Virémies de bas niveau (Low-Level Viremia)

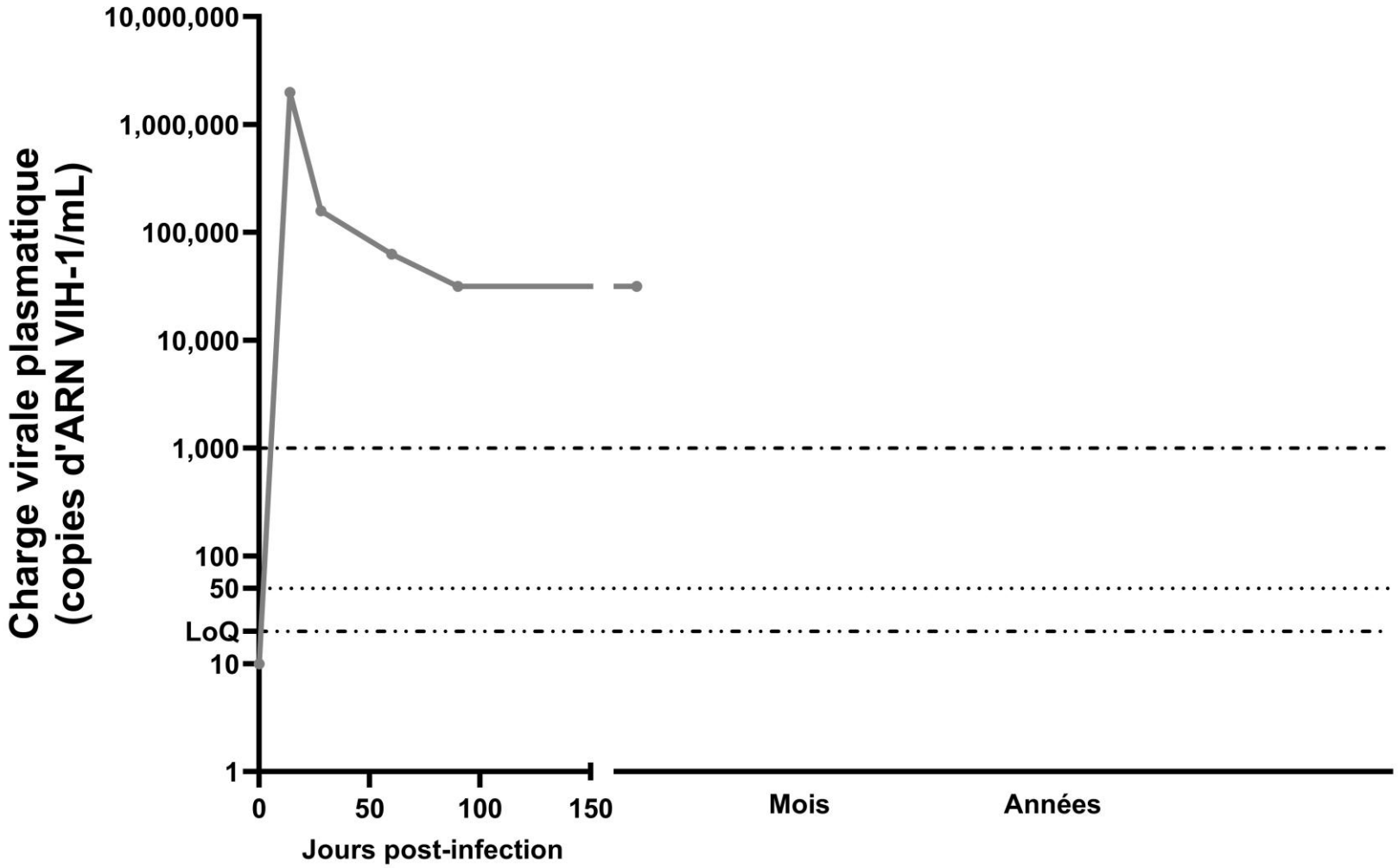
Dr Laurent HOCQUELOUX

SMIT – CHU d'Orléans

Agenda

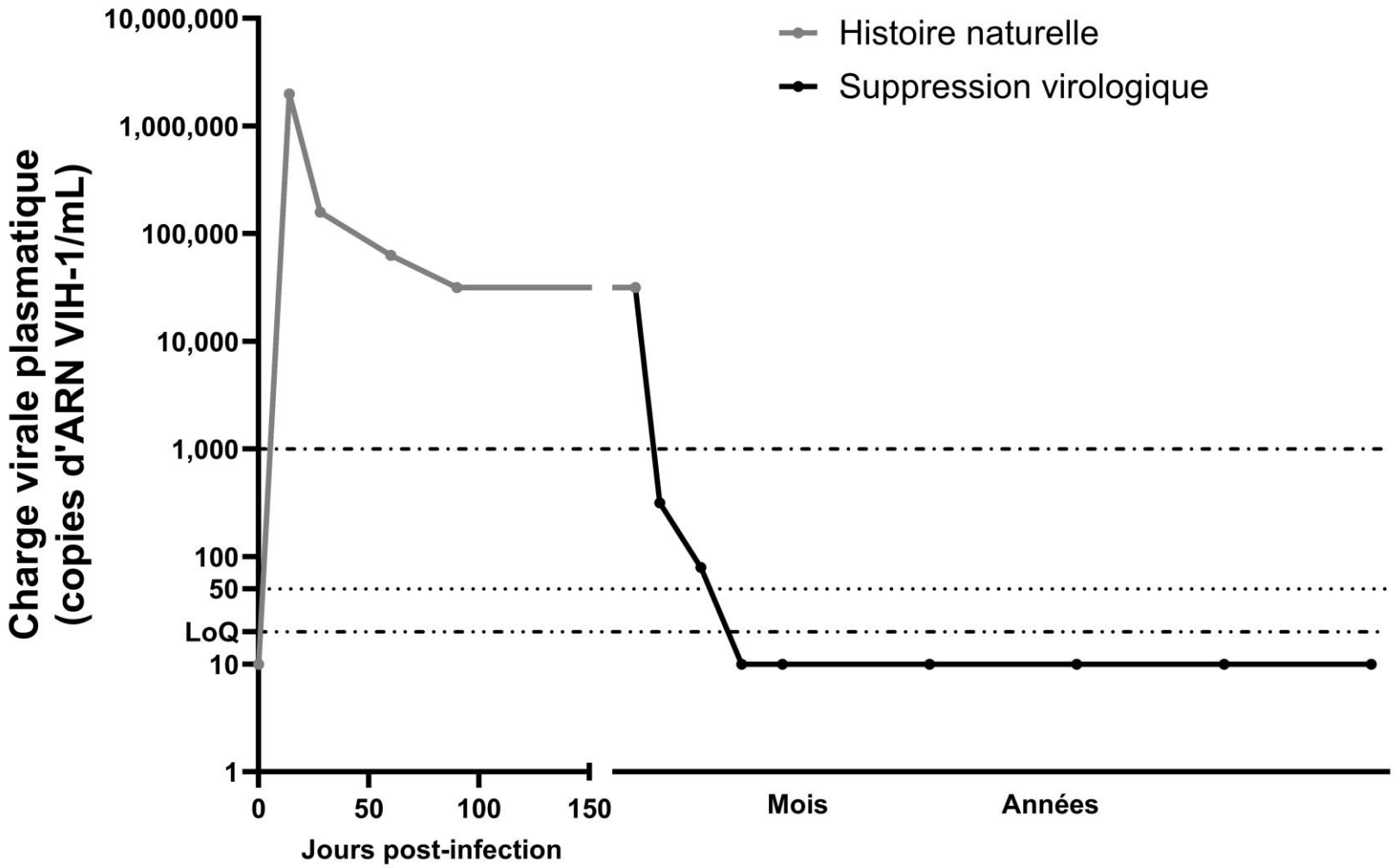
- LLV : de quoi parle-t-on ?
- LLV : que risque-t-on ?
- Quelles sont les principales causes d’une LLV ?
- Une cause émergente : les virémies non-suppressibles (VNS)
- LLV sous injectables de longue durée d’action
- CAT devant une LLV

Qu’est-ce qu’une LLV ?



