Low-Level Viremia despite ART

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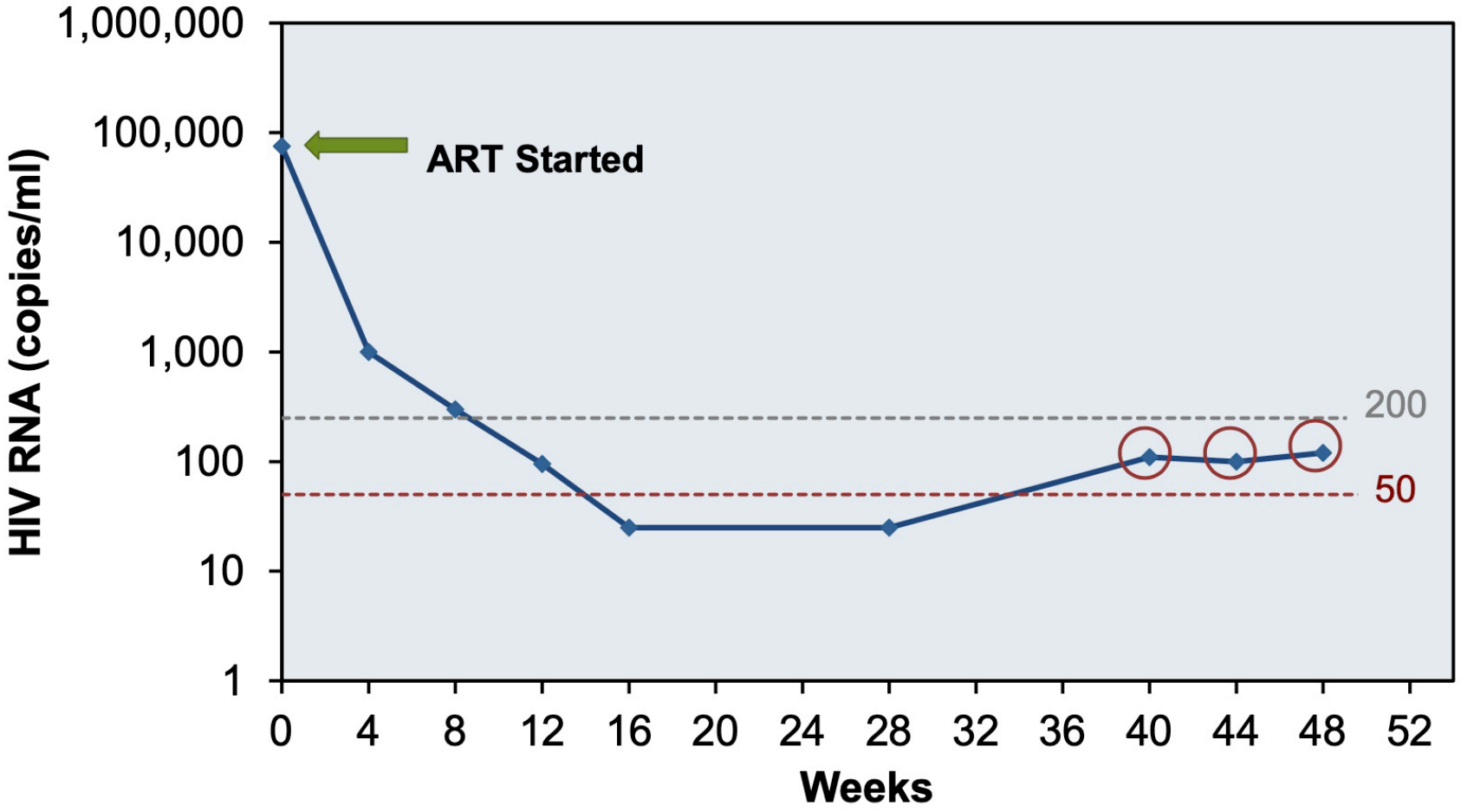
David W. Haas, MD
Professor of Medicine, Pharmacology, Pathology,
Microbiology & Immunology
Vanderbilt University School of Medicine
Associate Director
Tennessee Center for AIDS Research (CFAR)

Objectives

Regarding low-level viremia (LLV) on ART…

- provide an overview
- consider predictors and mechanisms
- discuss implications for management

