Underlying mechanisms of low-level viraemia

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Disclosures 2023-2024

- Personal payments from Abbott, Gilead, GSK, MSD, Roche, ViiV
- Research funding to Institution from Gilead, Roche, ViiV
- Editor in Chief, Sexually Transmitted Infections, *British Medical Journal*
- British HIV Association Guidelines Committee
- British HIV Association for Sexual Health & HIV Education Committee

LLV during ART: Why do we worry?

- May reflect ongoing virus replication
- May be associated with emergence of drug resistance
- May be followed by higher levels of viraemia
- May drive immune activation, immune senescence, inflammation[1]
- Typically leads to more frequent visits and lab tests
- Creates concern for both clinician and patient

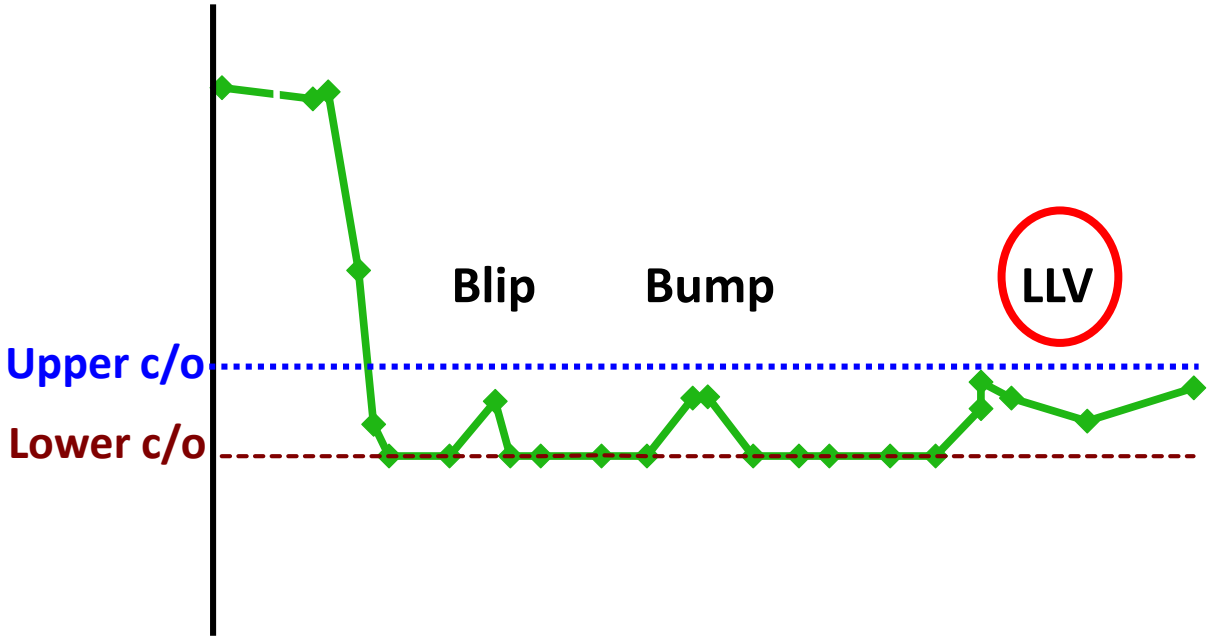
[1.] *Aguilar et al. CROI 2024 Abstract 348*

LLV during ART: Why do we worry?

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- May be followed by higher levels of viraemia **(~2 to 3-fold ↑risk[1-5])**
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[1]Laprise et al. Clin Infect Dis 2013; [2]Joya et al. Clin Infect Dis 2019; [3]Esber et al. Clin Infect Dis 2019; [4]Elvstam et al. Clin Infect Dis 2023; [5]Aldredge et al. CROI 2024 Abstract 822

Let's define low-level viraemia



c/o= Assay cut-off

IAS: 50-200 cps[1]
DHHS: >LLOD <200 cps[2]
EACS: >50 <200 cps[3]
WHO: 50-1000 cps[4]

LLOD= Lower limit of detection

[1]Gandhi et al. JAMA 2023; [2]DHHS Guidelines Feb 2024. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv;
[3]EACS Guidelines Oct 2023. https://www.eacsociety.org/media/guidelines-12.0.pdf; [4]WHO Guidelines 2021. https://www.who.int/publications/i/item/9789240031593

LLV has several possible mechanisms

Suboptimal drug potency



Modifying ART may help

A classic example:

PI/r monotherapy

LLV has several possible mechanisms

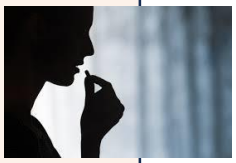
Suboptimal drug potency



Modifying ART may help

Suboptimal drug exposure

- Adherence
- Drug interactions
- Pharmacokinetics



Modifying ART may help

<u>A classic example:</u>

Interactions with multivalent cations (Ca^{2+}, Fe^{3+}, Mg^{2+}, Al^{3+}, Zn^{2+}) in mineral supplements and antacids with INSTIs

<u>A less common example:</u>

Sanctuary sites of viral replication

LLV has several possible mechanisms

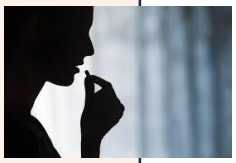
Suboptimal drug potency



Modifying ART may help

Suboptimal drug exposure

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- Pharmacokinetics



Modifying ART may help

”Physiological”



Does not indicate virus replication

Modifying ART does not help

“Nonsuppressible viraemia”

Bachmann et al. Nat Comm 2019; Palich et al. JAC 2020; Siliciano et al. J Cloin Invest 2020; Cole et al. Nat Commun 2021; Castillo-Mancilla et al. Open Forum Infect Dis 2021

Successful viral load suppression after starting ART



[1]*Riddler et al. J Infect Dis 2016*

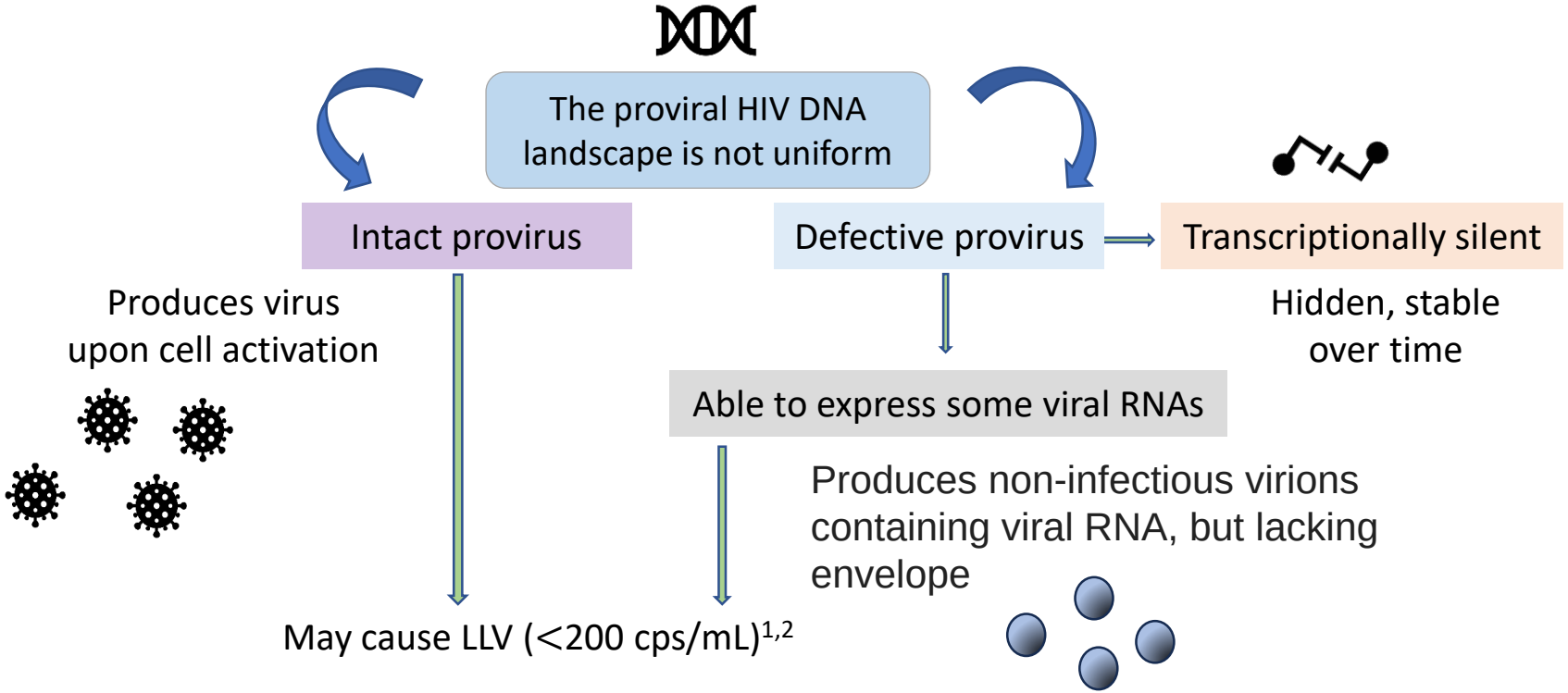
Successful viral load suppression after starting ART