Figures – Q. Le Hingrat

Qu’est-ce qu’une LLV ?



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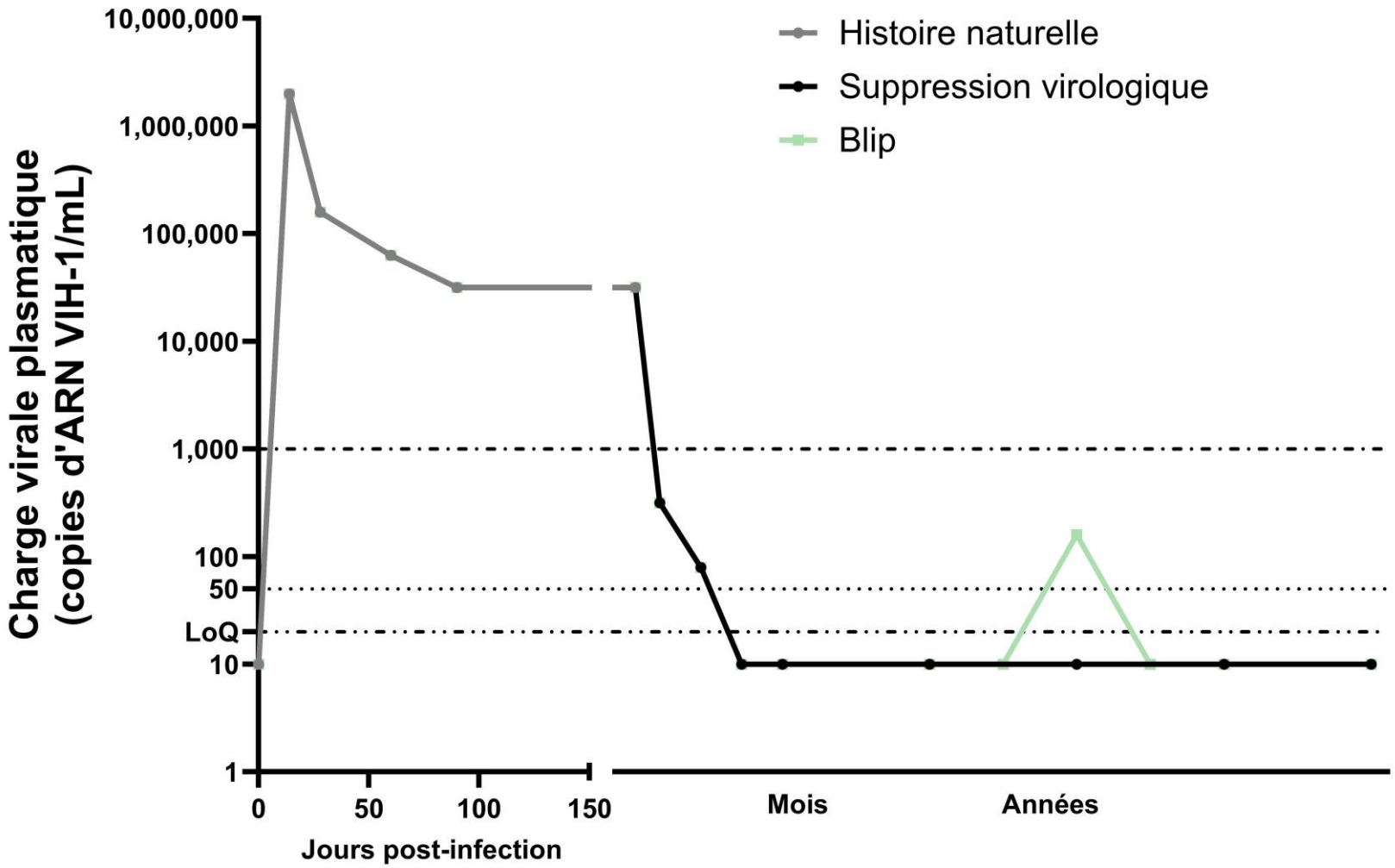