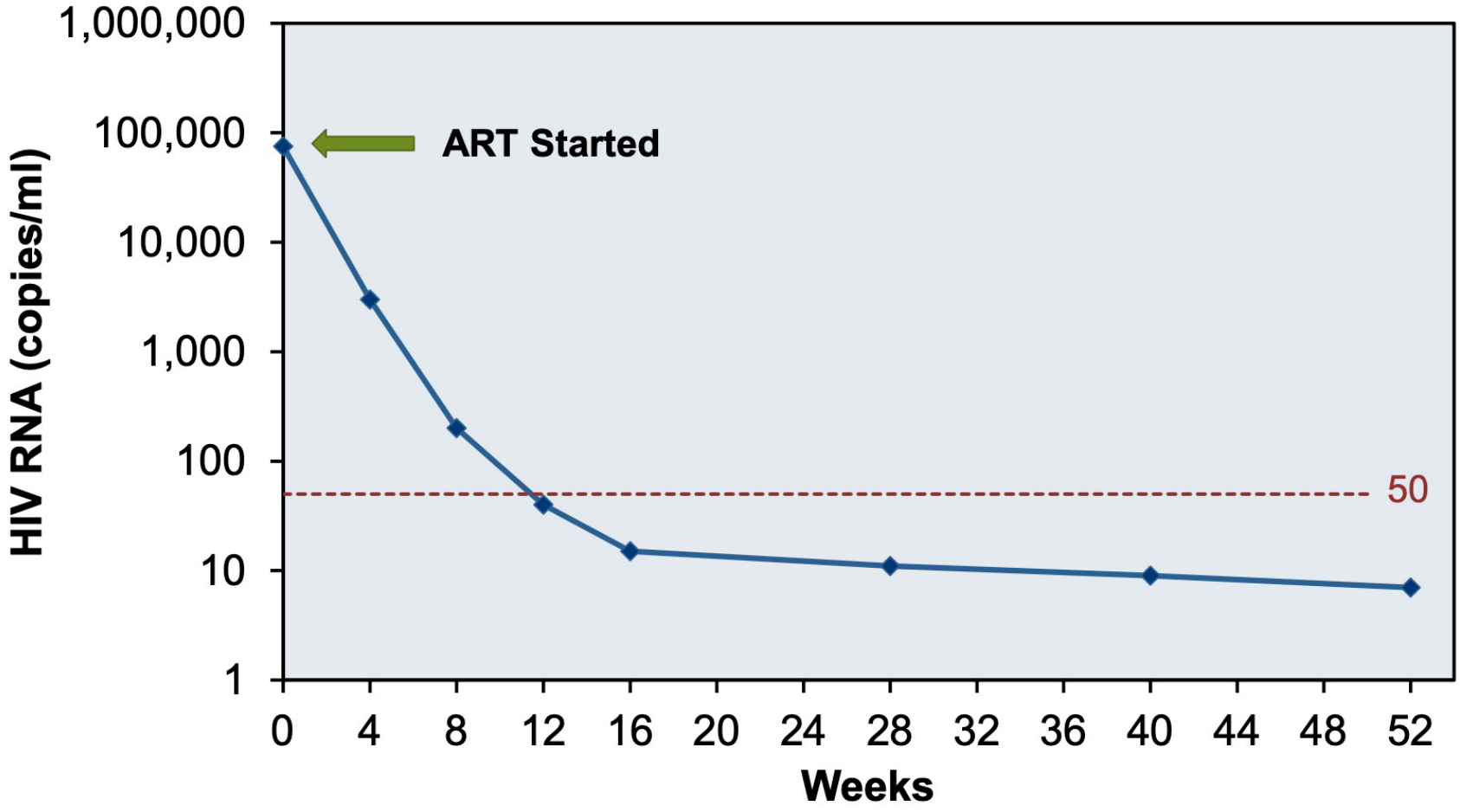
Low-Level Viremia (LLV)