Can be measured in~50% of stably treated individuals at ~3 cps/mL[2-4]

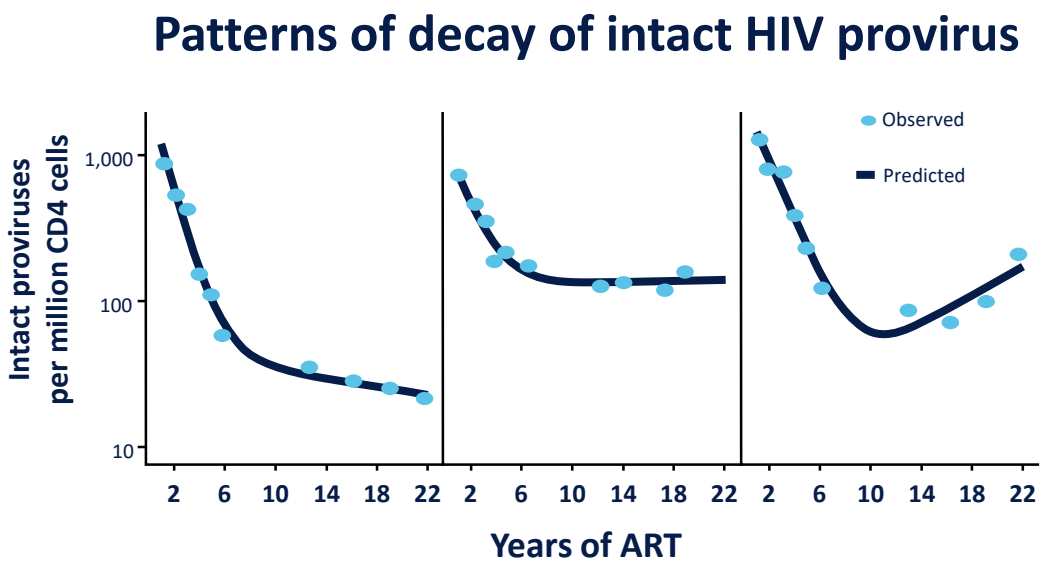
[1]Riddler et al. J Infect Dis 2016; [2]Ruggiero et al. EbioMed 2015; [3]Ruggiero et al. Open Forum Infect Dis 2018; [4]Cyktor et al. J Infect Dis 2021

The HIV DNA reservoir during suppressive ART



Adapted from Geretti AM. Infect Dis Ther 2022; [1]Cole et al. Cell Rep 2022; [2]White et al. J Clin Invest 2023

Intact HIV provirus during suppressive ART



- Progressive decay in the first 7 years
- Subsequent plateau or steady increase due to proliferation / reduced clearance of infected cells
- Persistence not due to failure of ART to fully suppress replication

Gandhi et al. J Infect Dis 2023; McMyn, Siliciano, Ward CROI 2023

Baseline HIV parameters are associated with LLV

High HIV DNA burden

- More frequent virus release
- High HIV DNA in blood

Persistent immune dysfunction

- Reduced clearance of infected cells

Sanctuary site persistence

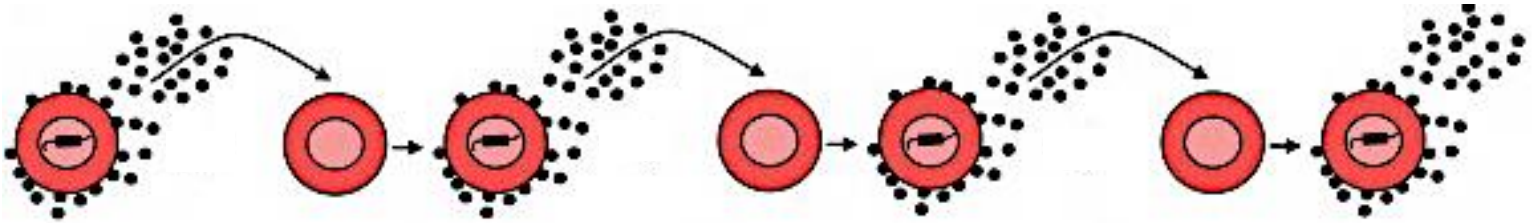
- Lymphoid tissue
- Brain, etc

A nadir CD4 count <200 cells and high pre-ART viral load increase the risk of both ongoing virus replication and “physiological” LLV