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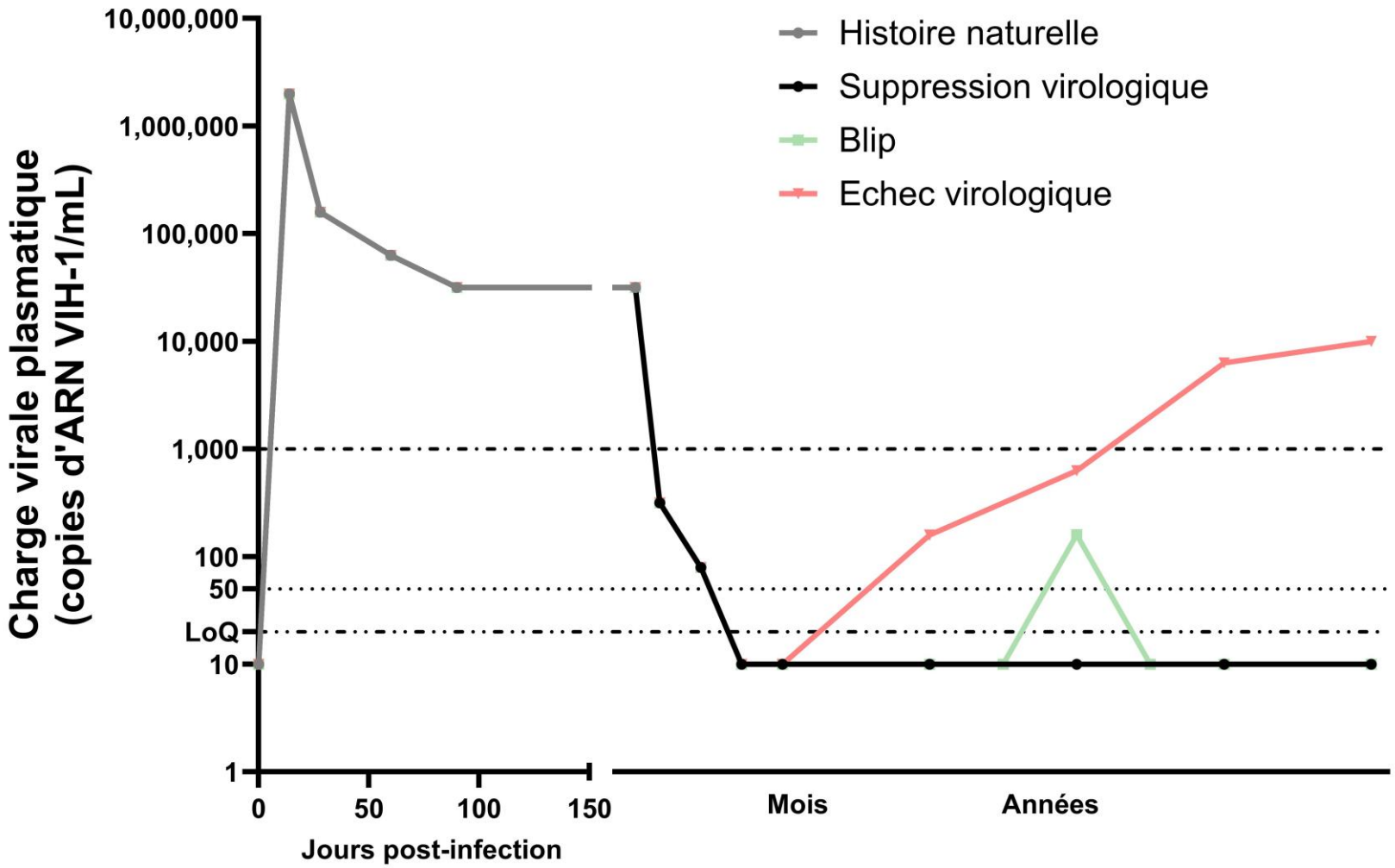
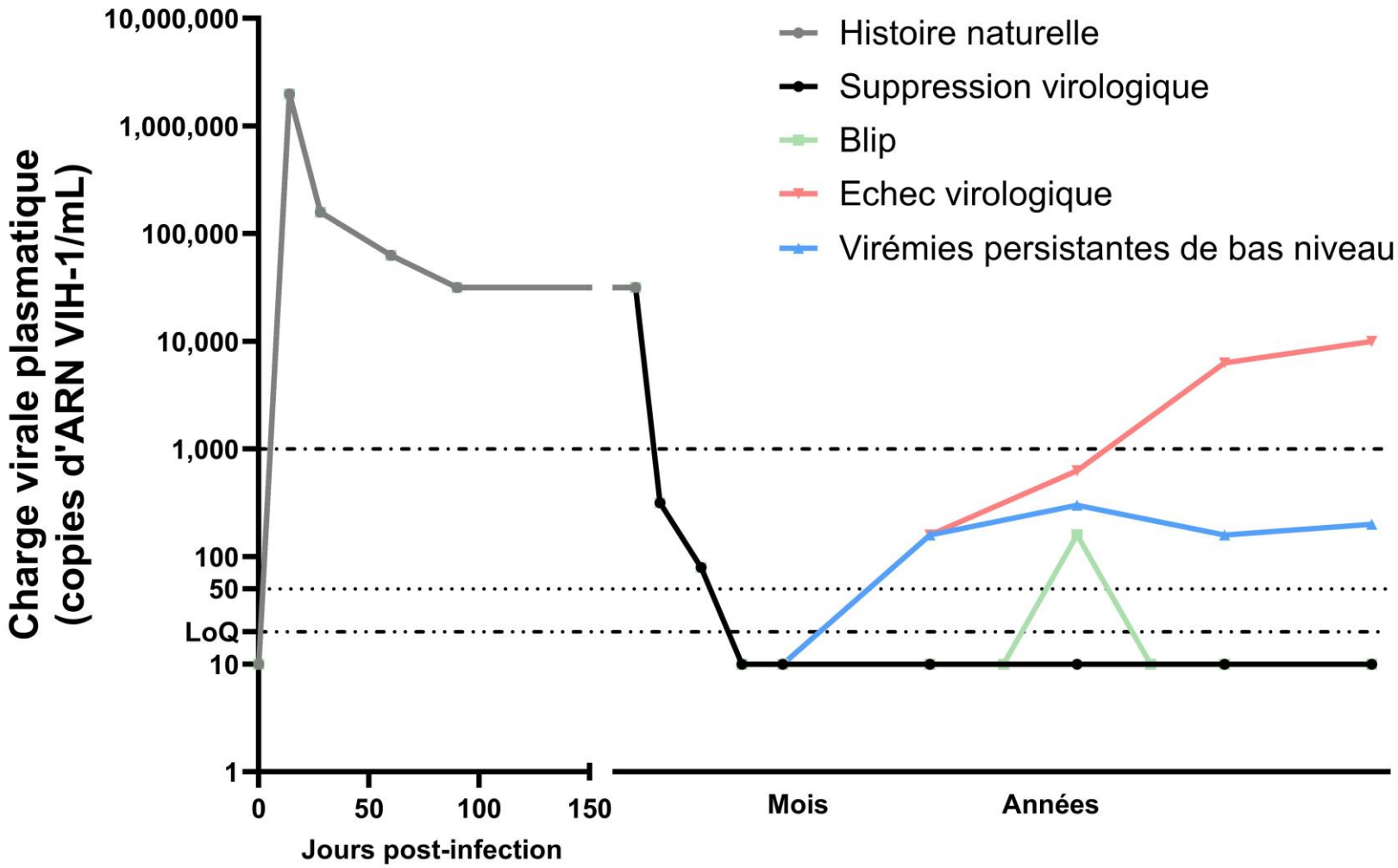
Qu’est-ce qu’une LLV ?



Figures – Q. Le Hingrat

Qu’est-ce qu’une LLV ?



Figures – Q. Le Hingrat

Qu’est-ce qu’une LLV ?

❑ Pas de définition consensuelle dans les recommandations (niveau / durée)

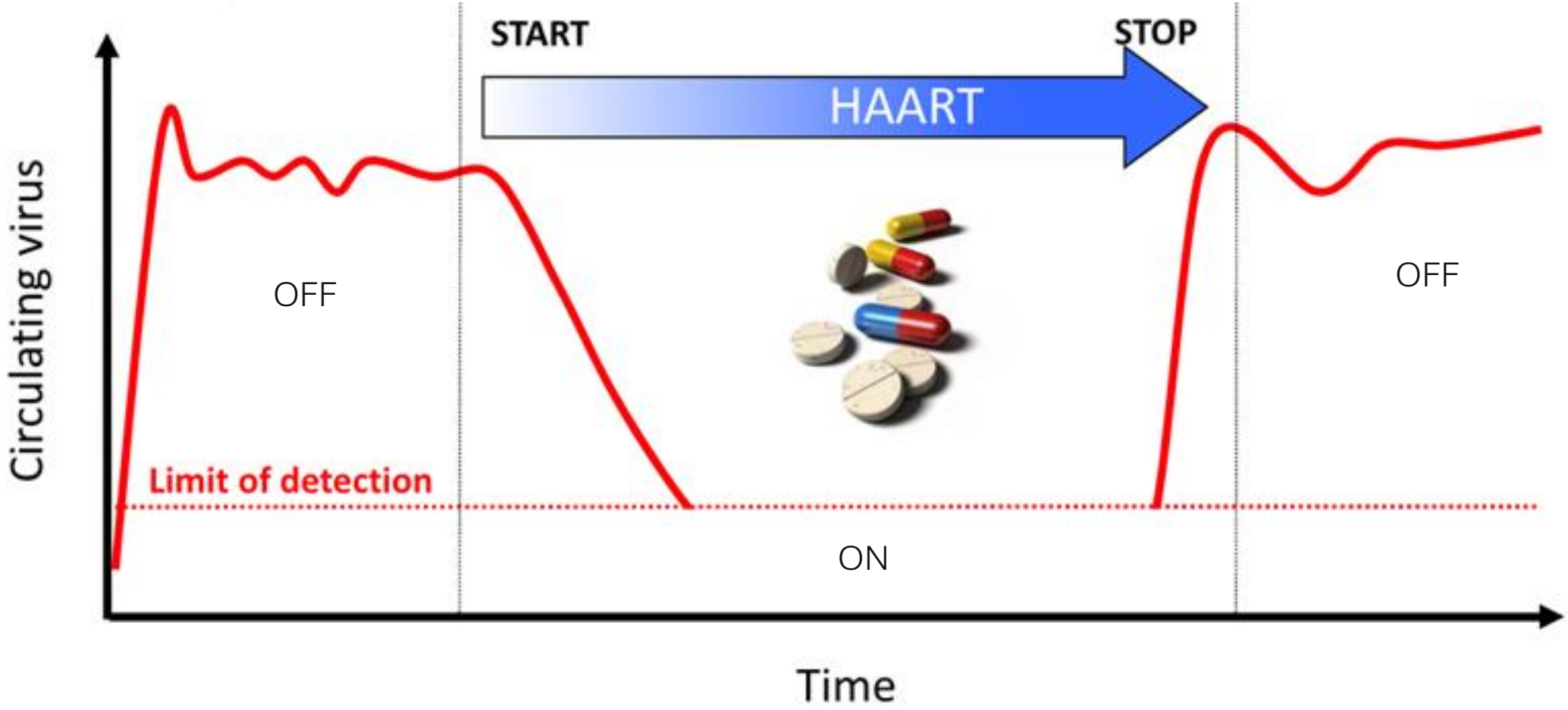
Recommandations	France	Europe (EACS)	G-B (BHIVA)	USA (NIH)	WHO
Définition	50 à 200 c/mL	ND	50 à 200 c/mL	50 à 200 c/mL	50 à 1000 c/mL