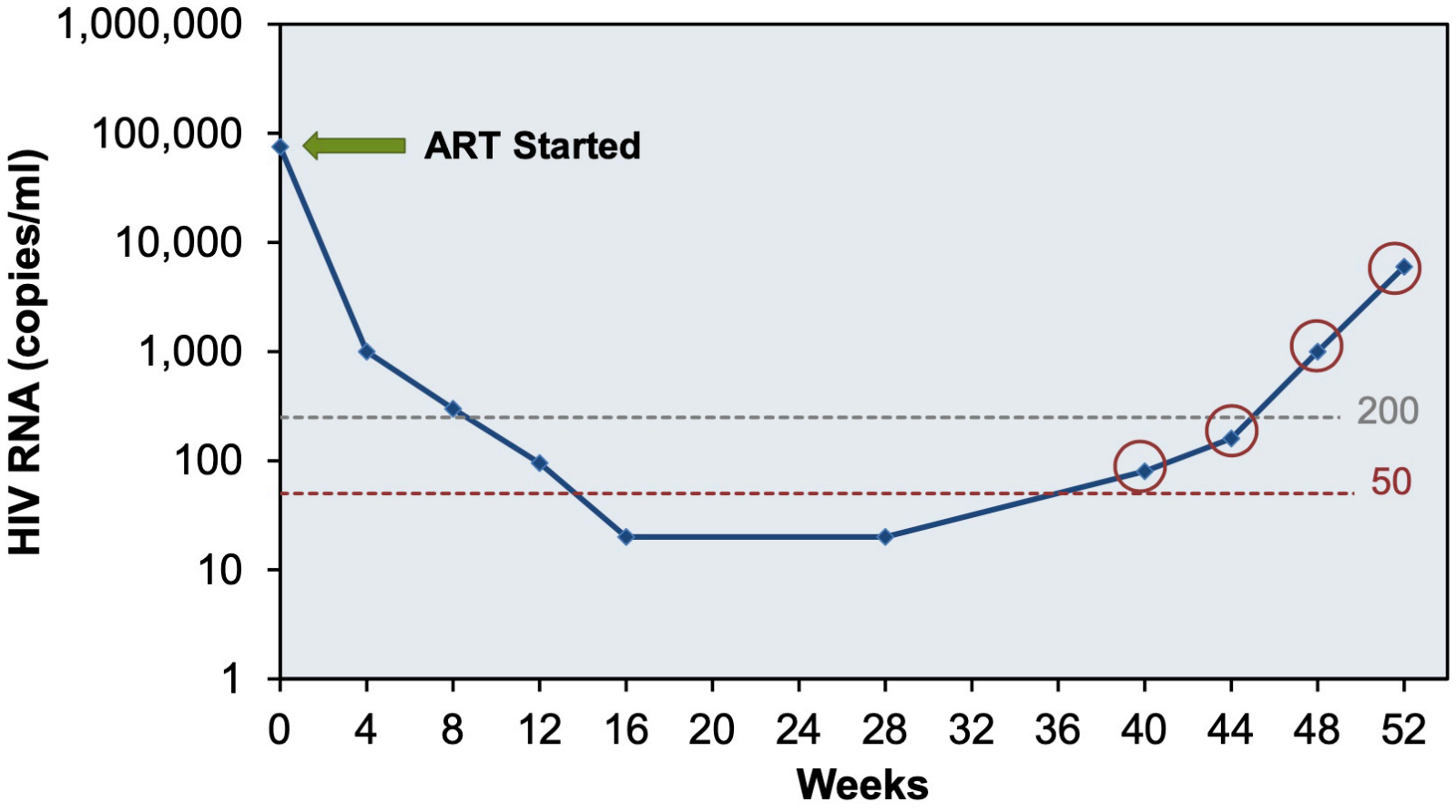
DHHS Panel Definitions

- Low-level viremia (LLV): persistent HIV RNA between lower limit of detection of the assay and 200* copies/ml
- Adequate virologic response: HIV RNA reduction to below limit of detection of the assay within 3-6 months
- Very low-level viremia (VLLV): persistent detected HIV RNA below limit of quantification of assay (ie. <40 or <20 copies/ml)
- Virological failure: HIV RNA increase to above 200* copies/ml
- Virological blip: isolated detectable HIV RNA followed by return to suppression