The association persists with DTG-based regimens

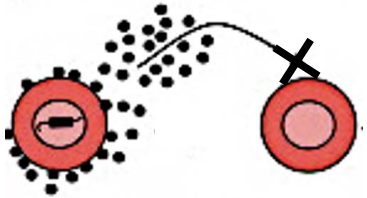
Nightingale et al. J Neurovirol. 2016; Bachmann et al. Nat Comm 2019; Palich et al. JAC 2020; Cole et al. Nat Commun 2021; Rasmussen et al. Clin Infect Dis 2022; Tang et al. J Clin Invest 2023; Alvarez et al. Clin Infec Dis 2023

Infectious virus release and ongoing virus replication



Infectious virus release with ART halting virus replication



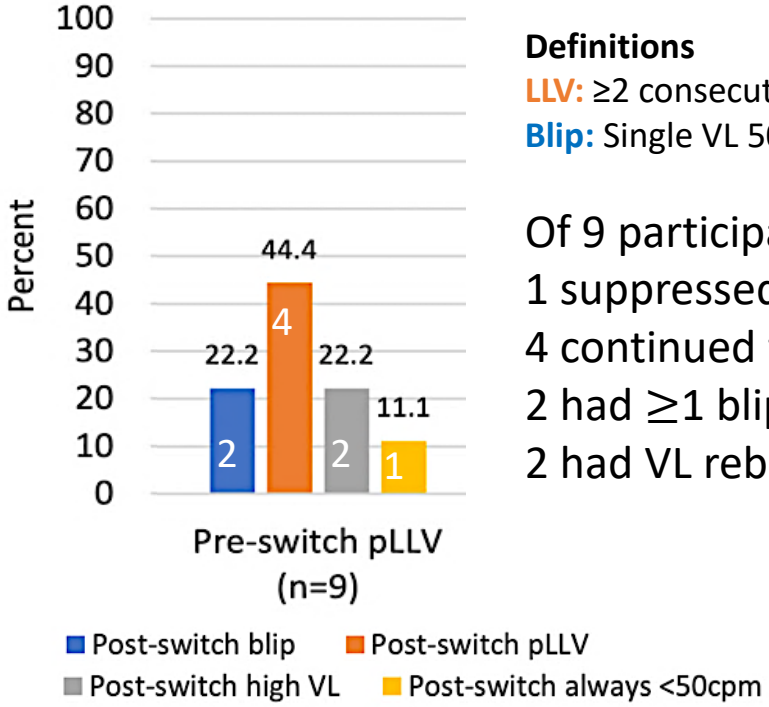


Non-infectious virus release

In LLV, it is important to differentiate between scenarios

Outcomes of LLV after switching to CAB RPV LA

Retrospective cohort who switched to LA with LLV (n=9 of 144)
Mean follow-up 40 weeks post-switch



Definitions

LLV: ≥2 consecutive VL 50-199 c/mL

Blip: Single VL 50-199 cps/mL with adjacent values <50 cps/mL

Of 9 participants:
1 suppressed <50 cps
4 continued to have LLV
2 had ≥1 blip
2 had VL rebound ≥200 cps

