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 2: Start | Summary slide

Discussion 2: Objectives

Case #1

Case 1: HPI

A **37 y/o F** with PMH including beta thalassemia minor, **HIV** (Dx 7 years ago) who presents at **32 weeks gestation** for HIV management

Case 1: HPI

A **37 y/o F** with PMH including beta thalassemia minor, **HIV** (Dx 7 years ago) who presents at **32 weeks gestation** for HIV management

- 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**

Case 1: HPI

A **37 y/o F** with PMH including beta thalassemia minor, **HIV** (Dx 7 years ago) who presents at **32 weeks gestation** for HIV management

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

Case 1: HPI

A **37 y/o F** with PMH including beta thalassemia minor, **HIV** (Dx 7 years ago) who presents at **32 weeks gestation** for HIV management

- 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**
- **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

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
Neut abs (%)	4800 (64%)
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!

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
Neut abs (%)	4800 (64%)
Lymph abs (%)	2320 (31%)

CD4/CD8	Result
CD8 abs (%)	940 (47%)
CD4 abs (%)	**738** (37%)
CD4:CD8	0.8

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

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
Neut abs (%)	4800 (64%)
Lymph abs (%)	2320 (31%)

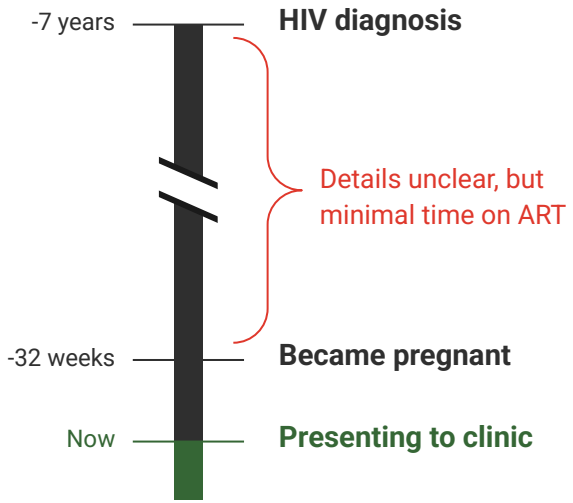
CD4/CD8	Result
CD8 abs (%)	940 (47%)
CD4 abs (%)	**738** (37%)
CD4:CD8	0.8

HIV PCR	Result
Viral load	**283**
Log VL	2.45

Case 1: Summary

A **37 y/o F** with PMH including beta thalassemia minor, **HIV** (diagnosed 7 years ago) who presents at **32 weeks gestation** for HIV management

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"



CD4/CD8	Result
CD8 abs (%)	940 (47%)
CD4 abs (%)	738 (37%)
CD4:CD8	0.8

HIV PCR	Result
Viral load	283
Log VL	2.45

Is she right?

Does she need treatment for HIV?

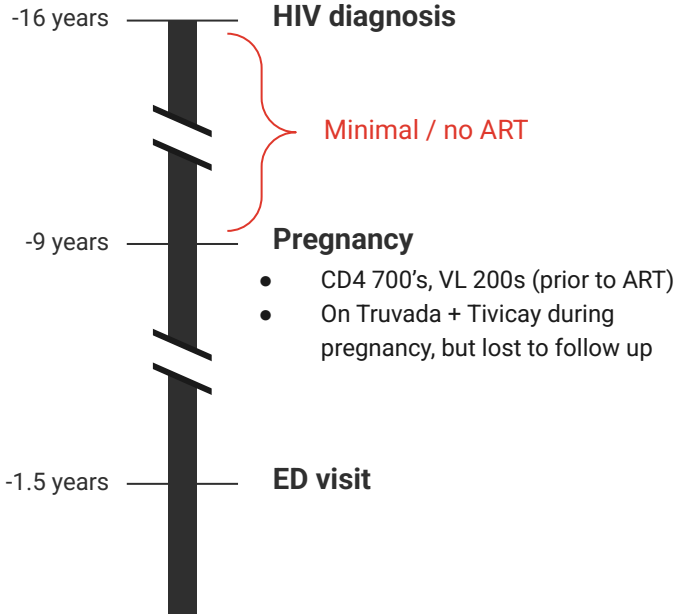
- During pregnancy?
- After pregnancy?
- Even if she doesn’t want to?

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

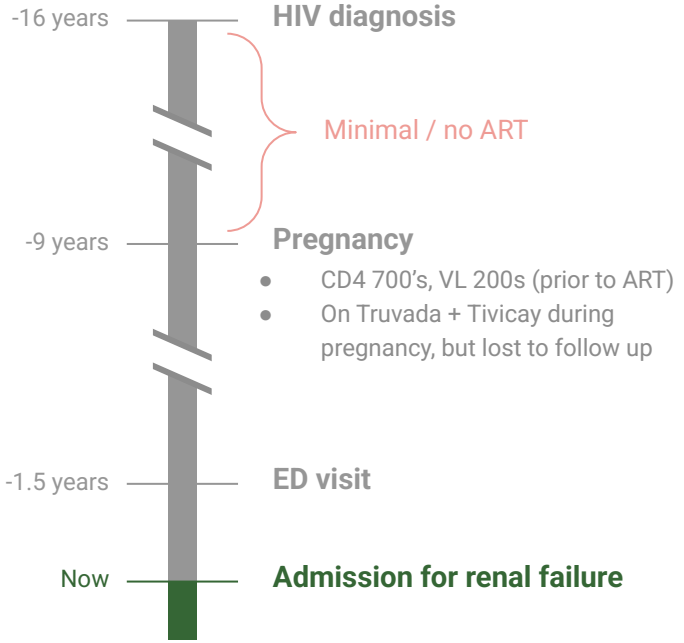


Case 1: Interim history

- **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

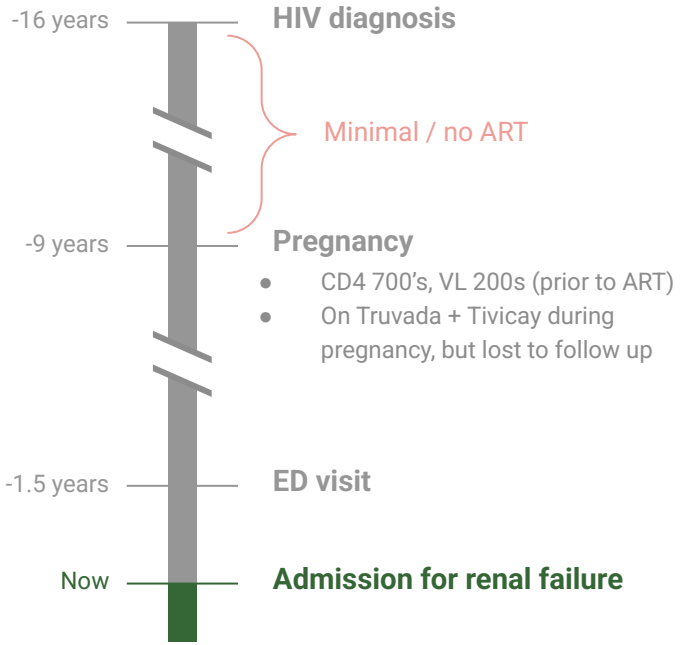
Fast forward to present day

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



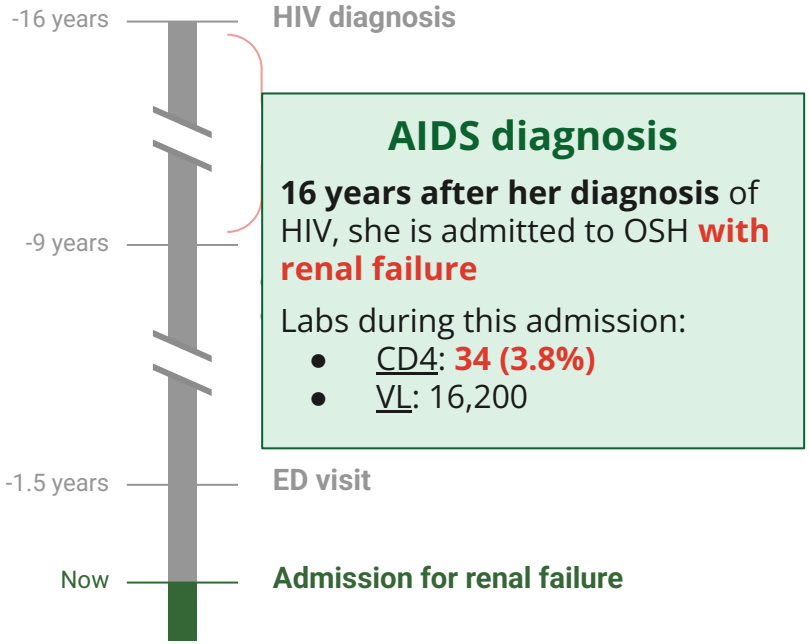
Case 1: Interim history - renal failure

Admitted for **lethargy / AMS**



Case 1: Interim history - renal failure

Admitted for **lethargy / AMS**

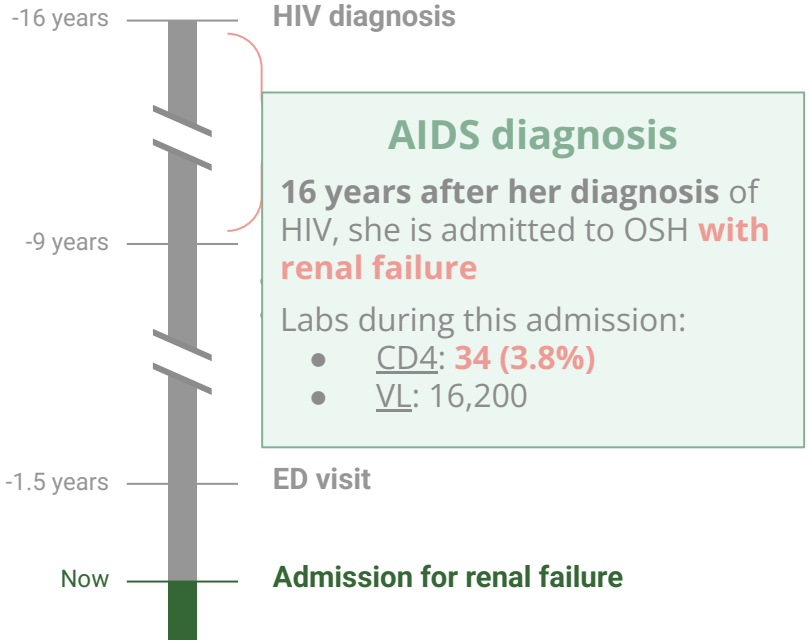


Case 1: Interim history - renal failure

Admitted for **lethargy / AMS**

 # Renal failure / ESRD

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



Case 1: Interim history - renal failure

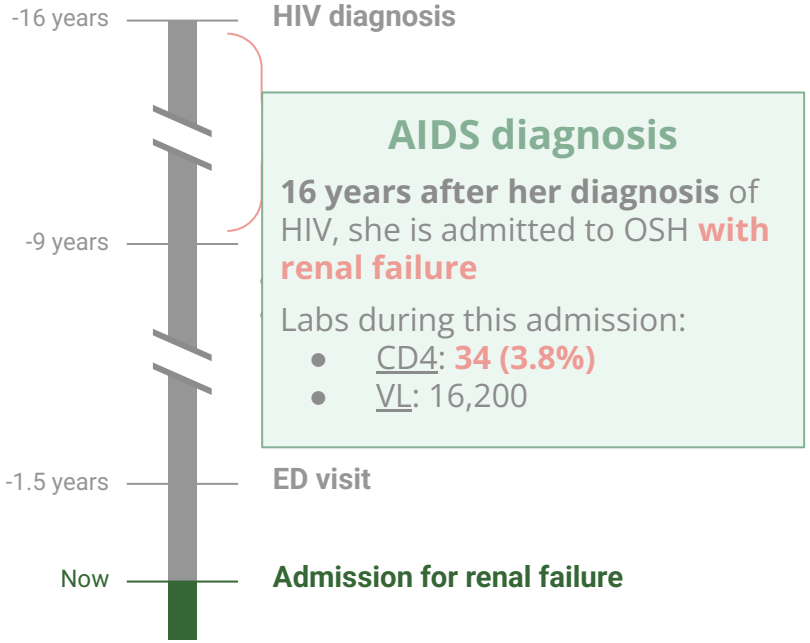
Admitted for **lethargy / AMS**

 # Renal failure / ESRD

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

 # Anemia, thrombocytopenia (severe)

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



Case 1: Interim history - renal failure

Admitted for **lethargy / AMS**

 # Renal failure / ESRD

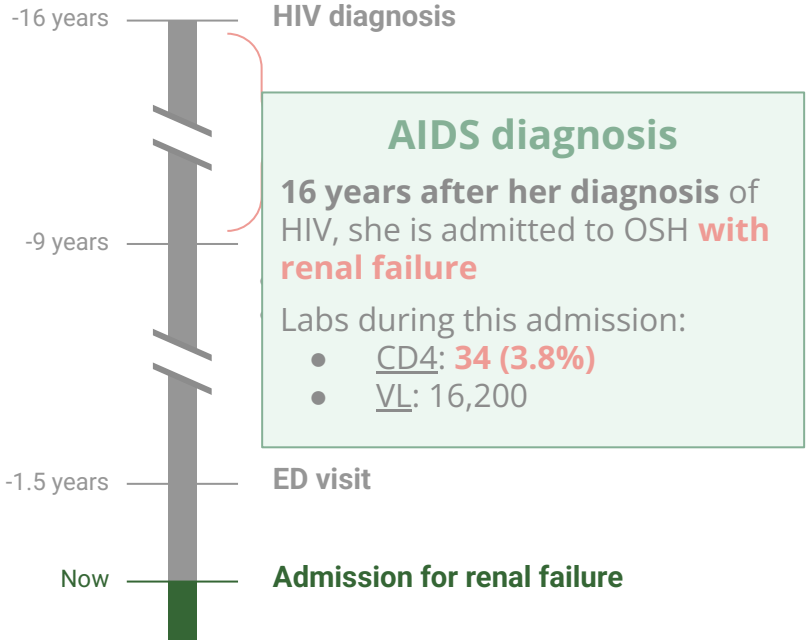
- Found to be in renal failure
  - **Nephrotic range** proteinuria (>14g)
  - Started on iHD

 # Anemia, thrombocytopenia

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

 # HIV / AIDS

- Seen by tele-ID, said to **start Biktarvy**



Case 1: Interim history - renal failure

Admitted for **lethargy / AMS**

 # Renal failure / ESRD

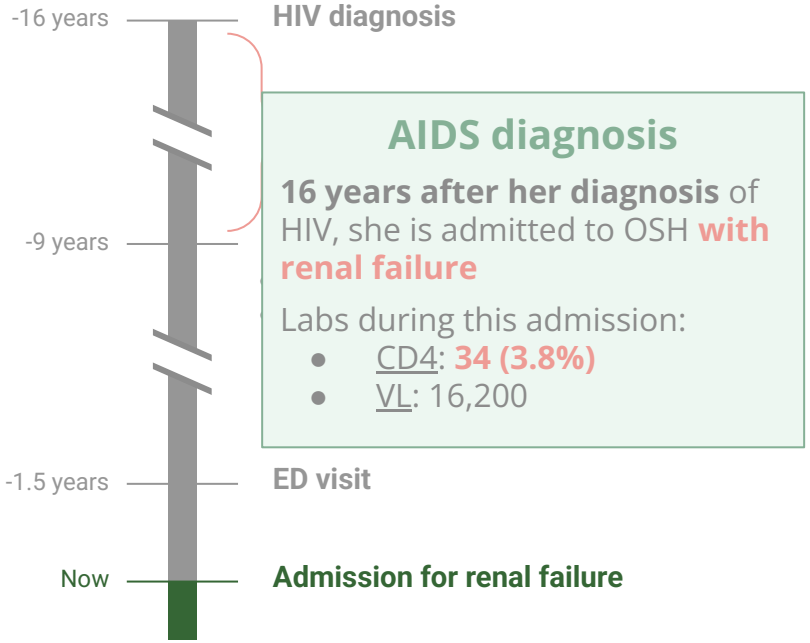
- Found to be in renal failure
  - **Nephrotic range** proteinuria (>14g)
  - Started on iHD