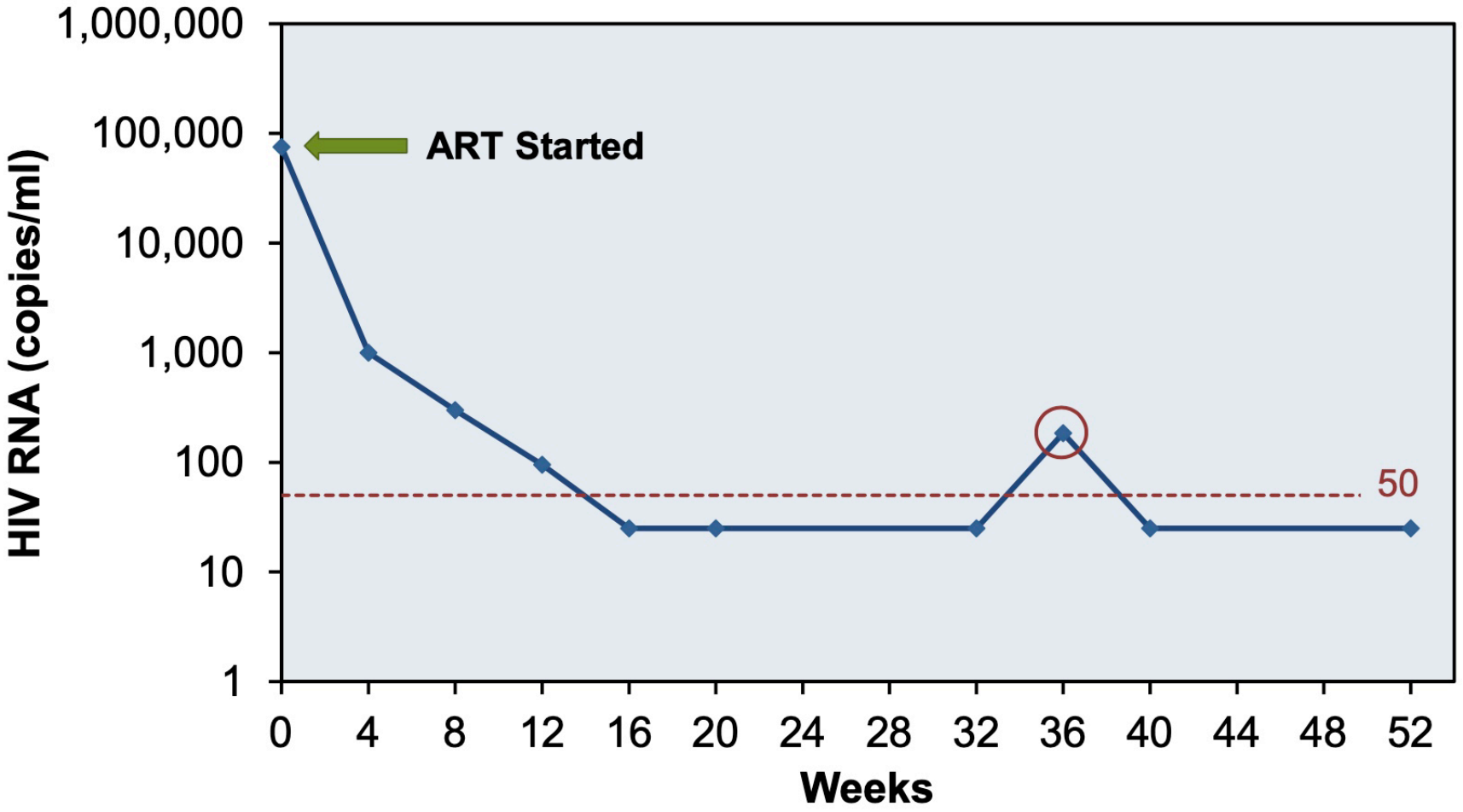
Virologic Suppression



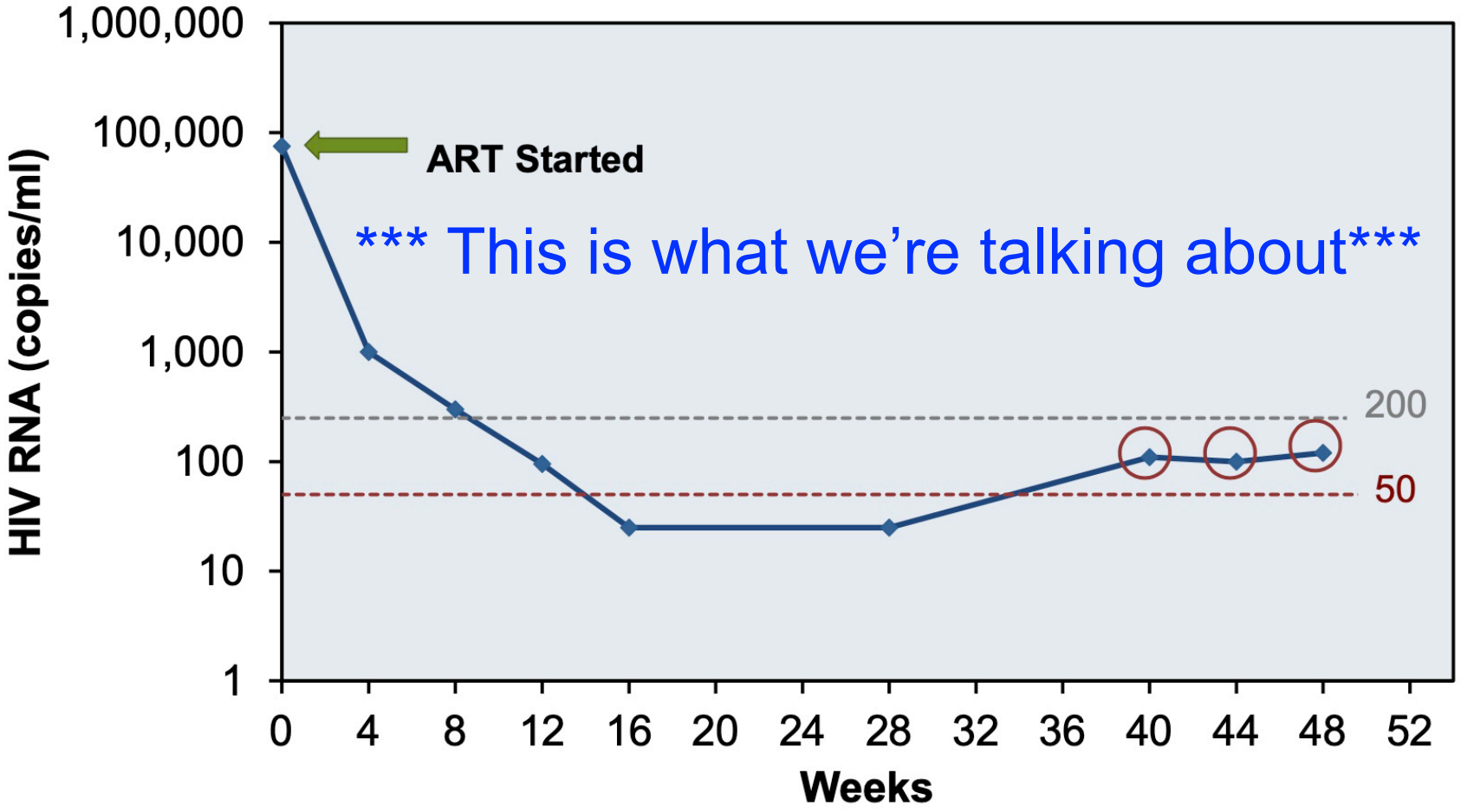
Virologic Rebound



Virologic Blip



Low-Level Viremia (LLV)



A Caveat about LLV Cut-offs

- True “cut-off” or “threshold” values in biology are extremely rare
- 200 copies/mL is not a strict cut-off for LLV. It is on a continuum of risk for future virologic failure
- Many factors affect how much to “worry” about LLV
  - In some patients, LLV 50 - 200 may be of great concern
  - In some patients, LLV 200 - 500 is of almost no concern

What Predicts Low-level Viremia on ART?