❑ Dans la littérature :

- 21-49 c/mL: Very LLV => virémie résiduelle ?
- **50-200 c/mL: LLV** **=> définition la plus commune**
- 201-999 c/mL: High LLV => déjà un échec pour la plupart des recommandations
- Parfois distinction entre intermittente et permanente…

Rapport Delobel, 2024; EACS Guidelines, 2022; BHIVA Guidelines, 2022; HIV.gov, 2023; WHO guidelines, 2021

Vision simpliste du contrôle virologique sous ARV



En fait, c’est un peu plus compliqué…

- La CV est une « coupe transversale » d’un état dynamique, plus ou moins stable, qui résulte de l’interaction du VIH, de la réponse de son hôte et du traitement :
  - ❑ VIH : capacité réplicative, résistances, taille des réservoirs, activation des cellules infectées…
  - ❑ Hôte : efficacité de la réponse adaptative anti-VIH, observance au traitement
  - ❑ ARV : puissance, mécanisme d’action, PK/PD, interactions médicamenteuses, diffusion (sanctuaires)…

- Le contrôle virologique ce n’est pas « OUI-NON » mais un continuum qui va du contrôle spontané jusqu’à l’échec virologique sous traitement : la LLV est au milieu

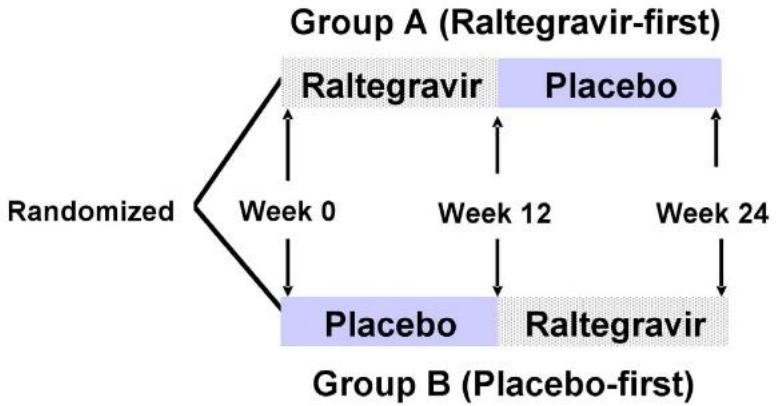
Virémie « résiduelle » (non-suppressible)

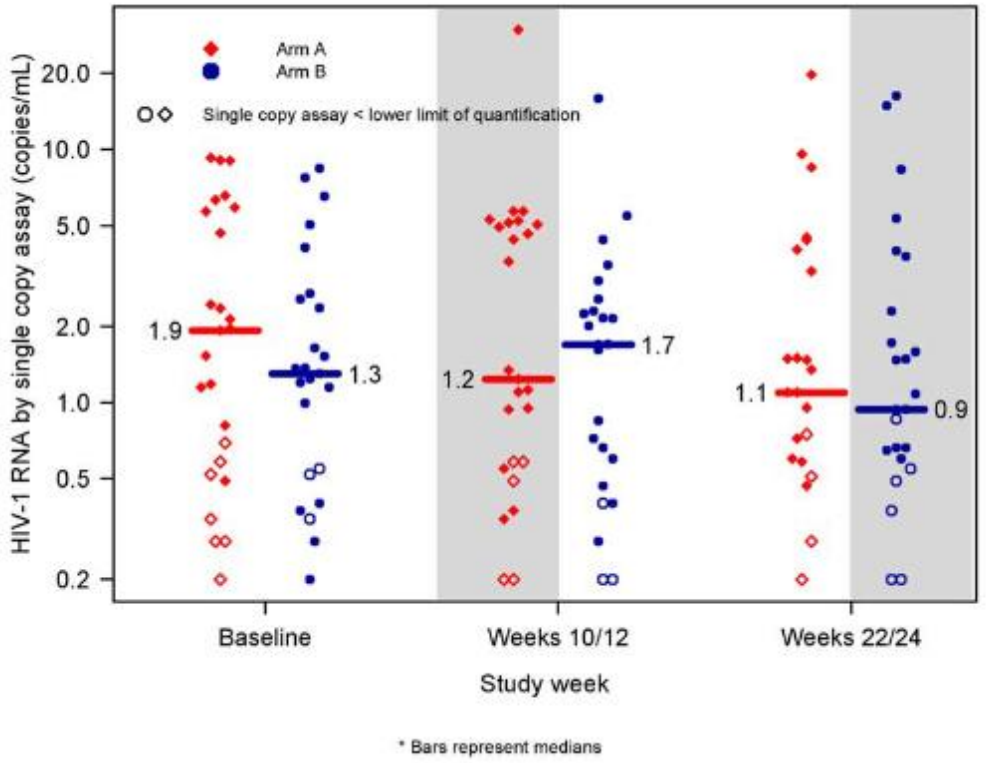
- Avec un seuil à 1 cp/mL la majorité des PVVIH <50 cp/mL deviennent détectables / quantifiables
- Et intensifier le traitement ARV ne change rien
- Pas d'évolution du virus = pas de cycle complet

OPEN ACCESS Freely available online PLoS MEDICINE

The Effect of Raltegravir Intensification on Low-level Residual Viremia in HIV-Infected Patients on Antiretroviral Therapy: A Randomized Controlled Trial

