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LOW LEVEL HIV VIREMIA - VIROLOGICAL AND CLINICAL IMPACT.

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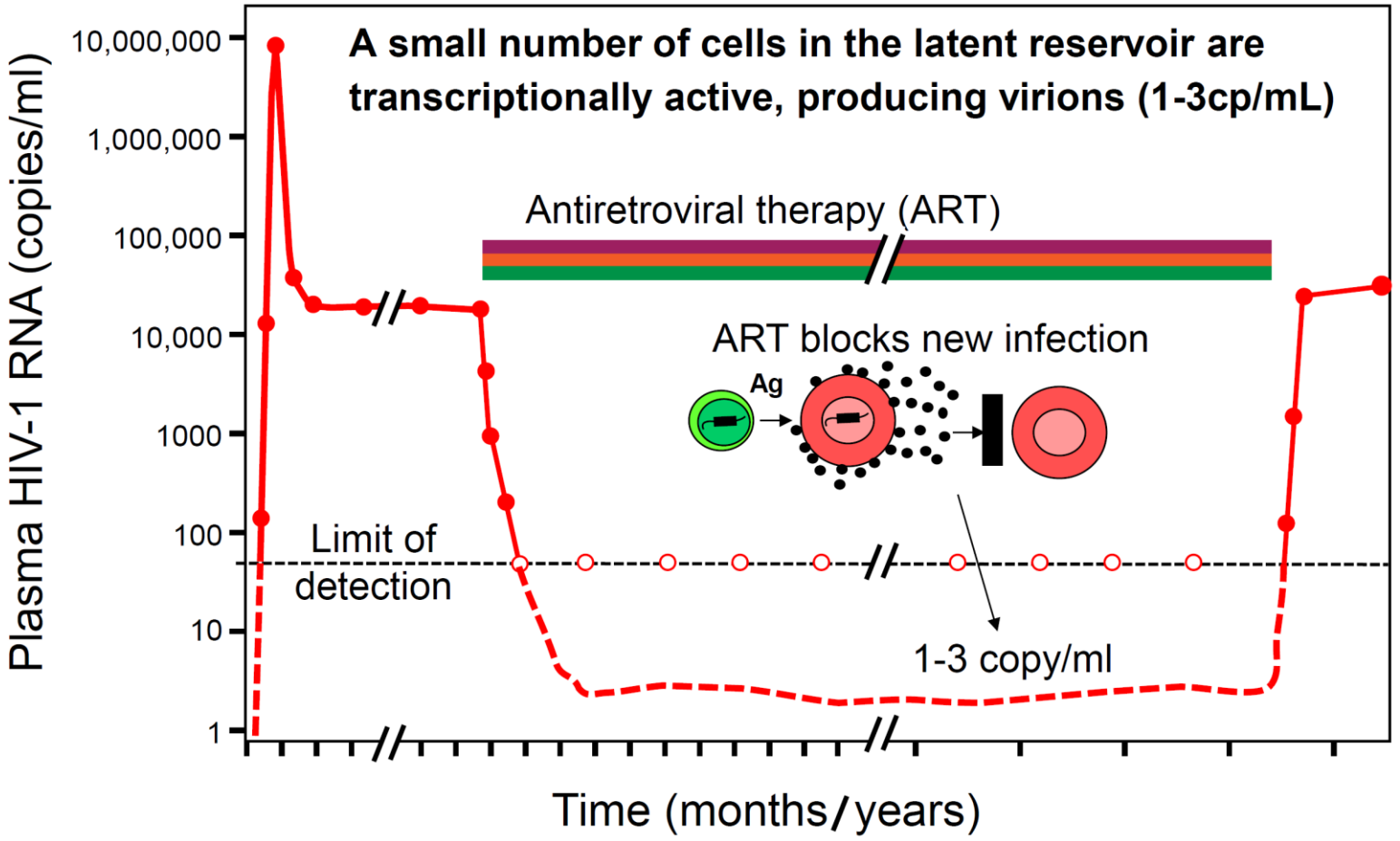
- Expert testimony, Gilead Sciences.
- Serve as a member in the panel of the Spanish Antiretroviral Treatment Guidelines (GeSIDA).

Flow

- **Definition** of LLV
- **Prevalence** of LLV
- Impact on **VF and HIV resistance selection**
- Impact on **HIV transmission**
- **Pathogenesis** of LLV
- **Checklist to complete in the management** of LLV

The vast majority of PWH on ART with undetectable plasma HIV-RNA have residual viremia on ultrasensitive assays.



Definitions and prevalence of virological non-suppression events.

Virological suppression: HIV-1 RNA <50 copies/mL (even if threshold is 40 or 20 c/mL)
No viral evolution, no resistance selection

Low-level viremia (2.1-7%)*: **≥2 consecutive HIV-1 RNA 51–199** c/mL

Residual viremia ("22.2%")*: detectable and quantifiable **HIV-1 RNA below 50 c/mL or TND**

Viral blip (9.6-16%)*: **isolated HIV-1 RNA >50 c/ml** (usually <200 c/mL) with pre- and post- VL <50 c/mL