- Higher VL before ART initiation, especially >1 million copies/mL
  - In a study of ~1,100 patient starting ART, 2.2-fold greater risk of persistent viremia (50 - 1,000 copies/mL) if high pre-ART viral load

    Taiwo et al *J Infect Dis*. 2011 (PMC3203388)
- Reduced medication adherence
  - Assessed by medication refill data, measuring tenofovir in dried blood spots

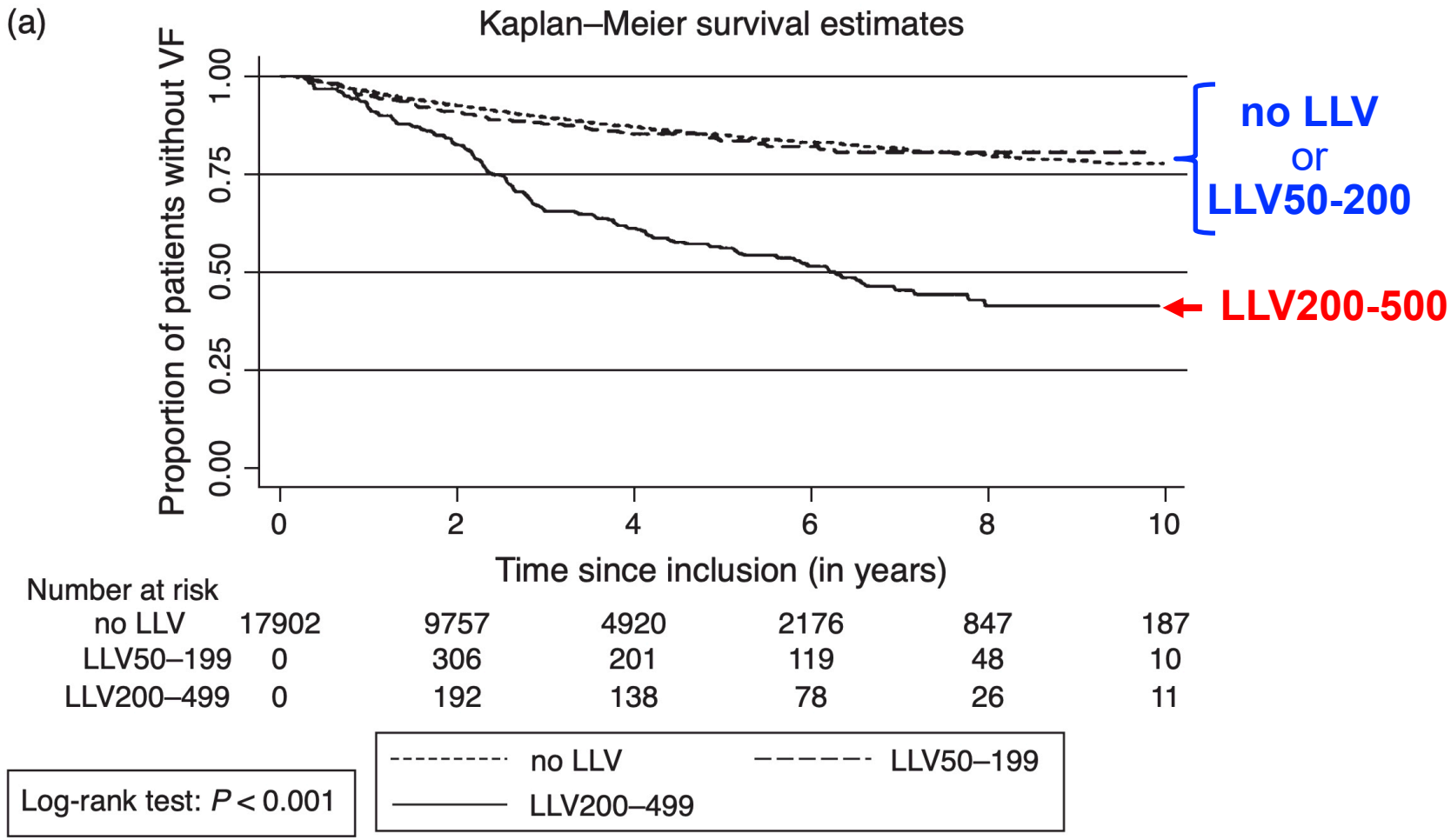
    Goupil de Bouillé et al *AIDS Care* 2021 (32794406)
    Maggiolo et al *Pragmat Obs Res* 2017 (PMC5457149)
    Castillo-Mancilla et al. *Open Forum Infect Dis* 2021 (PMC8465325)

Risk of Virologic Failure Following Low-Level Viremia (LLV)

- Analysis of ~18,000 patients from 18 cohorts in Europe and North America (ART-CC)
- All achieved VL<50 within 3-9 months of starting ART
- Definitions
  - $LLV_{50\text{-}200}$ = 2 consecutive VLs of 50-200 copies/mL
  - $LLV_{200\text{-}500}$ = 2 consecutive VLs of 50-500, with at least 1 of 200-500 copies/mL
- $LLV_{200\text{-}500}$ strongly associated with virological failure, with adjusted hazard ratio (aHR) of ~4
- $LLV_{50\text{-}200}$ weakly associated with virological failure, with aHR ~1.4

Antiretroviral Therapy Cohort Collaboration (ART-CC) *AIDS* 2015 (PMID: 25686685)

Risk of Virologic Failure Following Low-Level Viremia (LLV) in ART-CC



Antiretroviral Therapy Cohort Collaboration (ART-CC) *AIDS* 2015 (PMID: 25686685)

