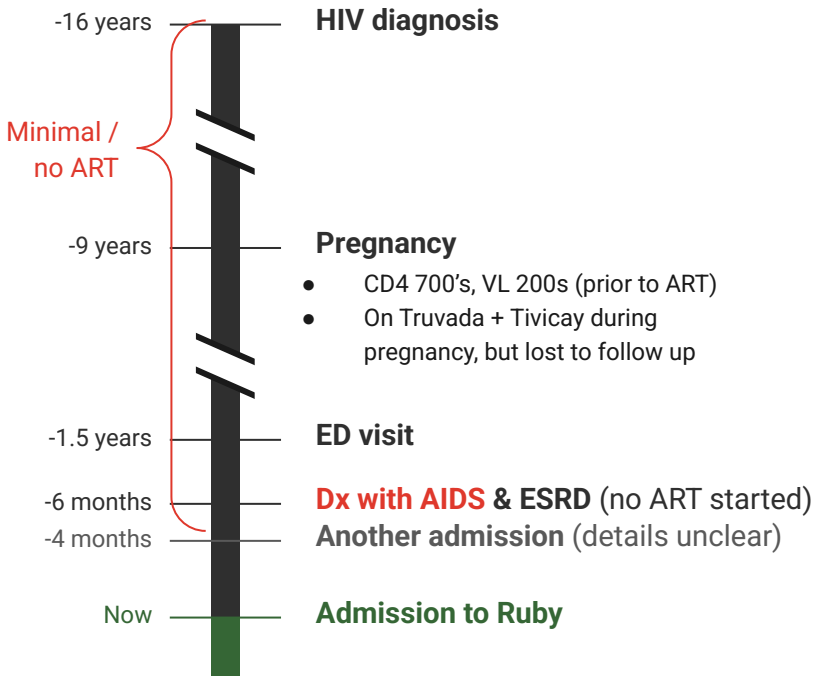
Labs show **thrombocytopenia** (70) and **lymphopenia** (ALC 340) but otherwise pretty normal (for ESRD)



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Viral load	283	38,100	16,200	???

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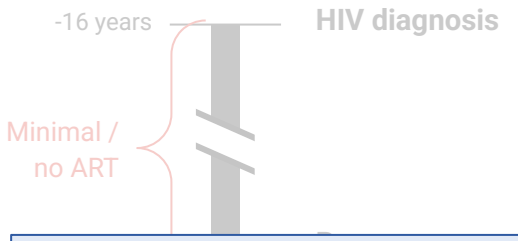

Beta-blocker toxicity

MICU suspected beta-blocker toxicity

- Renally cleared (so **buildup w/o HD**)
- Clinical presentation:
  - **Bradycardia** w/ **hypotension**
  - **Hypothermia**
  - **Altered mental status** / seizures
  - **Bronchospasm** w/ **respiratory depression**
- Responded well to treatment
- But she still **does have an infection**...

Tim… dia…				…yr …VU
CD4				?
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CT C/A/P
Subtle groundglass nodule and **opacities in the RLL** may represent infectious / inflammatory process

Case

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CD4 abs
CD4 %
Viral load

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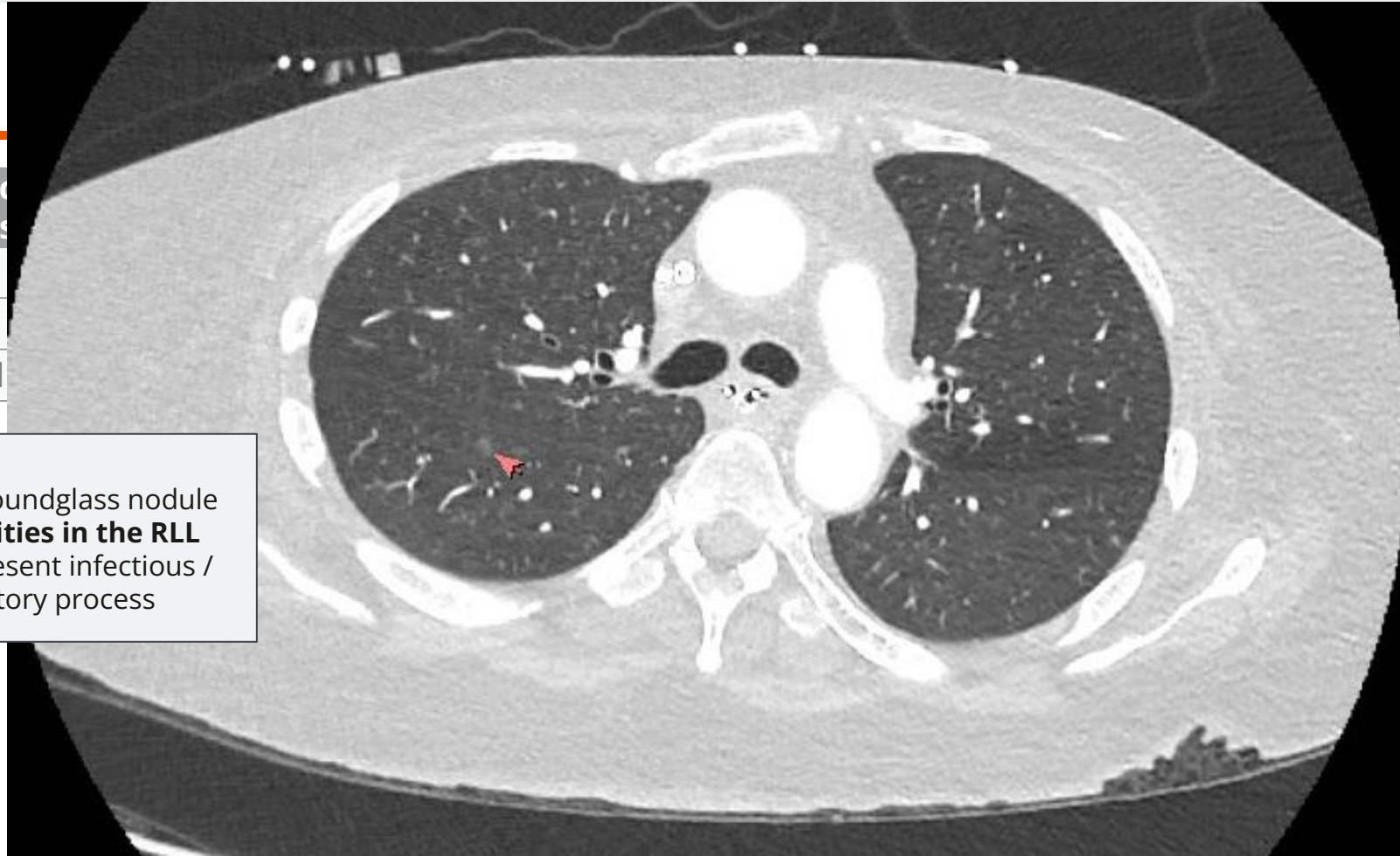

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MRI brain W/WO
Unremarkable

TTE
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Hep B	

Spirochetes	
Lyme	
Syphilis	

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Routine	
AFB blood	

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Serum fungal	
Serum CrAg	
Serum AspGM	
Fungitell	

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Respiratory	
Resp Biofire	
Urine Strep	
uLegionella	
Culture	

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Serum CrAg	Neg
Serum AspGM	Neg
Fungitell	<31

Case 1: Workup

Time since diagnosis	7 yr pregnancy	15 yr ED	16 yr Dx: ESRD	16.5 yr @WVU
CD4 abs	738	75	34	104
CD4 %	37%	9.4%	3.8%	30%
Viral load	283	38,100	16,200	71

Respiratory	
Resp Biofire	Neg
Urine Strep	Neg
uLegionella	**Pos**
Culture	**Pos**

Sputum Cx
1+ E cloacae (**CRE**)
1+ Kleb pneumo (**CRE**)
1+ Pseudomonas

CT C/A/P
Subtle groundglass nodule and **opacities in the RLL** may represent infectious / inflammatory process

MRI brain W/WO
Unremarkable

TTE
Unremarkable

Blood cultures	
Routine	Neg
AFB blood	**TBD**

Hepatitis screen	
Hep C	Neg
Hep B	wnl

Spirochetes	
Lyme	Neg
Syphilis	Neg

Serum fungal	
Serum CrAg	Neg
Serum AspGM	Neg
Fungitell	<31

Case 1: Workup

Respiratory Cx	1+ E cloacae	1+ Kleb pneumo	1+ Pseudomonas
Pip/tazo	R	R	S
Cefepime	SDD (8)	R	S (2)
Ceftazidime	R	R	S
Meropenem	R	R	S
Ceftaz/avibactam	**?**	**?**	**?**
Ceftolozane/tazo	**?**	**?**	**?**
Levofloxacin	?	?	?
Ciprofloxacin	?	?	?
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Levofloxacin	**S (<0.12)**	**S (<0.12)**	**S (1)**
Ciprofloxacin	**S**	**S**	**S (0.5)**
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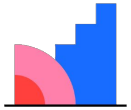
EKG: QTc **490s** (x2)

Would you use a quinolone?



Mentimeter

Remember, she came in for heart stuff...

Case 1: Hospital course

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- **Resumed Biktarvy**
- **Treated pneumonia** (both CRE and legionella) with **levofloxacin**
  - QTc was fine on treatment

Discussion

Links to articles discussed here

Objectives

Long term non-progressors & elite controllers

- Define **elite controllers** (EC) and **long term non-progressors** (LTNP)
  - Distinguish between **immunologic control** and **virologic control**
  - Contrast the **natural history** of these conditions
  - Describe the **rates** and **risk factors for progression**
- Investigate the current understanding of the **pathophysiology in EC & LTNP**, including
  - Factors related to the **viral strain of HIV**
  - Differences in their immune function (humoral vs **cellular immunity**)
- Evaluate the **inflammation & immunologic aging** that occurs in EC/LTNP
  - Abnormal **monocyte activation**
  - **Shorter telomere** lengths
  - **Consequences** of this aging
- Assess the risk/benefits of **starting ART** in this population, and review the 2025 **guidelines from HHS**

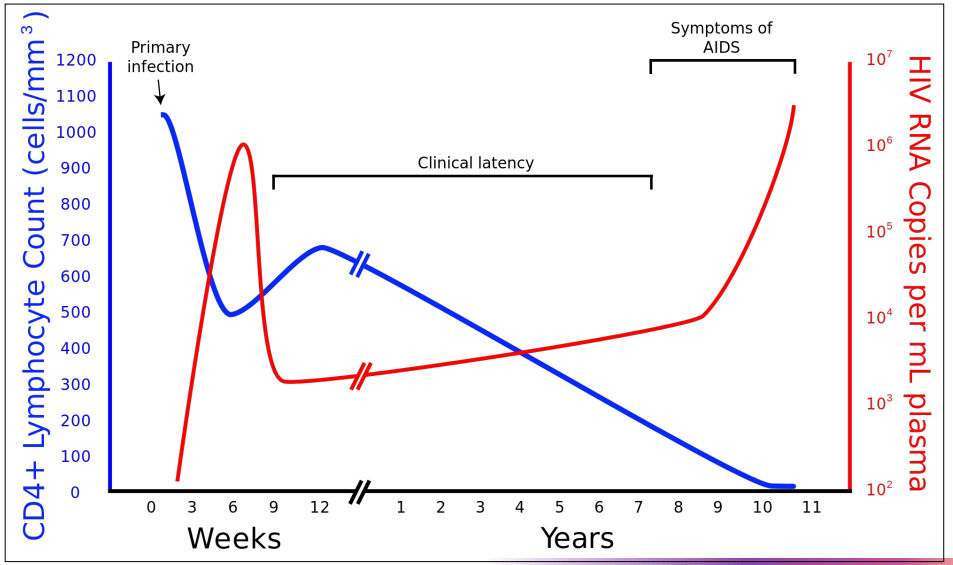
Spectrum of HIV phenotypes [4]

- **Rapid progressors**: Rapidly progress to AIDS in just a few year (not a focus for today)

Rapid progressors | **Typical progressors** | **Long term non-progressors** | Viremic controllers | **Elite controllers**

Spectrum of HIV phenotypes [4]

- **Typical progressors**: The majority of people living with HIV



Rapid progressors

Typical progressors

Long term non-progressors

Viremic controllers

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- **Viremic controllers**: People with HIV who maintain **low viral loads** (but detectable) without therapy
- **Elite controllers**: PLWH who remain virologically suppressed without therapy (virologic control)

Spectrum of HIV phenotypes [2]

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Prevalence	~5% of PLWH	0.3-0.5% of PLWH [1] • Subset of **LTNP**

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Virologic control

Immunologic control

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LTNP are defined as those who did not have immunologic progression by 10 years.