Virological failure (2.1%)*: Confirmed HIV-RNA ≥200 c/mL

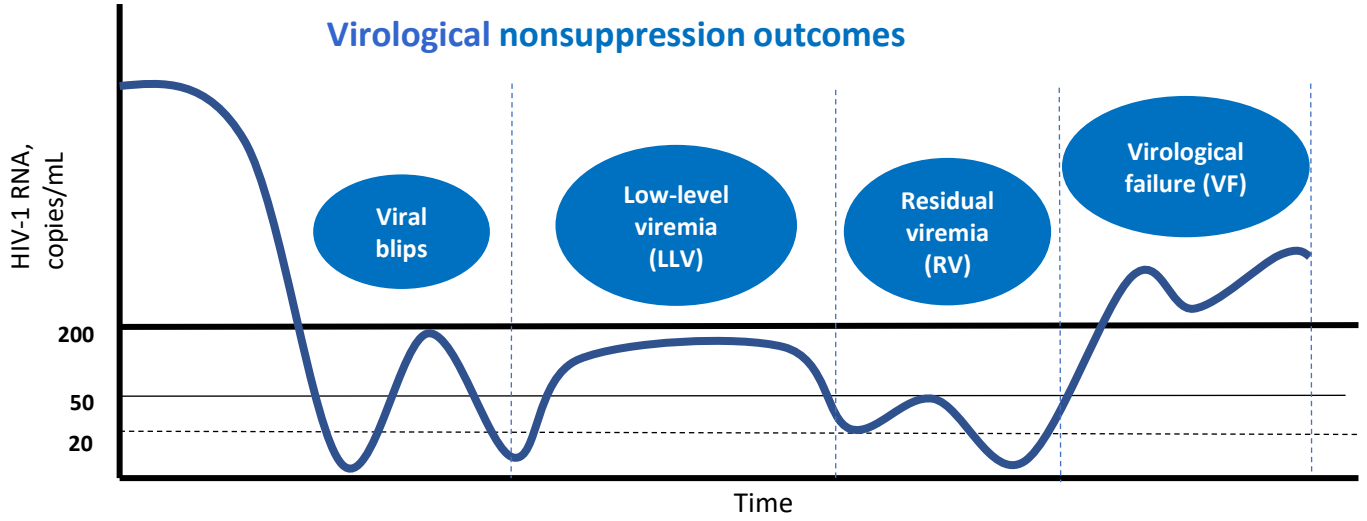


Figure: Courtesy of Hortensia Alvarez, Coruña, Spain.

* H Alvarez, JM Llibre. Clin Infect Dis 2023;77(4):593–605. O Elvstam. Clin Infect Dis 2024; doi/10.1093/cid/ciac762/6696999. C Lanz. Clin Infect Dis 2025. DOI: 10.1093/cid/ciae569

Discordant (contradictory) results on LLV and VF and/or HIV resistance

- **Disagreement in definitions** of LLV in studies (VL <200, <500, <1000 c/mL)
- **Low rates of Genotypic succesful amplification**
- **Not analysed by ART regimens** (high or low resistance barrier)
- Not compared to baseline HIV resistance (**new HIV resistance emergence vs re-emergence**)
- **Different treatment situations**: naives, switch, switch with previous resistance, salvage ART regimens…

O Elvstam. Clin Infect Dis 2024; doi/10.1093/cid/ciac762/6696999; LV Rindi. Sex Transm Infect 2024;0:1–8; R Palich. J Antimicrob Chemother 2020; 75: 2981–2985; P Ryscavage. AAC 2014; 58(7):3585–3598.
A Esteban-Cantos. Lancet HIV 2024; https://doi.org/10.1016/S2352-3018(24)00063-8

LLV: Risk of virological failure and resistance selection. EuResist DB

- EuResist Database. 22 523 participants, 81 837 p-y of follow-up.
- 1424 events of VF: 17 per 1000 p-y.

- **Only 7 participants with well-defined LLV had new DRMs at VF (but amplification rates low: 8% !!).**
- **M184V/I and K103N/S, most frequent DRMs.**
- **Only with low resistance barrier regimens.**

Cox regression models for VF with blips or LLV

	Unadjusted Model (n = 22 523)	Fully Adjusted Model[a] (n = 6650)
Virologic suppression	1 (Ref.)	1 (Ref.)
Viral blips	1.4 (1.2–1.7)	1.7 (1.3–2.2)
LLV 51–199 copies/mL	2.6 (2.3–3.1)	2.2 (1.6–3.0)

aHR 2.0 (1.4–2.9)
(LLV= 51-199 c/mL)

Subset INSTI (lower n): aHR 1.0 (0.2–4.3)

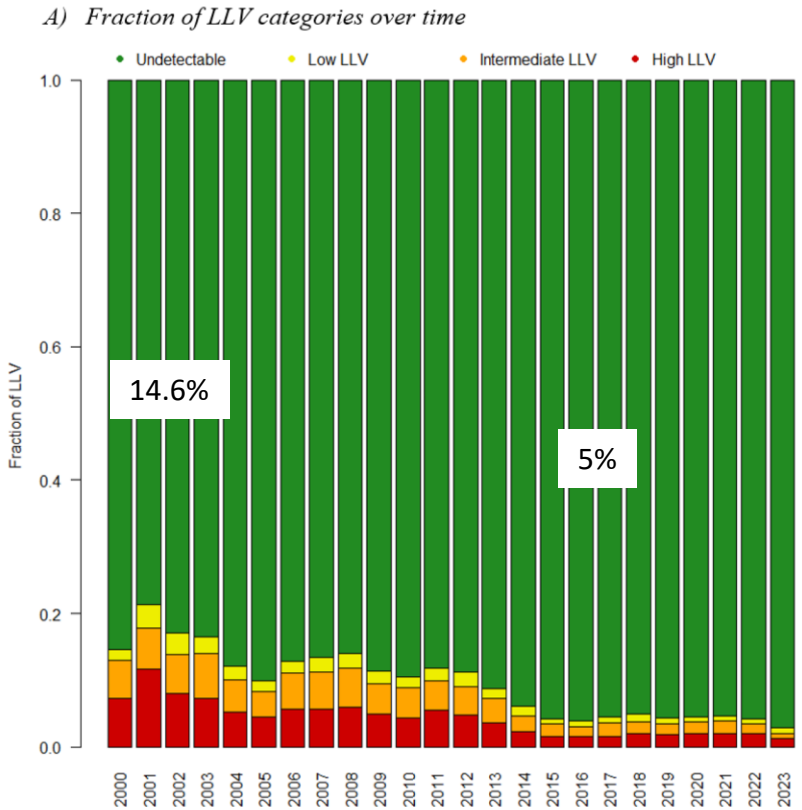
Table 3. Drug Resistance Mutations Among Participants With Virologic Failure