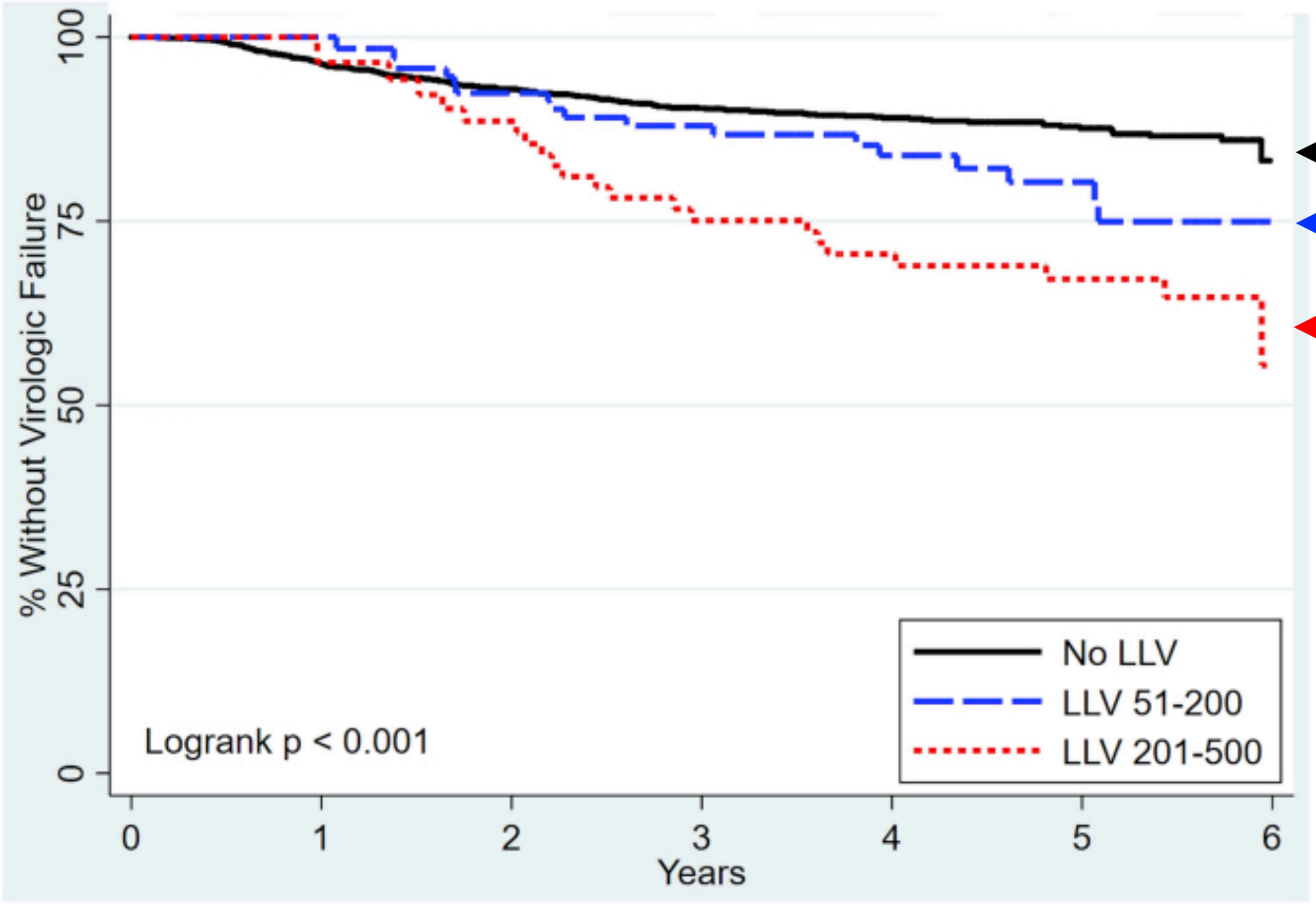
Risk of Virologic Failure Following Low-Level Viremia (LLV)

- Analysis of ~2800 patients from 17 clinics in the US (HIV Research Network)
- Definitions
  - $LLV_{50\text{-}200}$ = 2 consecutive VLs of 50-200 copies/mL
  - $LLV_{200\text{-}500}$ = 2 consecutive VLs of 50-500, with at least 1 of 200-500 copies/mL
- Both $LLV_{50\text{-}200}$ (aHR = 1.8) and $LLV_{200\text{-}500}$ (aHR = 4.3) were associated with virologic failure
- After excluding ART experienced patients, the risk in $LLV_{50\text{-}200}$ was not statistically significant

Suggests that, if VL 50-200, future failure more likely if ART experienced

Fleming et al (HIV Research Network). *AIDS* 2019 (PMC6774874)

Risk of Virologic Failure Following Low-Level Viremia (LLV) in HIV Research Network



Fleming et al (HIV Research Network). *AIDS* 2019 (PMC6774874)

Potential Causes of Low-Level Viremia

- Patient factors: adherence, absorption, food requirements
- Medication factors: drug-drug interactions
- Laboratory/collection error: e.g., plasma preparation tubes
- HIV resistance mutations: partially active ART
- “Repliclones”: activation of latently infected CD4 T-cells

Specimen Collection Factors

Increased Detectability of Plasma HIV-1 RNA after Introduction of a New Assay and Altered Specimen-Processing Procedures