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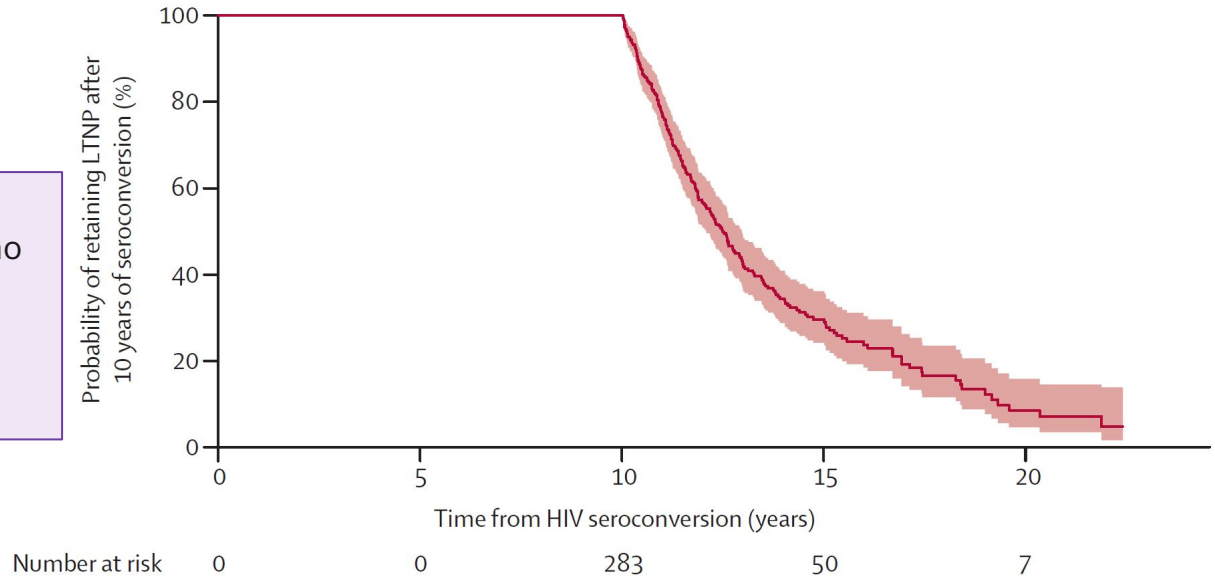

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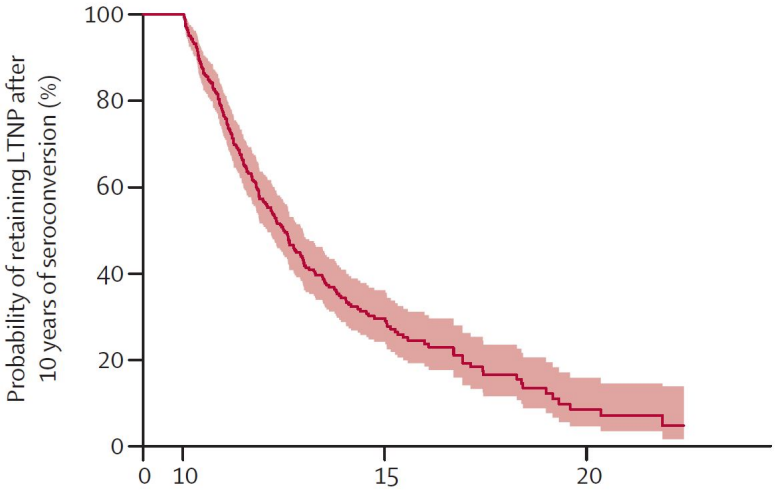

Fig 3 [3] Years after seroconversion

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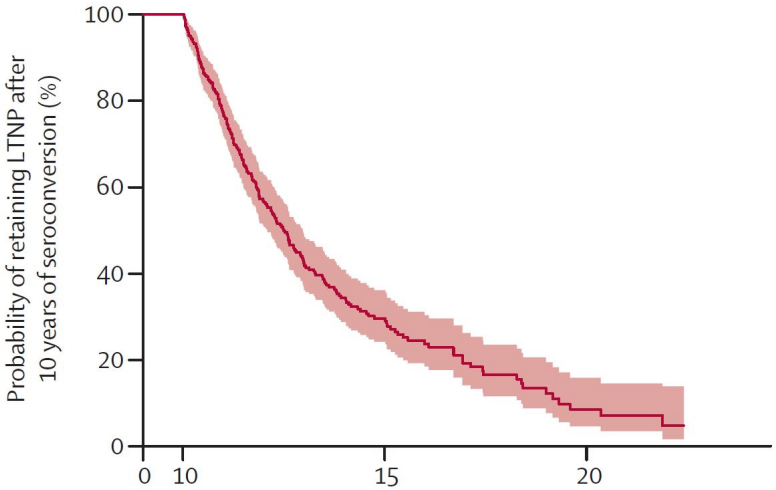
In a large, international database from 2014 [3] (25,629 PLWH)

- Inclusion: ART-naive & AIDS-free
- Defined **LTNP** as CD4 >500 at 10 years (n=283)

Predictors of progressing to CD4 <500:



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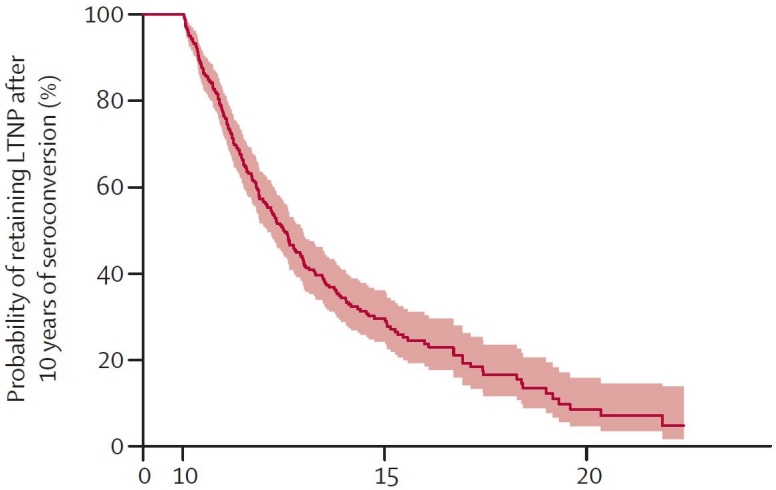

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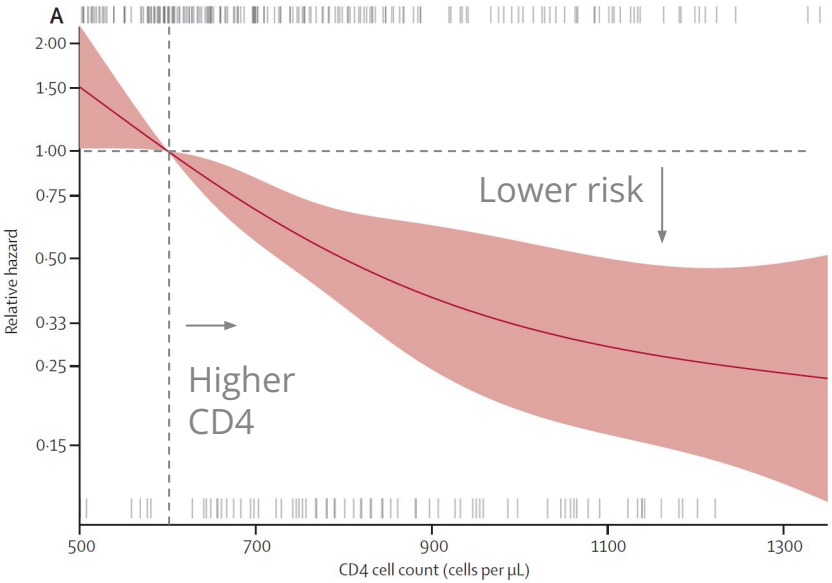

Fig 4a [3]

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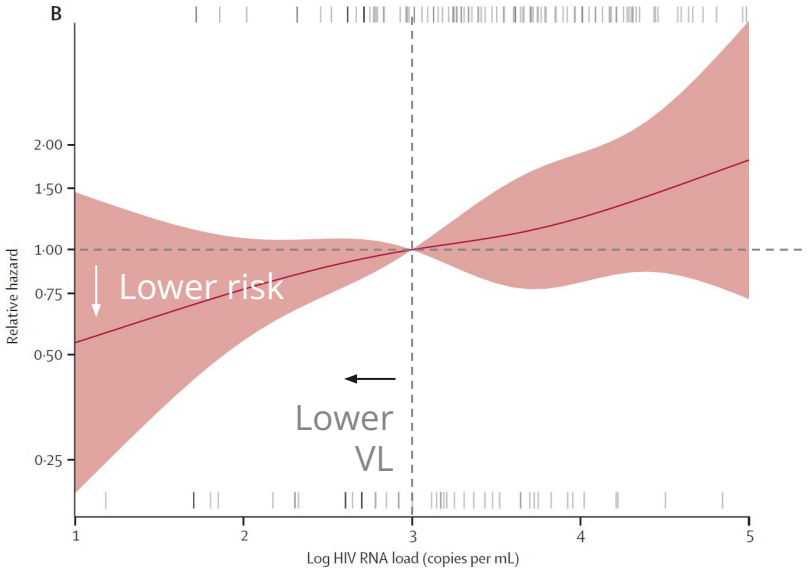

Fig 4b [3]

LTNP: Natural history

- Immunologic control is **temporary** [**1**][**3**,**4**,**5**]
- **Risk factors of progression** [**3**] are mainly based on **control at 10 years** (lower CD4, higher VL)

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    - This is highlighted by looking at studies with varying definitions of "LTNP" [see 5]

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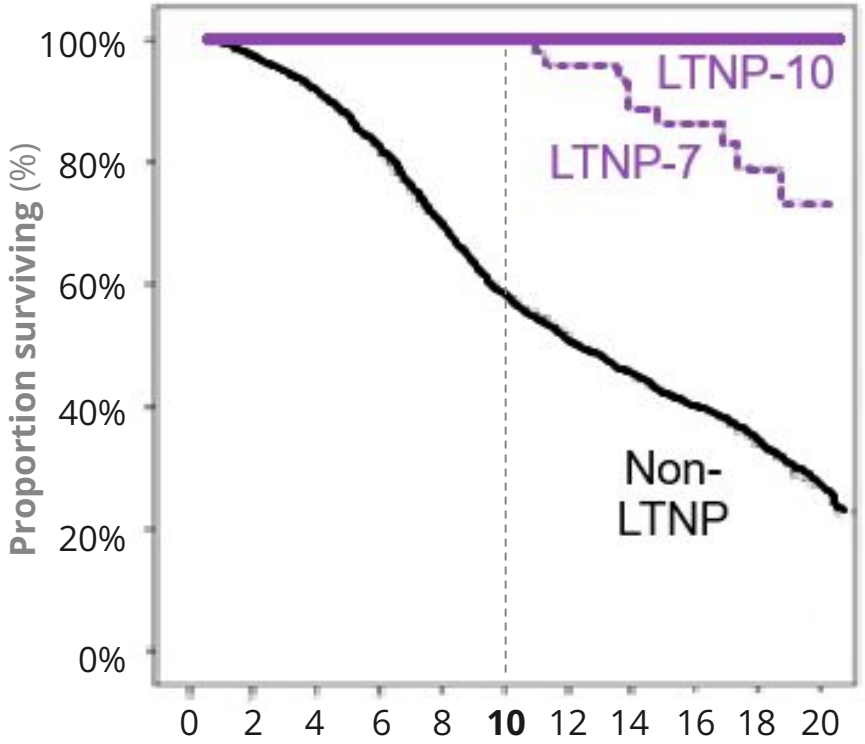

Fig 4C [5]

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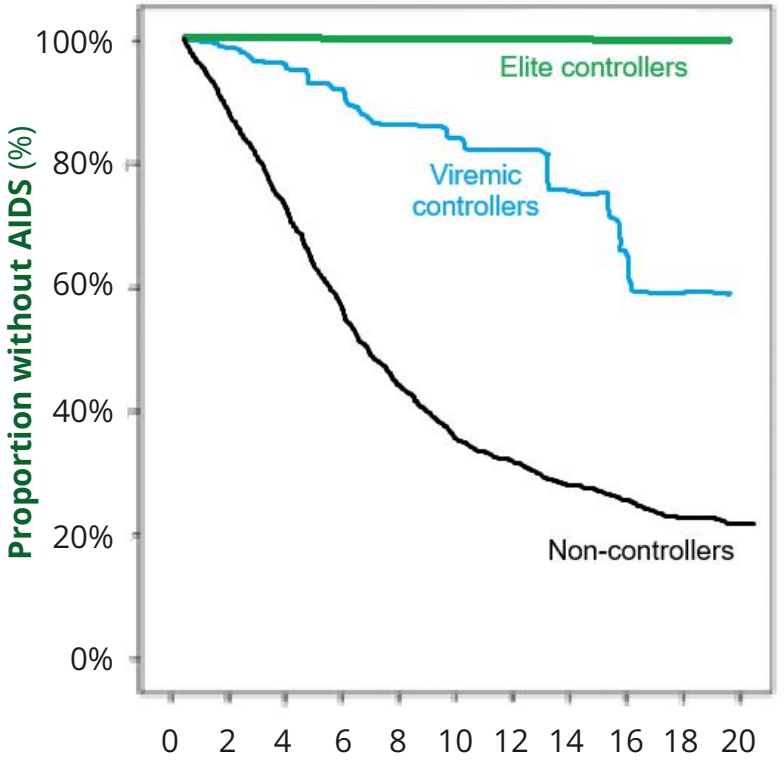

Fig 3C [5]

EC: Natural history

Compare this with **elite controllers**

- Tend to have **excellent immunologic control** [5]
- Degree of **viremia** is *partially* **predictive of loss of immunologic control**. Even differences as small as <1 copy vs 50 copies [**1**]

	Defined based on … control	Virologic control	Typical viral load
Elite controllers	**Virologic**	Excellent	<50 [2]
Viremic controllers	**Virologic**	Good	50 - 2,000 [6]
Long term non-progressors	**Immunologic**	Fair	1-10k [1] (usually 2k)

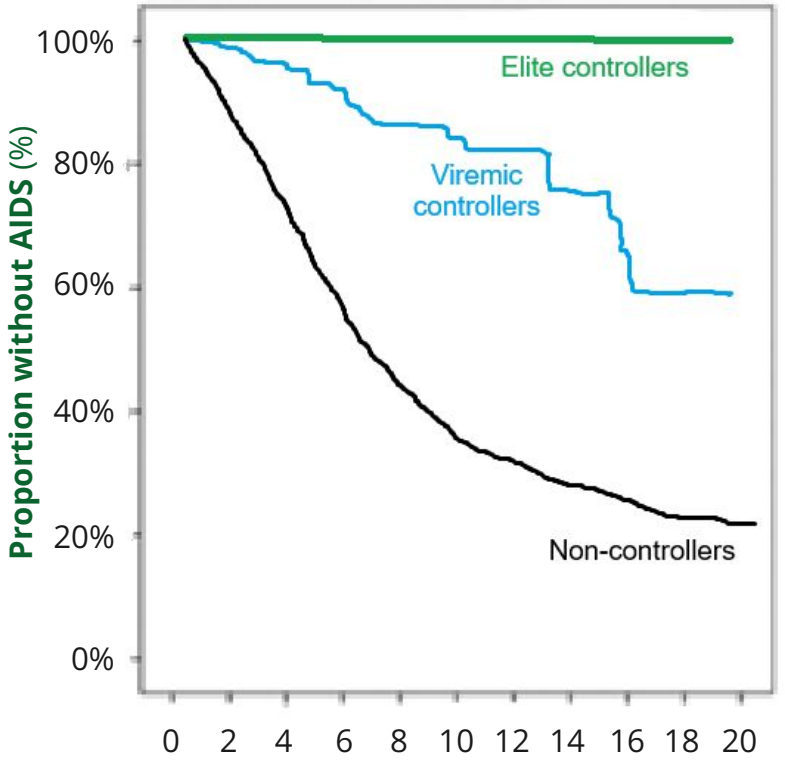

Fig 3C [**5**]

Elite controllers: Do they fail with time too?