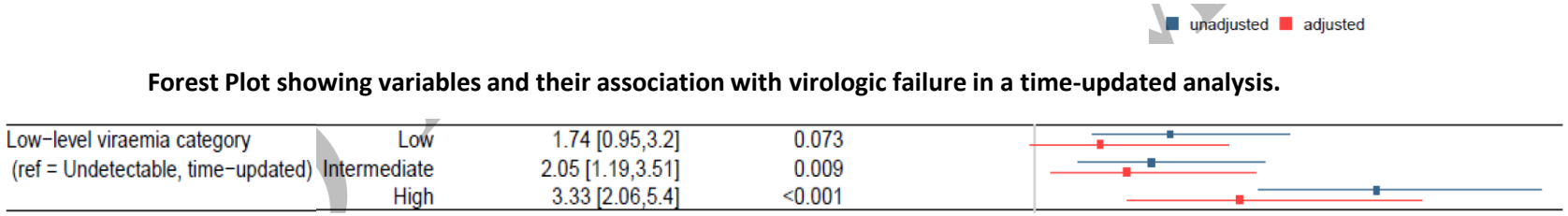
	Any Drug Resistance Mutations[a]	NRTI-resistance Mutations[b]	NNRTI-resistance Mutations[b]	PI-resistance Mutations[c]	INSTI-resistance Mutations[d]
Virologic suppression	113 (50%)	82 (37%)	74 (34%)	18 (8%)	10 (16%)
Viral blips	33 (59%)	23 (43%)	21 (40%)	4 (7%)	5 (21%)
LLV 51–199 copies/mL	24 (42%)	18 (33%)	13 (24%)	4 (7%)	3 (14%)

O Elvstam. Clin Infect Dis 2024; doi/10.1093/cid/ciac762/6696999

LLV: Risk of virological failure. Swiss HIV Cohort Study

- 8.132 participants, 49.579 person-years (since 1999).
- **LLV** (50-199 c/mL) **stratified in 3 categories** (low, intermediate, and high LLV) corresponding to AUC tertiles along time. **VF** defined as ≥200 copies/ml.
- 625 (**7.7%**) participants experienced **VF**.





C Lanz. Clin Infect Dis 2025. DOI: 10.1093/cid/ciae569

LLV: Risk of virological failure.

Women's Interagency HIV Study

Intermittent LLV (nonconsecutive detectable VL up to 199 copies/ml [blips]), **persistent LLV** (at least two consecutive detectable VL up to 199 copies/ml).
Of 1598 WWH, 58, **19, and 6% were categorized** as having virologic suppression, **iLLV, and pLLV** (17% had VF at baseline).