 # Anemia, thrombocytopenia

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

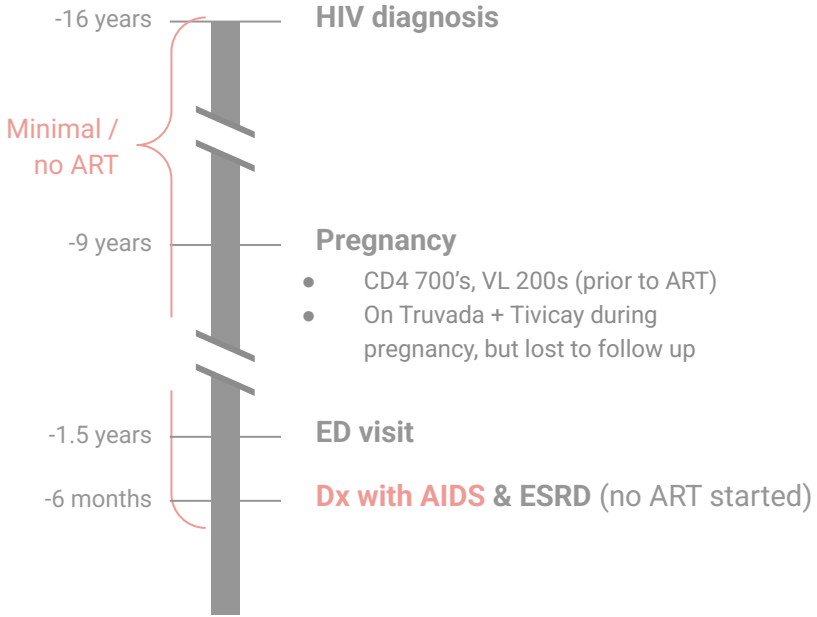
 # HIV / AIDS

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



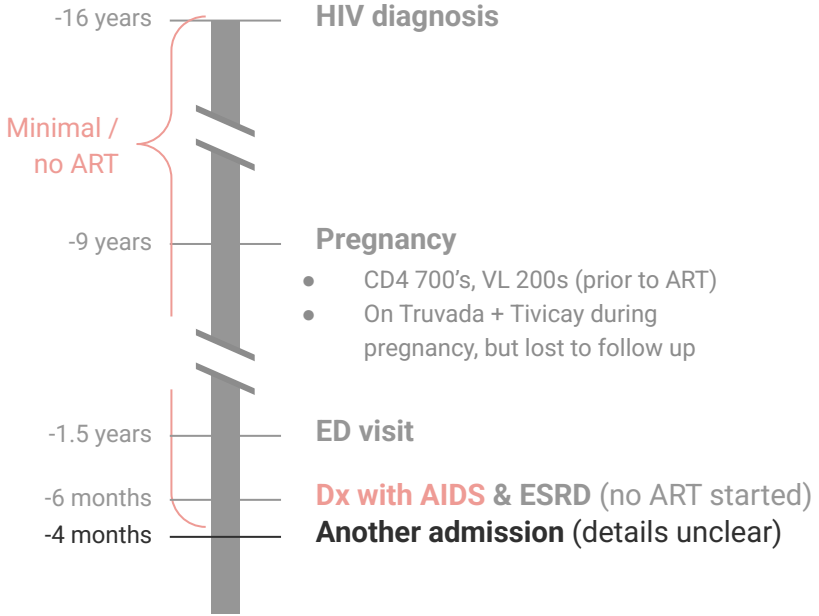
Case 1: Interim history

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



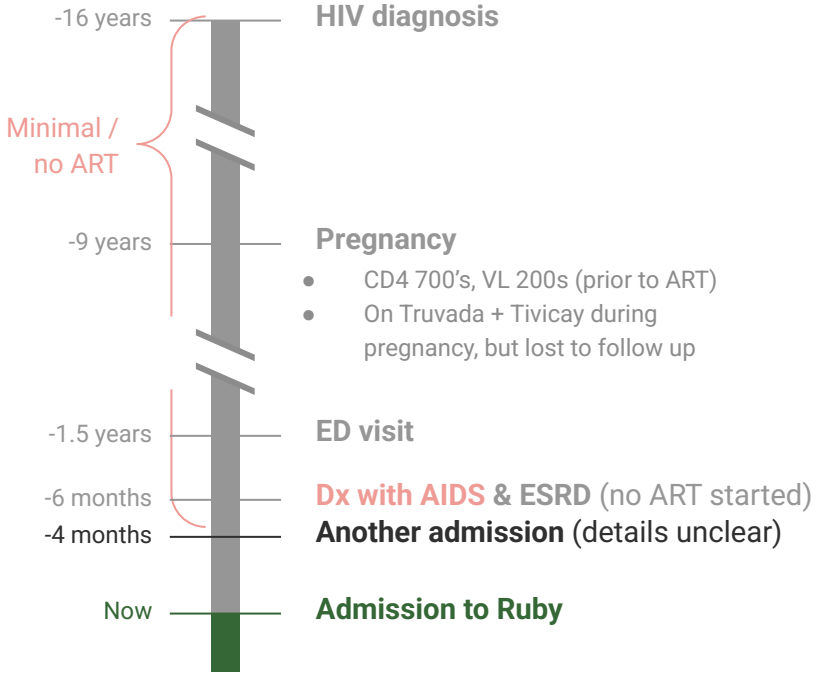
Case 1: Interim history

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



Case 1: Interim history

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

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

- Admitted to OSH (same day) with **dyspnea** and **feeling unwell**
- Had missed a few sessions of HD

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

- Admitted to OSH (same day) with **dyspnea** and **feeling unwell**
- Had missed a few sessions of HD

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

Case 1: Labs

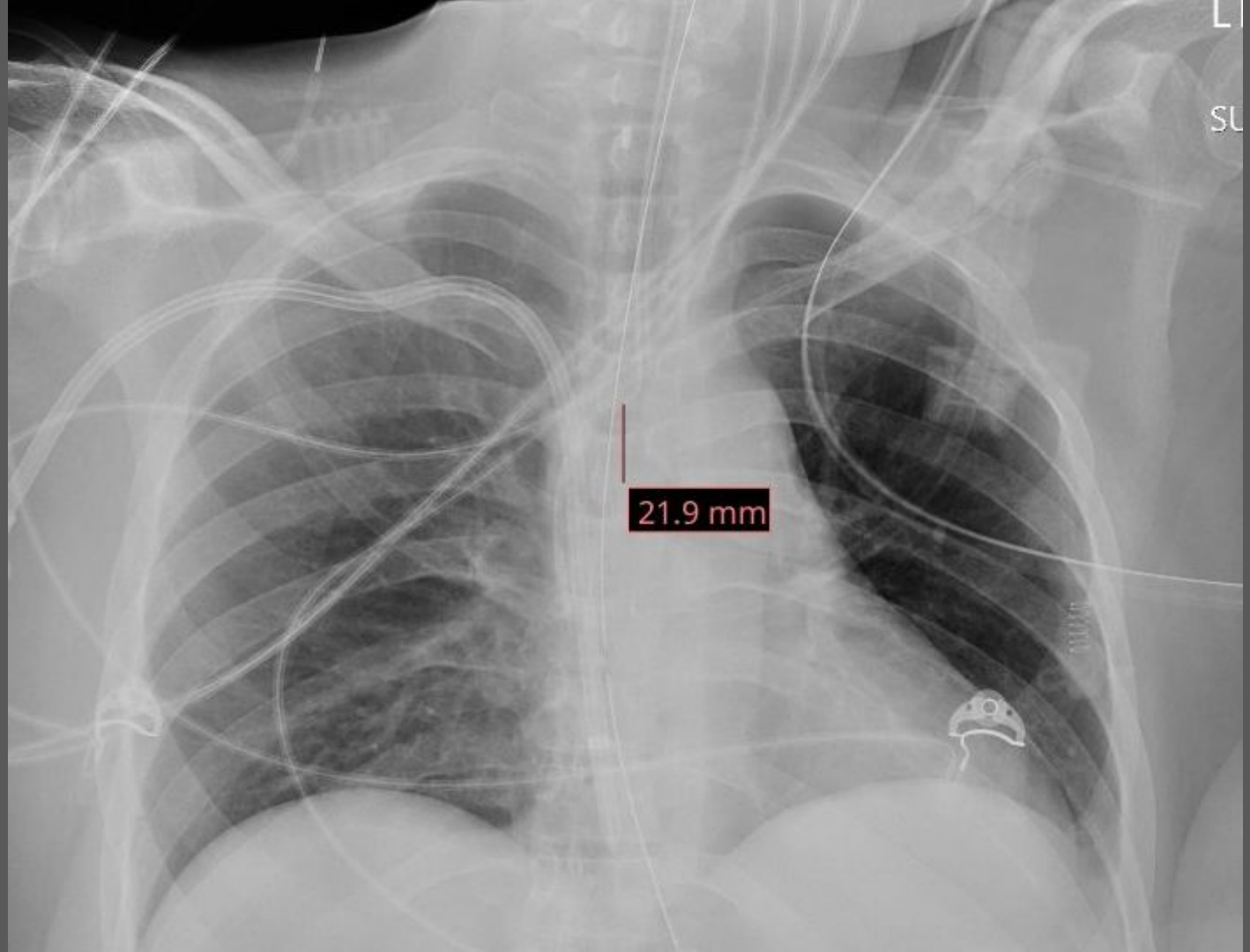
CBC	Result
WBC	8.6
Hgb	8.4
MCV	75
Platelets	70
Neut %	95%
Lymph %	4%
Lymph abs	340

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

Other	Result
LDH	203
Ferritin	5900
CRP	6.6

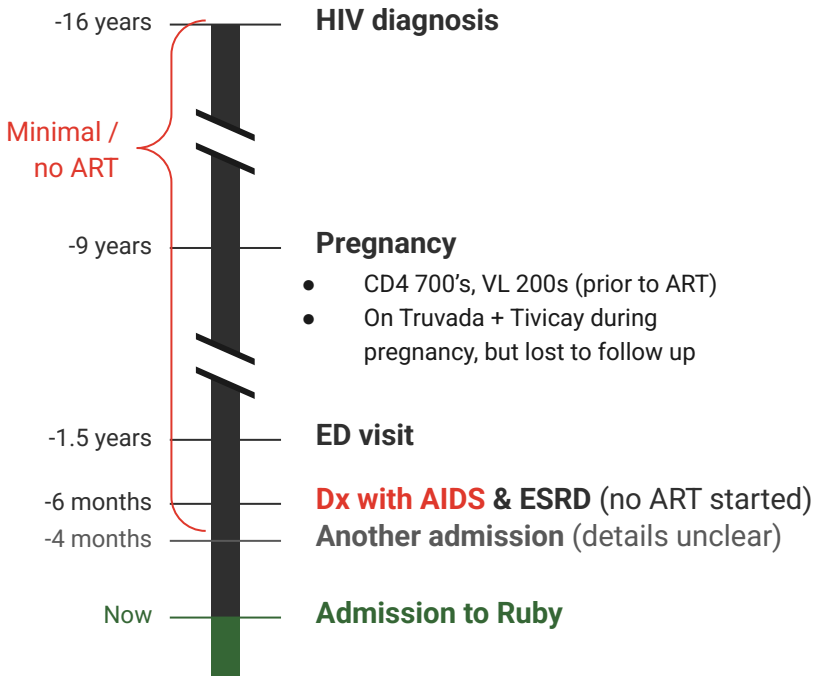
Endo	Result
TSH	10.7
Free T4	0.99
Cortisol	wnl


21.9 mm

Case 1: Summary

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** after missed HD sessions.

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

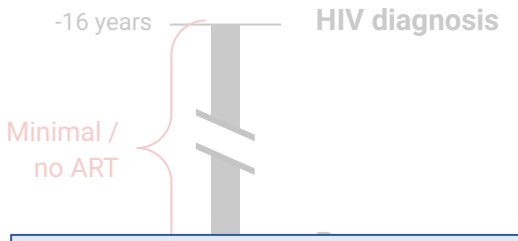


Time since diagnosis	7 yr pregnancy	15 yr ED	16 yr Dx: ESRD	16.5 yr @WVU
CD4 abs	738	75	34	???
CD4 %	37%	9.4%	3.8%	???
Viral load	283	38,100	16,200	???

Case 1: Summary

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** after missed HD sessions.

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



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				?
CD4 %	37%	9.4%	3.8%	???
Viral load	283	38,100	16,200	???

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	???
CD4 %	37%	9.4%	3.8%	???
Viral load	283	38,100	16,200	???

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

Case 1: Workup

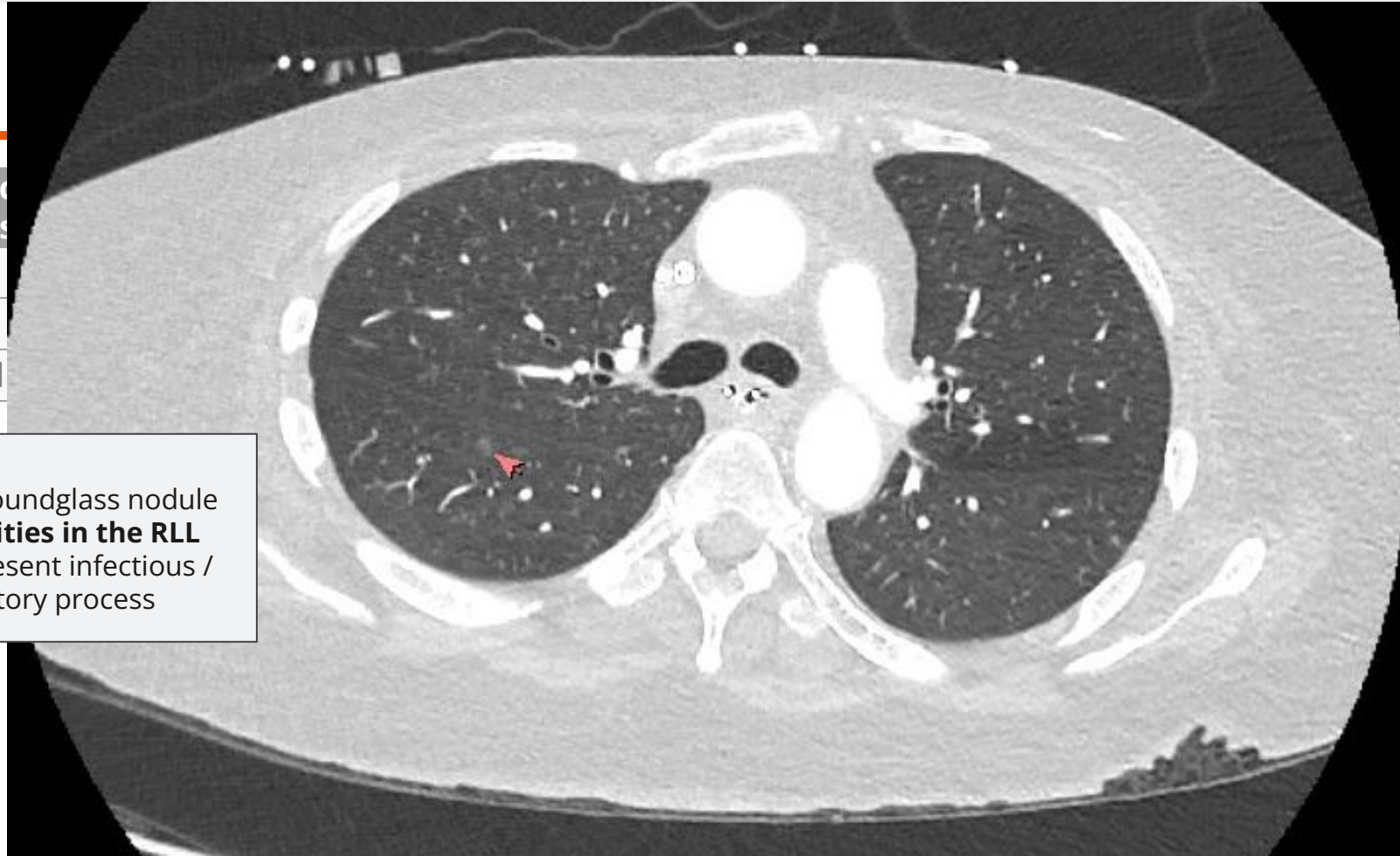
Time since diagnosis	7 yr pregnancy	15 yr ED	16 yr Dx: ESRD	16.5 yr @WVU
CD4 abs	738	75	34	104
CD4 %	37%	9.4%	3.8%	30%
Viral load	283	38,100	16,200	71

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

Case

Time sinc diagnosis
CD4 abs
CD4 %
Viral load

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



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

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

MRI brain W/WO
Unremarkable

TTE
Unremarkable

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

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

MRI brain W/WO
Unremarkable

TTE
Unremarkable

Hepatitis screen	
Hep C	
Hep B	

Spirochetes	
Lyme	
Syphilis	

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

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

MRI brain W/WO
Unremarkable

TTE
Unremarkable

Hepatitis screen	
Hep C	Neg
Hep B	wnl

Spirochetes	
Lyme	Neg
Syphilis	Neg

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

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	
AFB blood	

Hepatitis screen	
Hep C	Neg
Hep B	wnl

Spirochetes	
Lyme	Neg
Syphilis	Neg

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

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

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

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	
Serum AspGM	
Fungitell	

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

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

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	
Urine Strep	
uLegionella	
Culture	

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

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**

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

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	?	?	?
Gentamicin	?	?	?

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	**R**	**R**	**---**
Ceftolozane/tazo	**R**	**R**	**---**
Levofloxacin	?	?	?
Ciprofloxacin	?	?	?
Gentamicin	?	?	?

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	R	R	---
Ceftolozane/tazo	R	R	---
Levofloxacin	**?**	**?**	**?**
Ciprofloxacin	**?**	**?**	**?**
Gentamicin	**?**	**?**	**?**

Respiratory	
uLegionella	**Pos**
Culture	**NDM?**

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	R	R	---
Ceftolozane/tazo	R	R	---
Levofloxacin	**S (<0.12)**	**S (<0.12)**	**S (1)**
Ciprofloxacin	**S**	**S**	**S (0.5)**
Gentamicin	S	S	---

Respiratory	
uLegionella	**Pos**
Culture	**NDM?**

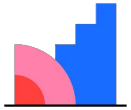
Case 1: Workup

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	R	R	---
Ceftolozane/tazo	R	R	---
Levofloxacin	S (<0.12)	S (<0.12)	S (1)
Ciprofloxacin	S	S	S (0.5)
Gentamicin	S	S	---

Respiratory	
uLegionella	**Pos**
Culture	**NDM?**

EKG: QTc **490s** (x2)

Would you use a quinolone?



Mentimeter

Remember, she came in for heart stuff...