Cases **elite controllers progression to AIDS is much less common** than with LTNP

- In one study [**5**], only one patient (of 25 elite controllers; **4%**) developed AIDS defining illness, **pulmonary TB**
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Some authors propose that **chronic immune activation** (e.g. aberrant T-cell activation) may drive these manifestations [1]

Themes thus far

1. "**Non-progressors**" can be categorized via immunologic control (e.g. **long term nonprogressors**) and virologic control (e.g. **elite controllers**)
    - These terms likely **exist on a continuum** [4]

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3. Progression of disease (i.e. loss of immunologic control) usually occurs due to **loss of virologic control** (just like untreated HIV in "typical progressors")
    - Think of these cases as **unfolding in slow motion** (compared to typical HIV off ART)

Pathophysiology

Long term non-progressors & elite controllers

- Define **elite controllers** (EC) and **long term non-progressors** (LTNP)
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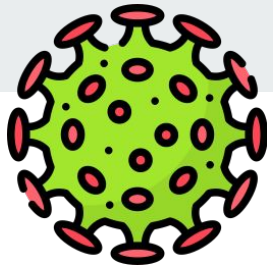
HIV control: **Viral factors**



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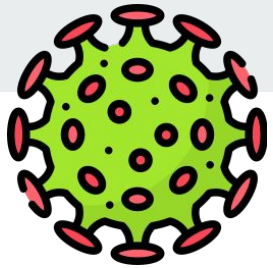

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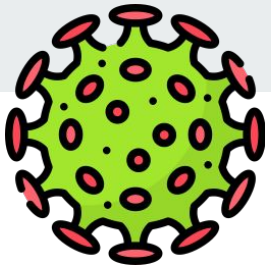

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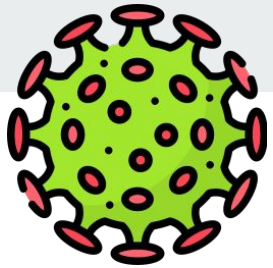

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However, **most LTNPs are infected with** fully pathogenic, **replication-competent viruses** [1]

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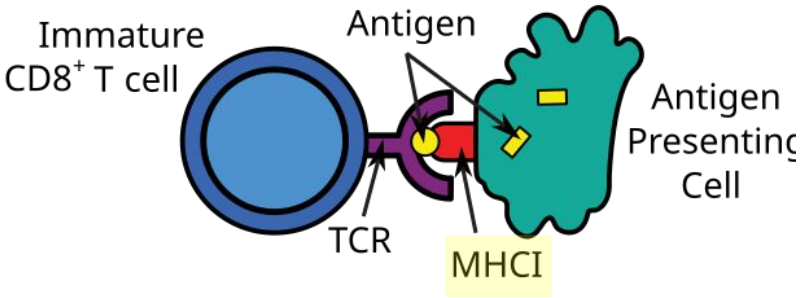
- Assess the risk/benefits of **starting ART** in this population, and review the 2025 **guidelines from HHS**

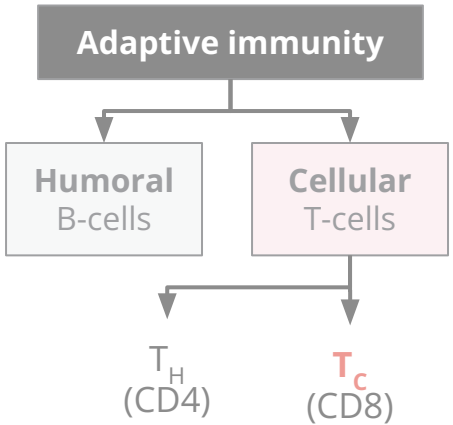
HIV control: The immune system

HLA genes encode major histocompatibility complex proteins

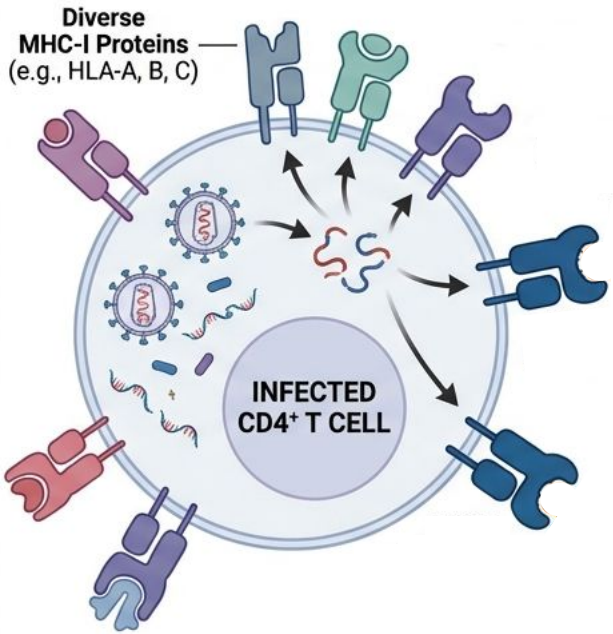
- In this case we care about **MHC-I** (HLA A-C)



	MHC-I	MHC-II
Presents	Endogenous proteins	Exogenous proteins
HLA genes	HLA-A HLA-B HLA-C	HLA-DP HLA-DQ HLA-DR



HIV control: Host genetics [2][10]



The strongest association with HIV control is the presence of specific HLA Class I alleles

- **Heterozygous HLA class-I genotype** is linked to slower disease development by allowing the presentation of a **broader spectrum of HIV peptides**

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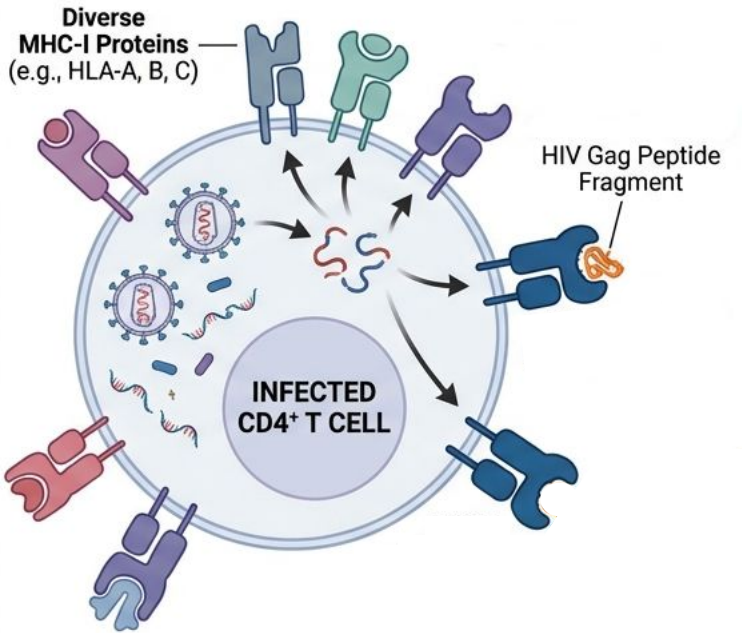

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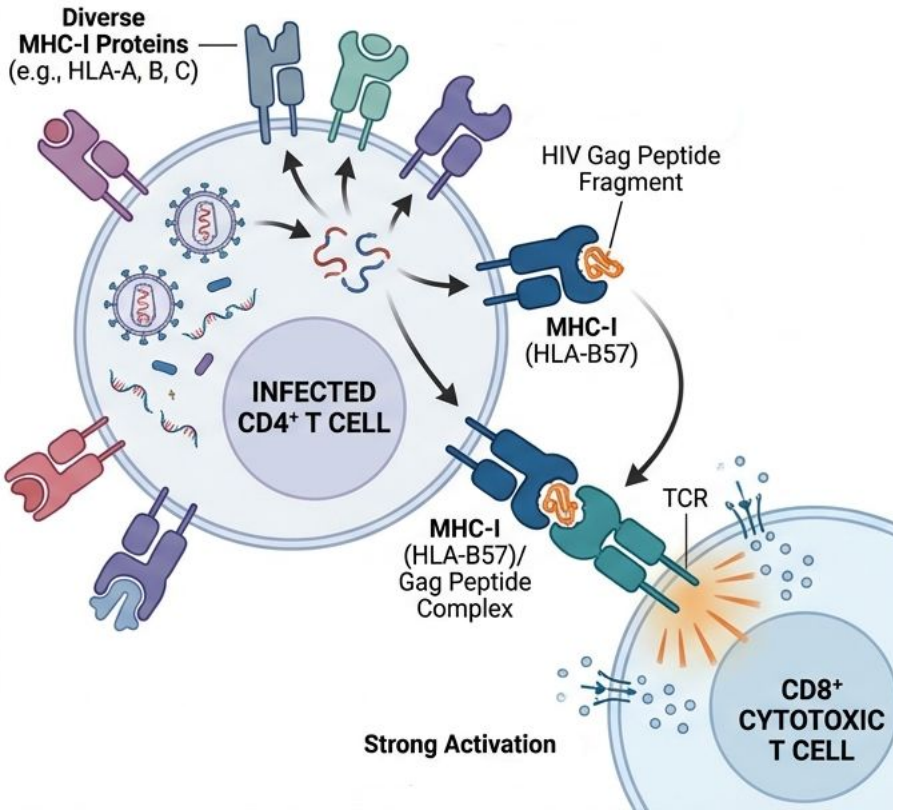

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  - This in turn leads to **strong activation of CD8+ cytotoxic T cells → Killing of infected CD4+ cells**

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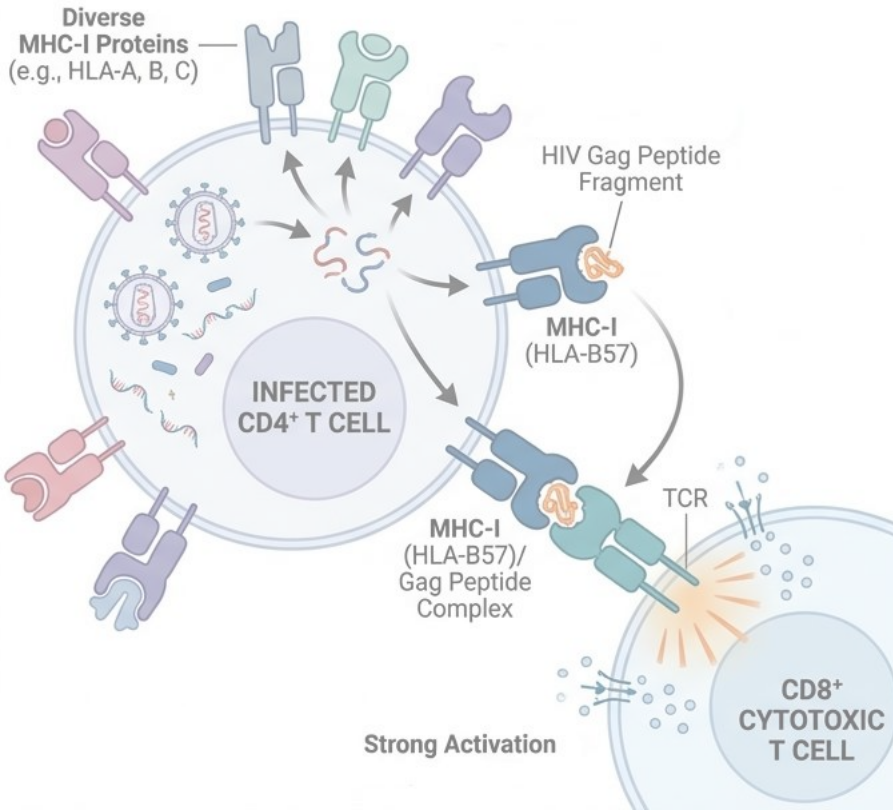

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- Studies of **LTNPs** with **the lowest viral loads** (<75) found that **B57 is found in considerably higher frequencies** (compared to typical progressors and healthy seronegative controls)

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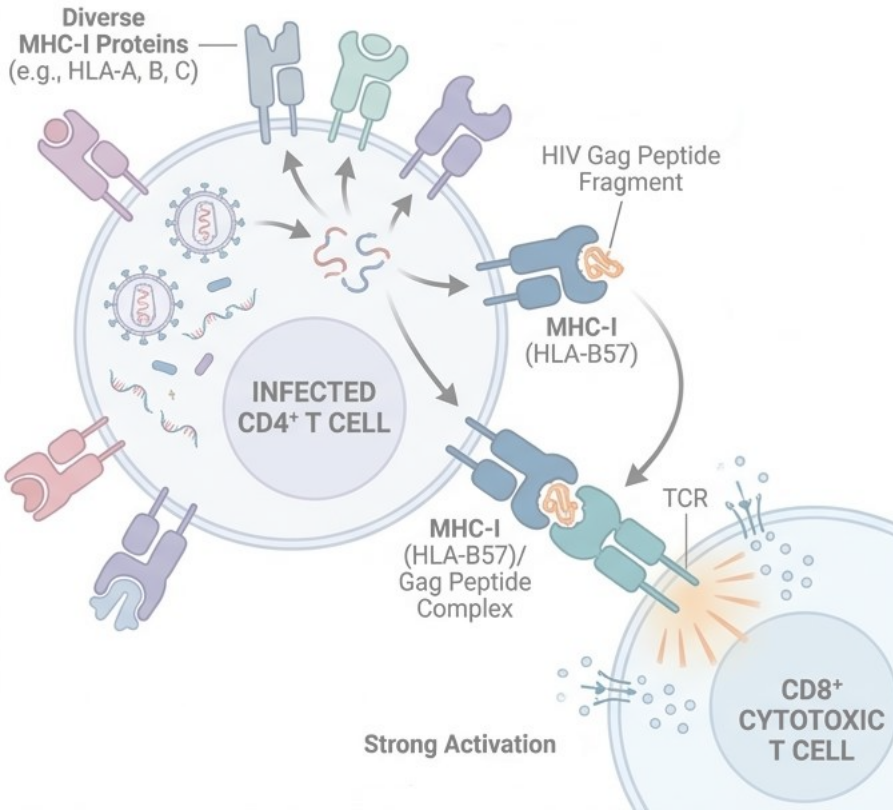