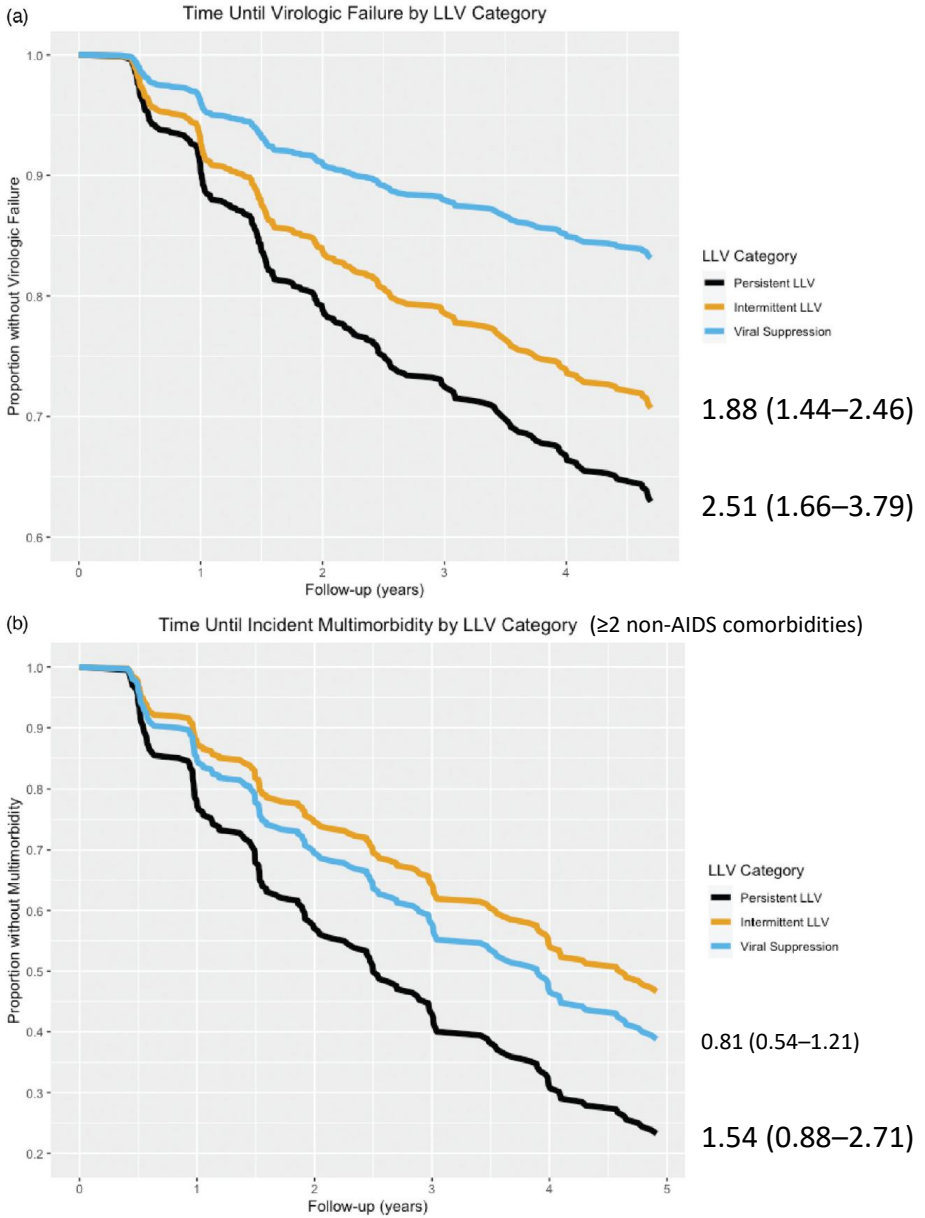


Fig. 3. Adjusted survival curves for (a) time to incident virologic failure and (b) time to Incident multimorbidity. (a) Model for virologic failure with $P < 0.0001$. (b) Model for multimorbidity with $P = 0.14$.

Amalia Aldredge. AIDS 2024, 38:1829–1838

Prevalence of DRMs in PWH on ART with LLV. China.

- 7635 PLHIV had received DRM testing: 789 LLV (50–999 c/mL) and 6846 high-level viremias (≥1000 c/mL).
- 85% NNRTI + NRTIs, 12% PI + NRTIs
- 470 sequences obtained.

Table 1. The amplification positive rates of different viremia categories

pVL range (copies/mL)	No. of all samples	No. of positive samples	Positive rate (%)
50–199	77	35	45.5
200–399	382	209	54.7
400–599	168	111	66.1
600–799	103	69	67.0
800–999	59	46	78.0

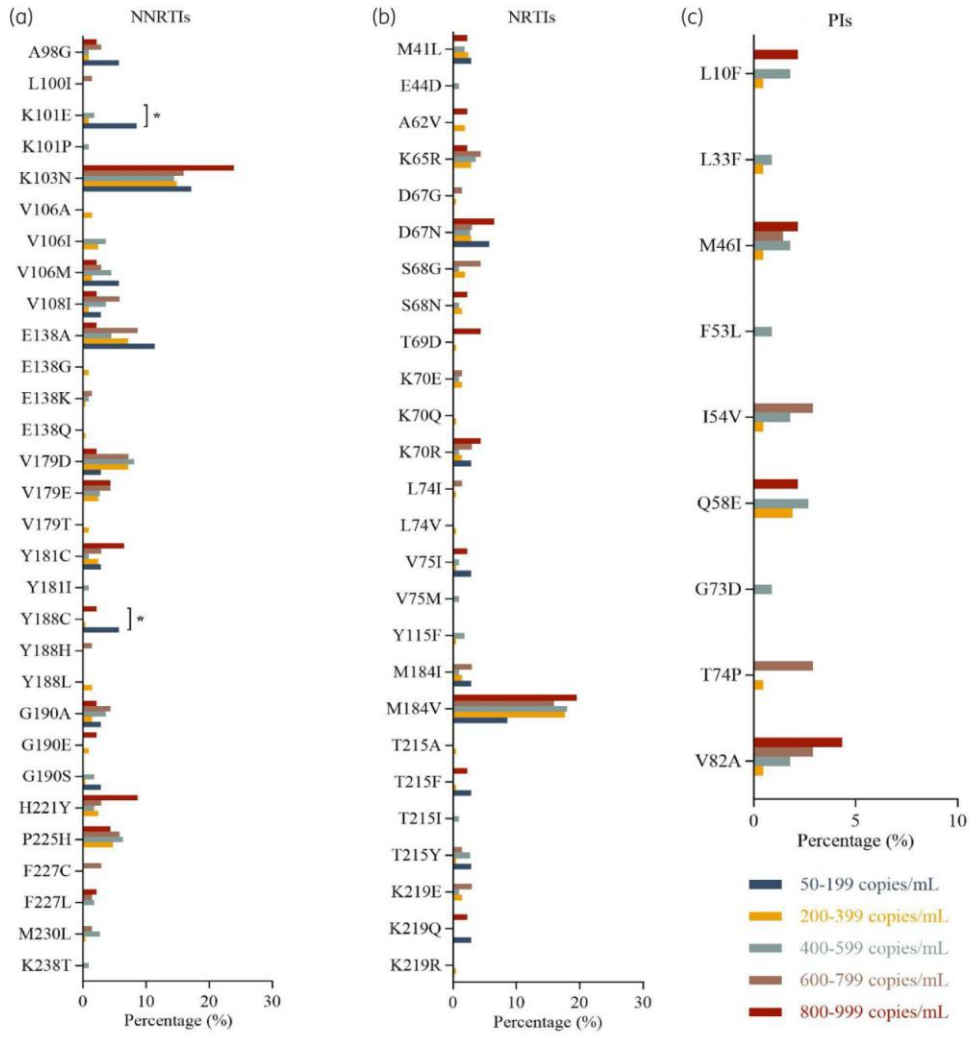


Figure 2. Prevalence of DRM sites with (a) NNRTIs, (b) NRTIs and (c) PIs stratified by LLV group. NNRTIs, non-nucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors. * indicates statistically significant differences ($P < 0.05$).

Yuanlu Shu. J Antimicrob Chemother 2025. https://doi.org/10.1093/jac/dkaf017

Impact of LLV on HIV transmission: systematic review.