Case 1: Hospital course

- We were actually consulted **asking if we should resume Biktarvy**

Case 1: Hospital course

- We were actually consulted **asking if we should resume Biktarvy**
  - During her prior hospital stay (OSF), infectious diseases there did an extensive workup for opportunistic infections (including a Karius?)
  - Seemed like she had been taking her Biktarvy since that discharge (was at a SNF)

Case 1: Hospital course

- We were actually consulted **asking if we should resume Biktarvy**
  - During her prior hospital stay (OSF), infectious diseases there did an extensive workup for opportunistic infections (including a Karius?)
  - Seemed like she had been taking her Biktarvy since that discharge (was at a SNF)
- **Resumed Biktarvy**

Case 1: Hospital course

- We were actually consulted **asking if we should resume Biktarvy**
  - During her prior hospital stay (OSF), infectious diseases there did an extensive workup for opportunistic infections (including a Karius?)
  - Seemed like she had been taking her Biktarvy since that discharge (was at a SNF)
- **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**

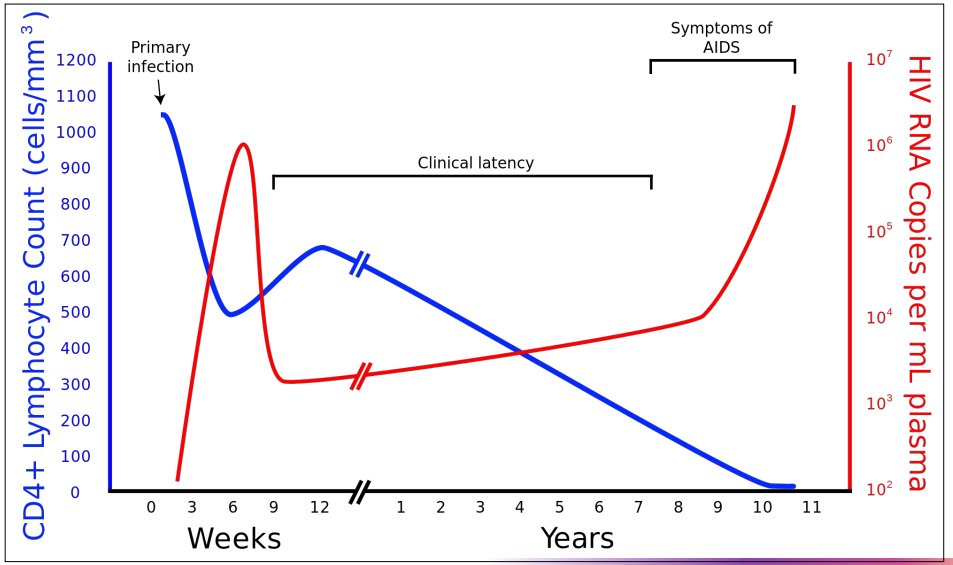
Spectrum of HIV phenotypes [4]

- **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

Elite controllers

Spectrum of HIV phenotypes [4]

- **Typical progressors**: The majority of people living with HIV
- **Long term non-progressors**: People infected with HIV but who remain clinically and immunologically stable (i.e. **normal CD4**) for extended periods without ART

Spectrum of HIV phenotypes [4]

- **Typical progressors**: The majority of people living with HIV
- **Long term non-progressors**: People infected with HIV but who remain clinically and immunologically stable (i.e. **normal CD4**) for extended periods without ART
- **Viremic controllers**: People with HIV who maintain **low viral loads** (but detectable) without therapy

Spectrum of HIV phenotypes [4]

- **Typical progressors**: The majority of people living with HIV
- **Long term non-progressors**: People infected with HIV but who remain clinically and immunologically stable (i.e. **normal CD4**) for extended periods without ART
- **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]

	Long term non-progressors	Elite controllers
Prevalence	~5% of PLWH	0.3-0.5% of PLWH [1] • Subset of **LTNP**

Spectrum of HIV phenotypes [2]

	Long term non-progressors	Elite controllers
Prevalence	~5% of PLWH	0.3-0.5% of PLWH [1] • Subset of **LTNP**
Definition (off of ART)	**CD4 >500** for **7-10 years**	**VL < 50** for **12 months**

Spectrum of HIV phenotypes [2]

	Long term non-progressors	Elite controllers
Prevalence	~5% of PLWH	0.3-0.5% of PLWH [1] • Subset of **LTNP**
Definition (off of ART)	**CD4 >500** for **7-10 years** • Defined by *immunologic control*	**VL < 50** for **12 months**
Immunologic control	**Yes** (for a while at least)	...
Virologic control	**No** (usually low-moderate viremia [1])	...

Virologic control

Immunologic control

Long term non-progressors — Elite controllers

Spectrum of HIV phenotypes [2]

	Long term non-progressors	Elite controllers
Prevalence	~5% of PLWH	0.3-0.5% of PLWH [1] • Subset of **LTNP**
Definition (off of ART)	**CD4 >500** for **7-10 years** • Defined by *immunologic control*	**VL < 50** for **12 months** • Defined by *virologic control*
Immunologic control	**Yes** (for a while at least)	**Usually**
Virologic control	**No** (usually low-moderate viremia [1])	**Yes**

Virologic control

Immunologic control

Long term non-progressors — Elite controllers

LTNP: Natural history

- Immunologic control is **rarely permanent [5]**
  - Most establish virologic control within a year of seroconversion

LTNP: Natural history

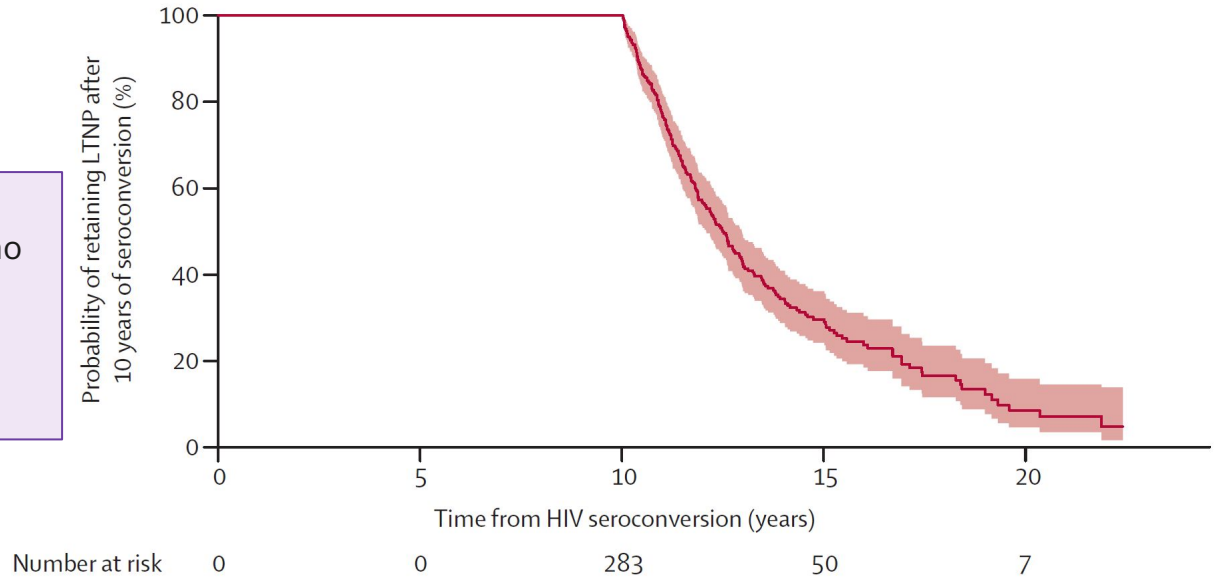
- Immunologic control is **rarely permanent** [5]
  - Most establish virologic control within a year of seroconversion
- After some time, most controllers will lose their ability to control the virus → **CD4 will drop eventually** [1][3-4]

LTNP: Natural history

- Immunologic control is **rarely permanent** [5]
  - Most establish virologic control within a year of seroconversion
- After some time, most controllers will lose their ability to control the virus → **CD4 will drop eventually** [1][3-4]

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

"**CD4 ≥500** for **7-10 years**"



LTNP: Natural history [5]

- Immunologic control is **rarely permanent**
- After some time, most controllers will lose their ability to control the virus → **CD4 will drop eventually** [1][3-4]
- **Median time** [3] to **loss of immunologic control** (after the 10 year period): **2.5 years**

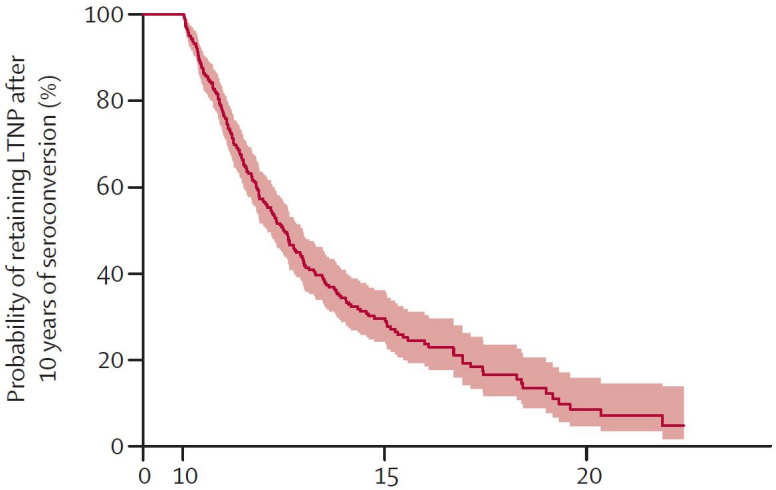


Fig 3 [3] Years after seroconversion

LTNP: Natural history [3]

- Immunologic control is **rarely permanent**
  - After some time, **CD4 will drop eventually** [1][3,4,5], median of **2.5 years** [3]

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:

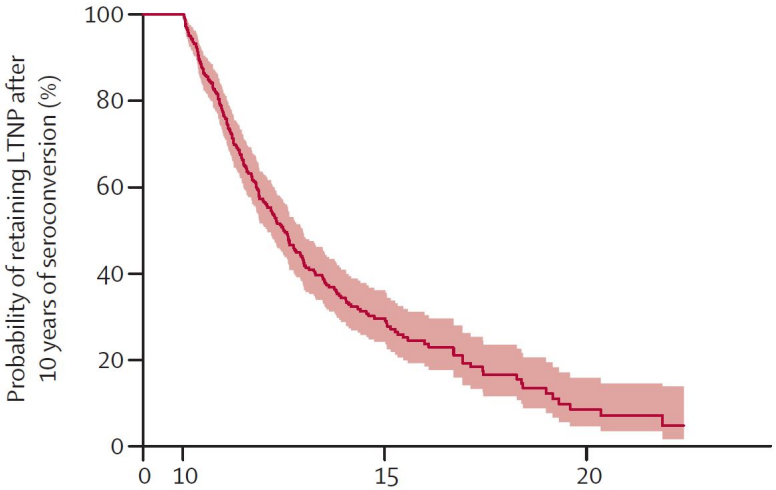


Fig 3 [3] Years after seroconversion

LTNP: Natural history [3]

- Immunologic control is **rarely permanent**
  - After some time, **CD4 will drop eventually** [1][3,4,5], median of **2.5 years** [3]

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:

- Not predictive: Age, sex, HIV risk factor
- Not predictive: Baseline or nadir CD4

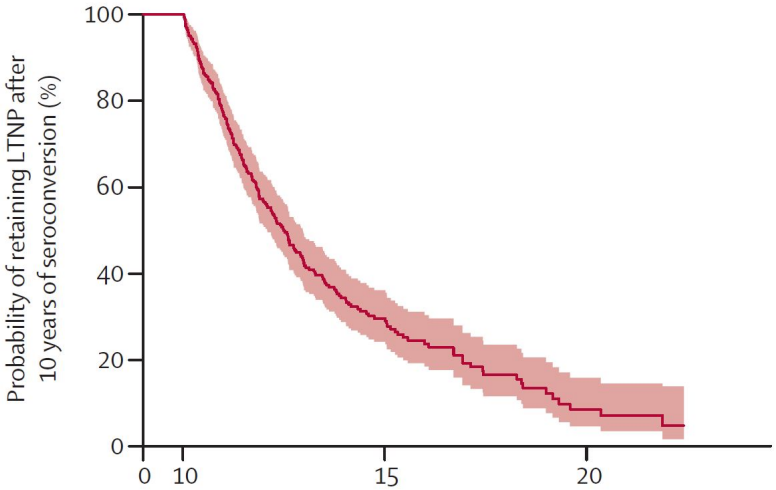


Fig 3 [3] Years after seroconversion

LTNP: Natural history [3]

- Immunologic control is **rarely permanent**
  - After some time, **CD4 will drop eventually** [1][3,4,5], median of **2.5 years** [3]

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:

- Not predictive: Age, sex, HIV risk factor
- Not predictive: Baseline or nadir CD4
- **CD4 count** at 10 years (↓ CD4 = ↑ risk)

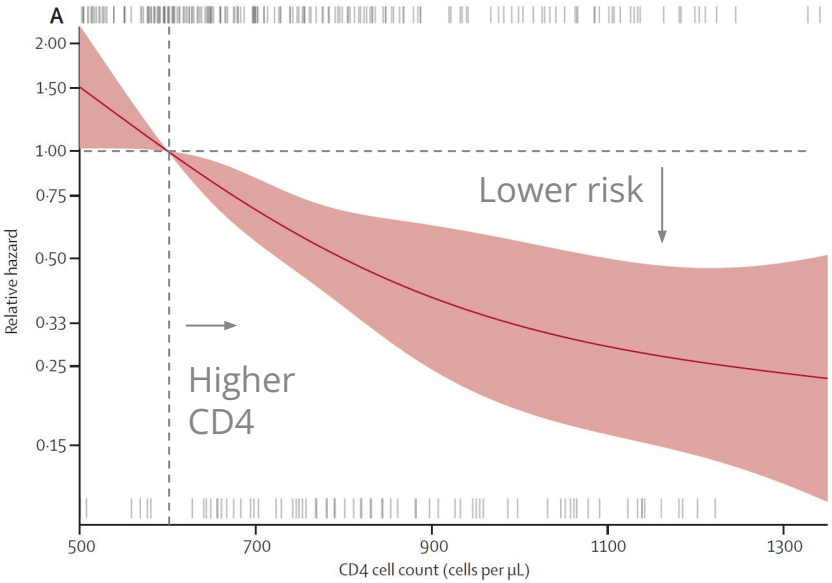


Fig 4a [3]

LTNP: Natural history [3]

- Immunologic control is **rarely permanent**
  - After some time, **CD4 will drop eventually** [1][3,4,5], median of **2.5 years** [3]

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:

- Not predictive: Age, sex, HIV risk factor
- Not predictive: Baseline or nadir CD4
- **CD4 count** at 10 years (↓ CD4 = ↑ risk)
- **Viral load** at 10 years (↑ VL = ↑ risk)

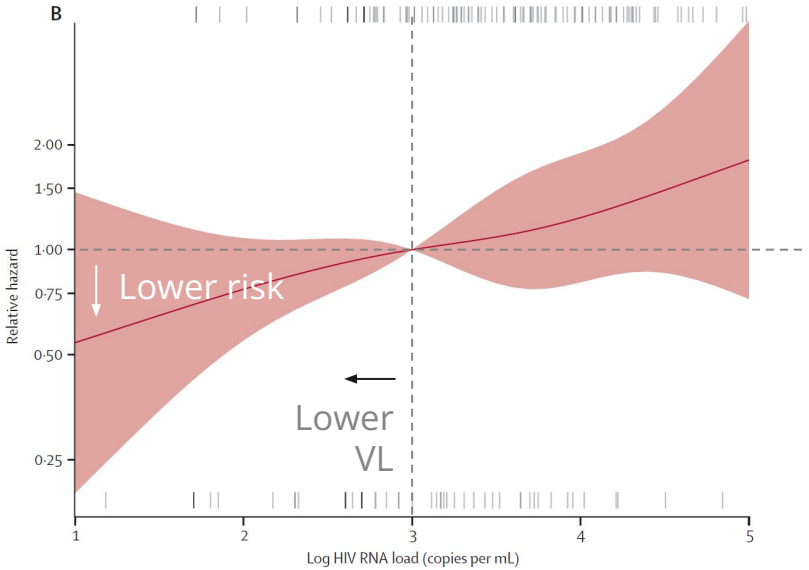


Fig 4b [3]

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)

- This has led some authors [**4**] to conclude that "long term non-progressors" may just be "slow progressors"

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)

- This has led some authors [4] to conclude that "long term non-progressors" may just be "slow progressors"
    - This is highlighted by looking at studies with varying definitions of "LTNP" [see 5]

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

"**CD4 ≥500** for **7-10 years**"

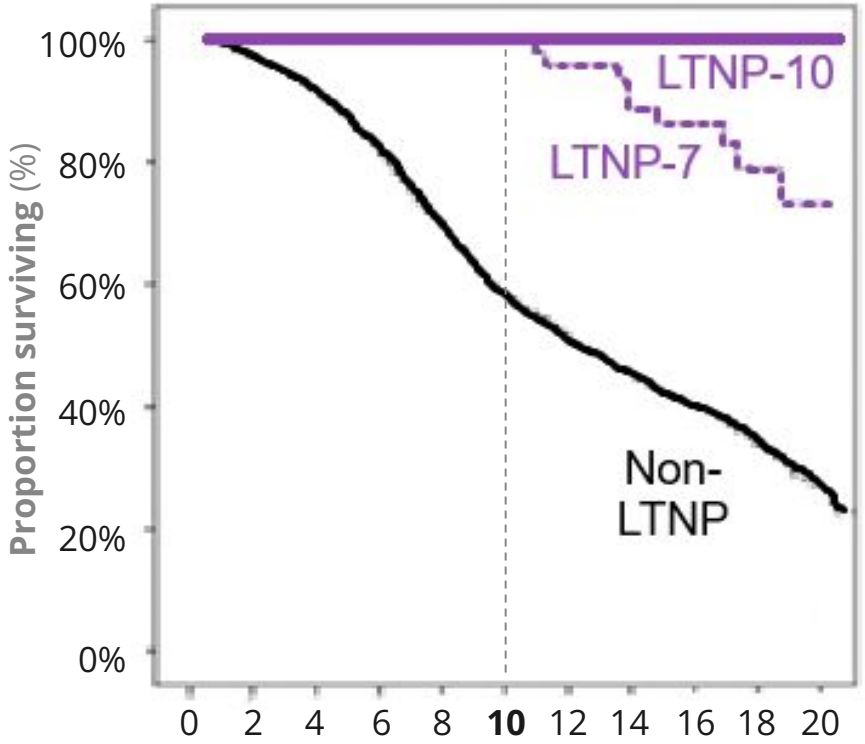


Fig 4C [5]

EC: Natural history

Compare this with **elite controllers** (those with extraordinary virologic control)

EC: Natural history

Compare this with **elite controllers** (those with extraordinary virologic control)

- Tend to have **excellent immunologic control** [5]