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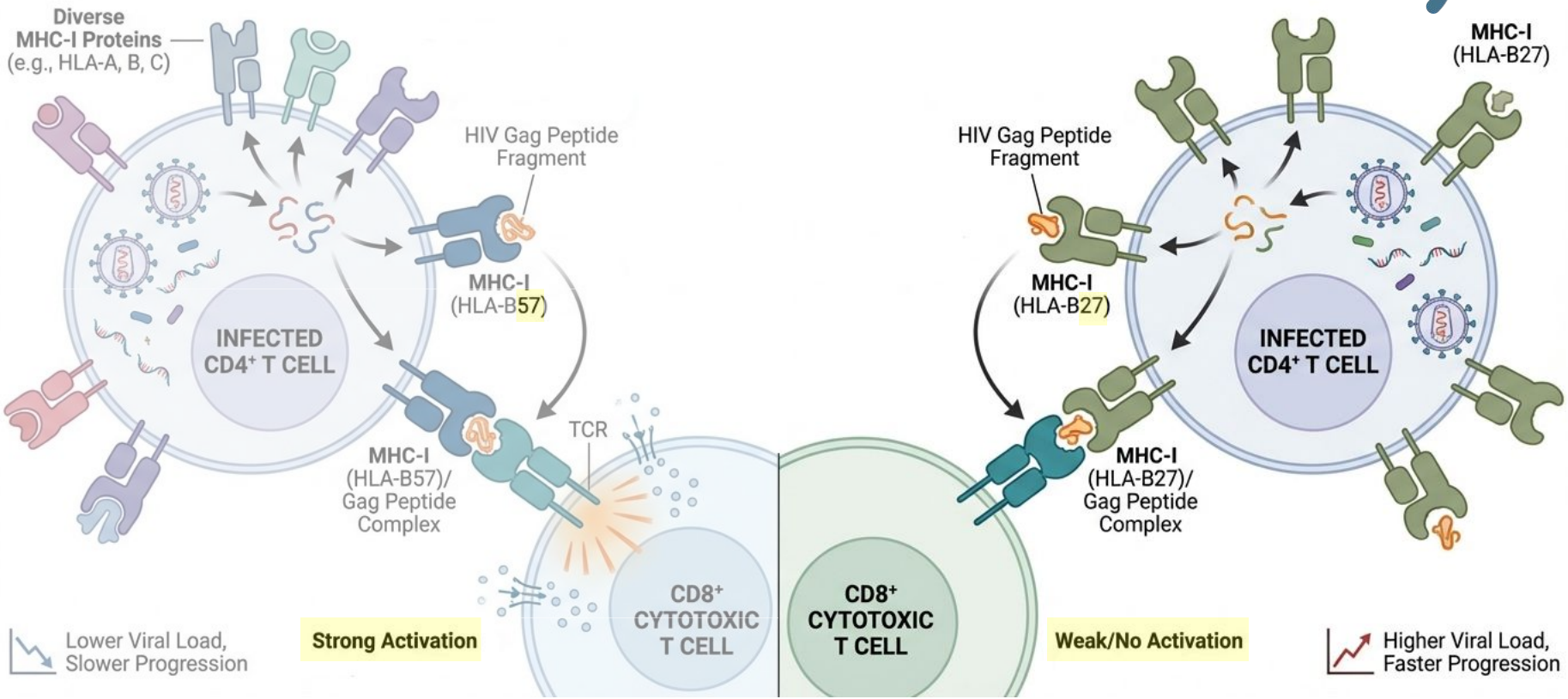
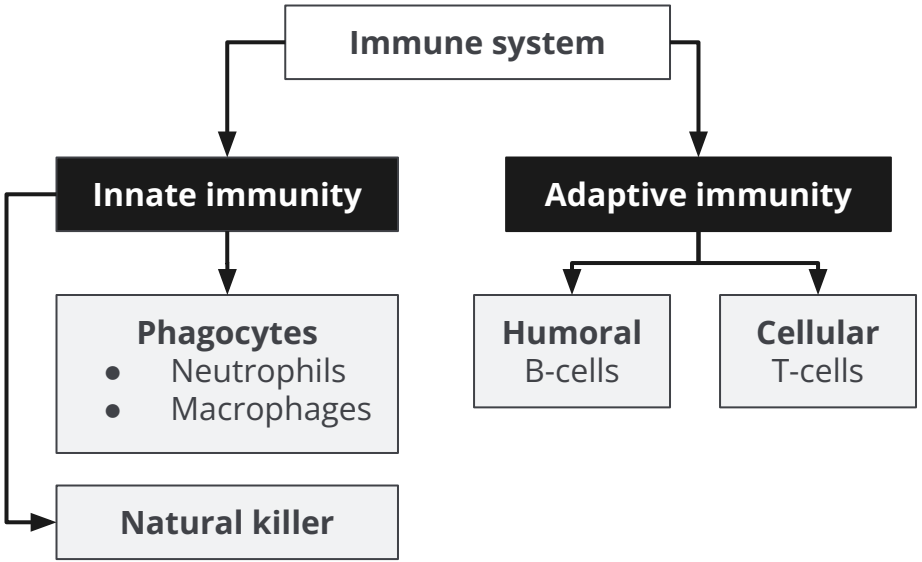
- Studies of **LTNPs** with **the lowest viral loads** (<75) found that **B57 is found in considerably higher frequencies** (compared to typical progressors and healthy seronegative controls)
- **90-95% of LTNPs** carry **at least one HLA-B allele** that mediate a slow rate of HIV progression
    - E.g. B57, B13, B15, B44, B51, B58

HIV control: Host genetics [2][10]



HIV control: The immune system



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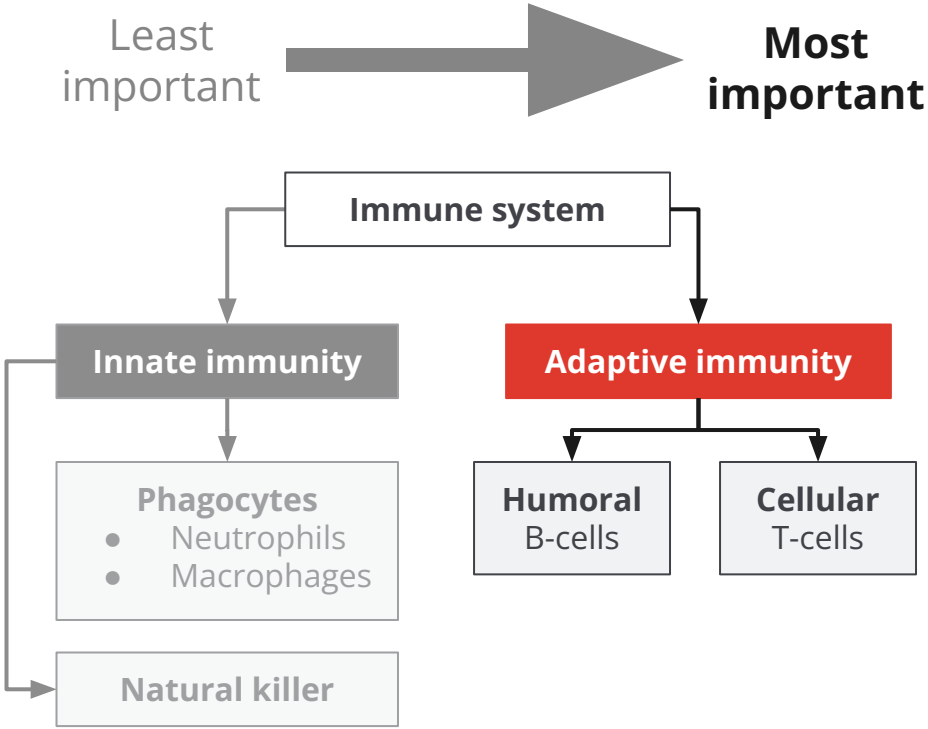

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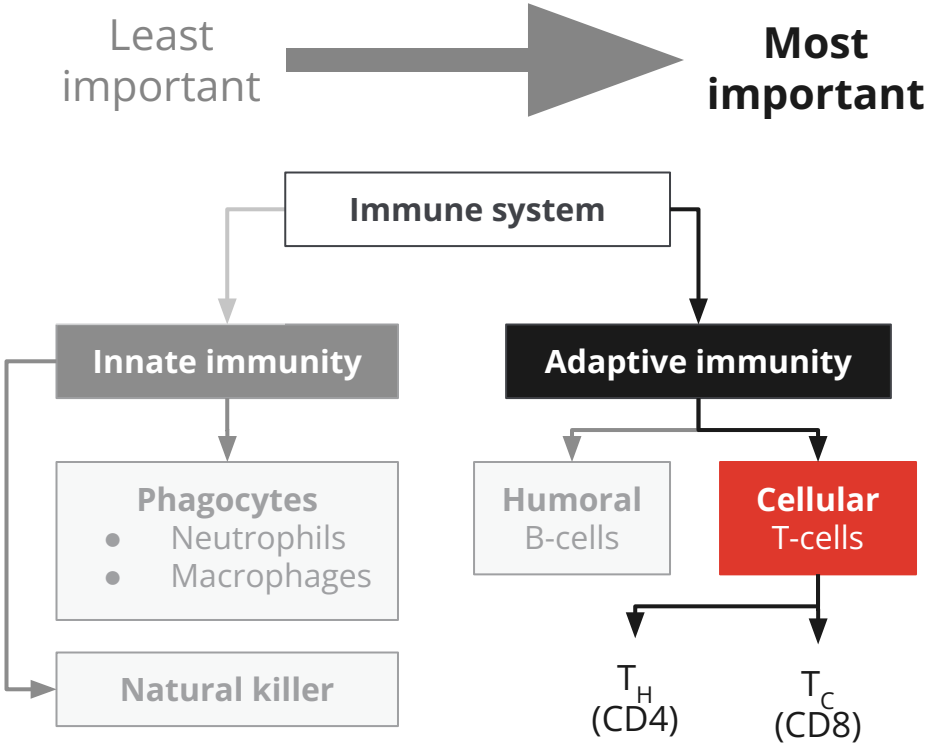

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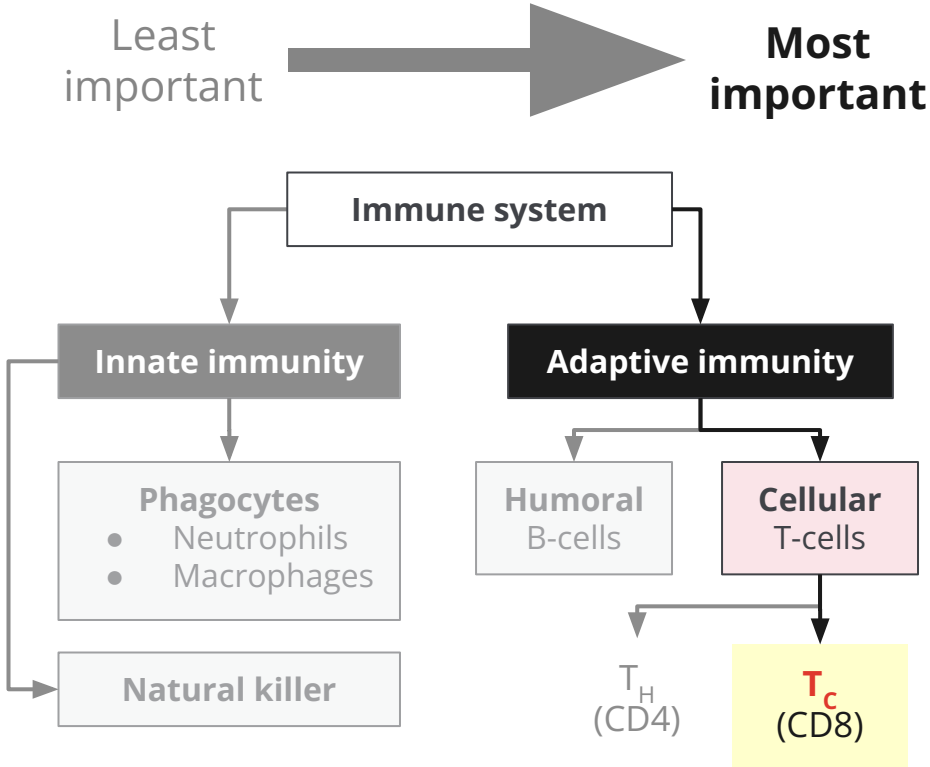
- **CD8** >> CD4



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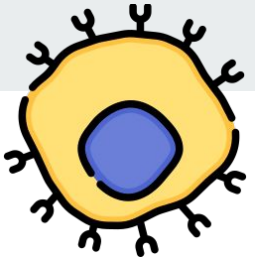

CD8+ cytotoxic T cells are **not** more numerous in LTNP/ECs [**10**]

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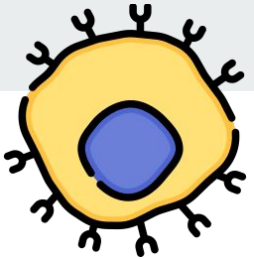

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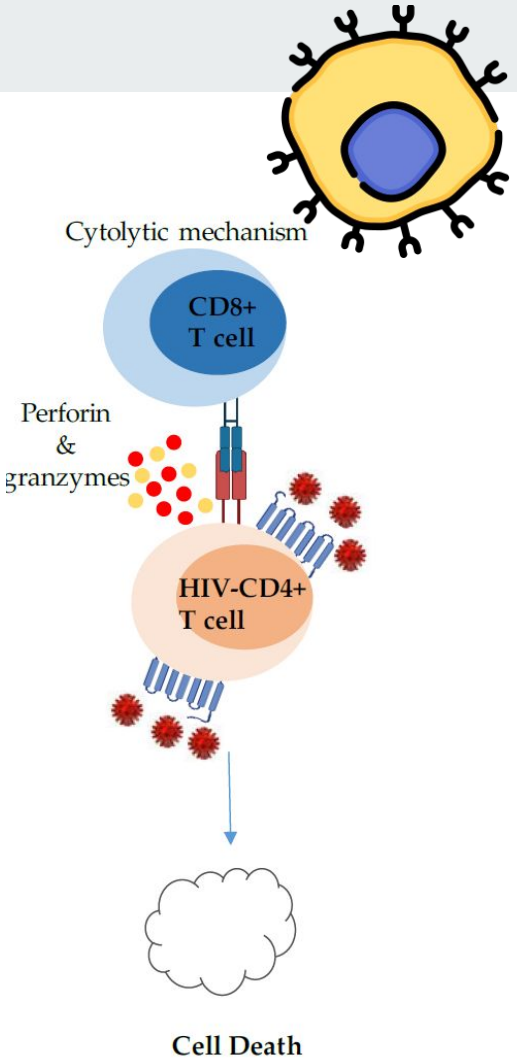