- **8 studies** with **7762 serodiscordant couples**, across 25 countries.
- HPTN 052, Opposites Attract, PARTNER, PARTNER 2, Partners PrEP, Rakai (Uganda), Zambia, Thailand.
- **323 transmission events** at varying HIV viral loads.
- Most included phylogenetic linkage analysis.
- 2 “possible” transmissions with HIV VL 600 – 1000 copies/mL, but done >50 days before transmission.

No HIV transmission when the partner living with HIV had a VL <200 copies/mL.
U=U message can be maintained in PWD on ART with VL < 200 c/mL.

Interpretation There is almost zero risk of sexual transmission of HIV with viral loads of less than 1000 copies per mL.

LN Broyles. Lancet 2023; https://doi.org/10.1016/S0140-6736(23)00877-2

Determinants of LLV. Analysis of the RESPOND cohort.

4310 treatment-naive PWH, RESPOND multicohort. 72% started INSTI-based ART.
Rate of LLV at 48 weeks: **2.1%**

Determinants at baseline (any ART):

- HIV-RNA ≤10.000 c/mL: **aHR 0.38** (0.16 - 0.91)
- HIV-RNA >100.000 c/mL: **aHR 2.41** (1.60 - 3.62)
- CD4+ ≤200, 200-350, 351-500 cells/µL: **aHR 5.07, 3.71, 2.25** (all p<0.01)

Subset receiving INSTIs:

- HIV-RNA >100.000 c/mL: **aHR 2.85** (1.76 - 4.62)
- CD4+ ≤200, 200-350, 351-500 cells/µL: **aHR 6.32, 4.46, 2.17** (all p<0.01)

Subset receiving DTG:

- HIV-RNA >100.000 c/mL: **aHR 2.87** (1.58 – 5.19)
- CD4+ ≤200, 200-350, 351-500 cells/µL: **aHR 11.82, 7.06, 4.82** ((all p<0.01)

Suggesting that a larger HIV reservoir is a lifelong determinant of LLV, with independence of the ART.

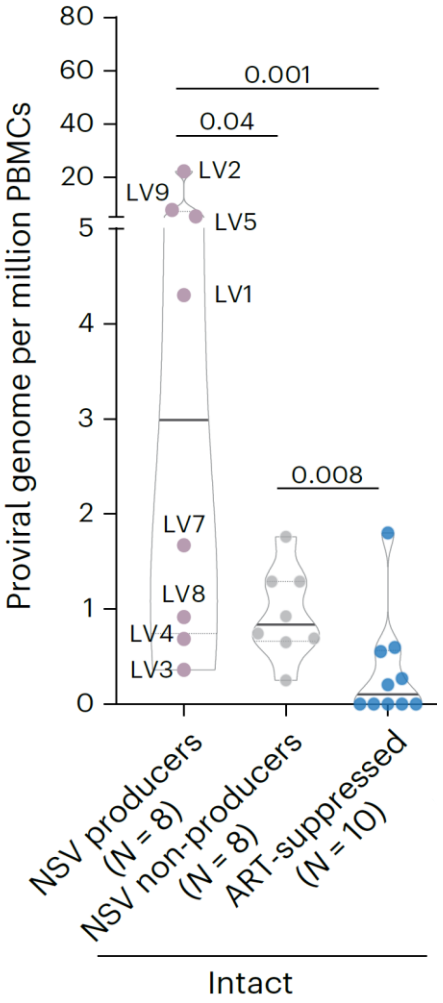
H Alvarez, JM Llibre. Clinical Infectious Diseases 2023;77(4):593–605. H Alvarez, JM Llibre. HIV Med 2022. DOI: 10.1111/hiv.13265

Persistent LLV in ART without evidence of non-adherence or significant drug resistance (**non-suppressible viremia**) is composed of **large defective clones without evidence of viral evolution** over time, **drug-sensitive viruses** and **relatively homogeneous viral populations,** integrated in transcriptionally permissive chromosomal regions.

These people have:

- **Larger HIV reservoirs** (low nadir CD4, nadir HIV-RNA >100.000 c/mL)
- **Disregulation of CD4+ T cells responses** (apoptosis)
- **Lower** (defective) **HIV-specific CD8+ T cell responses**
- **Independent of the ART received, INSTI or DTG.**

Intact reservoir size (n of proviral sequences per 10^6 PBMC cells) **for producer versus non-producer proviruses in participants with NSV** (non-suppressible viremia) **vs ART-suppressed individuals.**