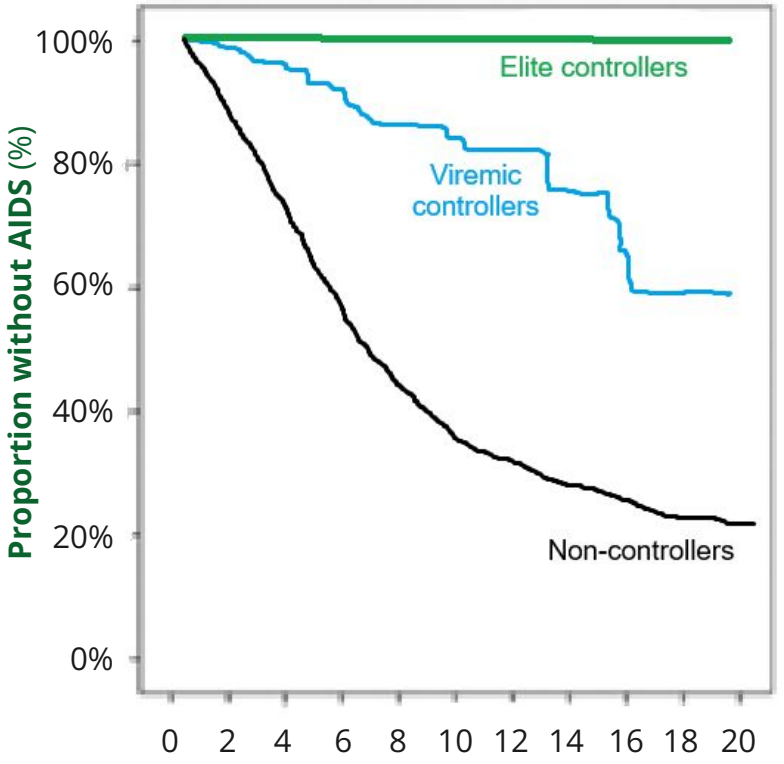


Fig 3C [5]

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)

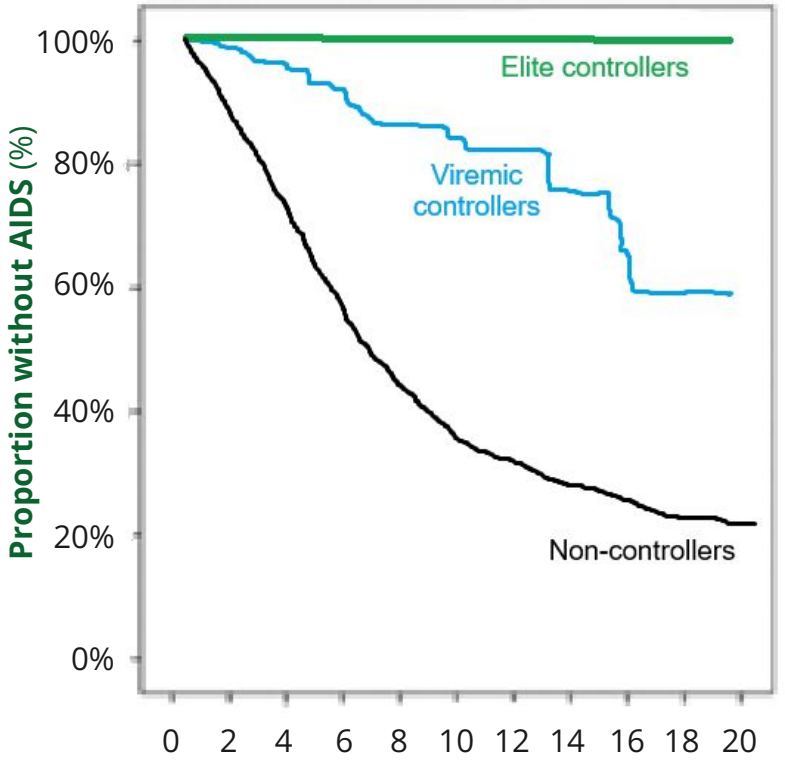


Fig 3C [**5**]

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**
  - This is much lower than the rate of AIDS defining illnesses in the cohort with a viral load >50 (25 events in 153 patients; **16%**)

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**
  - This is much lower than the rate of AIDS defining illnesses in the cohort with a viral load >50 (25 events in 153 patients; **16%**)
- In another study [1], the only AIDS defining illness was a case of **Kaposi sarcoma**
  - CD4 cell count was 630/μL

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**
  - This is much lower than the rate of AIDS defining illnesses in the cohort with a viral load >50 (25 events in 153 patients; **16%**)
- In another study [1], the only AIDS defining illness was a case of **Kaposi sarcoma**
  - CD4 cell count was 630/µL

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]

	Defined based on	Virologic control	Typical viral load	Immunologic control
Elite controllers	**Virologic** control	**Excellent** (by def)	<50 [2]	Usually **great** long term
Viremic controllers	**Virologic** control	Good	50 - 2,000 [6]	Good, for awhile
Long term non-progressors	**Immunologic** control	**Fair**, for awhile	1-10k [1] (usually 2k)	By definition (but **wanes** w/ time)

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]
2. Unless you have virologic control, immunologic control is **rarely permanent** [1]
   - Stable viral load generally → stable CD4 [5]

	Defined based on	Virologic control	Typical viral load	Immunologic control
Elite controllers	**Virologic** control	**Excellent** (by def)	<50 [2]	Usually **great** long term
Viremic controllers	**Virologic** control	Good	50 - 2,000 [6]	Good, for awhile
Long term non-progressors	**Immunologic** control	**Fair**, for awhile	1-10k [1] (usually 2k)	By definition (but **wanes** w/ time)

Themes thus far

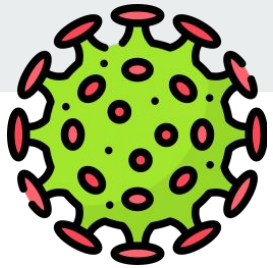
1. "**Non-progressors**" can be categorized via immunologic control (e.g. **long term nonprogressors**) and virologic control (e.g. **elite controllers**)
    - These terms likely **exist on a continuum** [4]
2. Unless you have virologic control, immunologic control is **rarely permanent** [1]
    - Stable viral load generally → stable CD4 [5]
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

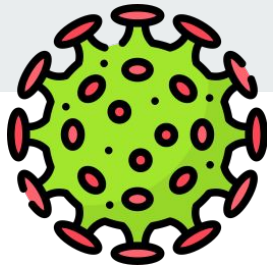
- Define **elite controllers** (EC) and **long term non-progressors** (LTNP)
  - Distinguish between **immunologic control** and **virologic control**
  - Contrast the **natural history**
  - Describe the **risk factors for progression**
- Investigate the current understanding of the **pathophysiology 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**

HIV control: **Viral factors**



Tempting to suspect that HIV control in these patients is due to **defective/attenuated viral strains**, but this **generally is not the case** [1], with the notable exceptions below:

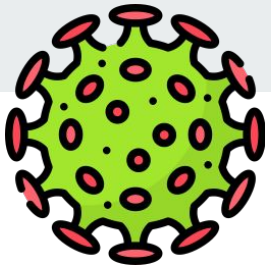
HIV control: **Viral factors**



Tempting to suspect that HIV control in these patients is due to **defective/attenuated viral strains**, but this **generally is not the case** [1], with the notable exceptions below:

- **Sydney blood bank cohort**: six recipients of blood (from a **LTNP**) developed HIV and became all **became LTNP as well** [**10**]
  - This viral strain had **deletions in the *nef* gene** [**2**]
  - Most of these LTNP eventually did have progression of their disease [**10**]

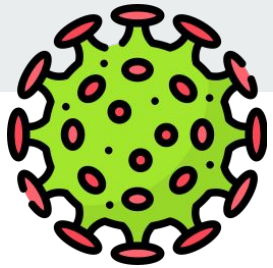
HIV control: **Viral factors**



Tempting to suspect that HIV control in these patients is due to **defective/attenuated viral strains**, but this **generally is not the case** [1], with the notable exceptions below:

- **Sydney blood bank cohort**: six recipients of blood (from a **LTNP**) developed HIV and became all **became LTNP as well** [10]
  - This viral strain had **deletions in the *nef* gene** [2]
  - Most of these LTNP eventually did have progression of their disease [10]
- Some strains (in other LTNP) have shown **other mutations** in genes that **reduce the rate of viral replication** (e.g. ↓ IL10 ⇒ ↓expression of CCR5) [2]

HIV control: **Viral factors**



Tempting to suspect that HIV control in these patients is due to **defective/attenuated viral strains**, but this **generally is not the case** [1], with the notable exceptions below:

- **Sydney blood bank cohort**: six recipients of blood (from a **LTNP**) developed HIV and became all **became LTNP as well** [10]
  - This viral strain had **deletions in the *nef* gene** [2]
  - Most of these LTNP eventually did have progression of their disease [10]
- Some strains (in other LTNP) have shown **other mutations** in genes that **reduce the rate of viral replication** (e.g. ↓ IL10 ⇒ ↓expression of CCR5) [2]

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

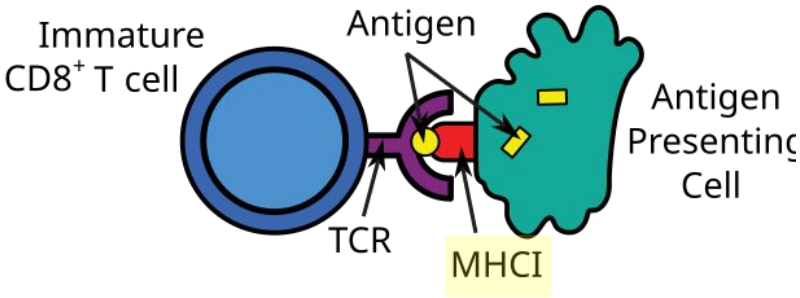
Pathophysiology: **Cell mediated immunity**

- 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**

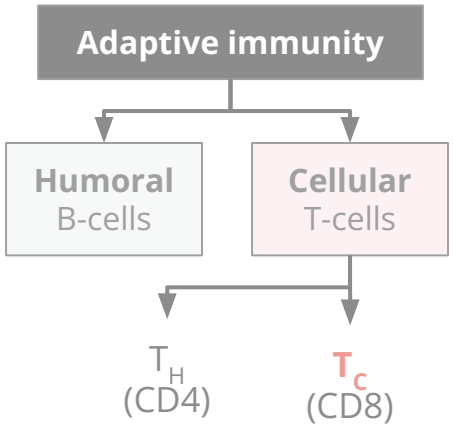
HIV control: The immune system

HLA genes encode major histocompatibility complex proteins

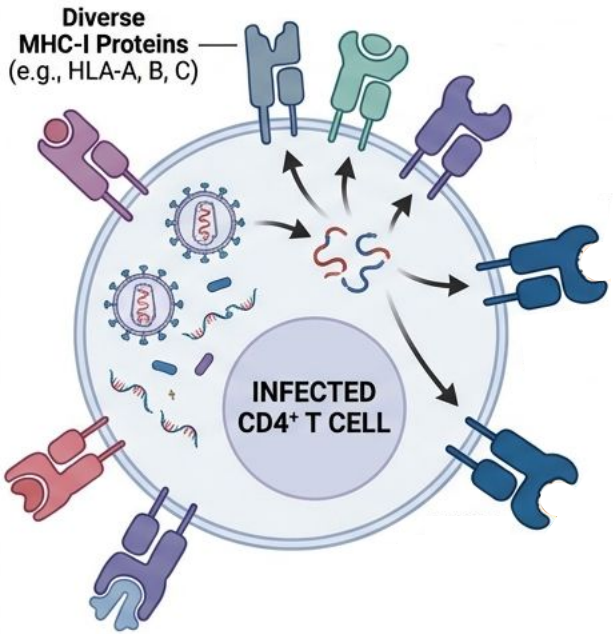
- In this case we care about **MHC-I** (HLA A-C)



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



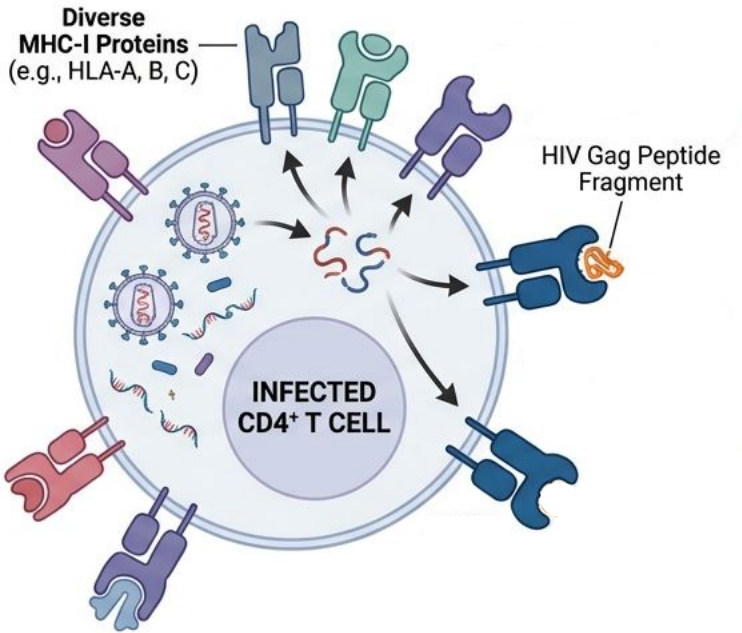
HIV control: Host genetics [2][10]



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**

HIV control: Host genetics [2][10]

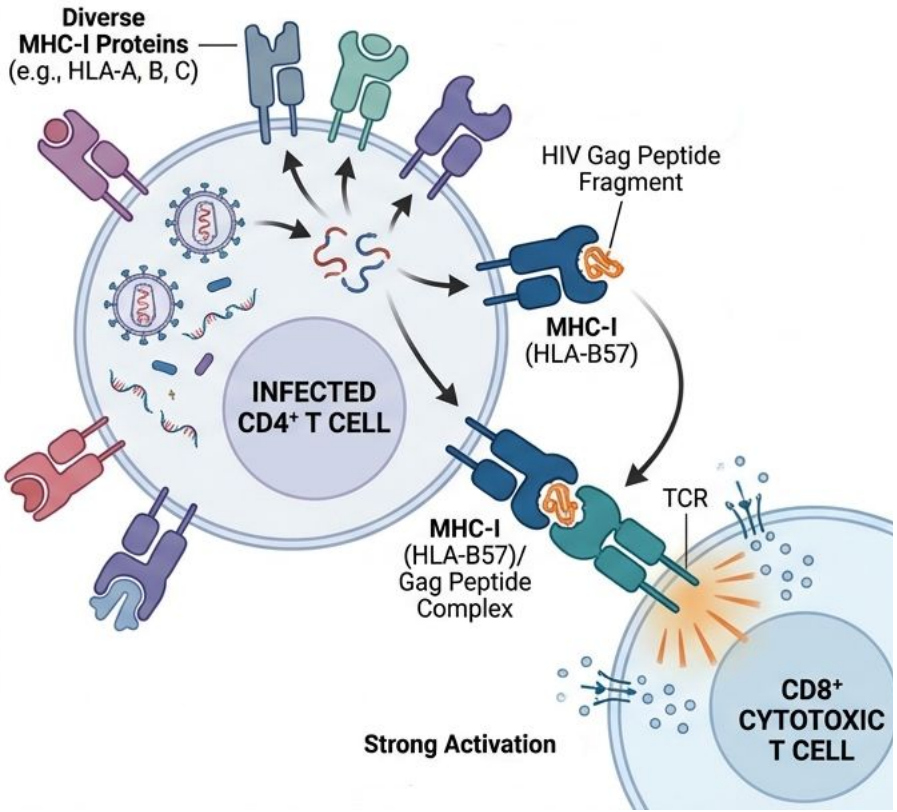


The strongest association with HIV control is the presence of specific HLA Class I alleles

- **Heterozygous HLA class-I genotype** is linked to slower disease development by allowing the presentation of a **broader spectrum of HIV peptides**
- **HLA-B57** variations (e.g. B5701 & B5703) in particular elicit a **strong response to the *Gag*** epitopes of HIV

Same one as for abacavir (but this time you want to have it)

HIV control: Host genetics [2][10]

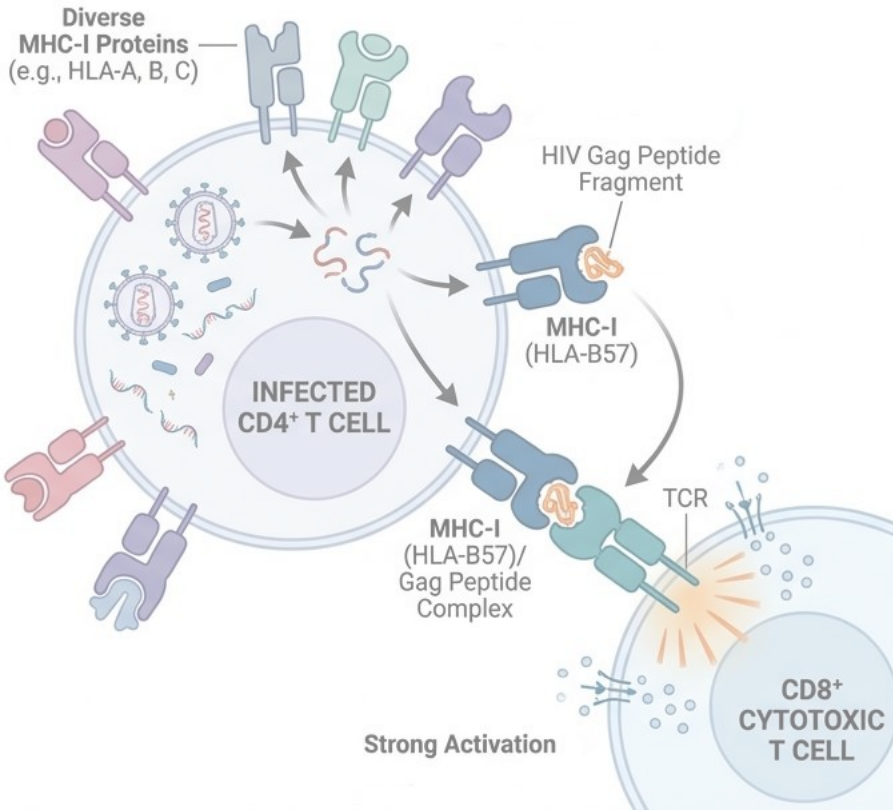


The strongest association with HIV control is the presence of specific HLA Class I alleles