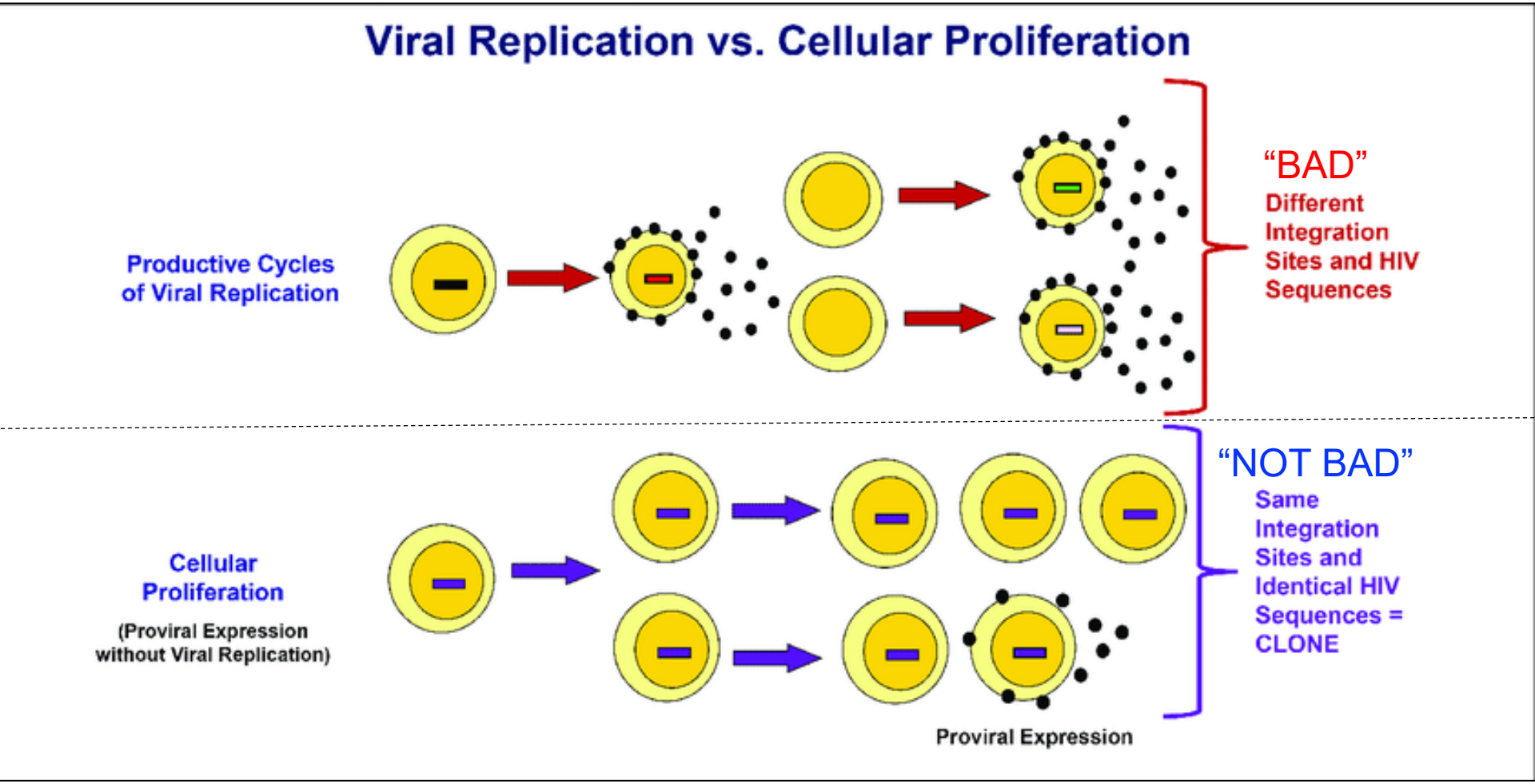
Peter F. Rebeiro,[1] Asghar Kheshti,[1,4] Sally S. Bebawy,[1] Samuel E. Stinnette,[1] Husamettin Erdem,[1] Yi-Wei Tang,[1,2] Timothy R. Sterling,[1,3] Stephen P. Raffanti,[1,4] and Richard T. D'Aquila[1]

[1]Division of Infectious Diseases, Department of Medicine, [2]Molecular Infectious Diseases Laboratory, Department of Pathology, and [3]Center for Health Services Research, Vanderbilt University School of Medicine, and [4]Comprehensive Care Center, Nashville, Tennessee

After changes to assay and specimen-processing methods, plasma human immunodeficiency virus type 1 (HIV-1) RNA was frequently detectable in patients who previously had well-suppressed HIV-1 RNA levels. This artifact is attributable to shipping frozen plasma in primary plasma preparation tubes and is not caused by the HIV-1 RNA detection assay; it can be avoided by shipping plasma in a secondary tube.