LLV can persist despite the adherence and absorption benefits of injectable ART

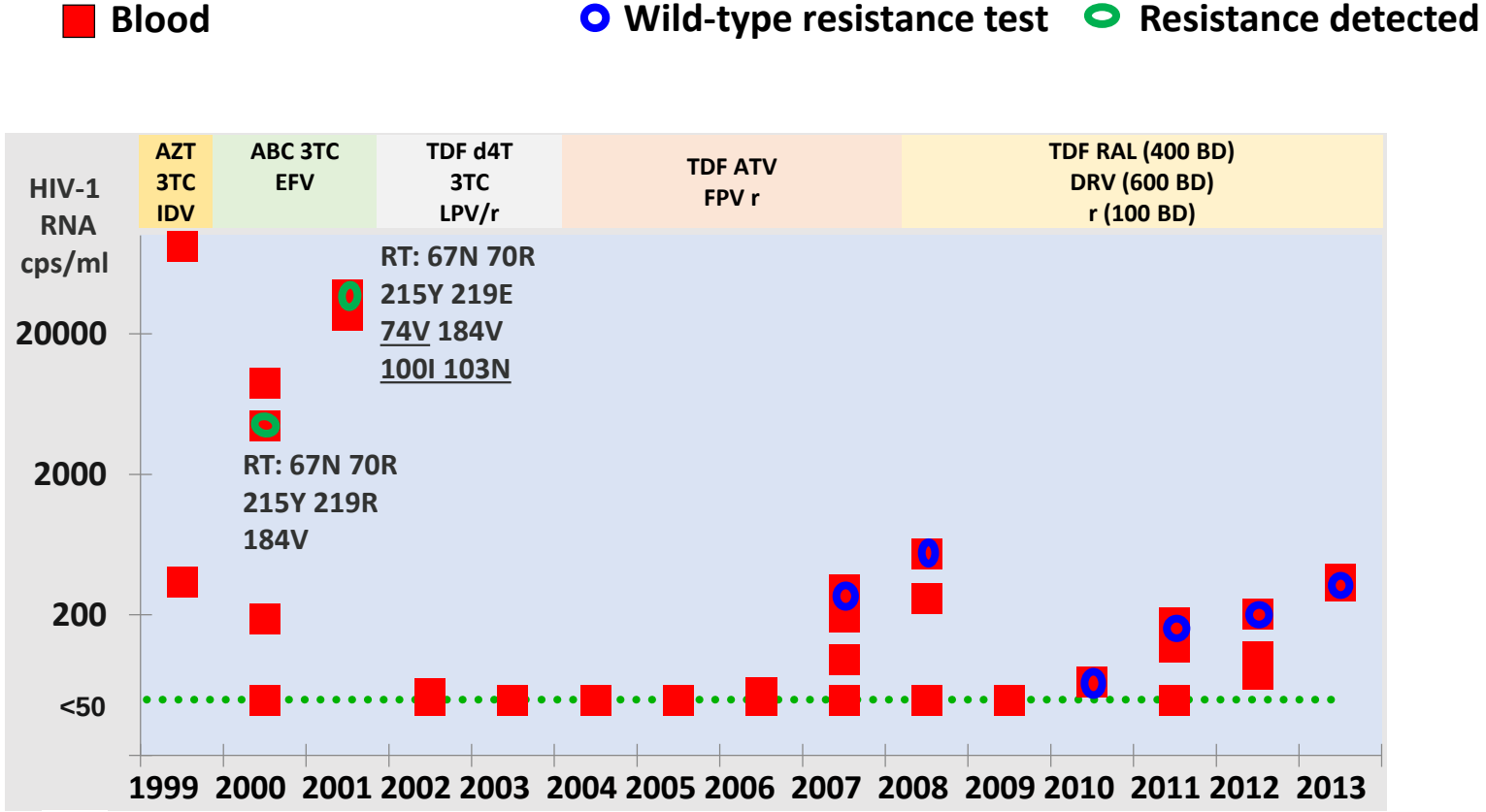
Hill et al. J AIDS 2023

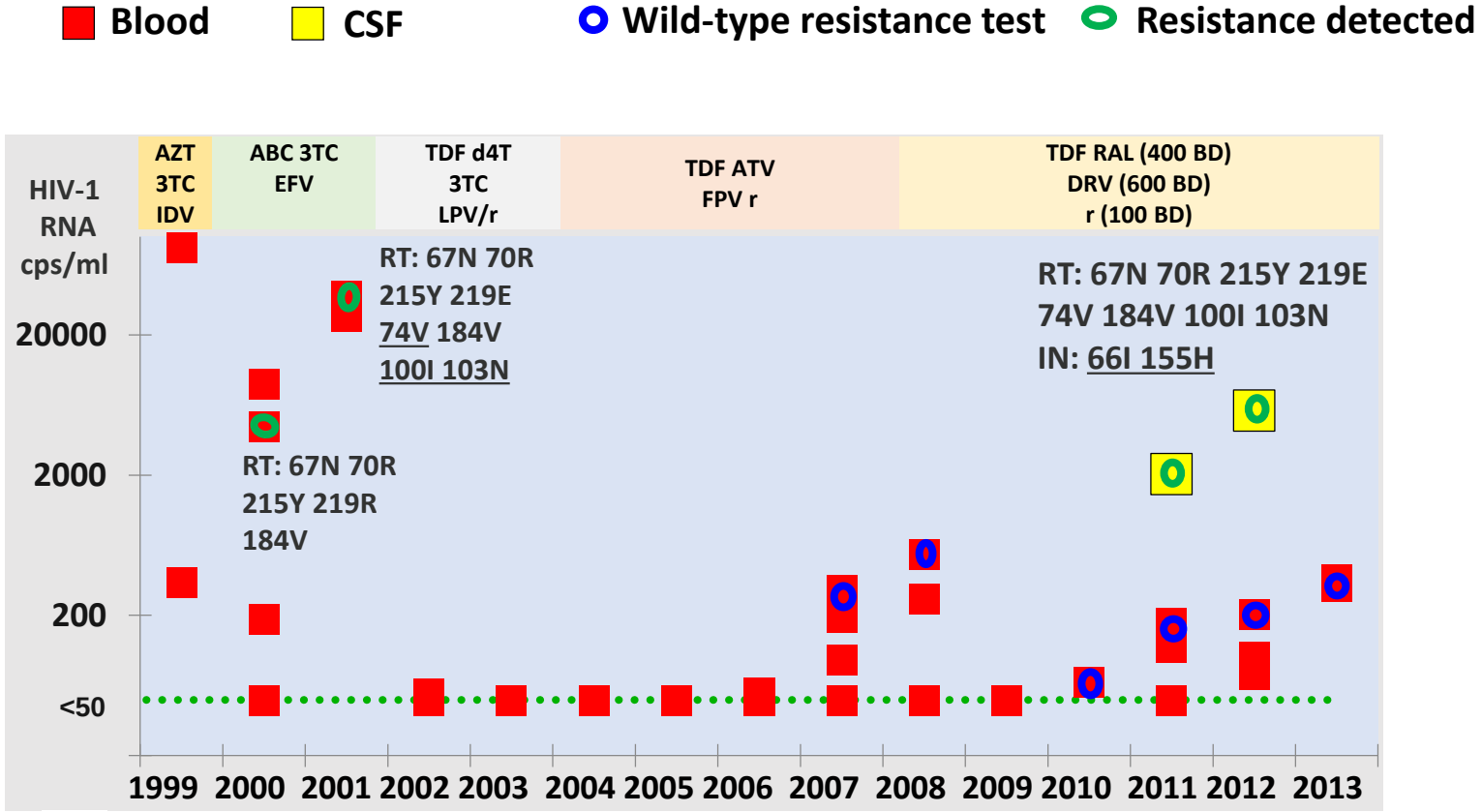
Case History

- 67 y.o. man
- HIV diagnosis in 1999 with Cryptococcus meningitis
- Baseline:
  - CD4 46 cells/mm^3
  - HIV RNA 83,000 c/mL
  - No resistance
  - Subtype C

Date	VL	ARVs
1999-2000	442	AZT 3TC IDV
2000-2001	37600	ABC 3TC EFV
2001-2004	<50	TDF 3TC d4T LPV/r
2004-2008	50-600	TDF ATV FPV r
2008-2013	50-200	TDF RAL DRV/r

NRTI and NNRTI resistance in 2000-2001;
None in 2006-2013 (x 6 tests)
Since 2011: Fatigue and poor memory


Blood
Wild-type resistance test
Resistance detected
HIV-1 RNA cps/ml
20000
2000
200
<50
AZT 3TC IDV
ABC 3TC EFV
TDF d4T 3TC LPV/r
TDF ATV FPV r
TDF RAL (400 BD) DRV (600 BD) r (100 BD)
RT: 67N 70R 215Y 219E 74V 184V 100I 103N
RT: 67N 70R 215Y 219R 184V
1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013



Compartmentalised evolution of drug resistance

LLV: Summary

Multiple possible sources, variable among individuals

Viral load 50 – 200 cps/mL

- **May be physiological**

Viral load >200 – 1000 cps/mL

- **Unlikely to be physiological**

Accepting LLV as physiological:

Only after assessing other potential mechanisms, considering the profile of the individual and temporal trends

1. DHHS Guidelines Feb 2024. https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv

Thank you