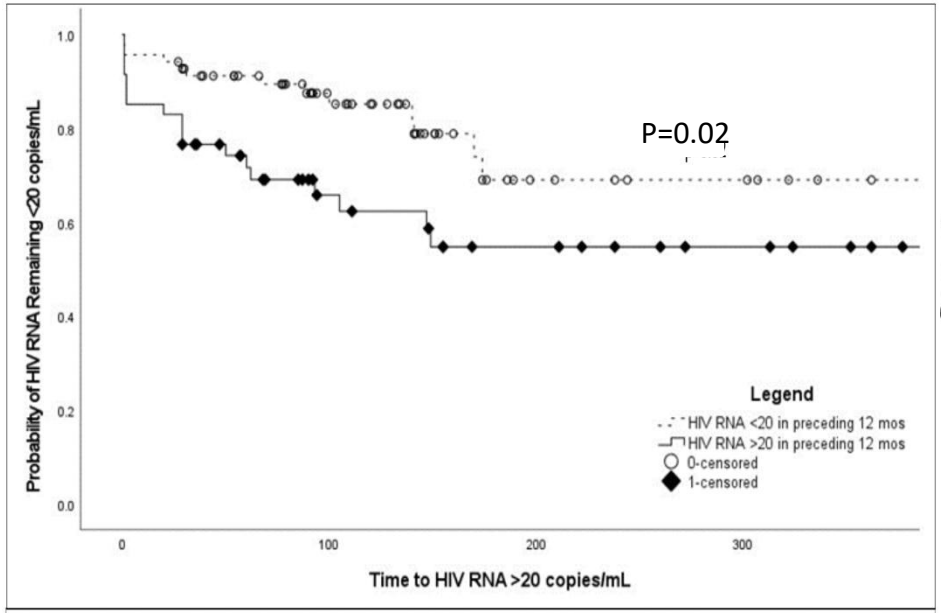


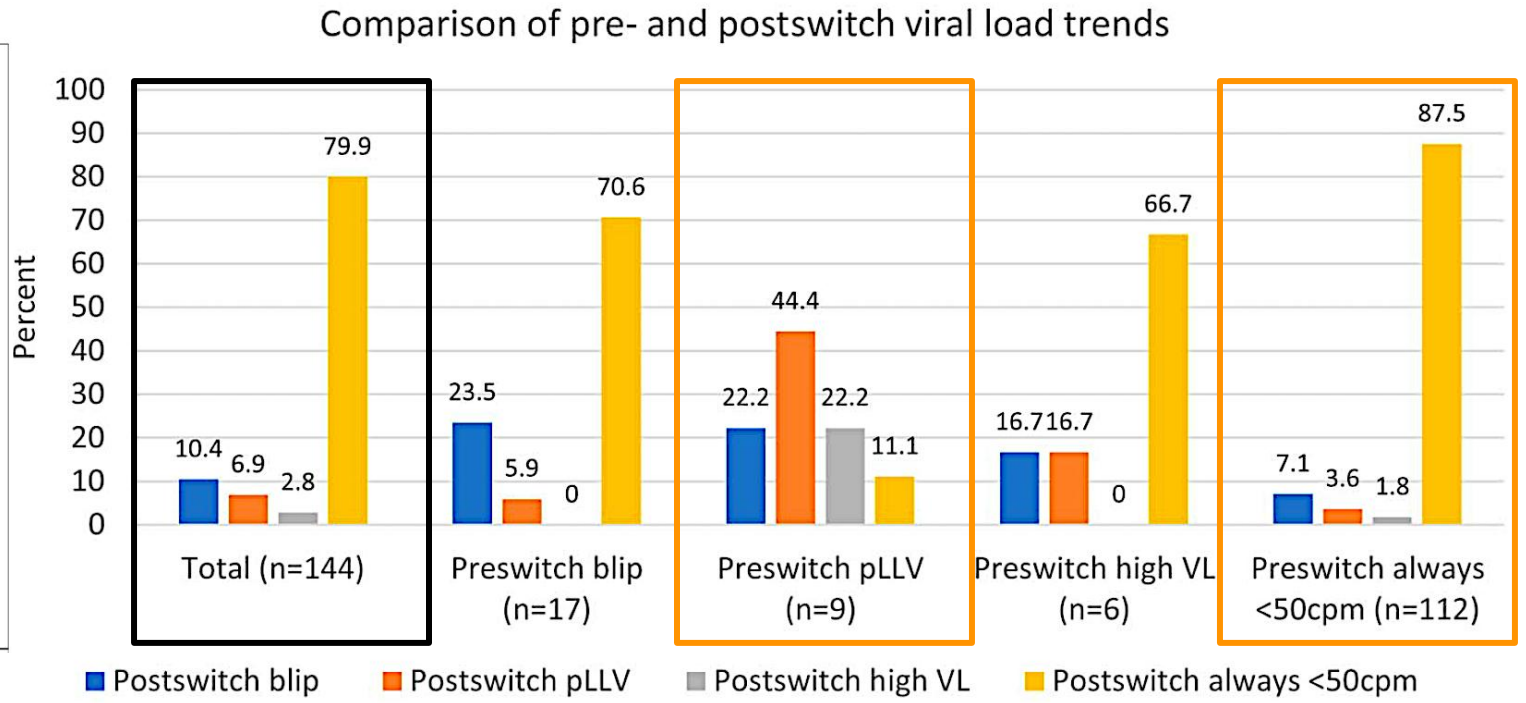
A Mohammadi. Nature Med 2023; https://doi.org/10.1038/s41591-023-02611-1 . H Alvarez, JM Llibre. Clin Infect Dis 2023;77(4):593–605.

True LLV could be independent of ART adherence: data on LA CAB+RPV

- Retrospective cohort. N=144. Median follow-up: 287 days.
- HIV RNA <200 copies/mL at the time of switch to CAB+RPV.

Those with pLLV before switch continued with pLLV after switch to LAI CAB/RPV despite 100% adherence.





L Hill. J Acquir Immune Defic Syndr 2024;95:90–96. S Kenney. CROI 2023, #516.

Factors associated with non-sustained Viral Suppression on LA CAB + RPV

173 PWH transition to LA CAB + RPV.
Intermittent viremia occurred in 34.7%, and persistent LLV in 4%.
VF (2 x VL≥200 c/mL) at 11 months: 2 (1.2%).

Low trough concentrations of CAB and RPV associated with episodes of detectable viremia exceeding 50 copies/mL in univariate but **not un multivariate models**.

Predictors of **non-sustained viral suppression:**

- **VL at HIV diagnosis** [AHR: 1.49 per $\log_{10}$ VL, 95% CI: 1.04-2.12, P =.027]
- **Detectable viremia on oral ART** [AHR: 2.45, 95% CI: 1.29-4.65, P =.006],
- **Being 20 c/mL at transition** [AHR: 0.38, 95% CI: 0.19-0.75, P =.004].