- **Heterozygous HLA class-I genotype** is linked to slower disease development by allowing the presentation of a **broader spectrum of HIV peptides**
- **HLA-B57** variations (e.g. B5701 & B5703) in particular elicit a **strong response** **to the *Gag*** epitopes of HIV
  - This in turn leads to **strong activation of CD8+ cytotoxic T cells → Killing of infected CD4+ cells**

Same one as for abacavir (but this time you want to have it)

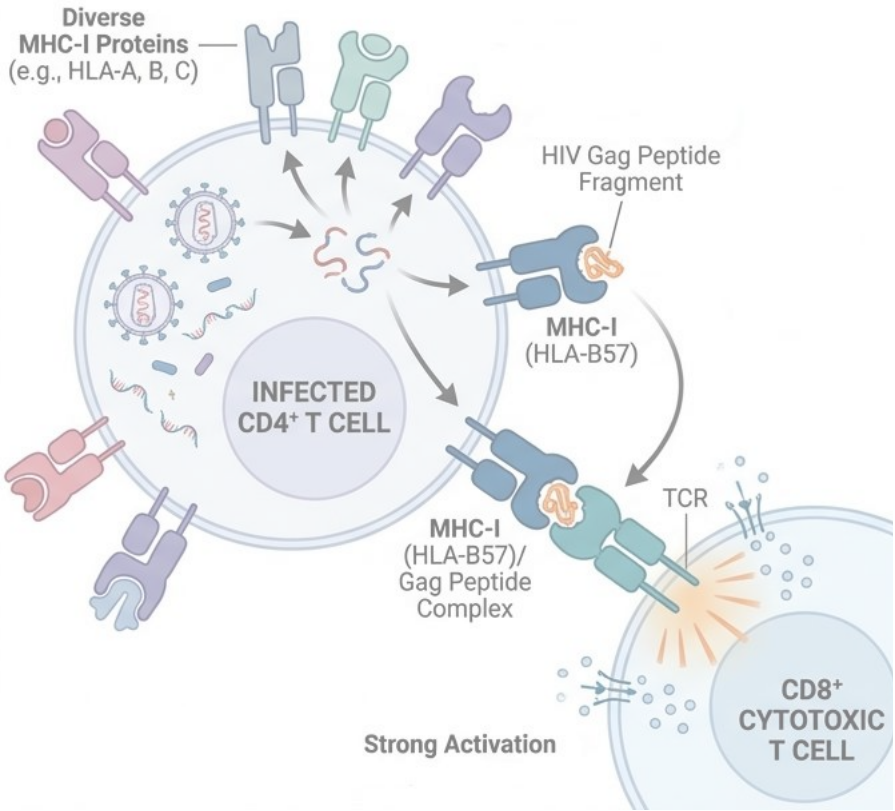
HIV control: Host genetics [2][10]



The strongest association with HIV control is the presence of specific HLA Class I alleles, specifically HLA-B57

- 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)

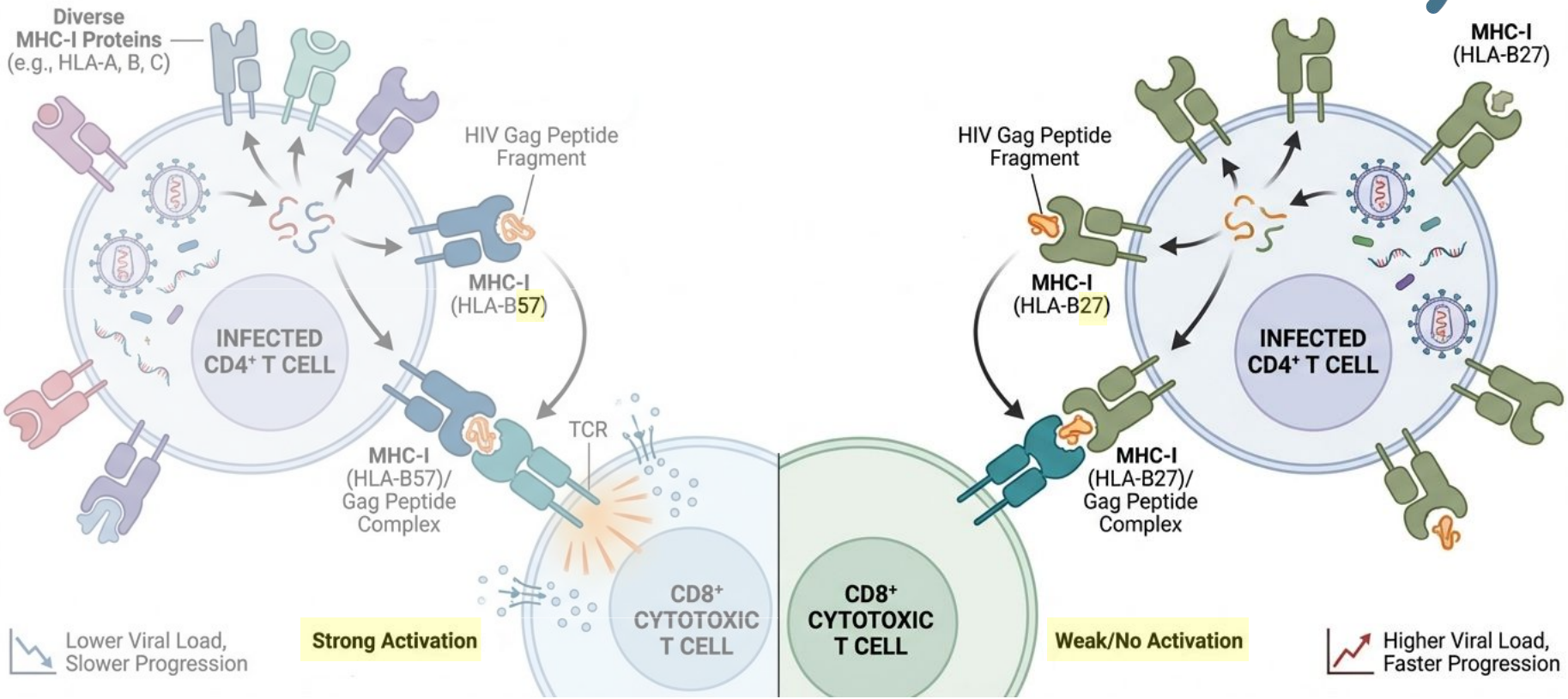
HIV control: Host genetics [2][10]



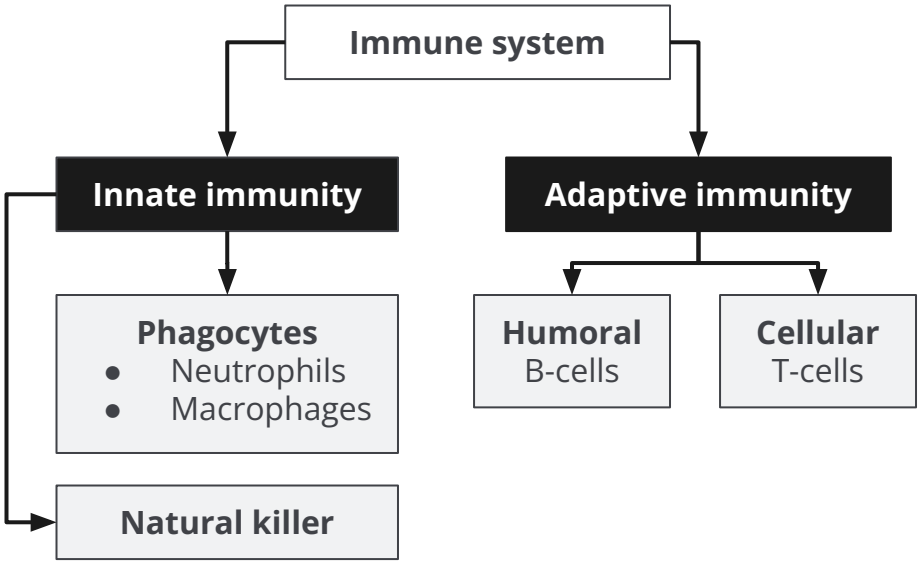
The strongest association with HIV control is the presence of specific HLA Class I alleles, specifically HLA-B57

- 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]

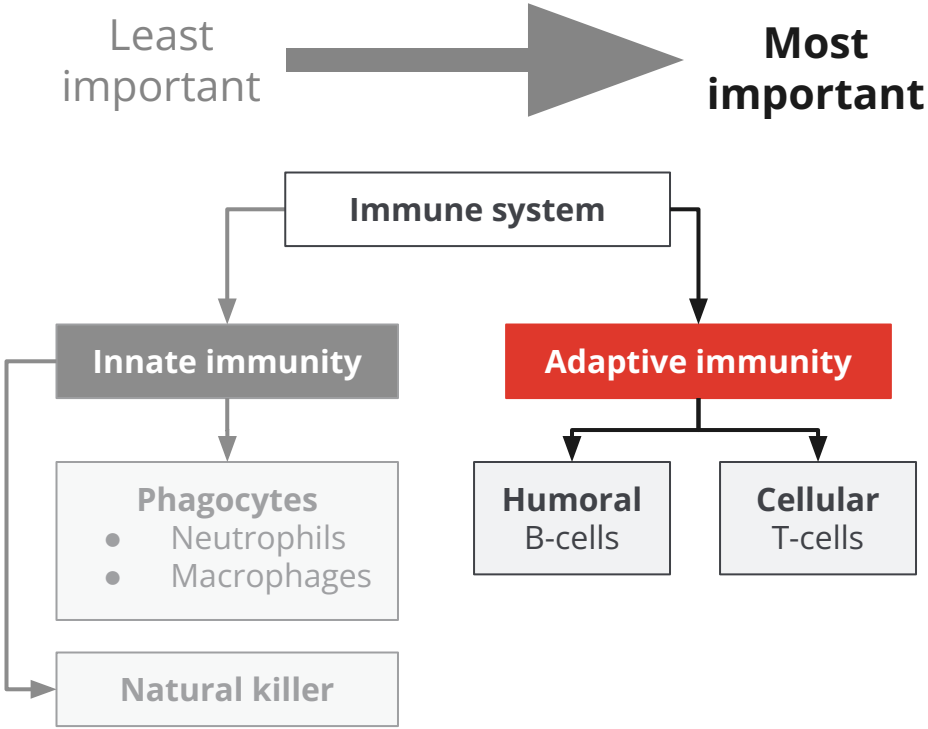


HIV control: The immune system



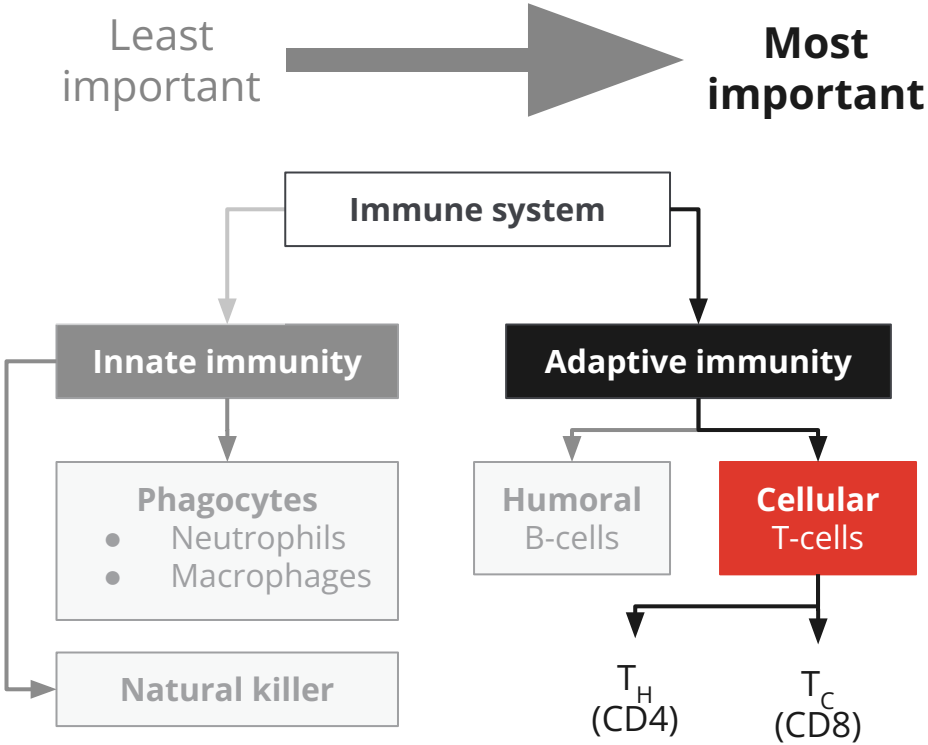
HIV control: The immune system

- **Adaptive** >>>> innate immunity
  - Innate immunity only matters early in the infection



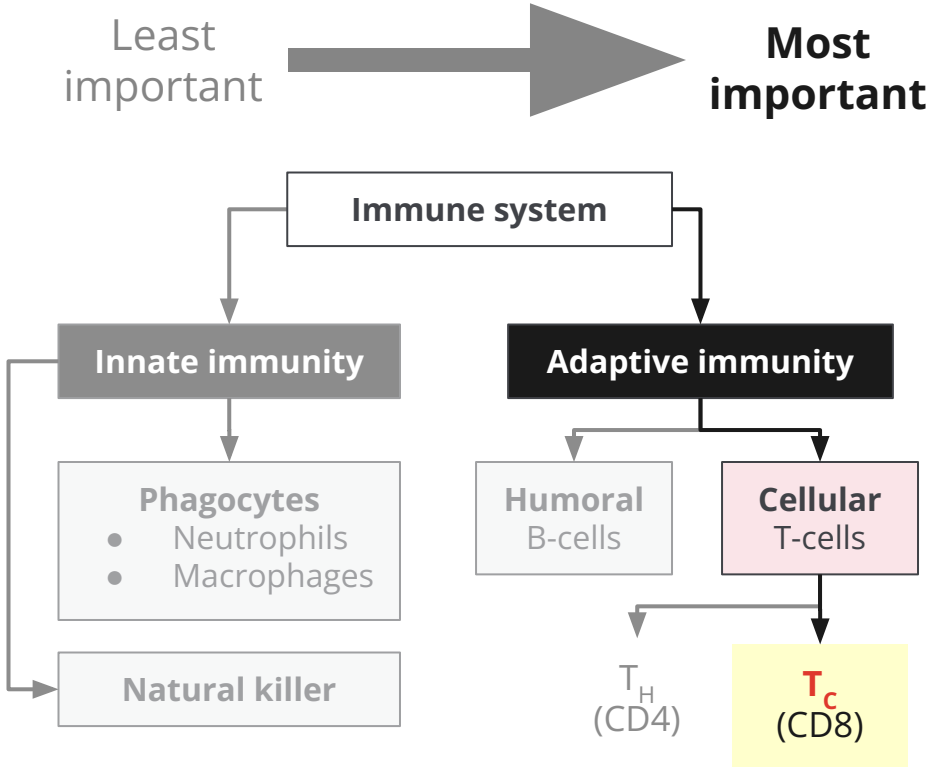
HIV control: The immune system

- **Adaptive** >>>> innate immunity
  - Innate immunity only matters early in the infection
- **Cellular** >>> humoral
  - Neutralizing antibodies develop too late in most infections

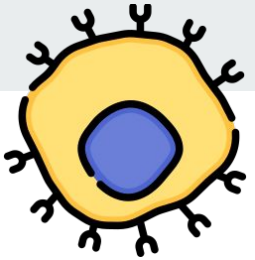


HIV control: The immune system

- **Adaptive** >>>> innate immunity
  - Innate immunity only matters early in the infection
- **Cellular** >>> humoral
  - Neutralizing antibodies develop too late in most infections
- **CD8** >> CD4

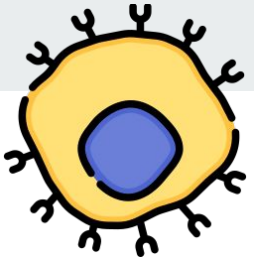


Cell-mediated immunity (CD8)



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

Cell-mediated immunity (CD8)

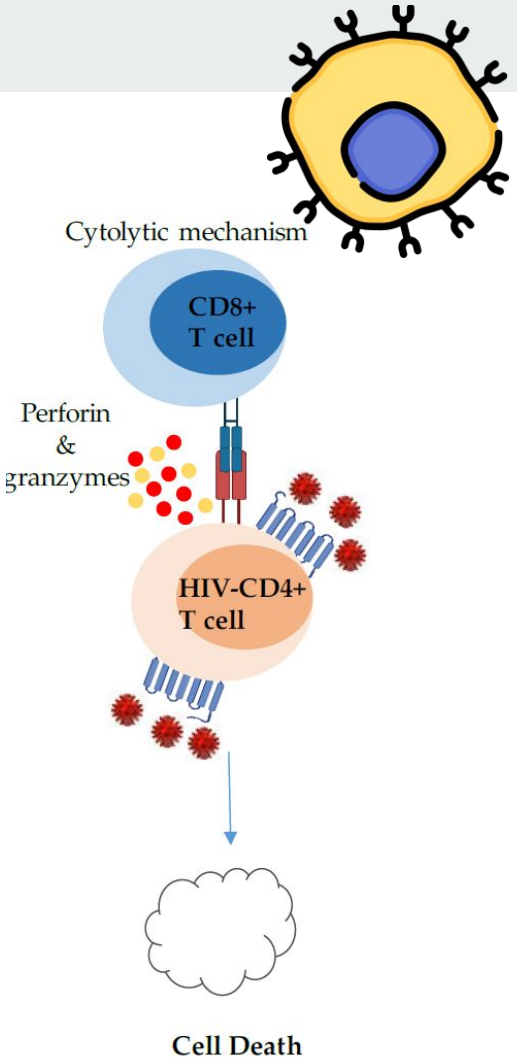


CD8+ cytotoxic T cells are not more numerous in LTNP/ECs, but are **polyfunctional**. **Quality matters** more than quantity [**10**]