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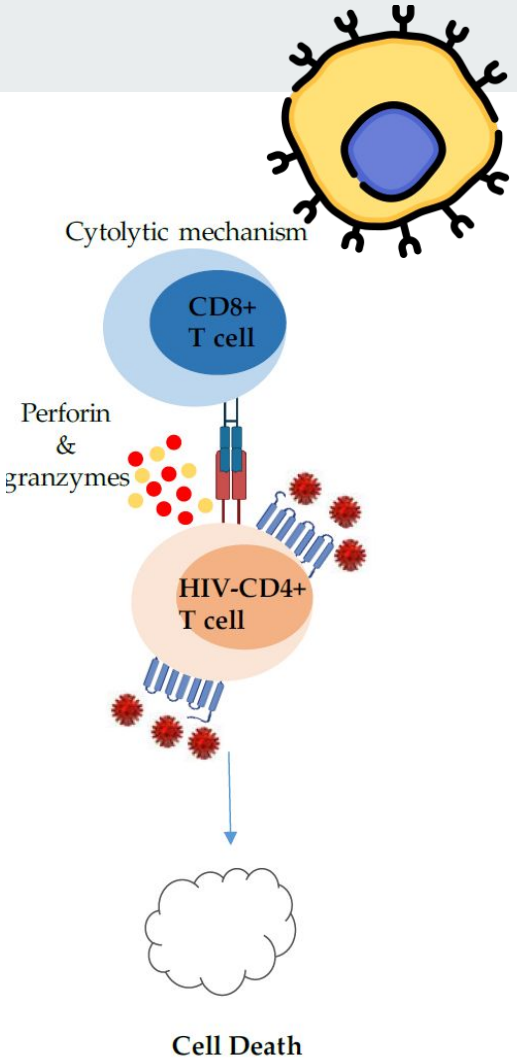

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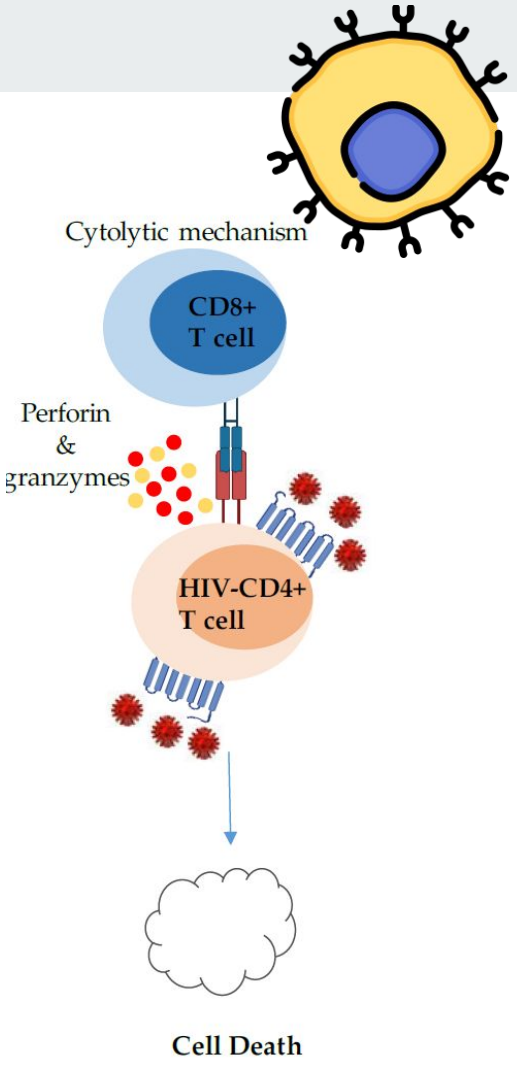

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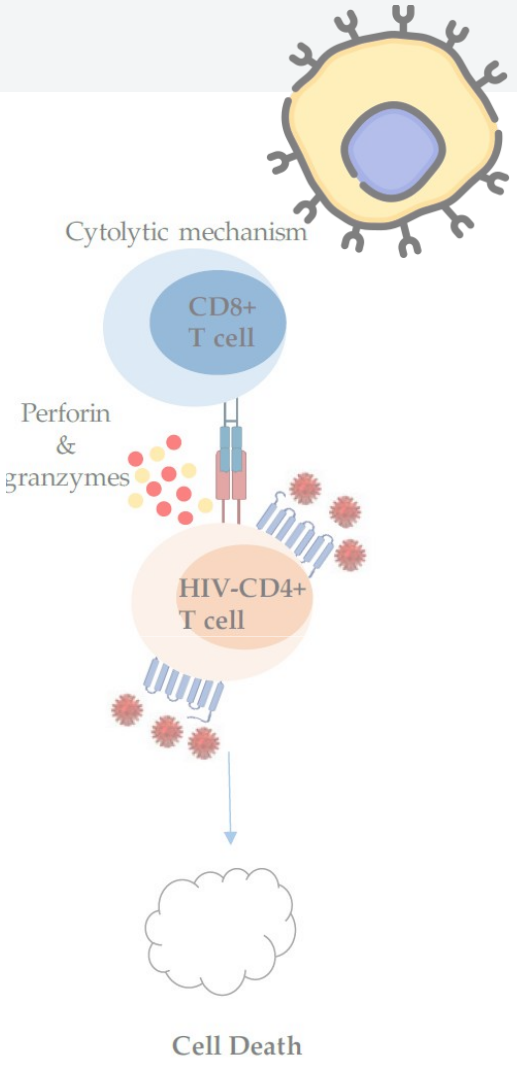
Speculation (on my part)
Does make one wonder if the ability of CD8 cells to recognize CD4 cells (prior to them transcribing new copies of HIV) is related to the ***high affinity MHC-I proteins*** expressed by certain HLA-B alleles [citation needed]



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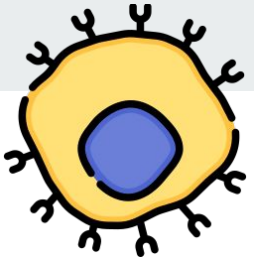

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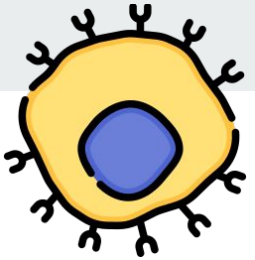
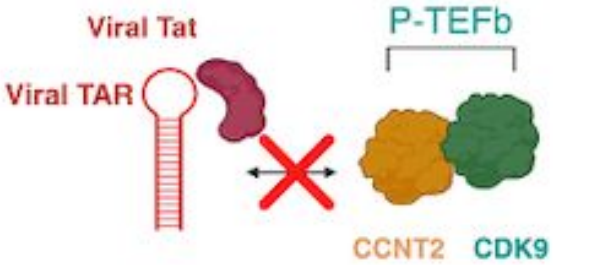


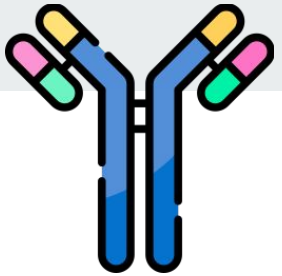
Although **CD8+ cytotoxic T cells are the main players** here, some elite controllers have **increased CD4+ expression of p21** [2]

- p21 is a cyclin-dependent kinase inhibitor
- Specifically, **p21 inhibits CDK9** (a cofactor for reverse transcription of HIV)



Pathophysiology: **Other mechanisms**

- Define **elite controllers** (EC) and **long term non-progressors** (LTNP)
  - Distinguish between **immunologic control** and **virologic control**
  - Contrast the **natural history**
  - Describe the **risk factors for progression**
- Investigate the current understanding of the **pathophysiology** **in EC & LTNP**, including
  - Factors related to the **viral strain of HIV**
  - Differences in their **immune function** (**humoral** vs cellular immunity)
  - Possible **other factors**
- Evaluate the **inflammation & immunologic aging** that occurs in EC/LTNP
- Assess the risk/benefits of **starting ART** in this population, and review the 2025 **guidelines from HHS**



Humoral immunity [2]

Long term non-progressors

- Some studies show LTNPs have **higher rates** of **broad acting neutralizing antibodies** (**NAbs**)
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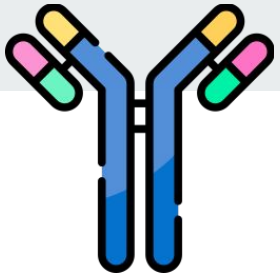

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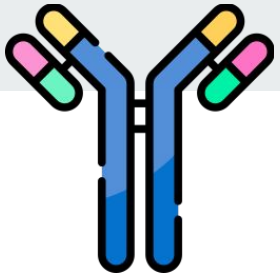

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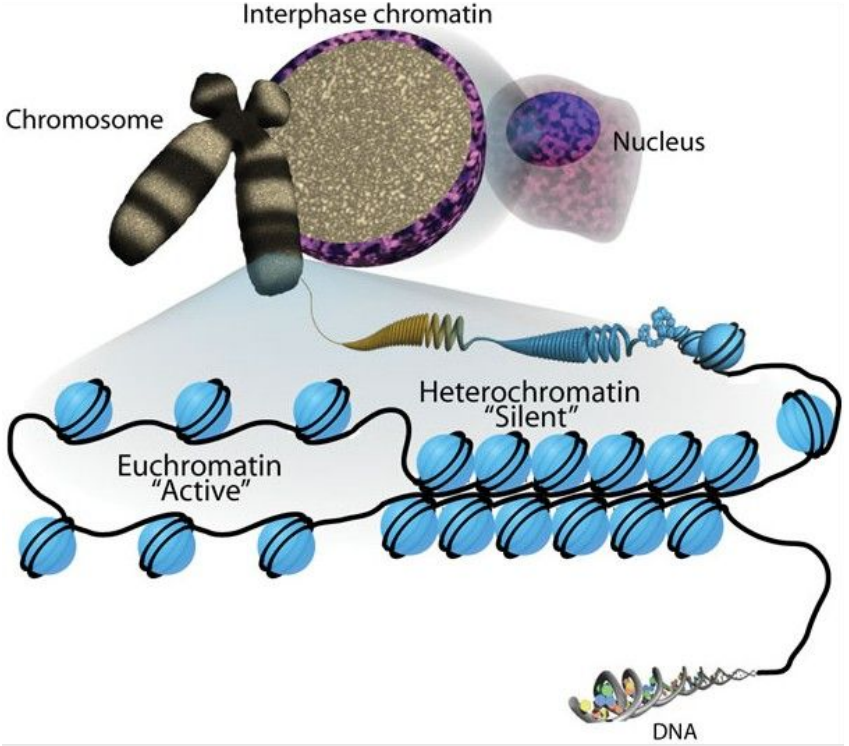
- Namely **antibody dependent cellular cytotoxicity**, which targets and kills infected cells **by recruiting natural killer cells**

HIV control: Location of integration [2][10]

In ECs, HIV proviruses are **disproportionately** found **integrated into non-coding regions** (“gene deserts”; e.g. heterochromatin)



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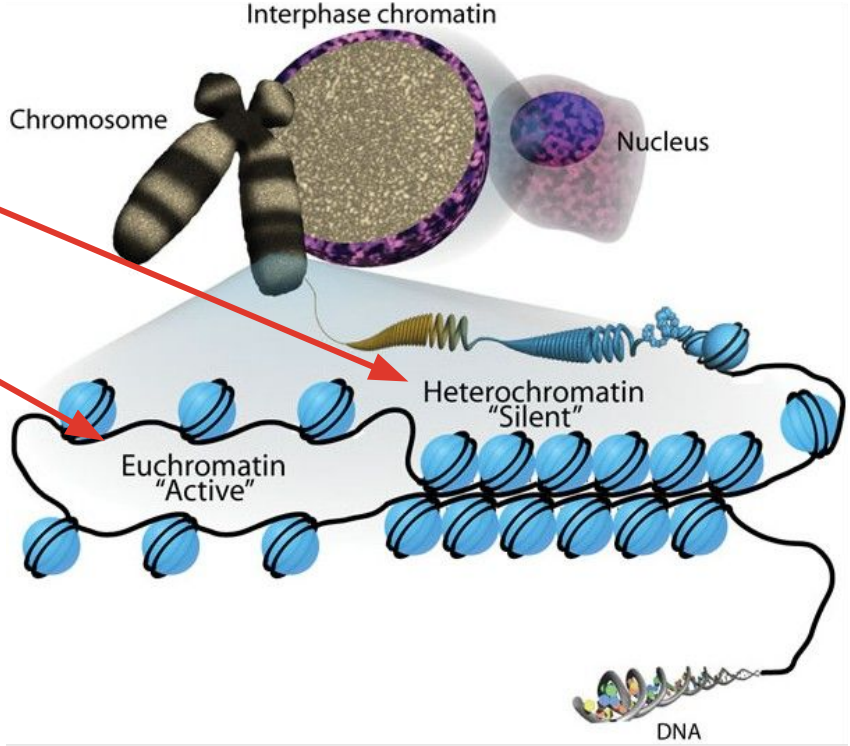

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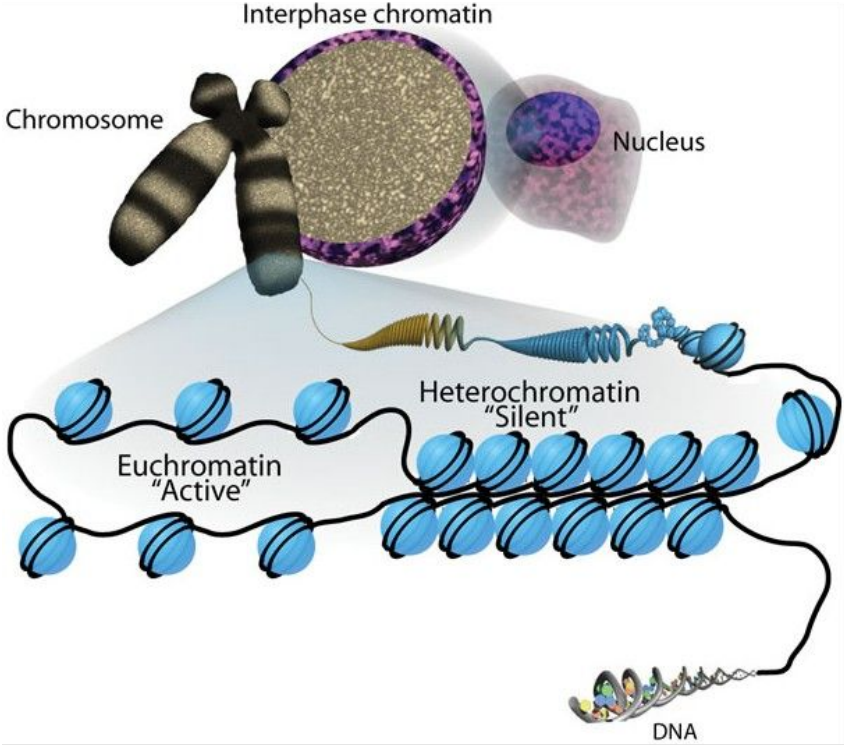
- This **partially explains why ECs have undetectable viral loads**
  - All of their ***actively*** **infected cells are being killed** by CD8 cells
  - Their **latent reservoir** “genome” is **not transcribed**