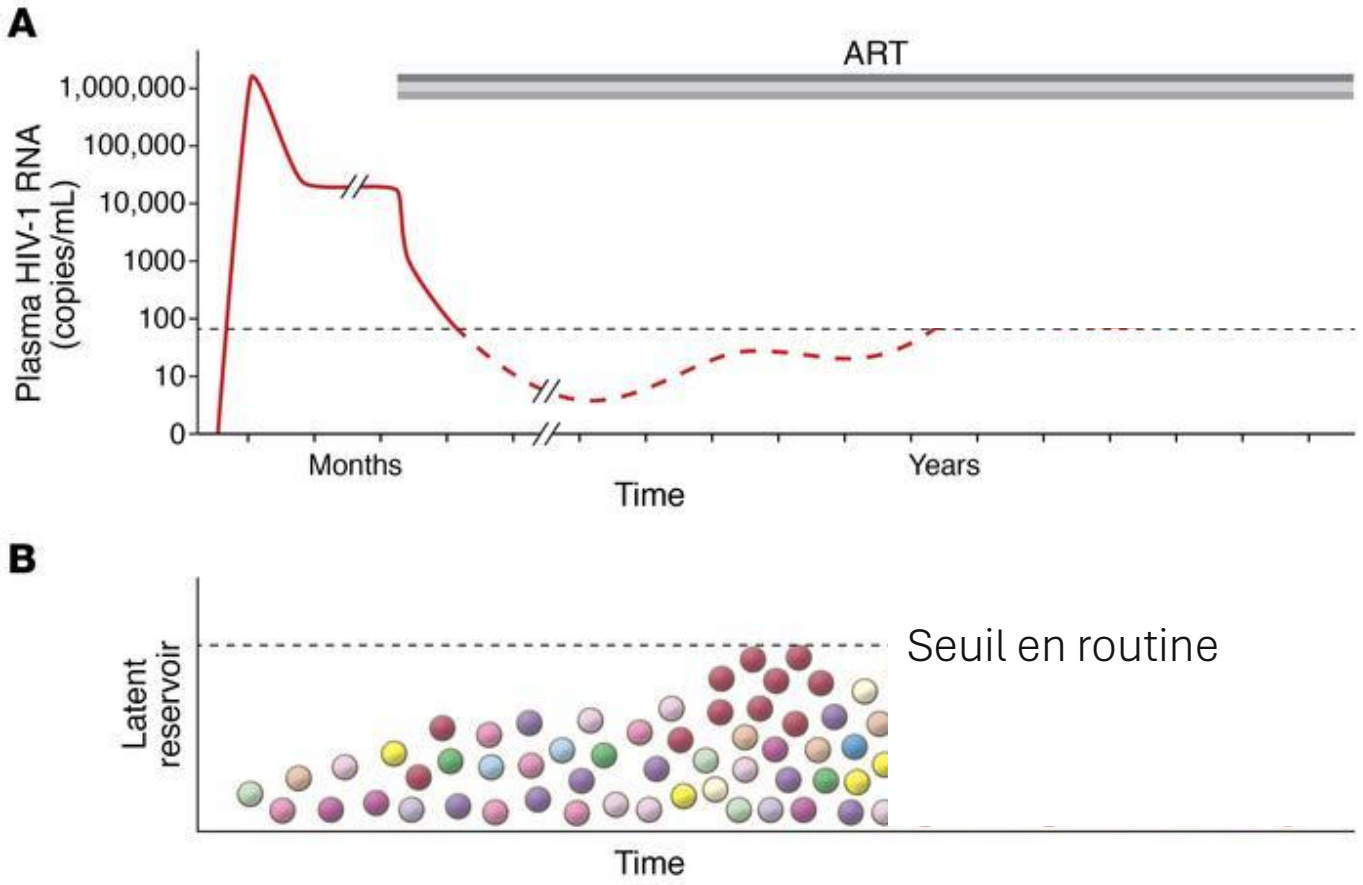
Rajesh T. Gandhi[1*], Lu Zheng[2], Ronald J. Bosch[2], Ellen S. Chan[2], David M. Margolis[3], Sarah Read[4], Beatrice Kallungal[5], Sarah Palmer[6], Kathy Medvik[7], Michael M. Lederman[7], Nadia Alatrakchi[8], Jeffrey M. Jacobson[9], Ann Wiegand[10], Mary Kearney[10], John M. Coffin[11], John W. Mellors[12], Joseph J. Eron[3], on behalf of the AIDS Clinical Trials Group A5244 team[¶]





Gandhi RT et al. PLoS Med 2010;7:e1000321.

Virémie « résiduelle » (non-suppressible)



Seuil en routine

Seuil en routine

Siliciano J et R. J Clin Invest 2020;130:5665-7.

Réservoirs viraux (ADN VIH)

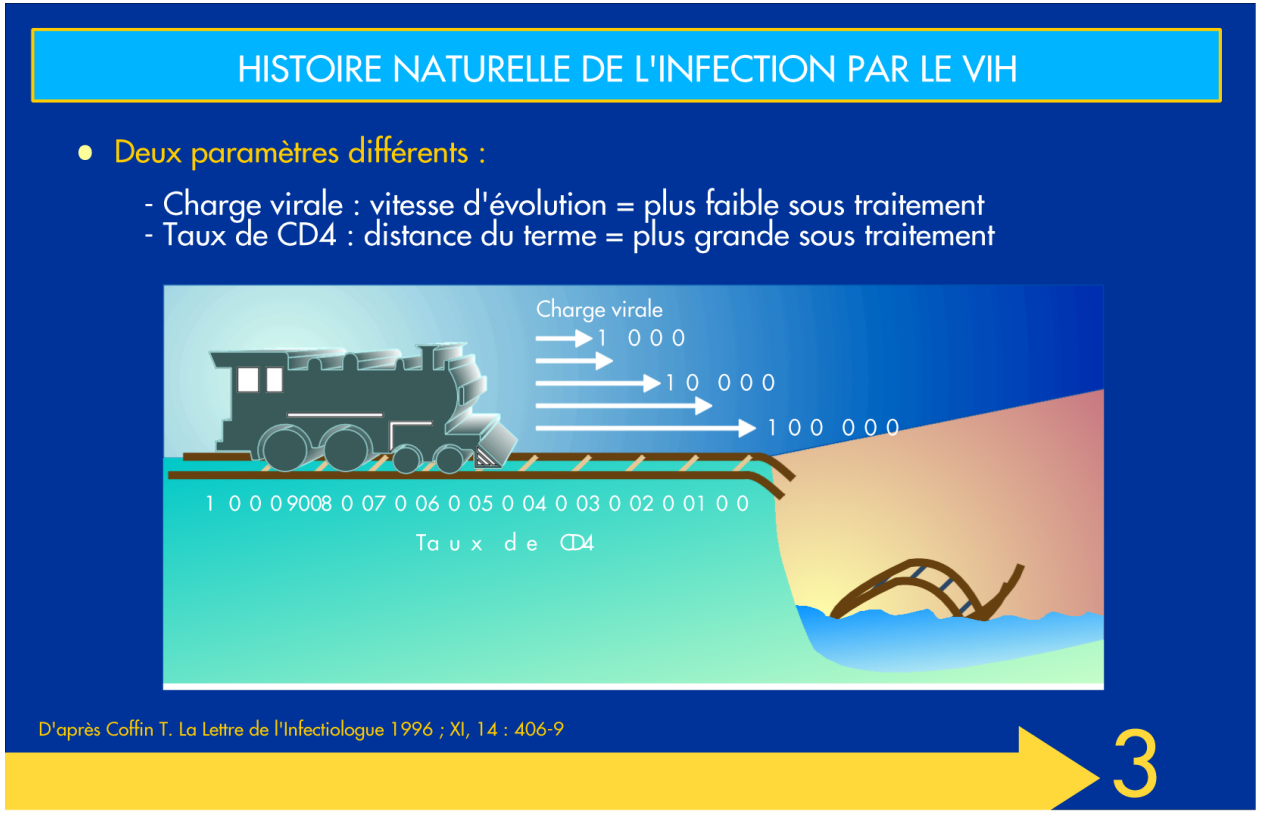
- Mémoire de l’infection

Rouzioux et al. JID 2005;192:46-55.
Avettand-Fènoël et al. CMR 2016;29:859-80.