Rebeiro et al. *Clin Infect Dis* 2008 (PMC2605467)

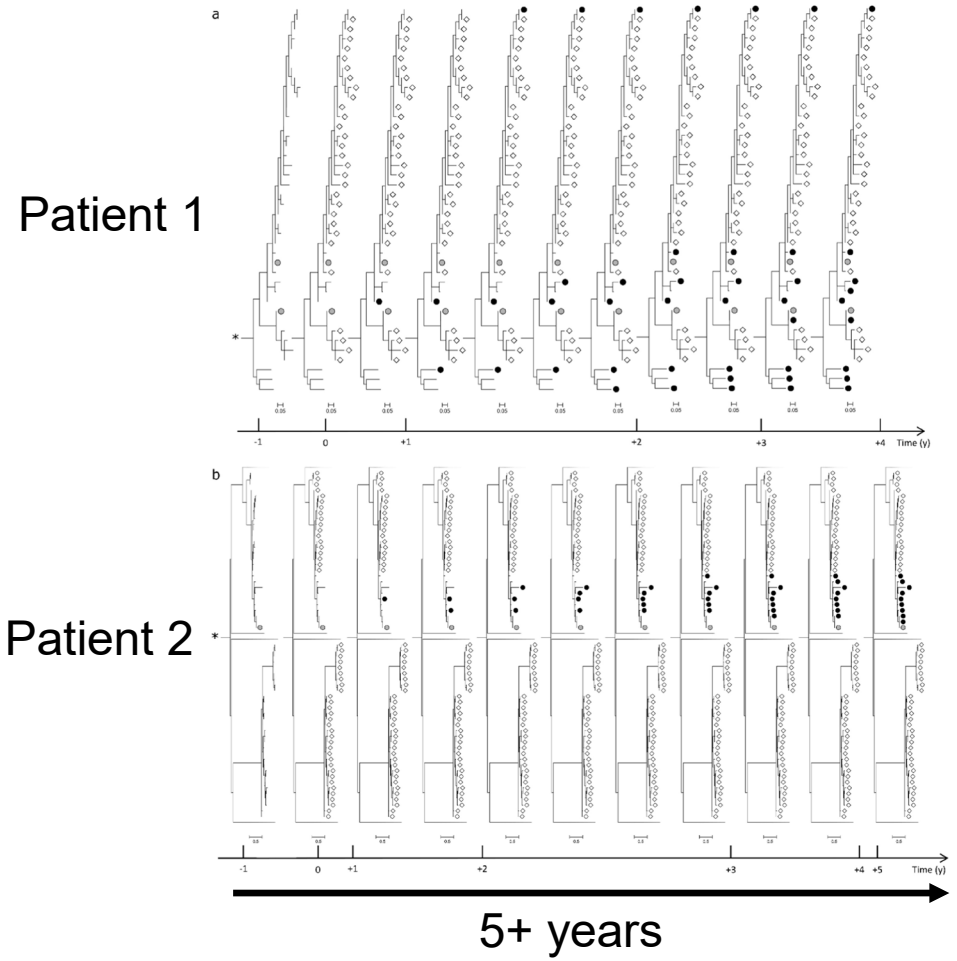
Low-level viremia despite ART: “repliclones” of CD4 T-cells



Jacobs et aL *Frontiers in Microbiology* 2019 (presenter added “bad” & “not bad”)

If Persistent LLV 20-250 copies/mL, HIV is Probably Not Replicating

- 18 patients on ART with VL 20 - 250 copies/mL on at least half of minimum 6 visits for >2.5 years
- Found no firm evidence that the virus was replicating (i.e., not evolving, **not becoming resistant**)



Vancoillie et al. *Virology* 2017 (28750322)

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HIV Proviral DNA Resistance Assays in Patients with Low-Level Viremia

- Standard HIV RNA genotype unlikely successful with LLV
- Proviral DNA resistance assay may help in selected cases
- GenoSure Archive assay, for example,
- May provide info about previously circulating resistant variants archived in proviral DNA
- May miss resistance mutations in HIV quasi-species, so interpret with caution
- Clinical utility of proviral DNA assays not fully determined
- May be very expensive

Managing Persistent Low-Level Viremia: 10 Things to Consider

1. What was pre-ART viral load (e.g., > 1 million)?
2. What was prior ART experience (i.e., likely resistance)?
3. How complete is adherence, how they take medications?
4. Are there drug interactions, drug absorption issues?
5. Maybe order HIV proviral DNA resistance assay?
6. Maybe change regimen, esp. if low resistance barrier?
7. Is there a problem with collection process?
8. Maybe a brief trial of “intensifying” ART (expect no effect)?
9. More frequent follow-up for a while (every 3 months)?
10. Consider referring to a research study…?

a currently-enrolling research study
for patients with low-level viremia

A5321

The ACTG HIV Reservoirs Cohort Study

(cohort 5 – low-level viremia despite ART)

A Multicenter Trial of the ACTG

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A5321 (cohort 5)
Low-level viremia despite ART

Why are we doing this study?

- One goal of HIV research is long-term cure or remission
- Understanding the HIV reservoir is important
- In many LLV patients comes from clonal proliferation of CD4 T cells (“repliclones”)
- Studying such patients will help understand what causes expansion of infected CD4 T cell clones and their fate

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A5321 (cohort 5)
Low-level viremia despite ART

Who is eligible for this study?

- Uninterrupted ART for >12 months before entry (interruptions up to 7 consecutive days allowed)
- At least 2 viral loads 20-1500 copies/mL within 24 months, and at least one 20-1500 within 12 months before entry
- Age ≥18 years
- No active HBV or HCV
- (There are other criteria)
- For Vanderbilt site, contact Joan Gottesman (joan.gottesman@vumc.org)

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A5321 (cohort 5)
Low-level viremia despite ART

What does the study involve?

- Study visits every 6 months
- Blood collections, questionnaires, clinical assessments
- Participants receive compensation per study visit

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Thank you
&
Questions?