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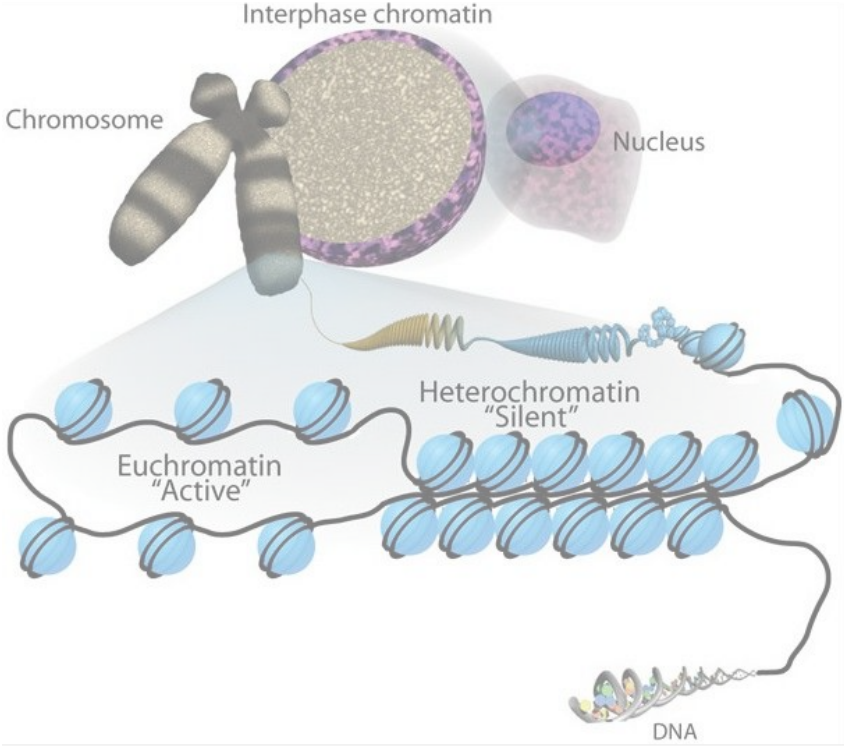

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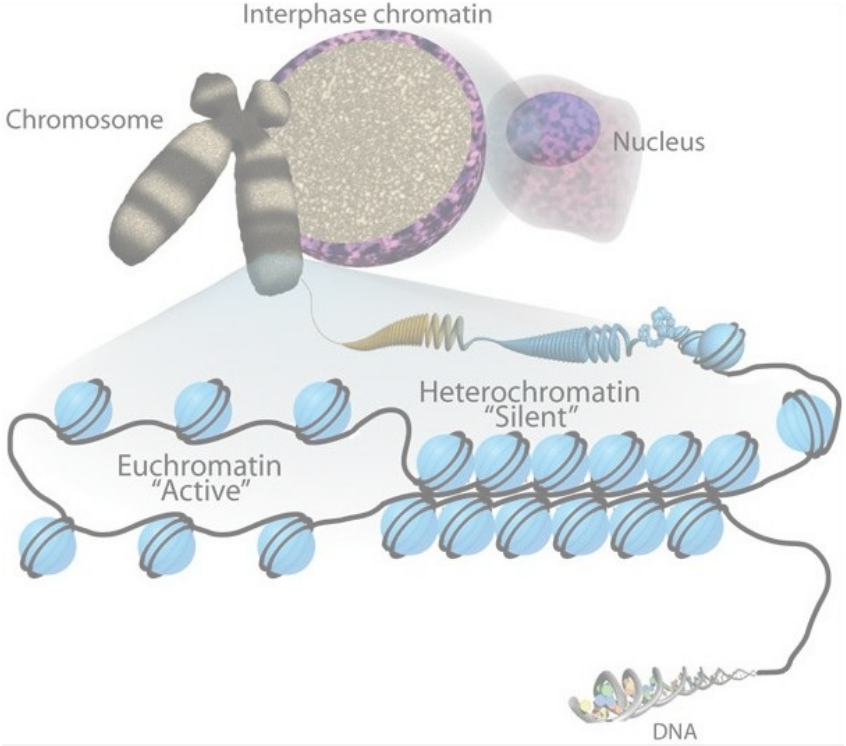
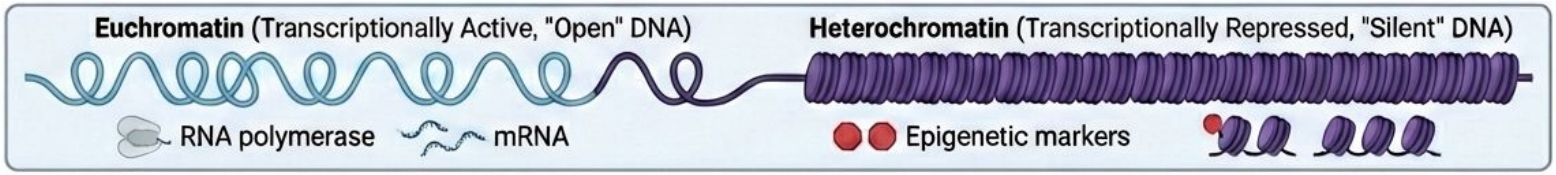
Both cases are thought to be **a result of selective pressure from the immune system**



HIV Elite Controllers: Preferential Proviral Integration into Heterochromatin via Immune Selection



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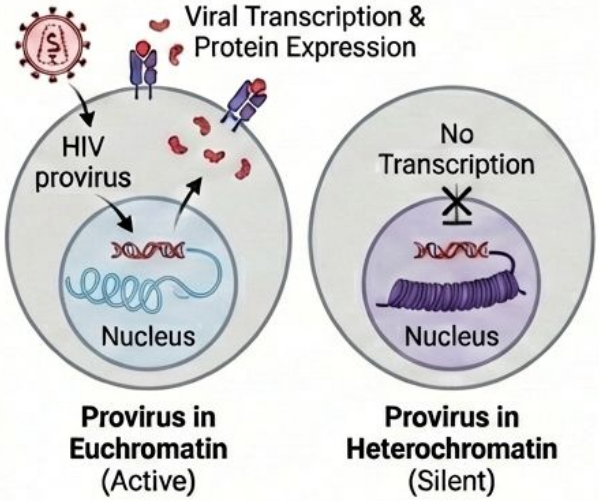

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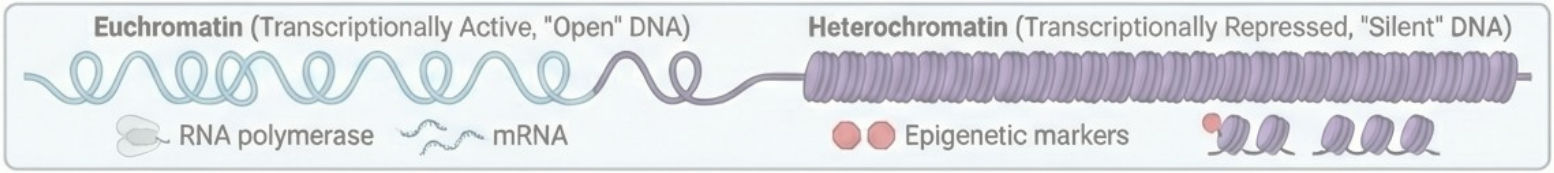

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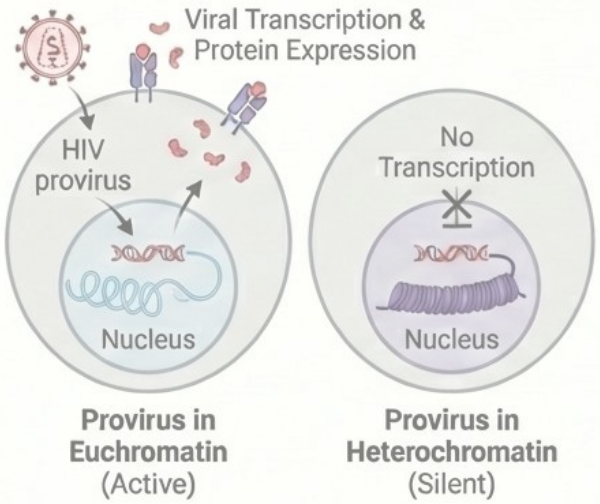
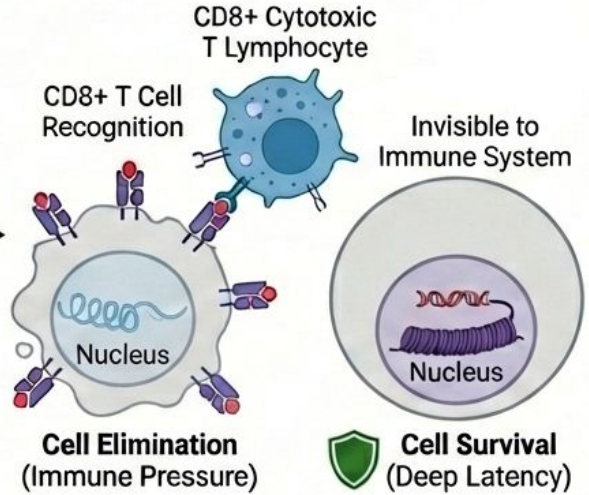


2. Immune Selection by CD8+ T Cells



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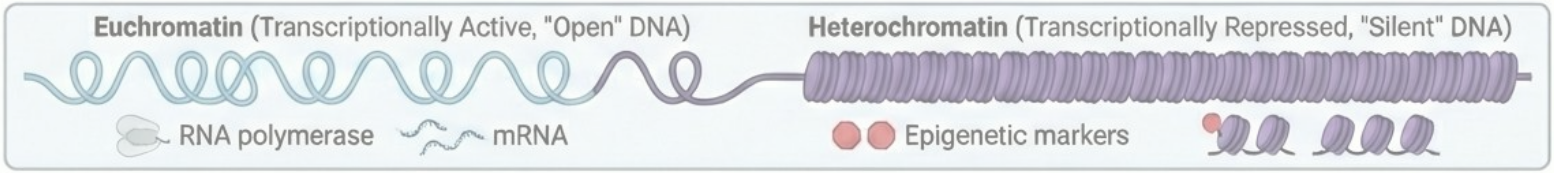

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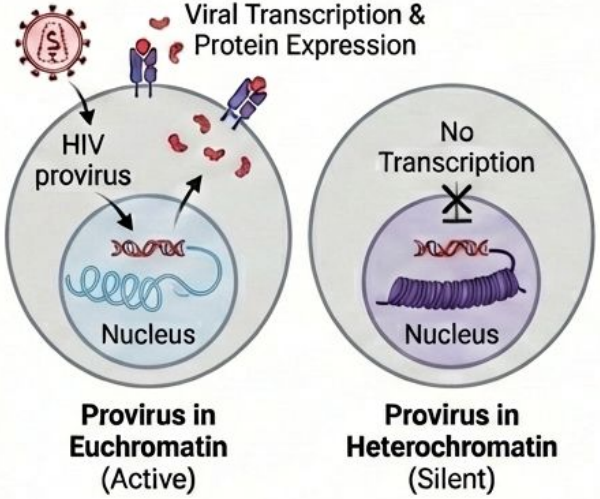

Provirus in Euchromatin (Active)

Provirus in Heterochromatin (Silent)

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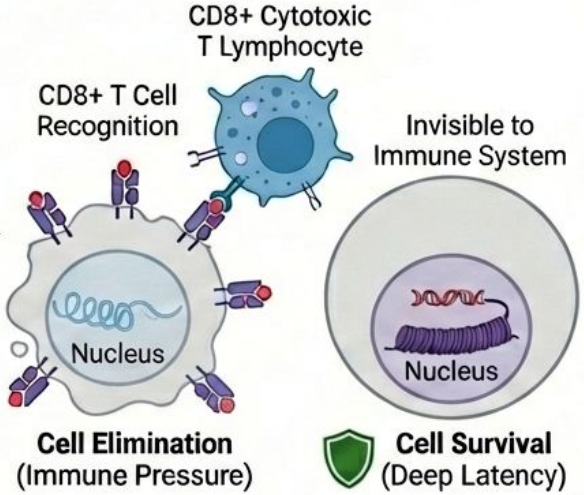
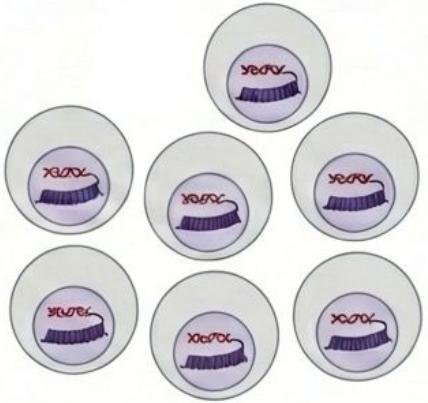


Cell Elimination (Immune Pressure)

Cell Survival (Deep Latency)

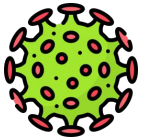
3. Elite Controller Reservoir Over Time



Reservoir Dominated by "Blocked" Proviruses in Heterochromatin

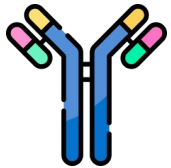
SUMMARY: Intense immune pressure by CD8+ T cells eliminates cells with active proviruses in euchromatin. In HIV elite controllers, this selective pressure leaves behind a reservoir of proviruses integrated into "silent" heterochromatin, which are **resistant to reactivation and invisible to the immune system, thus not contributing to viremia.**

HIV control: **Summary**



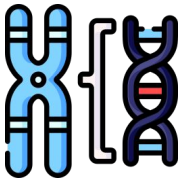
✗ Is it related to their virus?

Only in *rare cases* (Sydney blood bank)



✗ Produce more antibodies?