Réservoirs viraux (ADN VIH)

- Mémoire de l'infection

- Moteur de l'infection



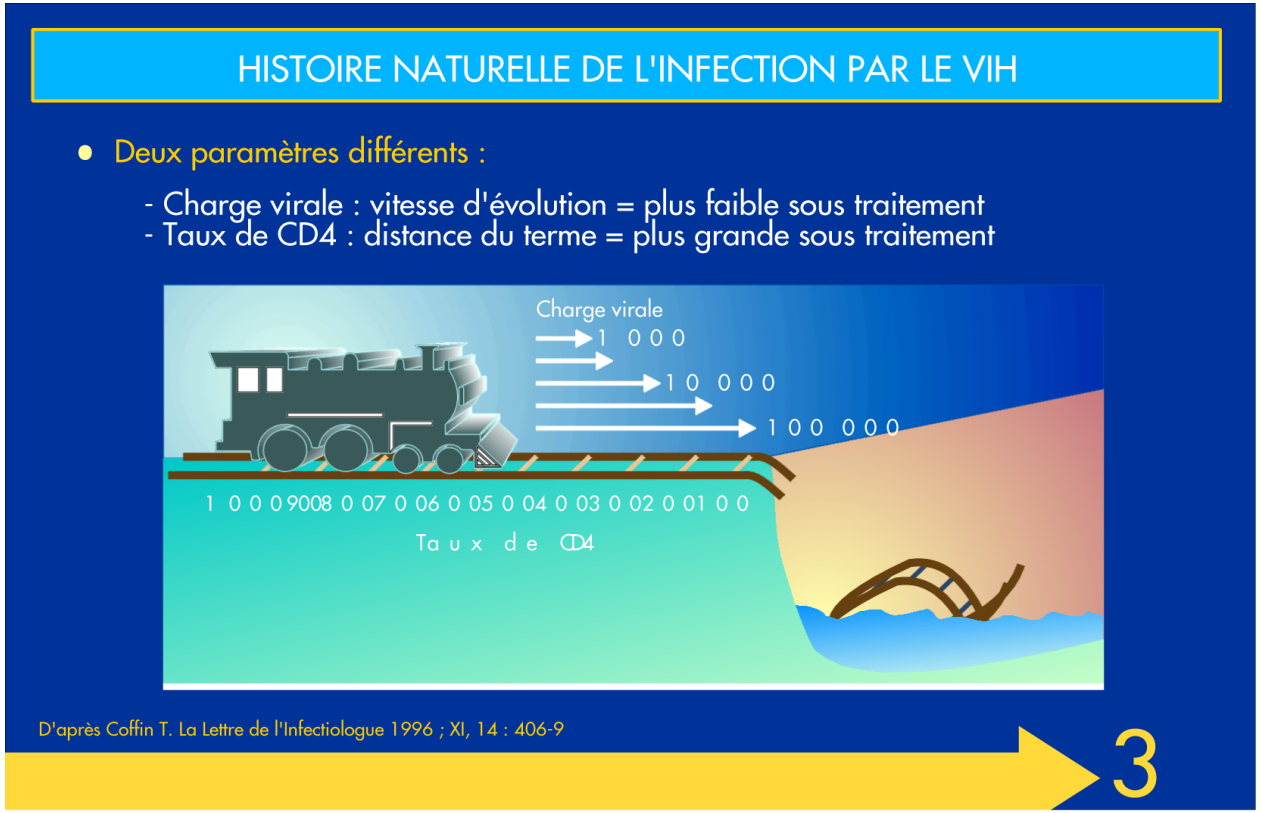
Rouzioux et al. JID 2005;192:46-55.
Avettand-Fènoël et al. CMR 2016;29:859-80.

Réservoirs viraux (ADN VIH)

- Mémoire de l'infection

- Moteur de l'infection

- Facteur pronostique



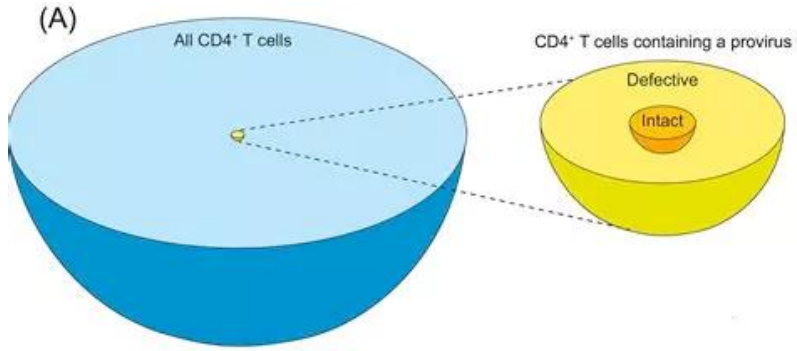
Early Levels of HIV-1 DNA in Peripheral Blood Mononuclear Cells Are Predictive of Disease Progression Independently of HIV-1 RNA Levels and CD4+ T Cell Counts

Christine Rouzioux,[1] Jean-Baptiste Hubert,[5] Marianne Burgard,[1] Christiane Deveau,[5] Cécile Goujard,[6] Marc Bary,[3] Daniel Séréni,[4] Jean-Paul Viard,[2] Jean-François Delfraissy,[6] and Laurence Meyer,[5] for the SEROCO Cohort Study Group[a]

Rouzioux et al. JID 2005;192:46-55.
Avettand-Fènoël et al. CMR 2016;29:859-80.

Réservoirs viraux (ADN VIH)

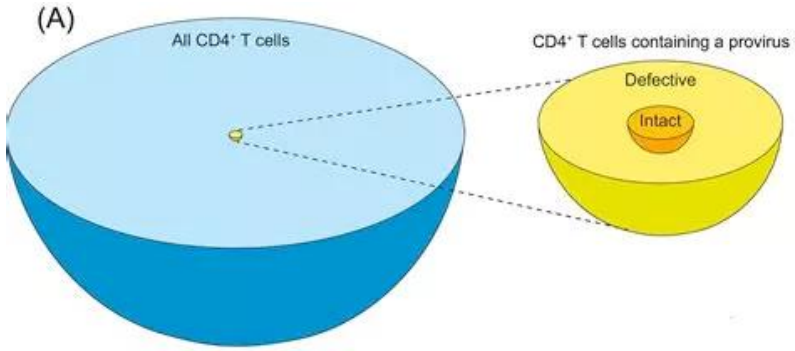
- Peu de cellules CD4+ sont infectées

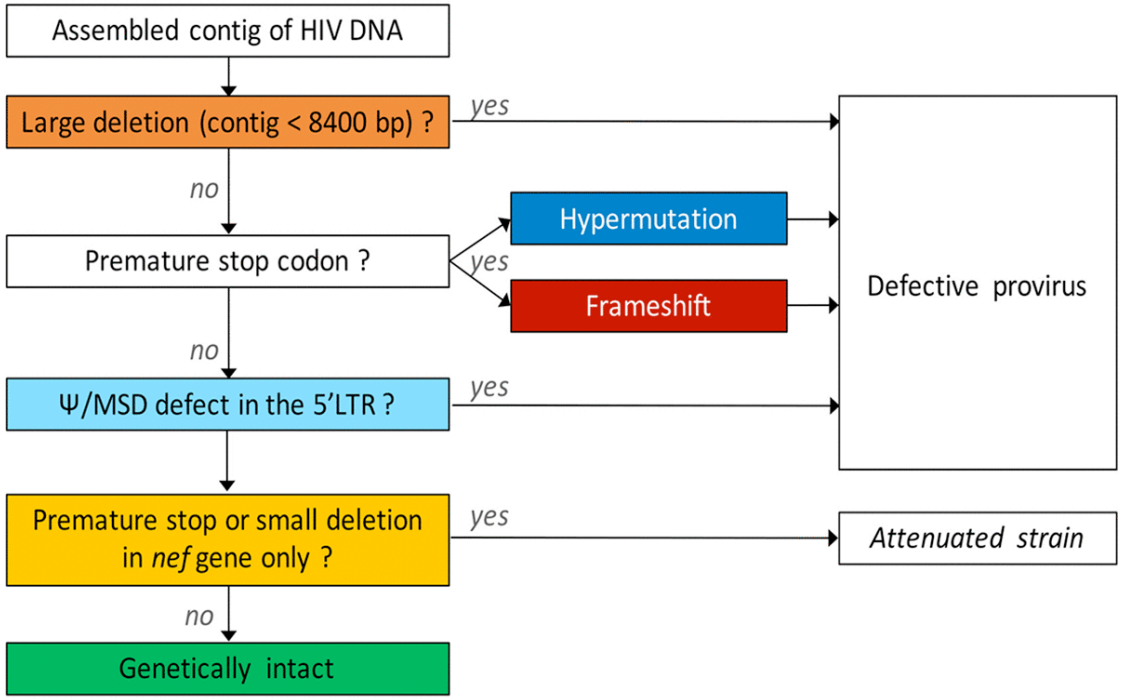


Trémeaux P et al. Microbiol Spectr 2023;11:e0326722.