Cell-mediated immunity (CD8)

CD8+ cytotoxic T cells are not more numerous in LTNP/ECs, but are **polyfunctional**. **Quality matters** more than quantity [**10**]

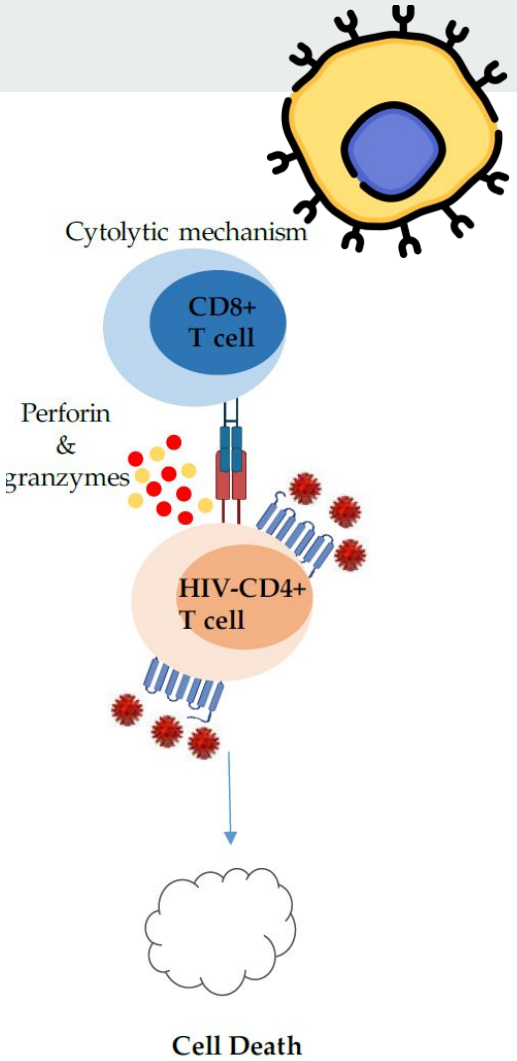
- They exhibit **higher expression of cytolytic enzymes** → better kill infected CD4 cells [**2**][**10**]



Cell-mediated immunity (CD8)

CD8+ cytotoxic T cells are not more numerous in LTNP/ECs, but are **polyfunctional**. **Quality matters** more than quantity [**10**]

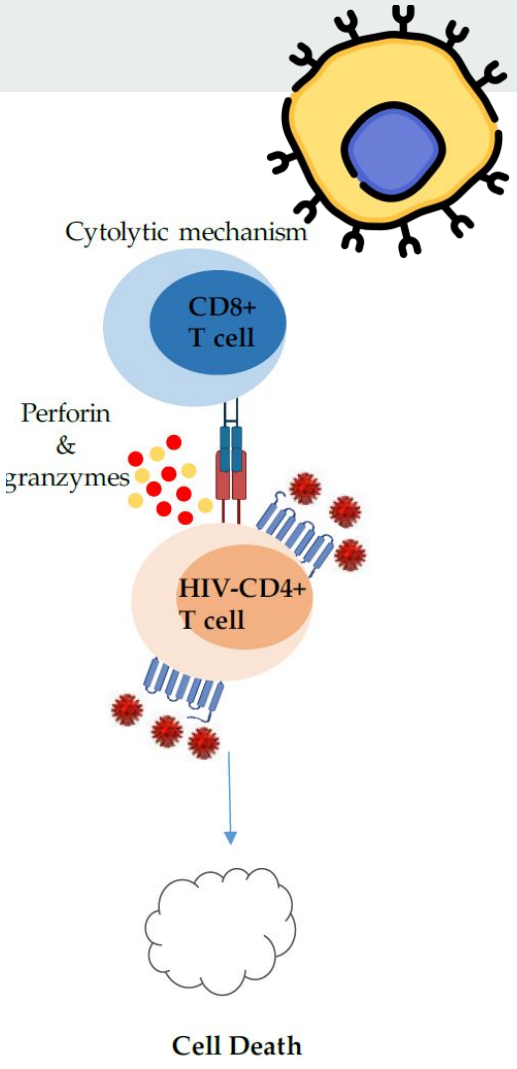
- They exhibit **higher expression of cytolytic enzymes** → better kill infected CD4 cells [**2**][**10**]
- Simultaneously, express high levels of **cytokines** (e.g. IL-2) **to sustain their own proliferative capacity** [**1**][**2**][**10**]



Cell-mediated immunity (CD8)

CD8+ cytotoxic T cells are not more numerous in LTNP/ECs, but are **polyfunctional**. **Quality matters** more than quantity [**10**]

- They exhibit **higher expression of cytolytic enzymes** → better kill infected CD4 cells [**2**][**10**]
- Simultaneously, express high levels of **cytokines** (e.g. IL-2) **to sustain their own proliferative capacity** [**1**][**2**][**10**]
- In some **ECs**, CD8+ cells are able to recognize (and kill) HIV infected CD4 cells even **before the CD4 cells become activated** or start producing new copies of HIV [**2**]

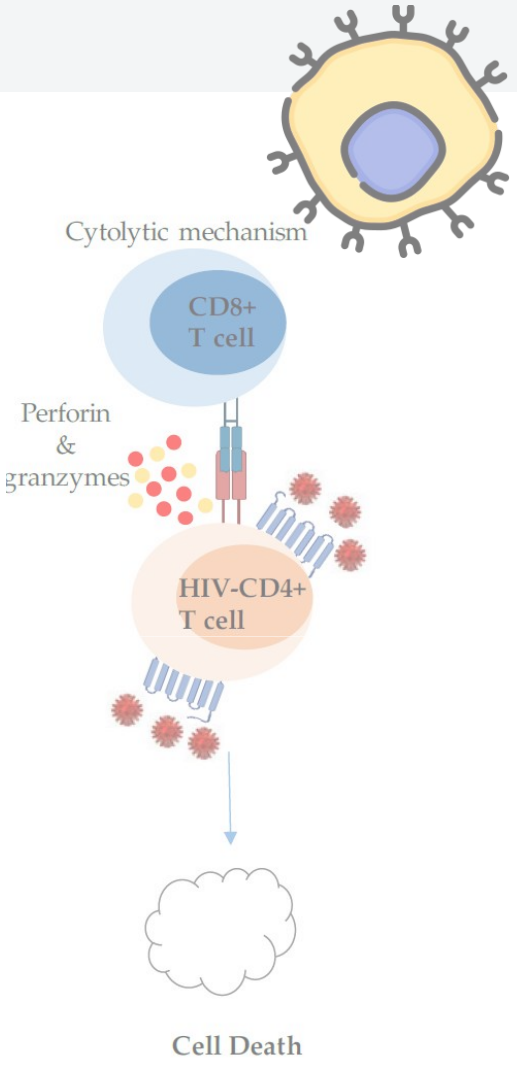


Cell-mediated immunity (CD8)

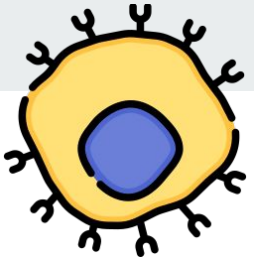
CD8+ cytotoxic T cells are not more numerous in LTNP/ECs, but are **polyfunctional**. **Quality matters** more than quantity [**10**]

- They exhibit **higher expression of cytolytic enzymes** → better kill infected CD4 cells [**2**][**10**]
- Simultaneously, express high levels of **cytokines** (e.g. IL-2) **to sustain their own proliferative capacity** [**1**][**2**][**10**]
- In some **ECs**, CD8+ cells are able to (recognize and) kill HIV infected CD4 cells even **before the CD4 cells become activated** or start producing new copies of HIV [**2**]

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]

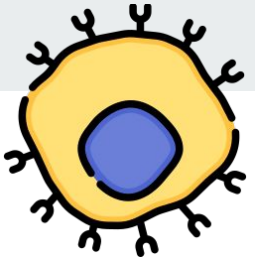


Cell-mediated immunity (CD4)



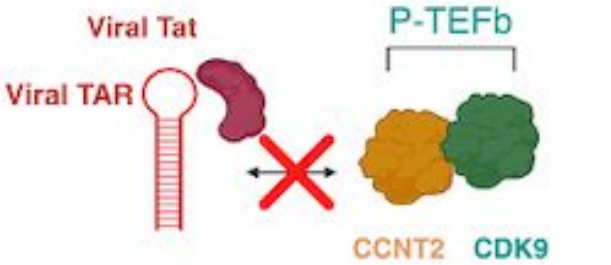
Although **CD8+ cytotoxic T cells are the main players** here, some elite controllers have **increased CD4+ expression of p21** [2]

Cell-mediated immunity (CD4)



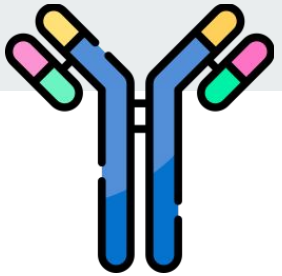
Although **CD8+ cytotoxic T cells are the main players** here, some elite controllers have **increased CD4+ expression of p21** [2]

- 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**

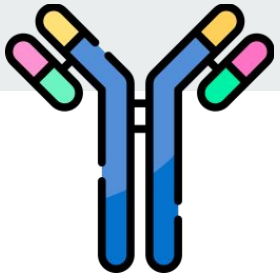


Humoral immunity [2]

Long term non-progressors

- Some studies show LTNPs have **higher rates** of **broad acting neutralizing antibodies** (**NAbs**)
- But others **could not replicate** this findings

Humoral immunity [2]



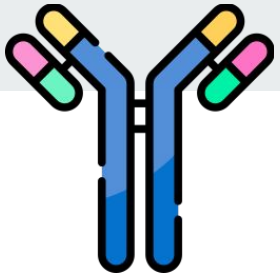
Long term non-progressors

- Some studies show LTNPs have **higher rates** of **broad acting neutralizing antibodies** (**NAbs**)
- But others **could not replicate** this findings

Elite controllers

- Generally do not have *higher rates* of **NAbs**, but instead the antibodies produced by ECs have **unique effector functions**

Humoral immunity [2]



Long term non-progressors

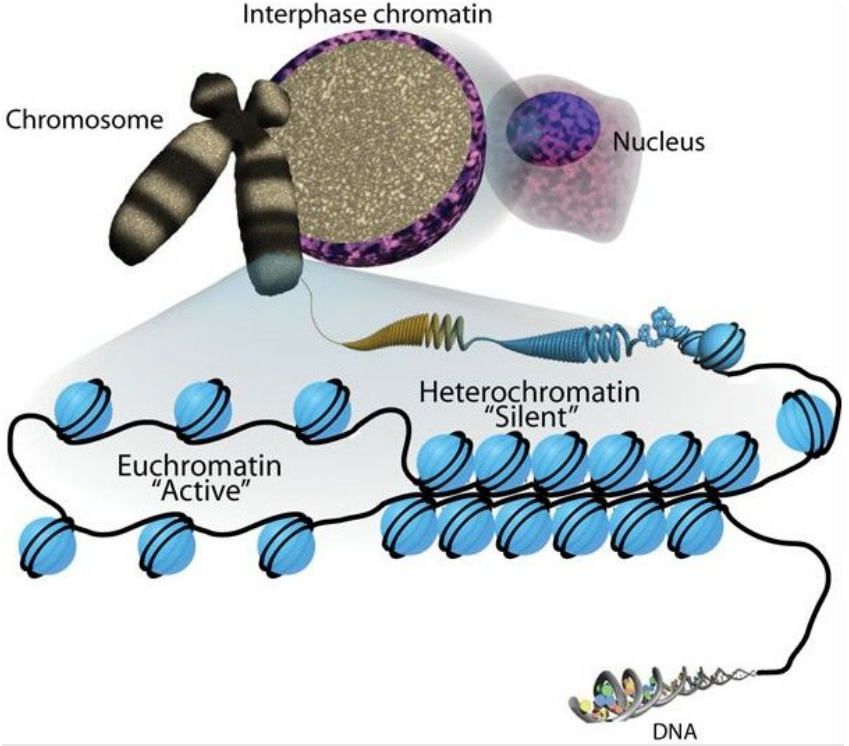
- Some studies show LTNPs have **higher rates** of **broad acting neutralizing antibodies** (**NAbs**)
- But others **could not replicate** this findings

Elite controllers

- Generally do not have *higher rates* of **NAbs**, but instead the antibodies produced by ECs have **unique effector functions**
- Namely **antibody dependent cellular cytotoxicity**, which targets and kills infected cells **by recruiting natural killer cells**

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

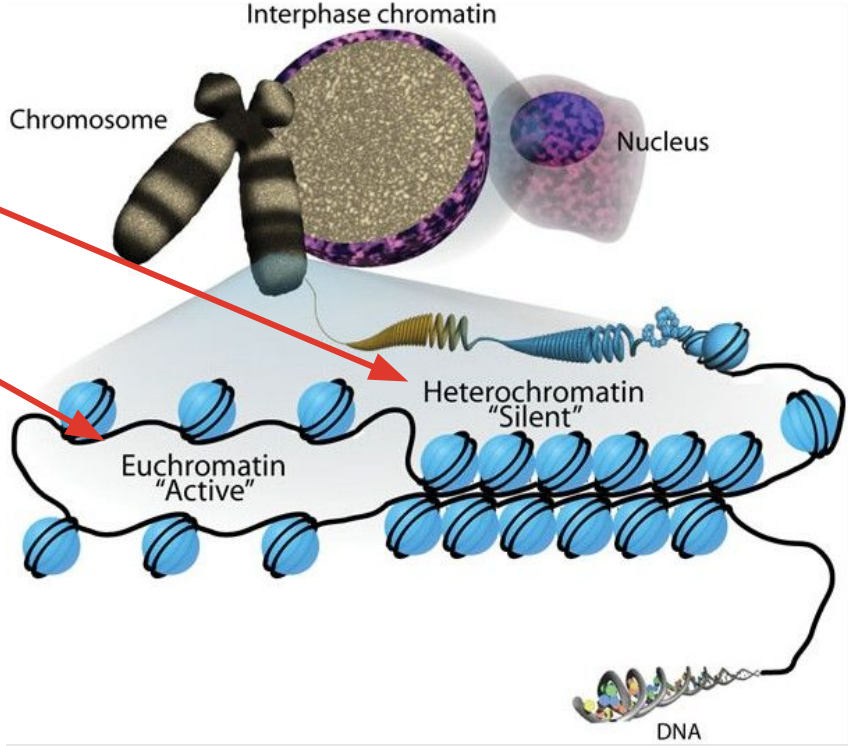
In ECs, HIV proviruses are **disproportionately** found **integrated into non-coding regions** (“gene deserts”; e.g. heterochromatin)



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

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

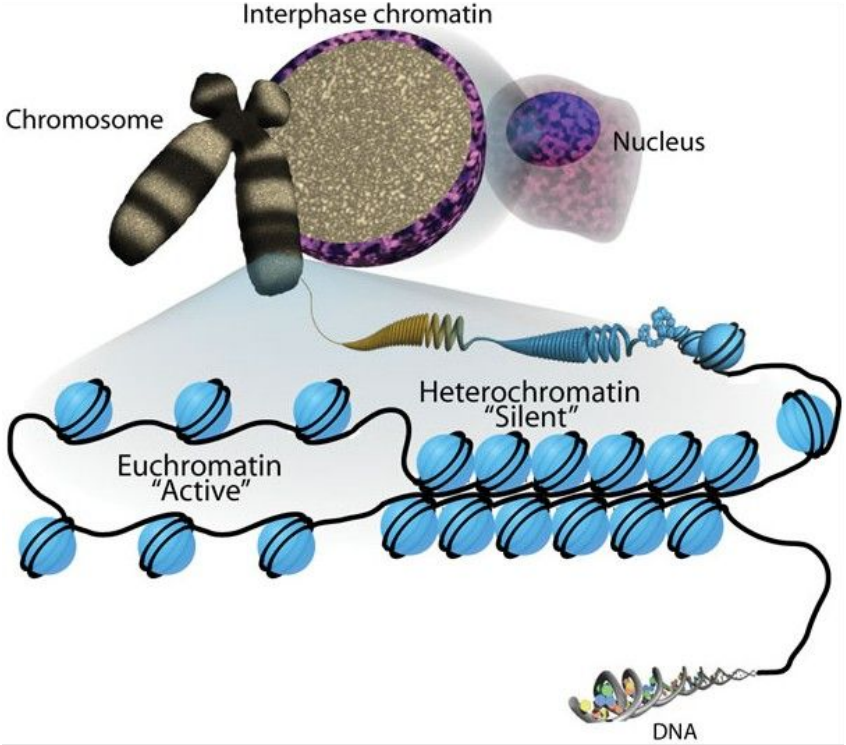
- Non-controllers (on ART) are more likely to have integration into euchromatin → more prone to reactivation