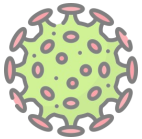
Mixed data on the *amount* of antibodies, but some studies showed ECs have Abs that help with ADCC via NK cells



? Site of HIV integration?

Integration into **transcriptionally repressed areas** of the host genome likely contributes ECs ability to have undetectable VL, but this may be a selective consequence from their elite control (not the cause of it)

HIV control: **Summary**

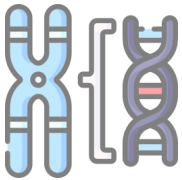


✗ **Is it related to their virus?**

Only in *rare cases* (Sydney blood bank)

✗ **Produce more antibodies?**

Mixed data on the *amount* of antibodies, but some studies showed ECs have Abs that help with ADCC via NK cells



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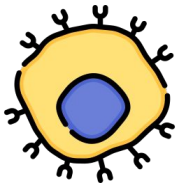
✓ **Host genetics? (MHC-I)**

Strong association with **HLA*B** (**B57**) in LTNPs, especially when **heterozygous alleles** since can better bind to fragments of HIV in infected cells → **allows CD8 cells to kill** infected cells



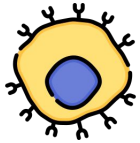
✓✓ **Cellular immunity (CD8 >> CD4)**

CD8 cytotoxic T cells in LTNP/ECs are *phenotypically unique* and **polyfunctional** (better at killing infected CD4 in a number of ways). CD4 cells likely play a minimal role in control

Possible mechanism? (speculative)

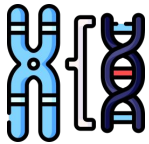
Host genetics
(MHC-I)

Encodes for **more effective CD8** cells



Cellular immunity
(CD8)

Polyfunctional CD8 T cells are better at killing infected cells that express HIV



Site of HIV integration

Selective pressure created to favor cells with HIV integrated into **transcriptionally repressed areas**

Likely multifactorial (and may be multiple mechanisms)

↓ **expression** of HIV → **fewer chances to mutate**
(and less likely to have virologic escape from the CD8 cells)

Inflammation & immunologic aging

Long term non-progressors & elite controllers

- Define **elite controllers** (EC) and **long term non-progressors** (LTNP)
  - Distinguish between **immunologic control** and **virologic control**
- Investigate the current understanding of the **pathophysiology in EC & LTNP**, including
  - Factors related to the **viral strain of HIV**
  - Differences in their immune function (humoral vs **cellular immunity**)
- Evaluate the **inflammation & immunologic aging** that occurs in EC/LTNP
  - Abnormal **monocyte activation** → CV risk & HAND
  - **Shorter telomere** lengths
  - **Consequences** of this aging
- Assess the risk/benefits of **starting ART** in this population, and review the 2025 **guidelines from HHS**

Immunologic aging

Both LTNP & EC still have **high levels of abnormal immune activation** [11]

- We will start with (~~the least technical~~ most familiar) example I could find, the CD4:CD8 ratio

Immunologic aging: **CD4:CD8**

CD4:CD8 ratio is helpful method of assessment of immune function

- **CD4:CD8 ratio <1 is bad** (even in LTNP/EC) and associated with [9]
  - Abnormal immune function
  - Serious non-AIDS events

T-cell subsets (during pregnancy)	
CD8 abs (%)	940 (47%)
CD4 abs (%)	**738** (37%)
CD4:CD8	0.8

Immunologic aging: **CD4:CD8**

- **CD4:CD8 ratio <1 is bad** (even in LTNP/EC) and associated with [9]
  - Abnormal immune function
  - Serious non-AIDS events
- Despite their normal CD4 levels, **ratio is often <1 in LTNP** compared to those with undetectable VL [7]

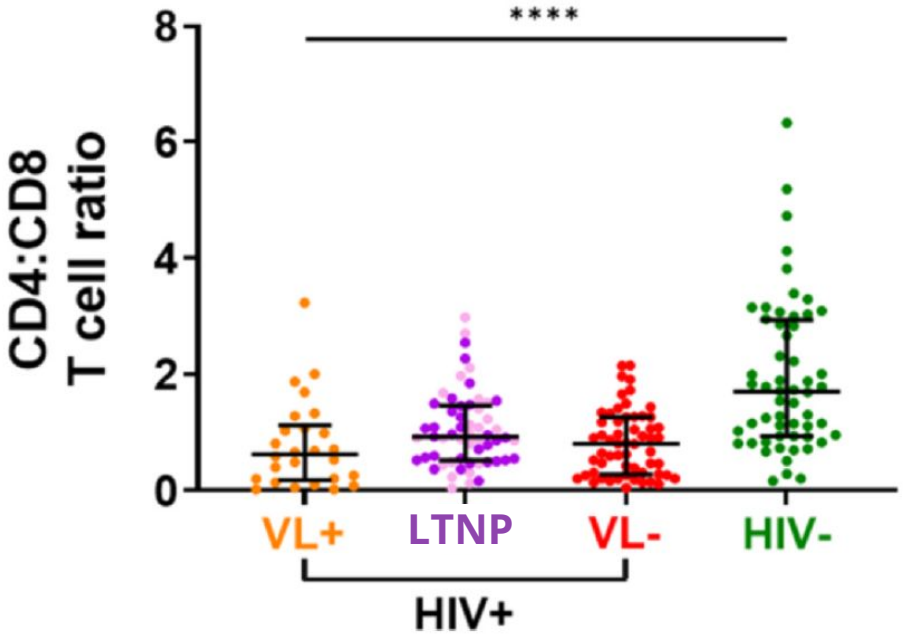


Figure 2A of citation [7]

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  - Serious non-AIDS events
- Despite their normal CD4 levels, **ratio is often <1 in LTNP** compared to those with undetectable VL [7]
- **Ratio remains abnormal** (<1) in LTNP, even ***after*** **starting ART** [9]

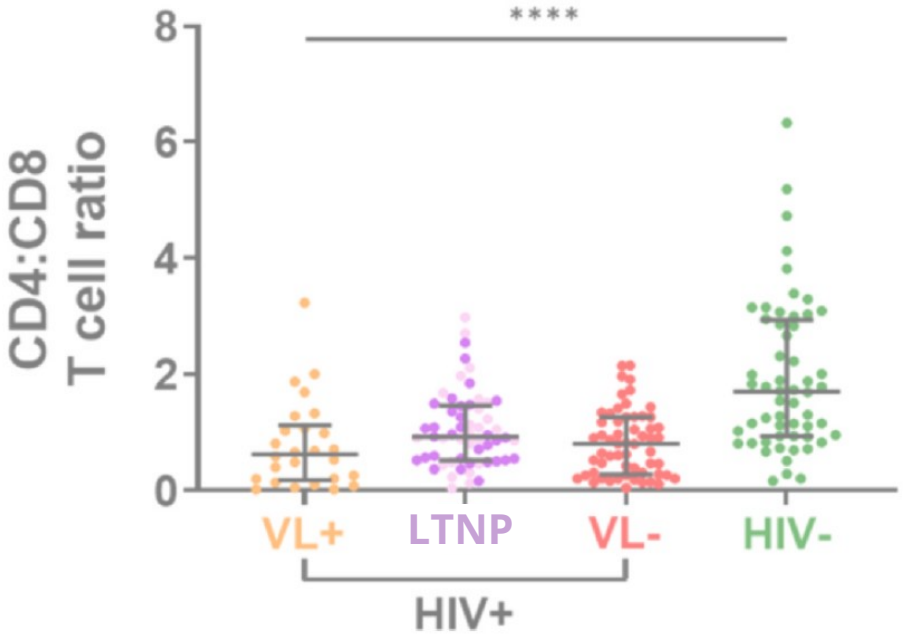

Figure 2A of citation [7]

Immunologic aging: **Monocytes [6]**

LTNP have **similar immune activation profiles** as other people with **HIV who are not on ART**

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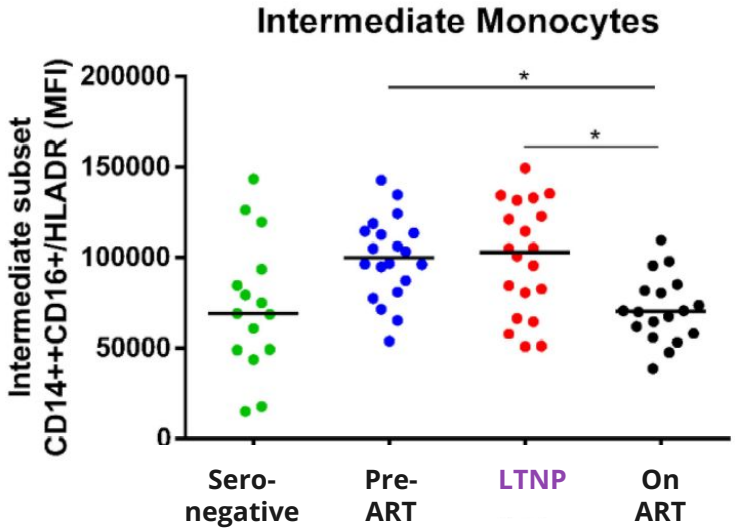


Figure 5B of citation [6]

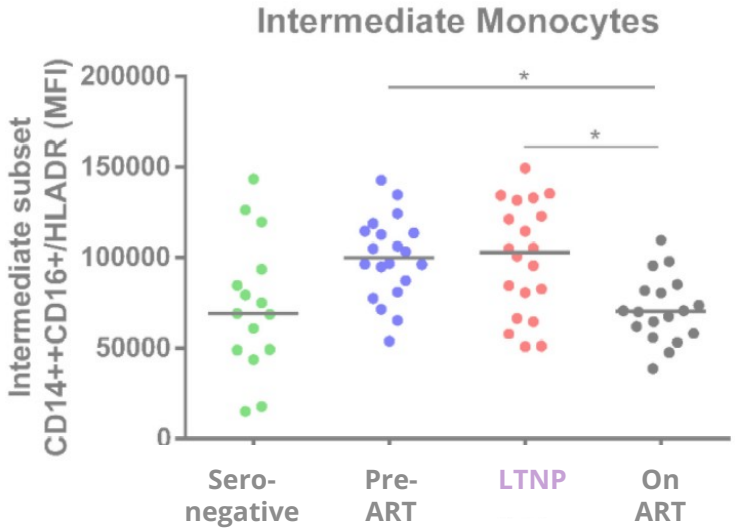
Immunologic aging: Monocytes [6]

LTNP have **similar immune activation profiles** as other people with **HIV who are not on ART**

- LTNP have increased levels of **pro-atherogenic monocyte subsets**

FYI, I'm <u>not</u> an immunologist (this is an immunology journal)

- Intermediate monocytes are **identified by CCR5**
- In animal models, **atherosclerotic plaque formation** is recruited in a **CCR5-dependent fashion**



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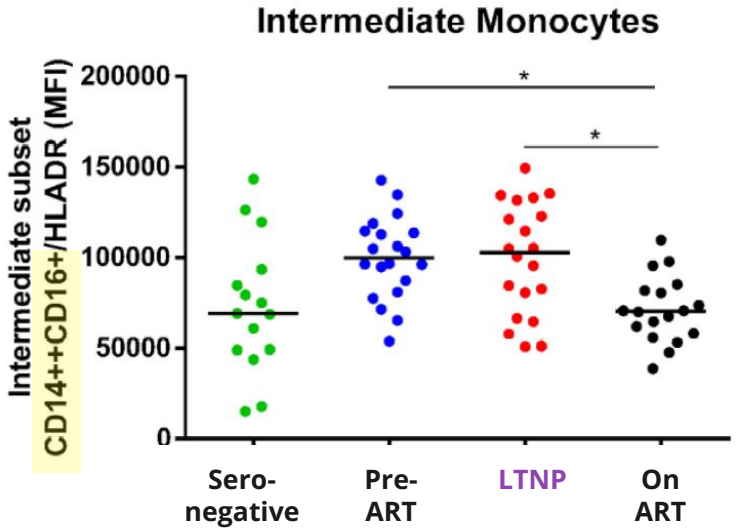
- LTNP have increased levels of **pro-atherogenic monocyte subsets**
- CD4+CD16+ **monocytes preferentially** transmigrate **across the blood brain barrier**
  - Increased monocyte activation (across the BBB) has been **associated with HAND** [**8**]



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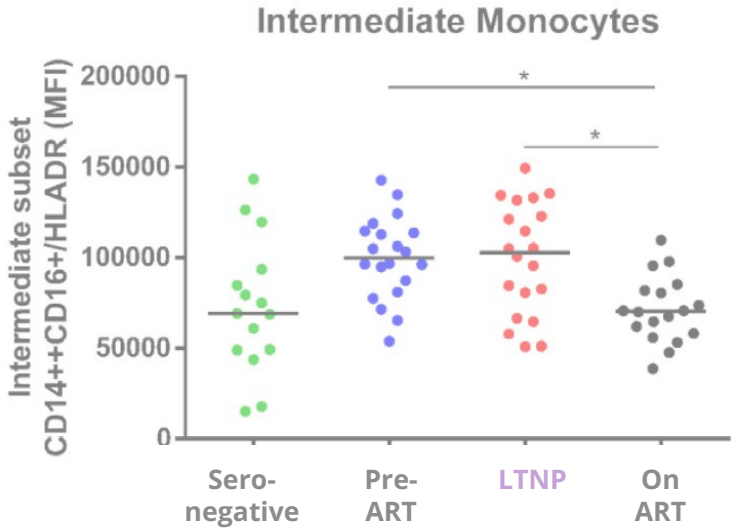
- CD4+CD16+ **monocytes preferentially** transmigrate **across the blood brain barrier**
  - Increased monocyte activation (across the BBB) has been **associated with HAND** [8]
- **Disequilibrium** between **activation markers persisted irrespective of disease progression** status (pre-ART vs LTNP)
  - But was **restored by ART**



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Immunologic aging: Telomere length [7]

LTNP have **shorter telomere length** compared to PWH on ART (or healthy controls)