Non-sustained viral suppression in PWH transitioning from stable oral ART to CAB+RPV LA linked to pre-existing factors before transition

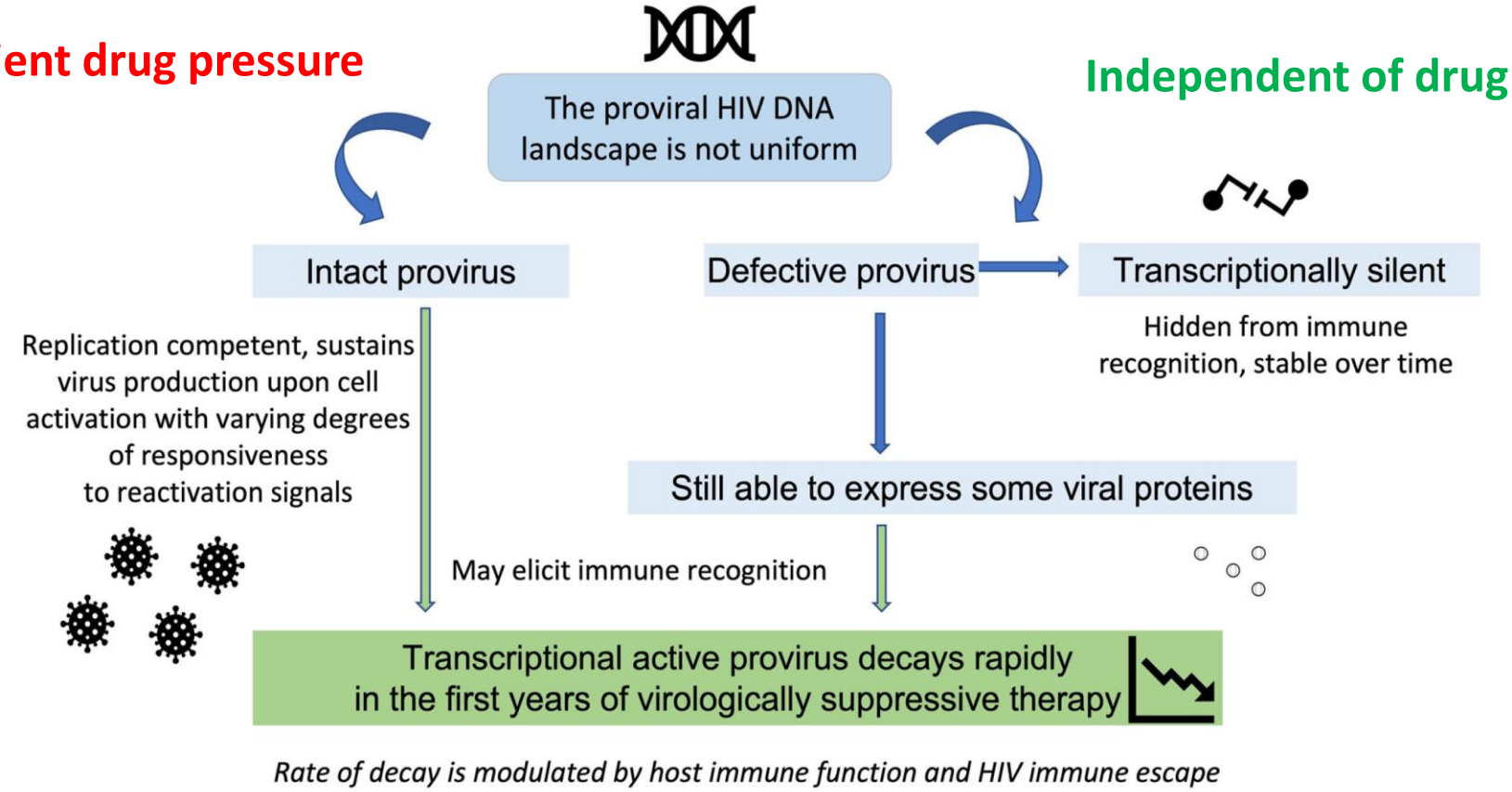
Felix Gutierrez. Clin Infect Dis 2024; DOI: 10.1093/cid/ciae475

The source of LLV: Viral Replication ≠ Clonal Expansion with Proviral Expression

The diverse HIV proviral landscape.

- **genetic heterogeneity** (errors in RT)
- **variation in the chromosomal integration site** of the HIV provirus

- **identical chromosomal HIV integration sites** in cell progeny
- **identical proviral sequences**
- **identical viral sequences** from the subset of cell in the clone that produce virus