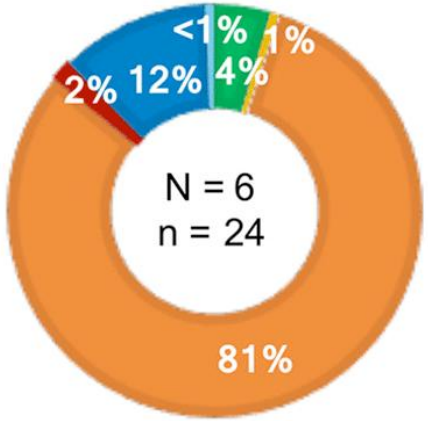
Réservoirs viraux (ADN VIH)

- Peu de cellules CD4+ sont infectées
- Au sein du réservoir : très peu de virus « intacts » et transcriptibles





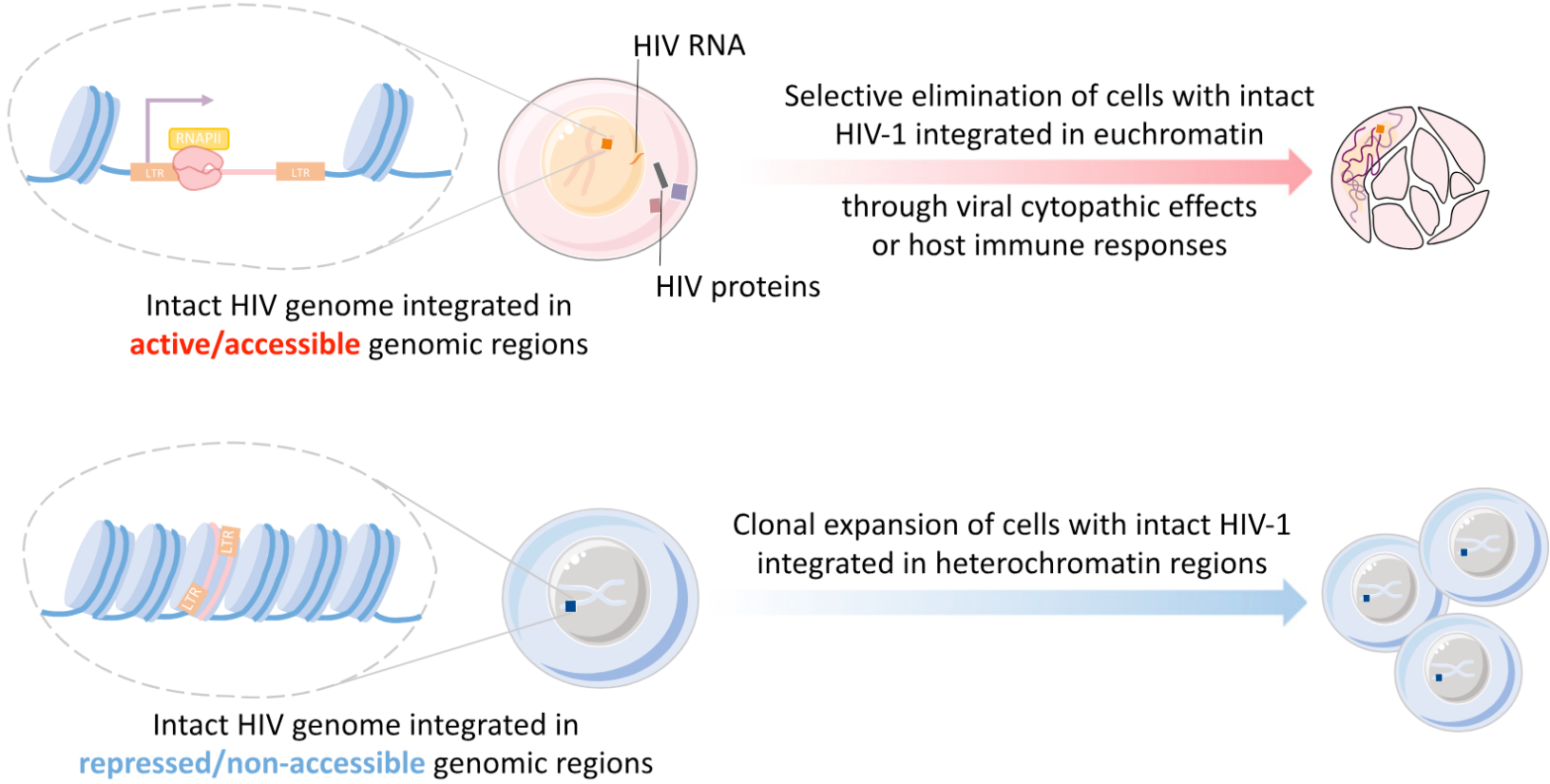
PVVIH traité en phase chronique



Trémeaux P et al. Microbiol Spectr 2023;11:e0326722.

Réservoirs viraux (ADN VIH)

- Après des décennies de traitement suppressif => concentration des virus intacts dans « culs de sac » génomiques



Lian X et al. Cell Host Microb 2023;31:83-96.

Réservoirs viraux (ADN VIH)

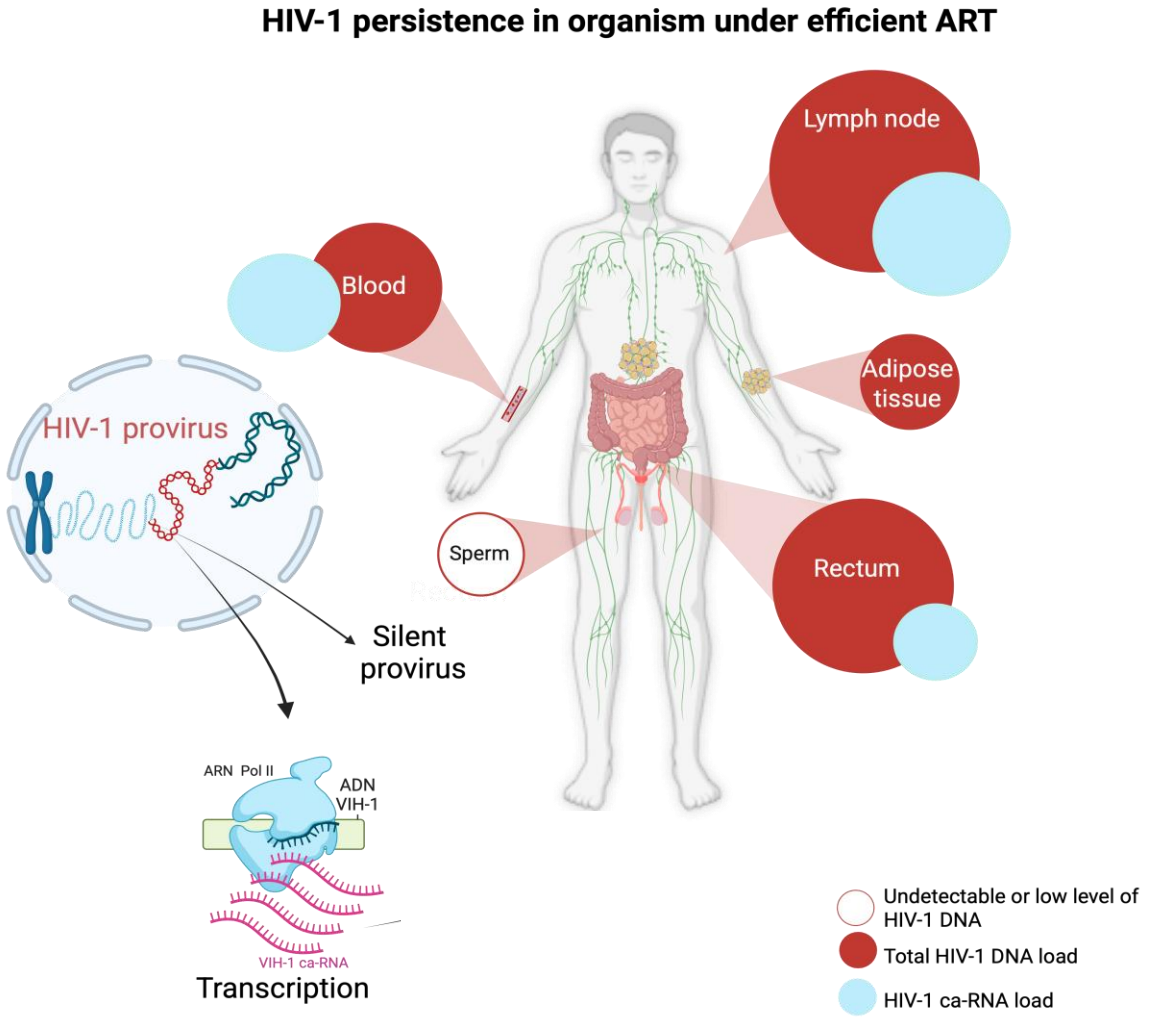
Néanmoins, quel que soit le traitement :