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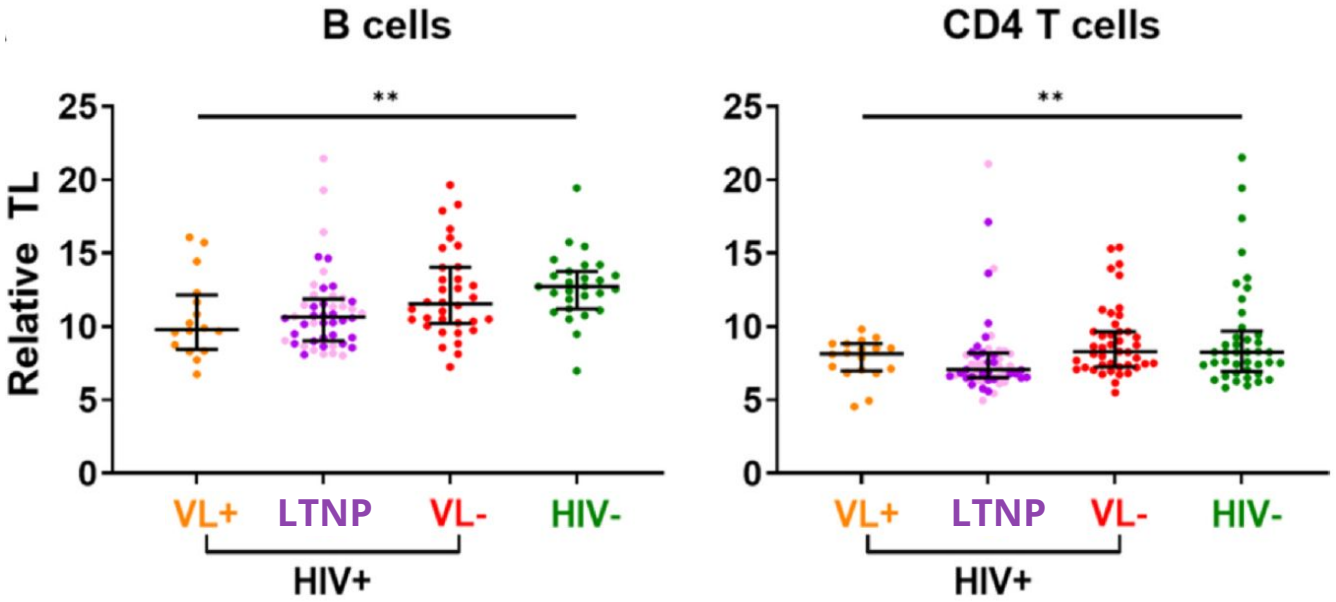
Fig 3 [7]: **Relative telomere length** (TL) compared to age+sex matched HIV groups



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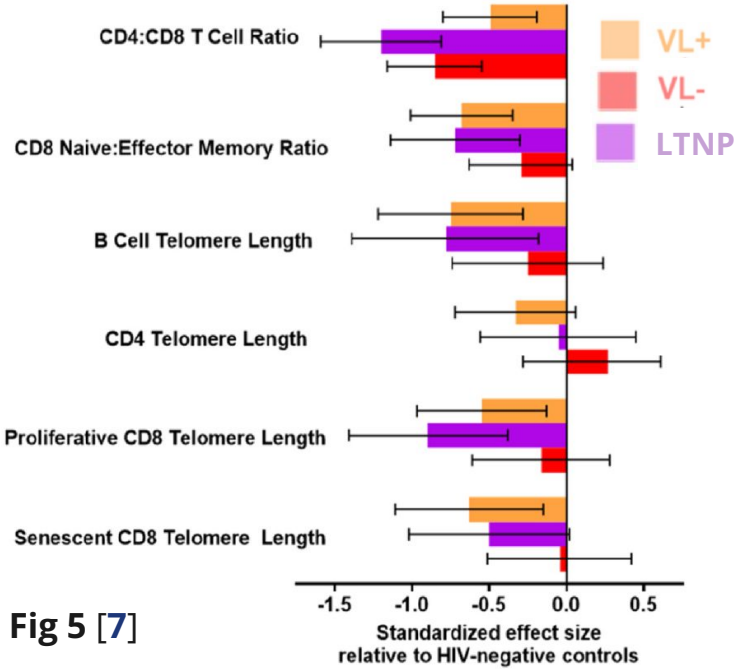

Fig 5 [7]

- Shorter telomere length seen in B cells, CD4, and CD8 cells
- Pattern **persisted even in elite controllers**

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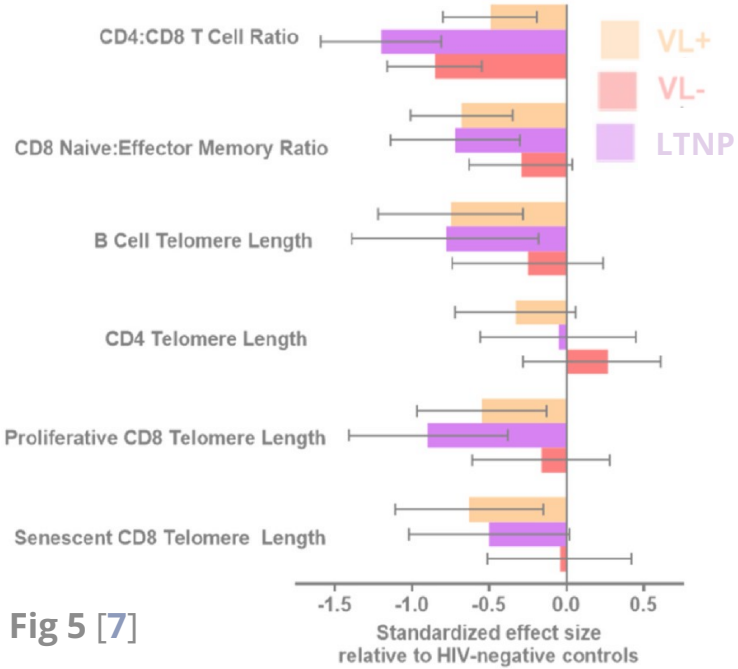

Fig 5 [7]

- Shorter telomere length seen in B cells, CD4, and CD8 cells
- Pattern **persisted even in elite controllers**

In some models, the **effect of LTNP status** can account for **more than a decade of immune aging**

- Their immune aging is **akin to** peers with **uncontrolled HIV**

Immunologic aging: **Outcomes**

- In one cohort, **elite controllers** not receiving ART were **hospitalized more often for cardiovascular and psychiatric disease** [**11**]

Immunologic aging: **Outcomes**

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- Another study found **LTNP** not receiving ART have nearly **four times higher mortality risk** [**9**]

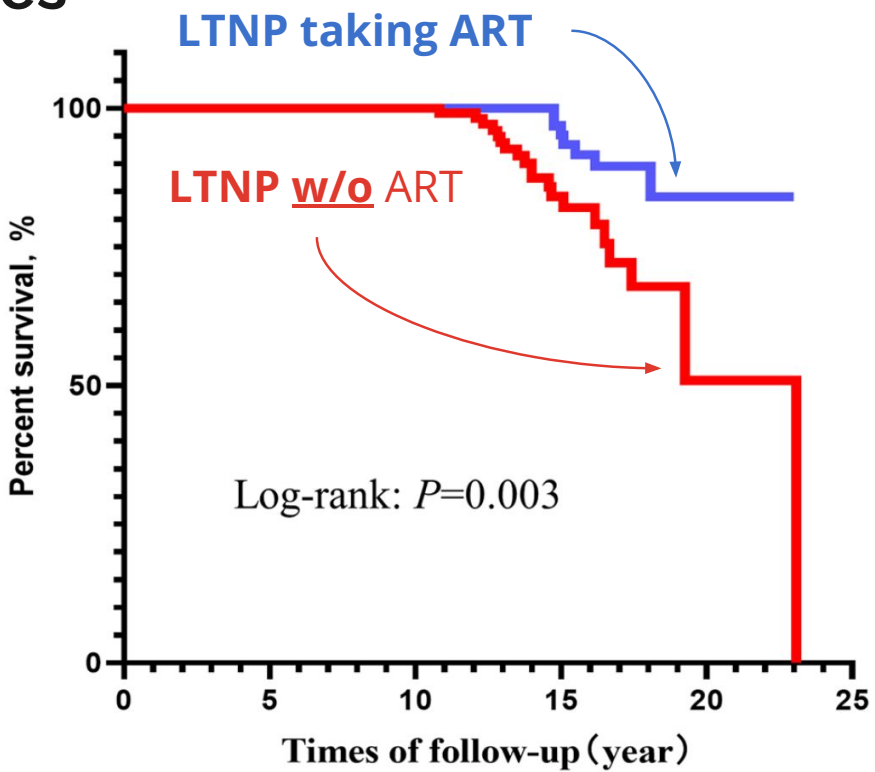
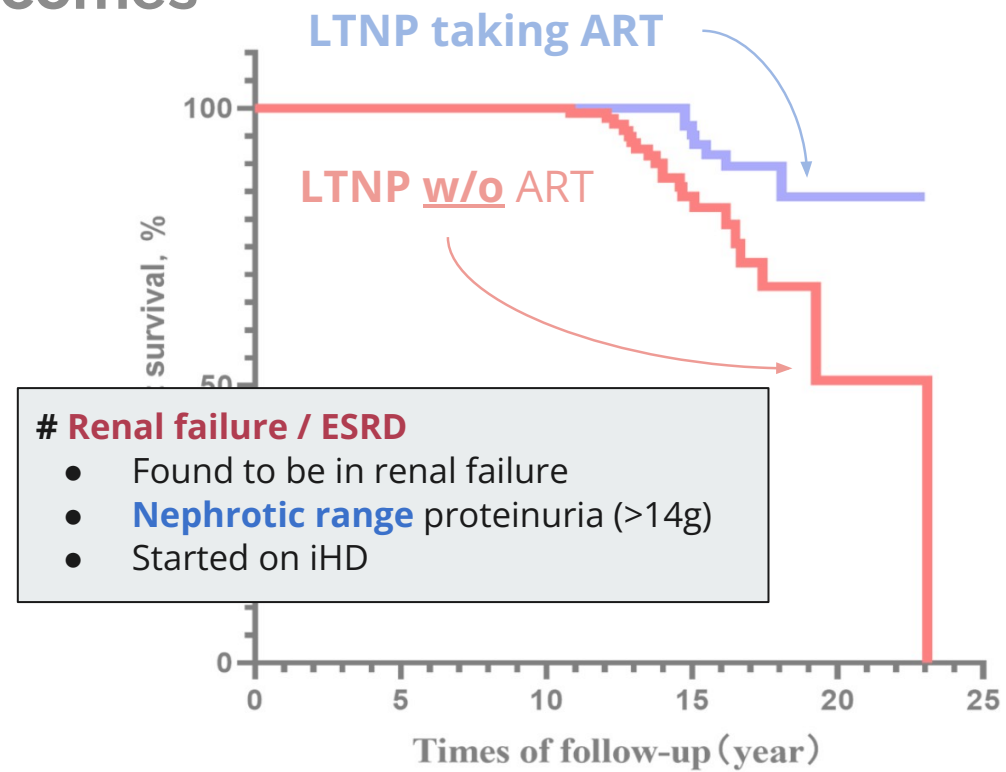


Figure 1C of citation [**9**]

Immunologic aging: Outcomes

- In one cohort, **elite controllers** not receiving ART were **hospitalized more often for cardiovascular and psychiatric disease** [11]
- Another study found **LTNP** not receiving ART have nearly **four times higher mortality risk** [9]

HIV associated nephropathy?
I couldn't find anything directly on this in LTNP, but it seems reasonable to conclude the patient's **LTNP status did not help** the kidneys



 # Renal failure / ESRD
- Found to be in renal failure
- **Nephrotic range** proteinuria (>14g)
- Started on iHD

Figure 1C of citation [9]

Should you start ART? [11]

Data is sparse, so **decision to start ART** in **elite controllers** should be **shared decision making**

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Data is sparse, so **decision to start ART** in **elite controllers** should be **shared decision making**

- No ART: Probable/possible risk of
  - Immune aging & inflammation (e.g. HAND)
  - Atherosclerosis
  - Increased mortality
- Starting ART: Small risk of
  - Bone issues
  - Renal issues
  - Other metabolic changes

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The **HHS guidelines** [**11**] “for the use of antiretroviral agents in adults and adolescents with HIV” were updated in 2025 to include:

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The Panel *strongly recommends* (**AIII**) ART for **elite controllers** with:

1. Evidence of HIV-related complications
2. Declining CD4 counts
3. Intermittent detectable viral load
4. Comorbidities (e.g., cardiovascular disease, cancer, HBV/HCV coinfection)
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This will likely be **many of the LTNP** (but not ECs)

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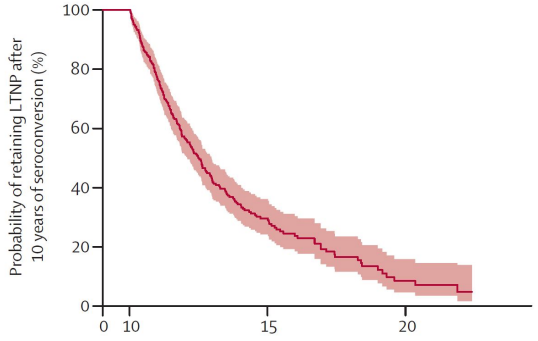

Fig 3 [**3**] Years after seroconversion

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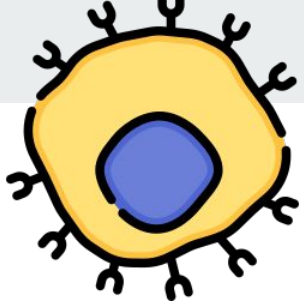
The Panel *recommends* (**BII**) initiation of ART for **all other elite controllers**

If ART is deferred, **elite controllers should be followed closely**, as some may experience CD4 count decline, loss of viral control, or complications related to HIV infection

Learning points & take aways

Learning points & take aways



- **LTNP**: CD4 >500 for 7–10 years off ART → **immunologic control**
  - Immunologic control is **usually temporary** (more like **slow progressors**)
  - After 10 years, median **time to progression 2.5 years**
- **Elite Controllers (EC)**: VL <50 copies for ≥12 months off ART → **virologic control**
  - EC are a small subset of LTNP (and only ~0.3-0.5% of PLWH)
- Control is associated with **host genetics** (**HLA-B57** and other HLA-B alleles) and **polyfunctional CD8+ T cells**
- Despite a normal CD4, the **immune system is not normal** → **accelerated immune aging**
  - When off ART, ↑ hospitalizations for **cardiovascular** (**pro-atherogenic monocyte** activation) and **psychiatric** (**BBB transmigrations**) events
- 2025 HHS ART guidance **recommends ART for most EC** (and likely all LTNP)
  - If ART is deferred, close monitoring is suggested due to risk of progression

Slides available on hunterratliff1.com/talk/; Citations available via QR code or via the "citations" button on the website