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

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

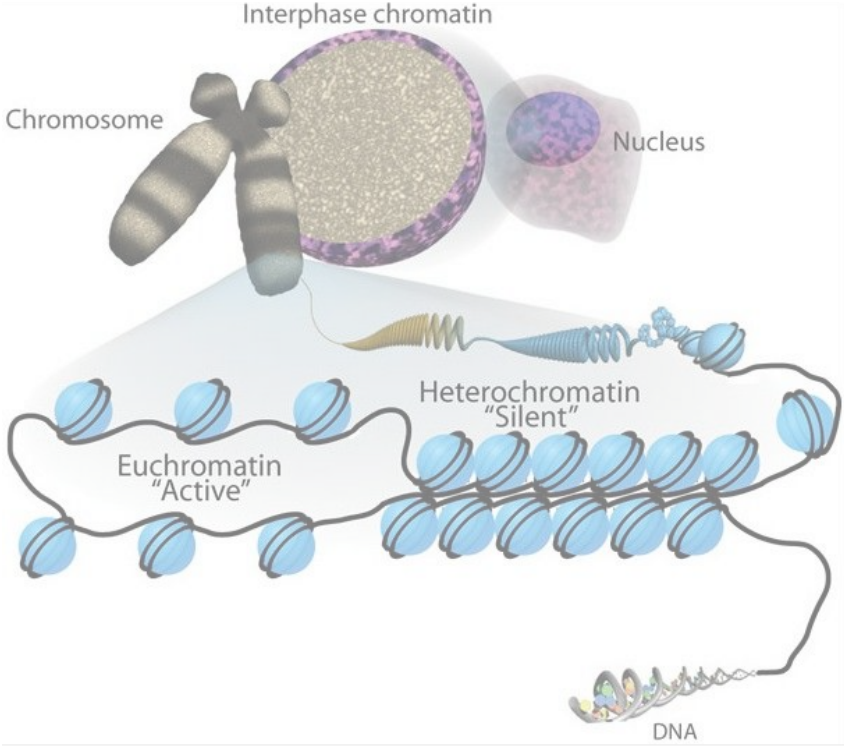
- Non-controllers (on ART) are more likely to have integration into euchromatin → more prone to reactivation
- This **partially explains why ECs have undetectable viral loads**
  - All of their ***actively*** **infected cells are being killed** by CD8 cells
  - Their **latent reservoir** “genome” is **not transcribed**



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

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

- Interestingly, **after prolonged ART** (>20 years), the **sites of integration** begins to **mimic elite controllers**

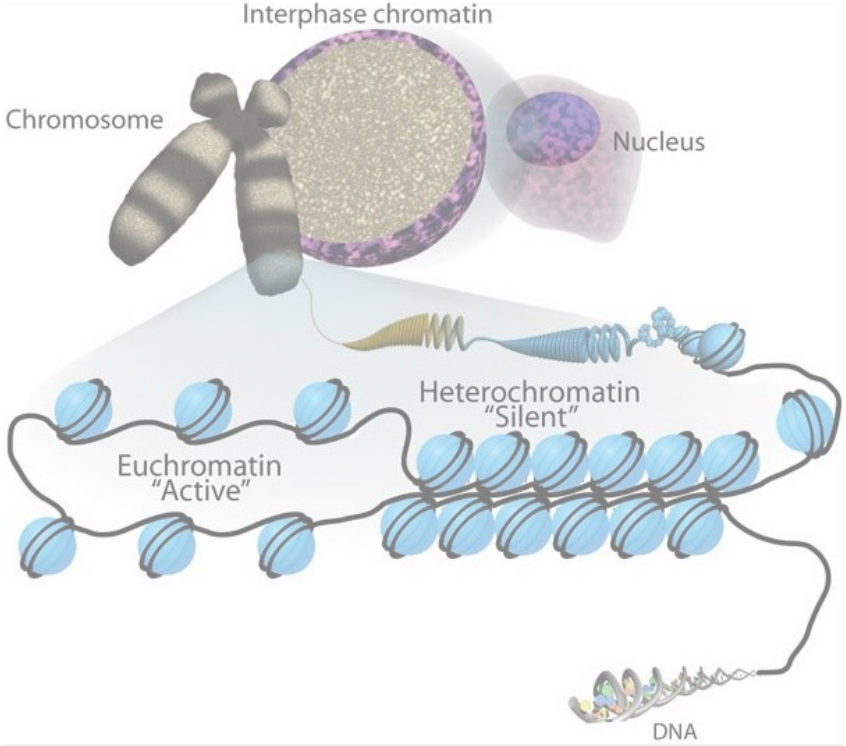


HIV control: Location of integration [2][10]

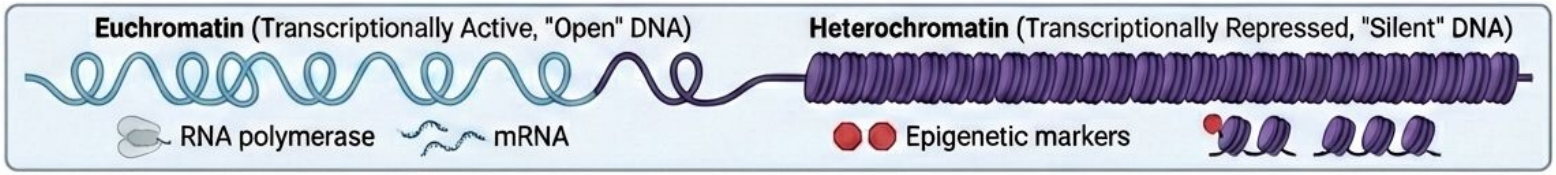
In ECs, HIV proviruses are **disproportionately** found **integrated into non-coding regions** (“gene deserts”; e.g. heterochromatin)

- Interestingly, **after prolonged ART** (>20 years), the **sites of integration** begins to **mimic elite controllers**

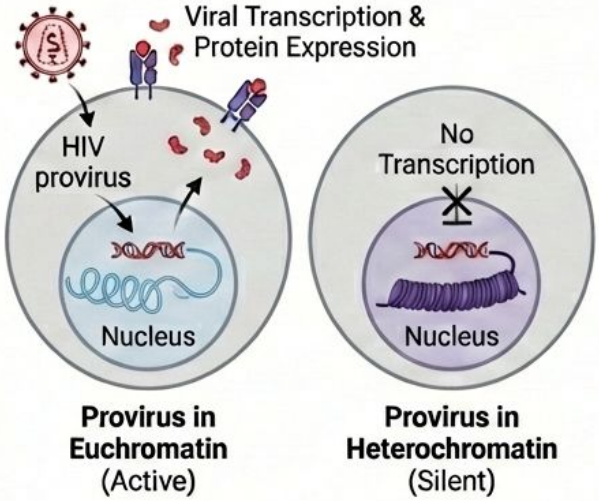
Both cases are thought to be **a result of selective pressure from the immune system**



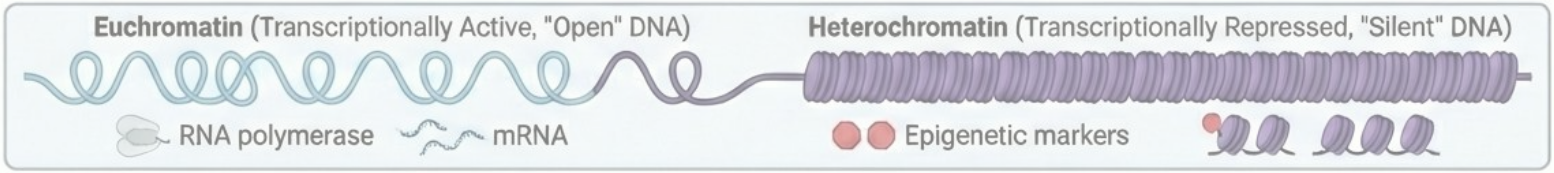
HIV Elite Controllers: Preferential Proviral Integration into Heterochromatin via Immune Selection



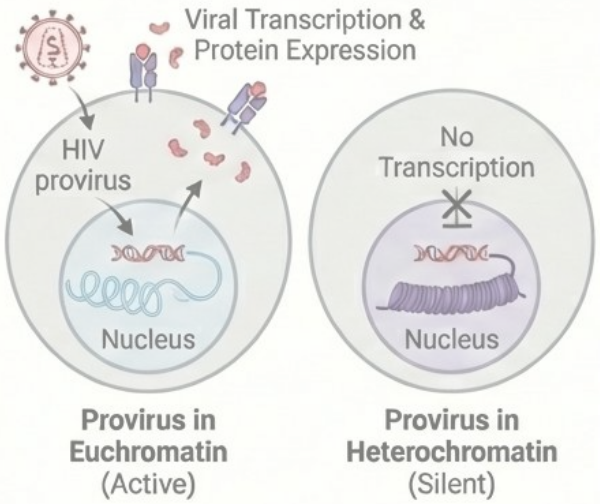
1. Initial Infection & Random Integration



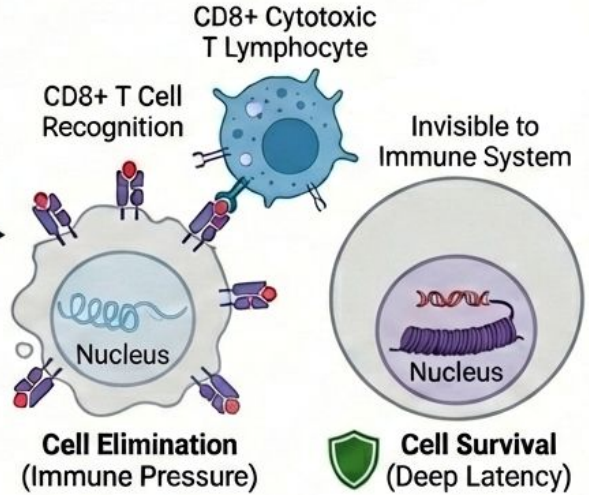
HIV Elite Controllers: Preferential Proviral Integration into Heterochromatin via Immune Selection



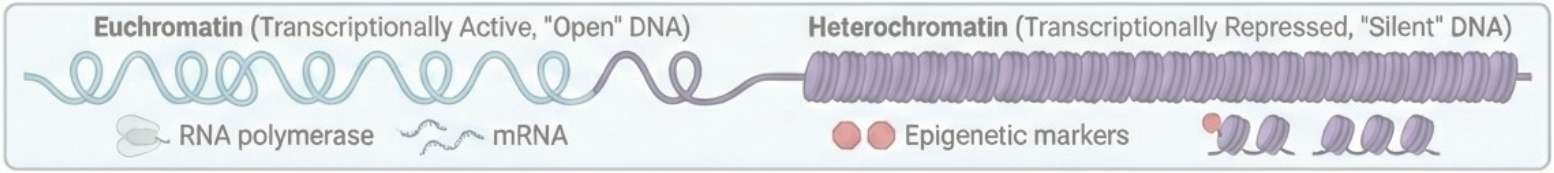
1. Initial Infection & Random Integration



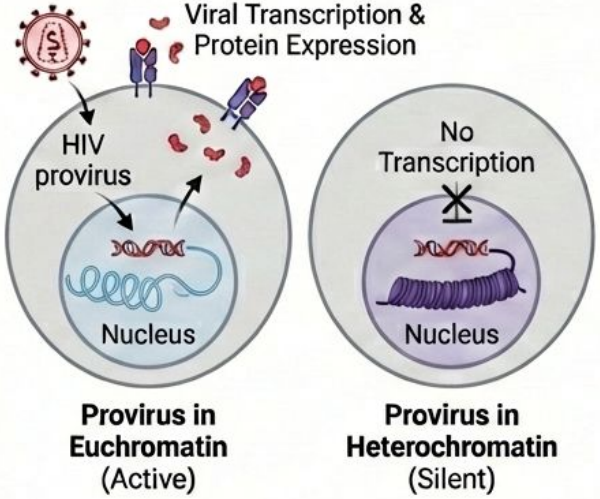
2. Immune Selection by CD8+ T Cells



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



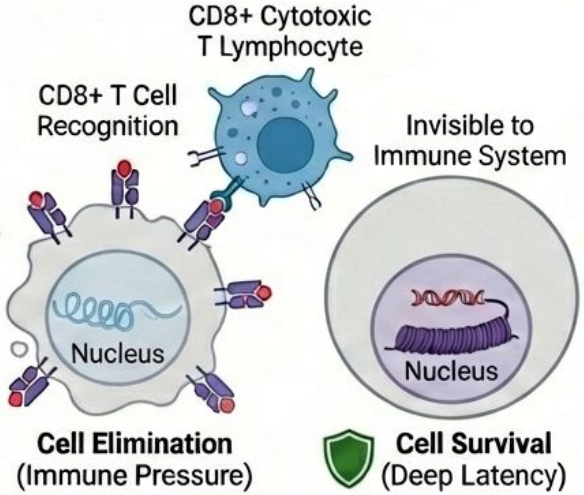
1. Initial Infection & Random Integration



Provirus in Euchromatin (Active)

Provirus in Heterochromatin (Silent)

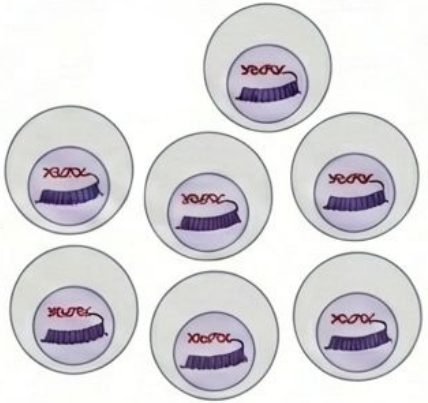
2. Immune Selection by CD8+ T Cells



Cell Elimination (Immune Pressure)

Cell Survival (Deep Latency)

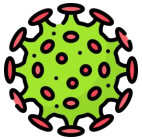
3. Elite Controller Reservoir Over Time



Reservoir Dominated by "Blocked" Proviruses in Heterochromatin

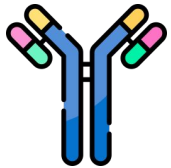
SUMMARY: Intense immune pressure by CD8+ T cells eliminates cells with active proviruses in euchromatin. In HIV elite controllers, this selective pressure leaves behind a reservoir of proviruses integrated into "silent" heterochromatin, which are **resistant to reactivation and invisible to the immune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

HIV control: **Summary**



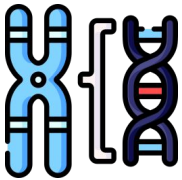
✗ Is it related to their virus?

Only in *rare cases* (Sydney blood bank)



✗ Produce more antibodies?

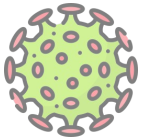
Mixed data on the *amount* of antibodies, but some studies showed ECs have Abs that help with ADCC via NK cells



? 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**

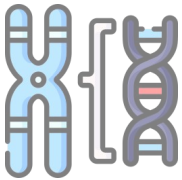


✗ **Is it related to their virus?**

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

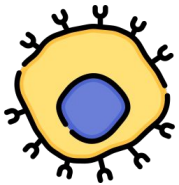


? Site of HIV integration?

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)

✓ **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



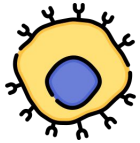
✓✓ **Cellular immunity (CD8 >> CD4)**

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)

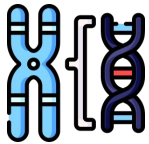
Host genetics
(MHC-I)

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]

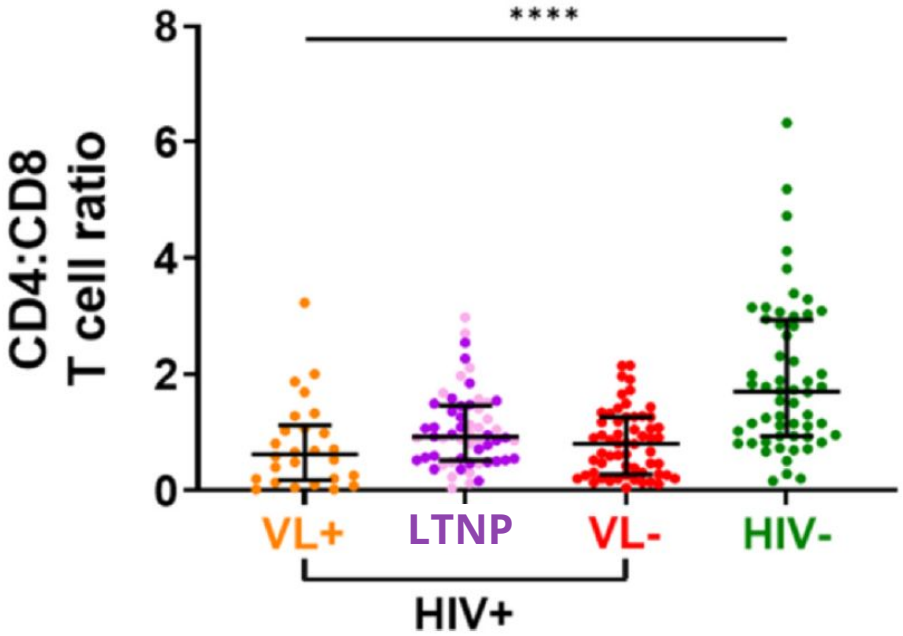


Figure 2A of citation [7]

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]
- **Ratio remains abnormal** (<1) in LTNP, even ***after*** **starting ART** [9]

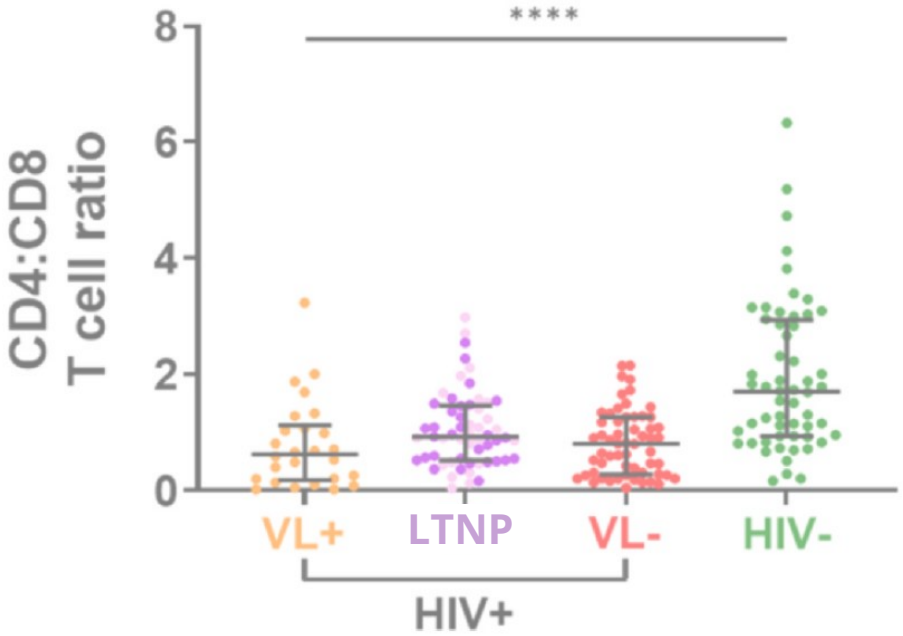


Figure 2A of citation [7]