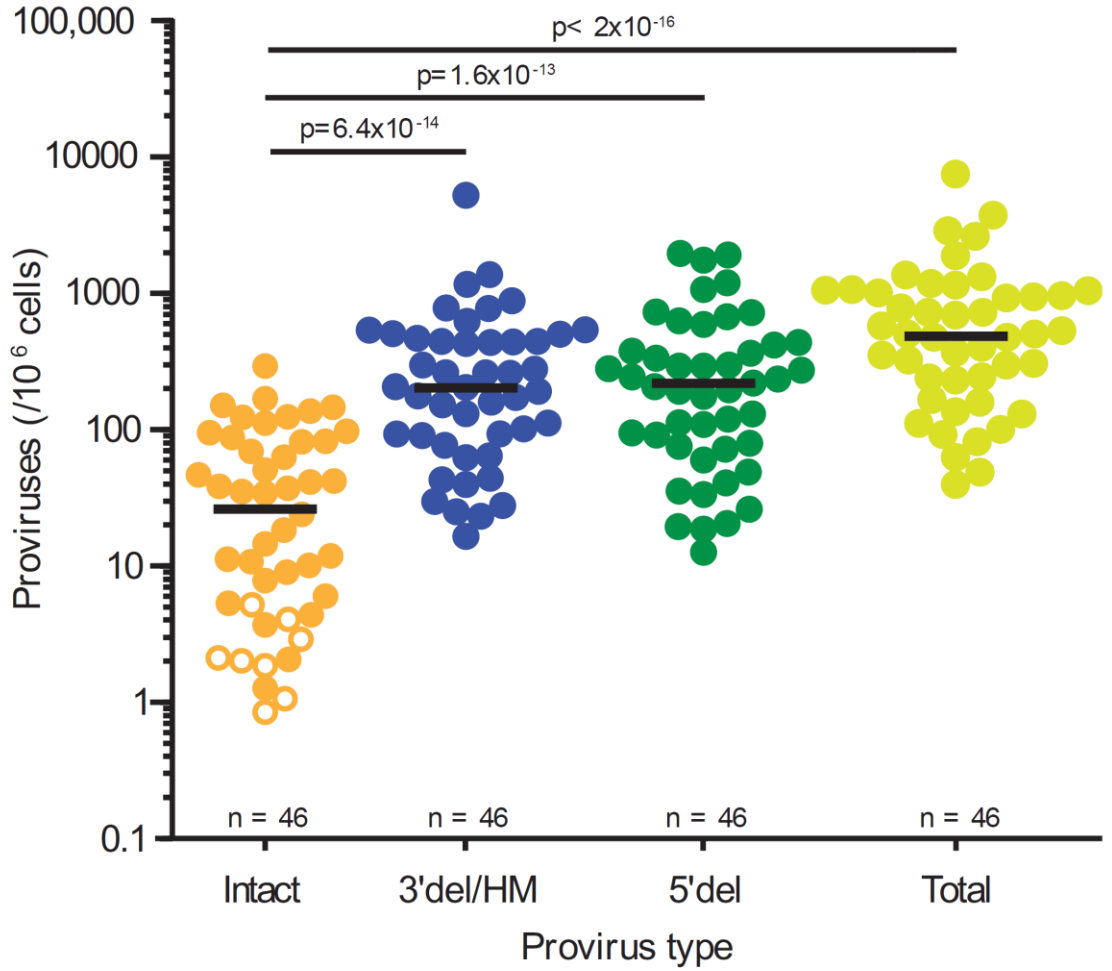


AM Geretti. Infect Dis Ther (2022) 11:1793–1803

Upon long-term ART defective proviruses outnumber intact proviruses.

- Under long-term suppressive ART, inducible **replication competent proviruses remain quite stable**, and **integrated mainly in transcriptionally inactive regions of the genome.**
- The expected decay in HIV reservoir with t½=44.2 months is no longer confirmed.
- **Along time, there is a gradual selection against inducible, intact proviruses, and defective viruses prevail**.

Frequency of intact and defective proviruses (3' deleted/hypermutated and 5' deleted) in resting CD4+ T cells of PWH on suppressive ART.



NF McMyn. J Clin Invest 2023; https://doi.org/10.1172/JCI171554.
V Hariharan. AIDS 22-26 July 2024, Munich. #OAA3503

Mandatory checklist in (confirmed) LLV management

- **Check for adherence / reinforce adherence.**
- **Check for change in lab reagents /techniques** (*LLV seen in a short time among different PWH*).

- **Confirm the current ART is optimal** based on all previous info (resistance & toxicity).
- Check for **ddI and food-drug interactions**.
- Remember InSTI interactions with multivalent cations (Ca^{2+}, Fe^{3+}, Mg^{2+}, Al^{3+}, Zn^{2+}).
- Check for **malabsorption**.
- **Perform HIV genotype despite LLV** (*more plasma to increase the amount of HIV RNA extracted, ultracentrifugation*). **HIV-1 proviral DNA might** have a role with low resistance barrier regimens.
- **Secure an ART regimen with a high resistance barrier**.
- No proven role of TDM.

RT Gandhi. JAMA. 2022; 329(1):63-84. HF Günthard. Clin Infect Dis 2019;68(2):177–87. EACS Guidelines v 12.0, Oct 2023. Available at: https://www.eacsociety.org/guidelines/eacs-guidelines/. DHHS Guidelines for the Use of Adults and Adolescents With HIV, 12 Sept 2024. Avalable at: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new.

BIC/F/TAF, DTG + F/TAF or DRV/c/F/TAF positioning in ALL treatment guidelines

- The importance of a high resistance barrier in Clinical practice -

- **Preferred regimen** in ALL guidelines **with no restrictions or caveats (BIC/F/TAF, DTG+TFV/XTC).**

1. Specifically recommended in **immediate ART initiation.**
2. Specifically recommended when **no baseline resistance available** (EACS 2023 ~~bDRV~~).
3. Specifically recommended in **subjects infected on PrEP** with TDF/FTC.
4. Specifically recommended in **low-level viremia**.
5. Specifically recommended in **switch in subjects with archived NRTI resistance**.

EACS Guidelines 12.0. October 2023. Available at: https://www.eacsociety.org/guidelines/eacs-guidelines/. IAS-USA Guidelines. RT Gandhi. JAMA. doi:10.1001/jama.2022.22246, Published online December 1, 2022. DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents With HIV, 12 Sept 2024. Avalable at: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/whats-new. GeSIDA/PNS TAR en adultos infectados por el VIH (Actualización enero 2023). Disponible en: https://gesida-seimc.org

Take homes.

- **LLV and "true" LLV are not uncommon**.
- LLV **complicates clinical care** and **can lead to unnecessary ART changes and tests**.
- When adherence and tech lab issues excluded, **mainly caused by leakage/propagation of defective HIV proviruses (clonal activation)**.
- More commonly seen in people with **greater HIV reservoirs** (*late presenters*).
- **No HIV transmission; no HIV resistance selection if on high resistance barrier regimens**.
- Once ART non-adherence and lab tech issues have been ruled out, **complete the checklist**, **keep calm and secure ART to a high resistance barrier regimen**.