Immunologic aging: **Monocytes [6]**

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

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**

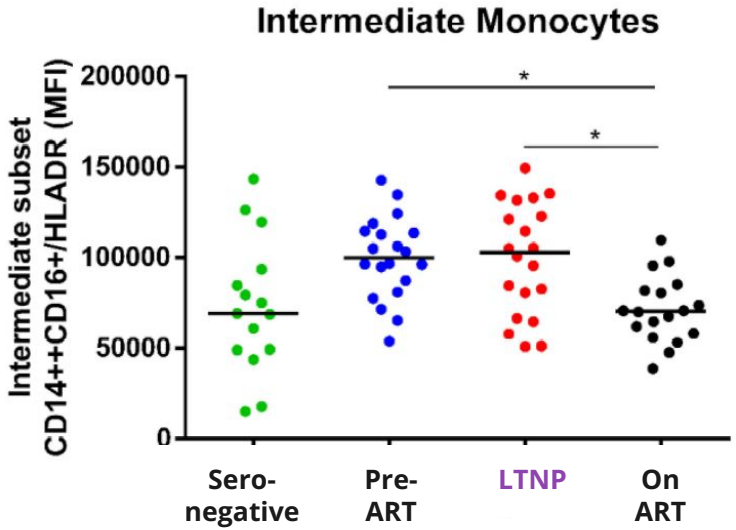


Figure 5B of citation [6]

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**

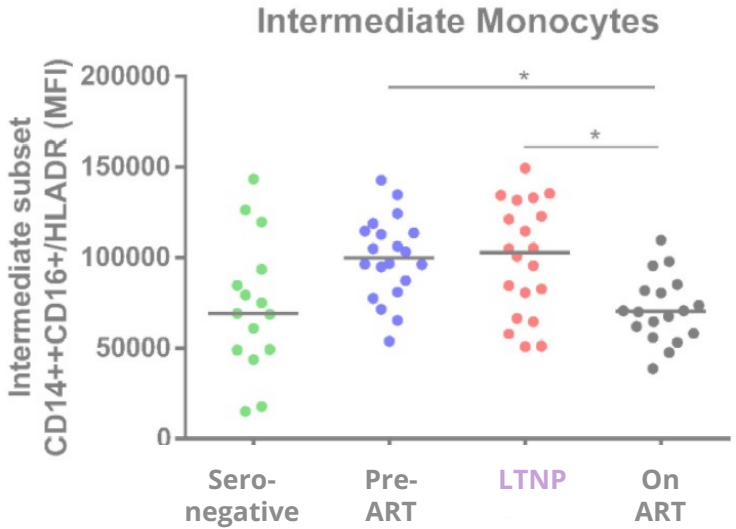


Figure 5B of citation [6]

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**
- CD4+CD16+ **monocytes preferentially** transmigrate **across the blood brain barrier**
  - Increased monocyte activation (across the BBB) has been **associated with HAND** [**8**]

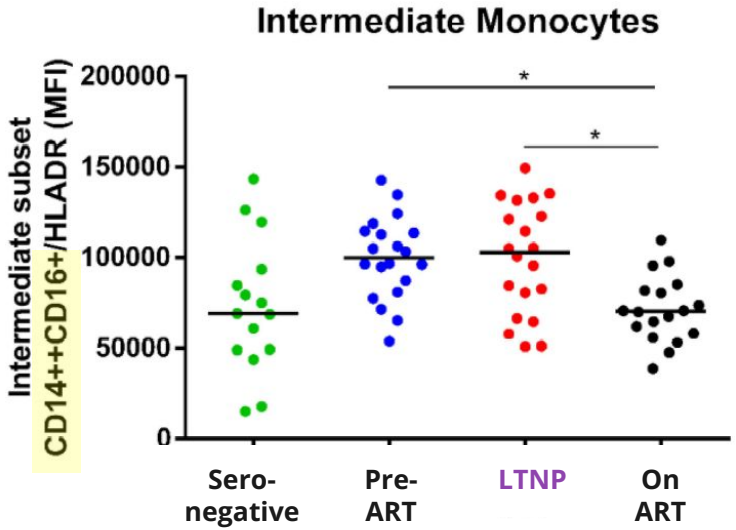


Figure 5B of citation [**6**]

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**
- 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**

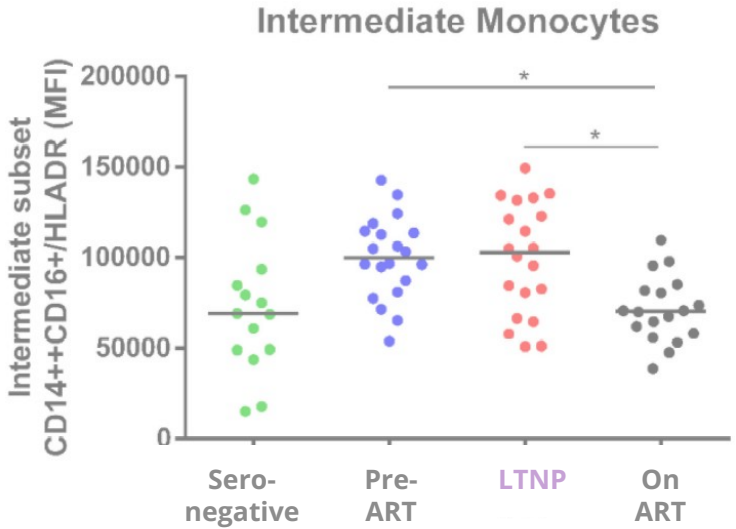


Figure 5B of citation [6]

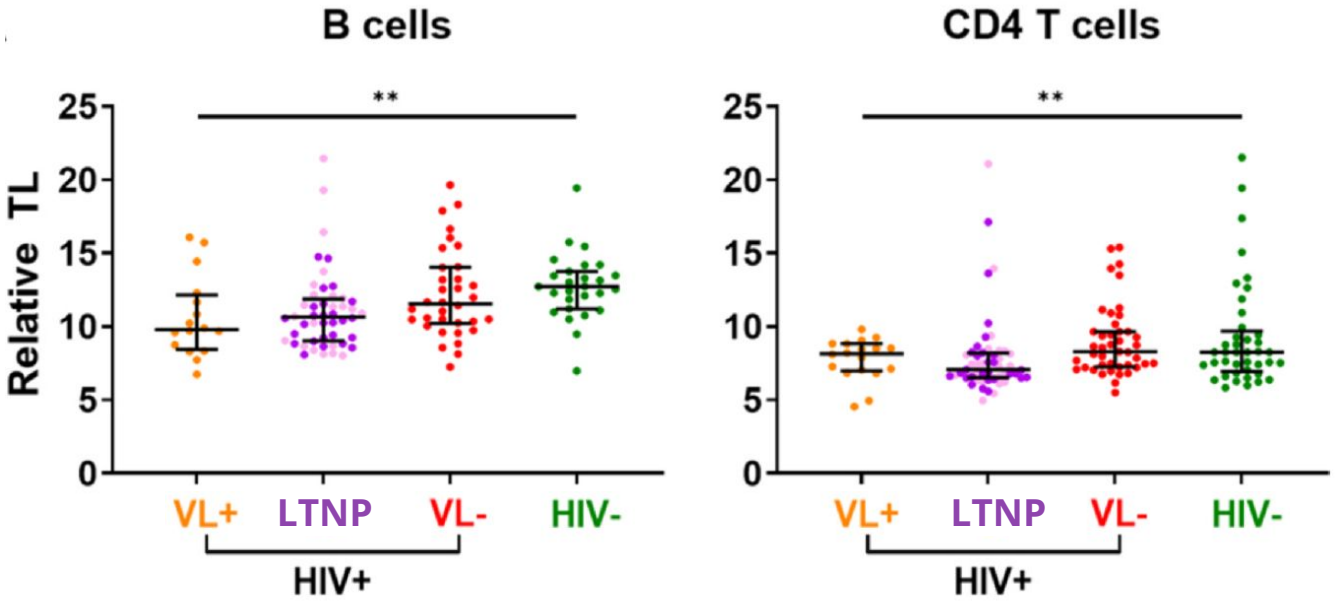
Immunologic aging: Telomere length [7]

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

Immunologic aging: Telomere length [7]

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

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



Immunologic aging: **Telomere length [7]**

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

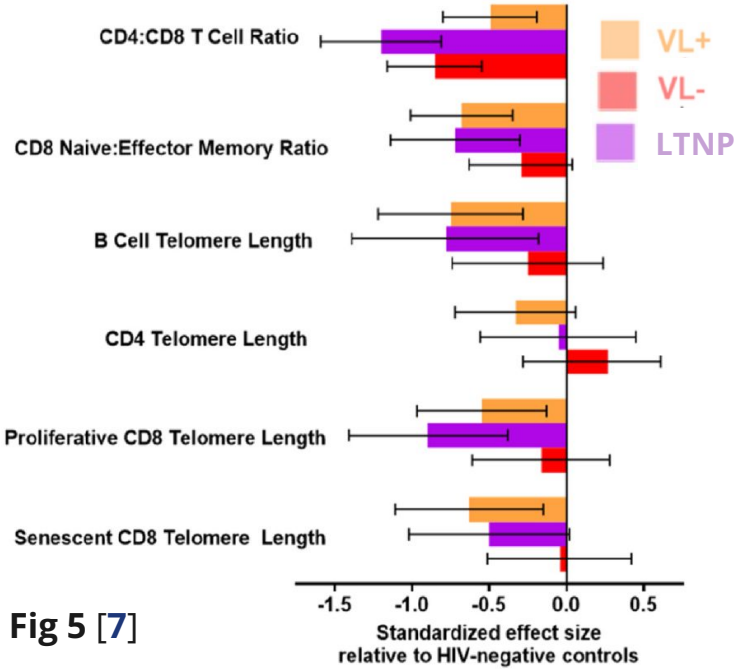


Fig 5 [7]

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

Immunologic aging: **Telomere length [7]**

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

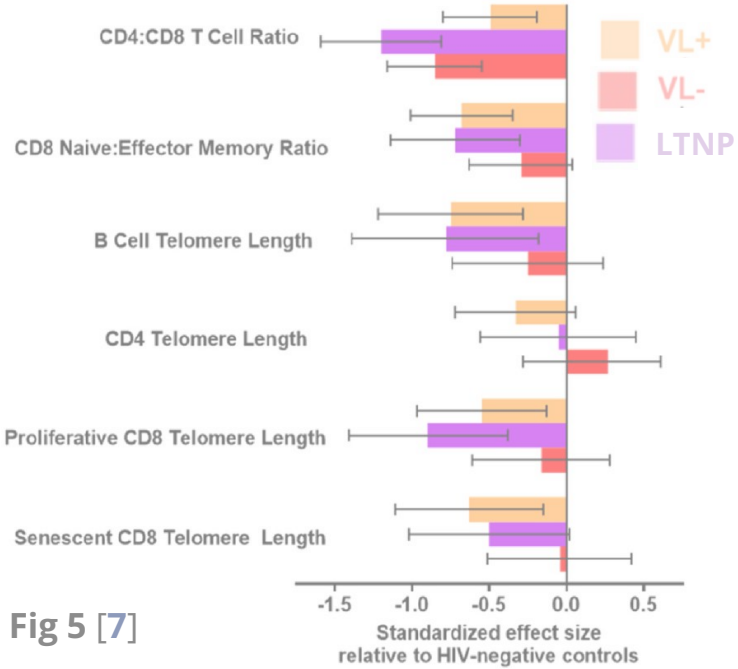


Fig 5 [7]

- 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**

- 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**]

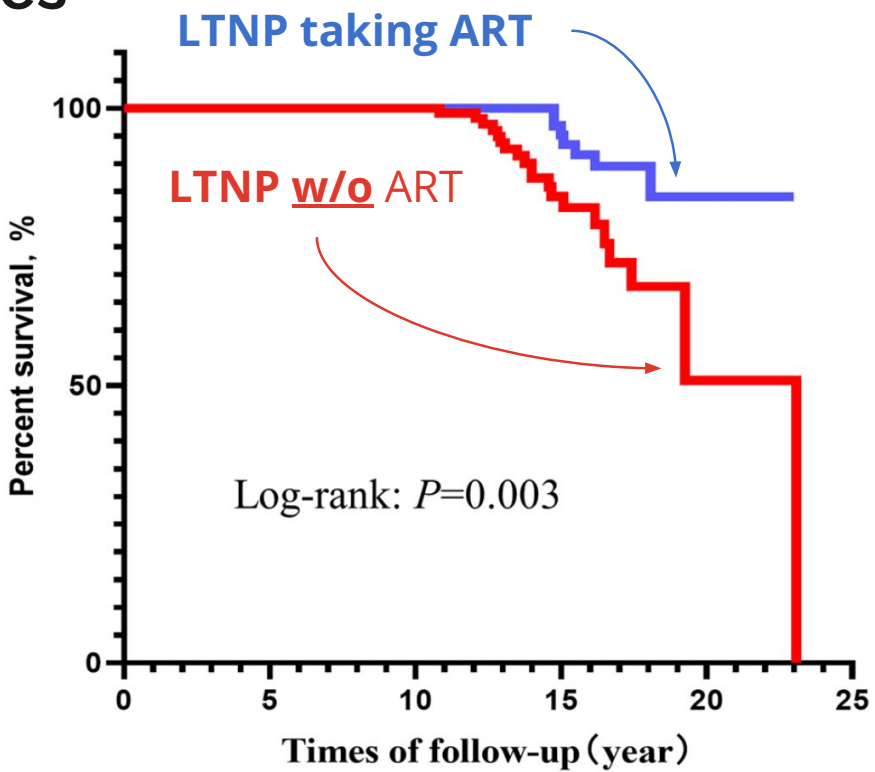
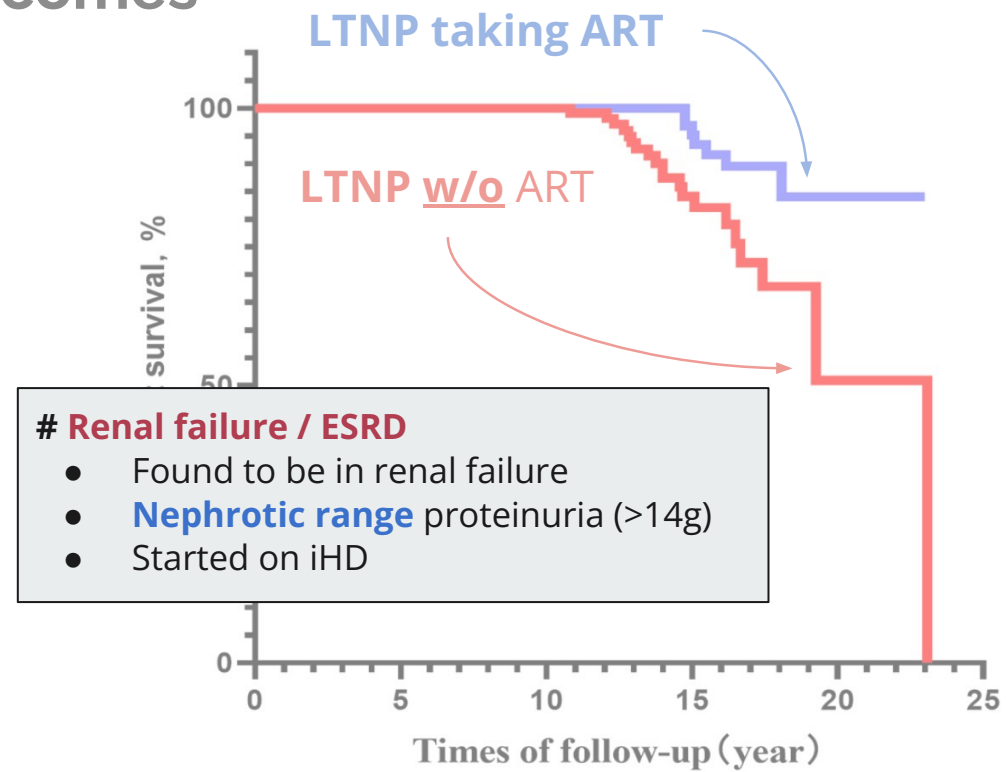


Figure 1C of citation [**9**]

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**

Should you start ART? [11]

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

Should you start ART? [11]

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

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

Should you start ART? [11]

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

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

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)
5. Pregnancy

Should you start ART? [11]

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

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

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)
5. Pregnancy

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

Should you start ART? [11]

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

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

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)
5. Pregnancy

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

This will likely be **many of the LTNP** (but not ECs)

Should you start ART? [11]

Data is sparse, so **decision to start ART** in **elite controllers** should b

The **HHS guidelines** [**11**] "for the use of antiretroviral agents in adults were updated in 2025 to include:

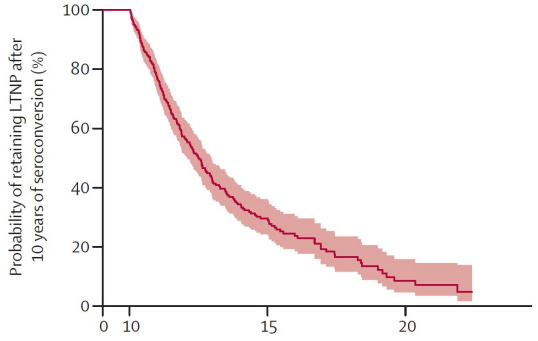


Fig 3 [**3**] Years after seroconversion

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

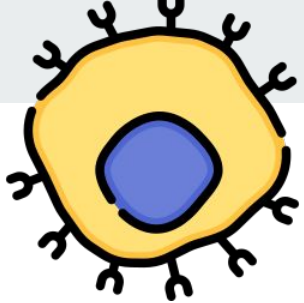
1. Evidence of HIV-related complications
2. Declining CD4 counts
3. Intermittent detectable viral load
4. Comorbidities (e.g., cardiovascular disease, cancer, HBV/HCV coinfection)
5. Pregnancy

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