- Du virus continue d'être transcrit
- Dans le sang / tissus ganglionnaires
- Sans cycle complet / évolution / résistance

ANRS EP64 (DOLUVOIR)

Caractérisation des réservoirs tissulaires :

- 20 PVVIH sous DTG (tri 70% et bithérapie 30%)
- CV <50 copies/mL depuis en médiane 52 mois



Mchantaf G. et al. Commun Med 2026;6:130.

LLV : quelle fréquence ?

Etude	France	Sweden	Europe	USA
Nombre de patients	2374	6956	22523	1598
Traitement ARV	2 NUCs + IP/r ou 2 NUCs + NNUC	Tous types	Tous types	Tous types
Durée de suivi	3 ans	5,7 ans	2,8 ans	1,5 ans
Définition de la LLV	2 CV entre 50-199 c/mL espacées de ≥ 1 mois	2 CV entre 50-999 c/mL espacées de ≥ 1 mois	2 CV entre 50-199 c/mL espacées de ≥ 1 mois	2 CV entre 20-199 c/mL espacées de ≥ 1 mois
Prévalence LLV à un moment du suivi	8.6%	13.7% (7.5% si 50-199 c/mL)	7.3%	5.9%
Durée médiane de la LLV	8.3 mois	N/A	N/A	N/A

Vandenhende et al., Antivir Ther, 2015; Elvstam et al., CID, 2021; Elvstam et al., CID, 2023; Aldredge et al., AIDS, 2024

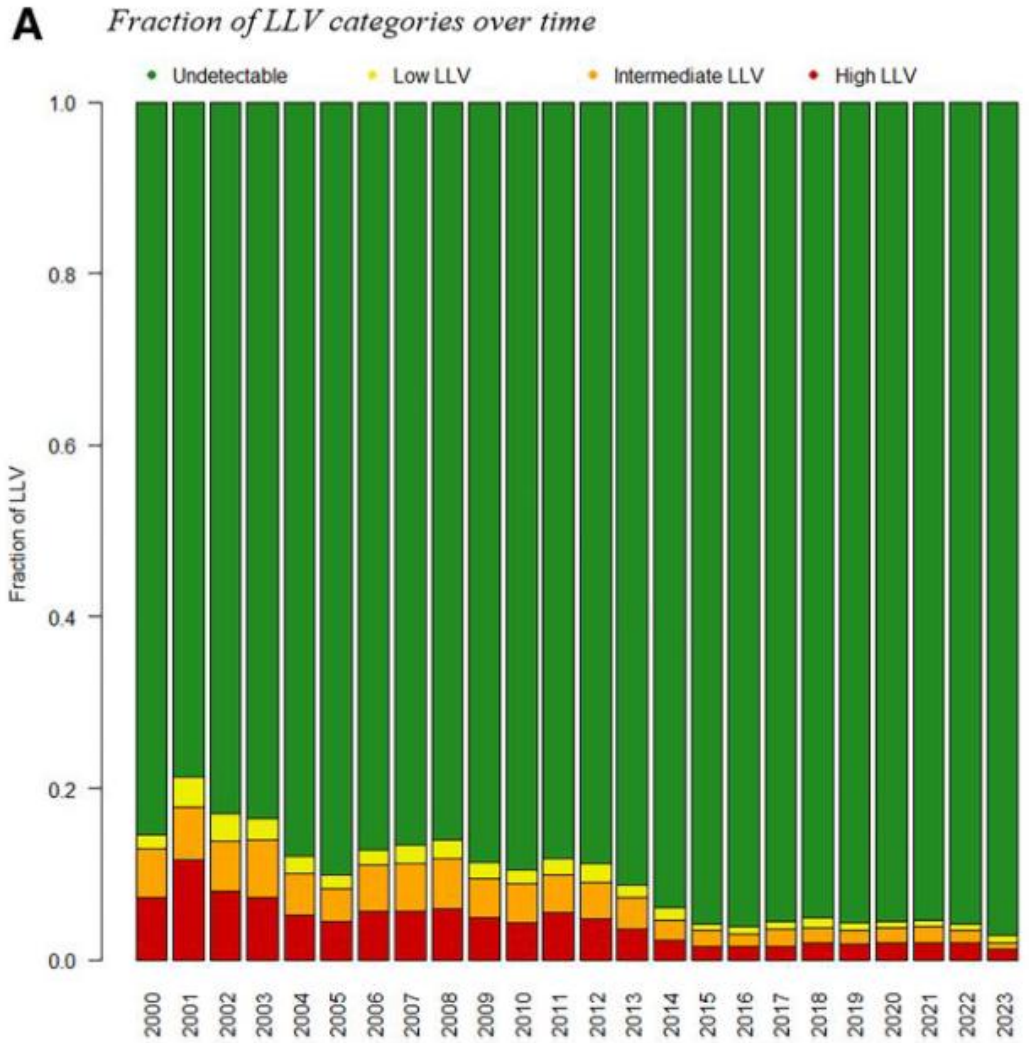
LLV : fréquence dans la cohorte suisse

Clinical Infectious Diseases
MAJOR ARTICLE
IDSA OXFORD

HIV-1 Low-Level Viremia Predicts Viral Failure in Participants on Antiretroviral Therapy in the Swiss HIV Cohort Study

Caroline Lanz,[1] Jan Meier,[2] Marcel Stöckle,[3,©] Hansjakob Furrer,[4,©] Alexandra Calmy,[5,©] Matthias Cavassini,[6,©] Enos Bernasconi,[7,©] Patrick Schmid,[8,©] Dominique L. Braun,[1,2] Roger D. Kouyos,[1,2] Tom Loosli,[1,2,a] Katharina Kusejko,[1,2,a,©] and Huldrych F. Günthard[1,2,a]; the Swiss HIV Cohort Study[b]

- Nette inflexion de la fréquence depuis 2015
- Avènement des INSTI 2e génération



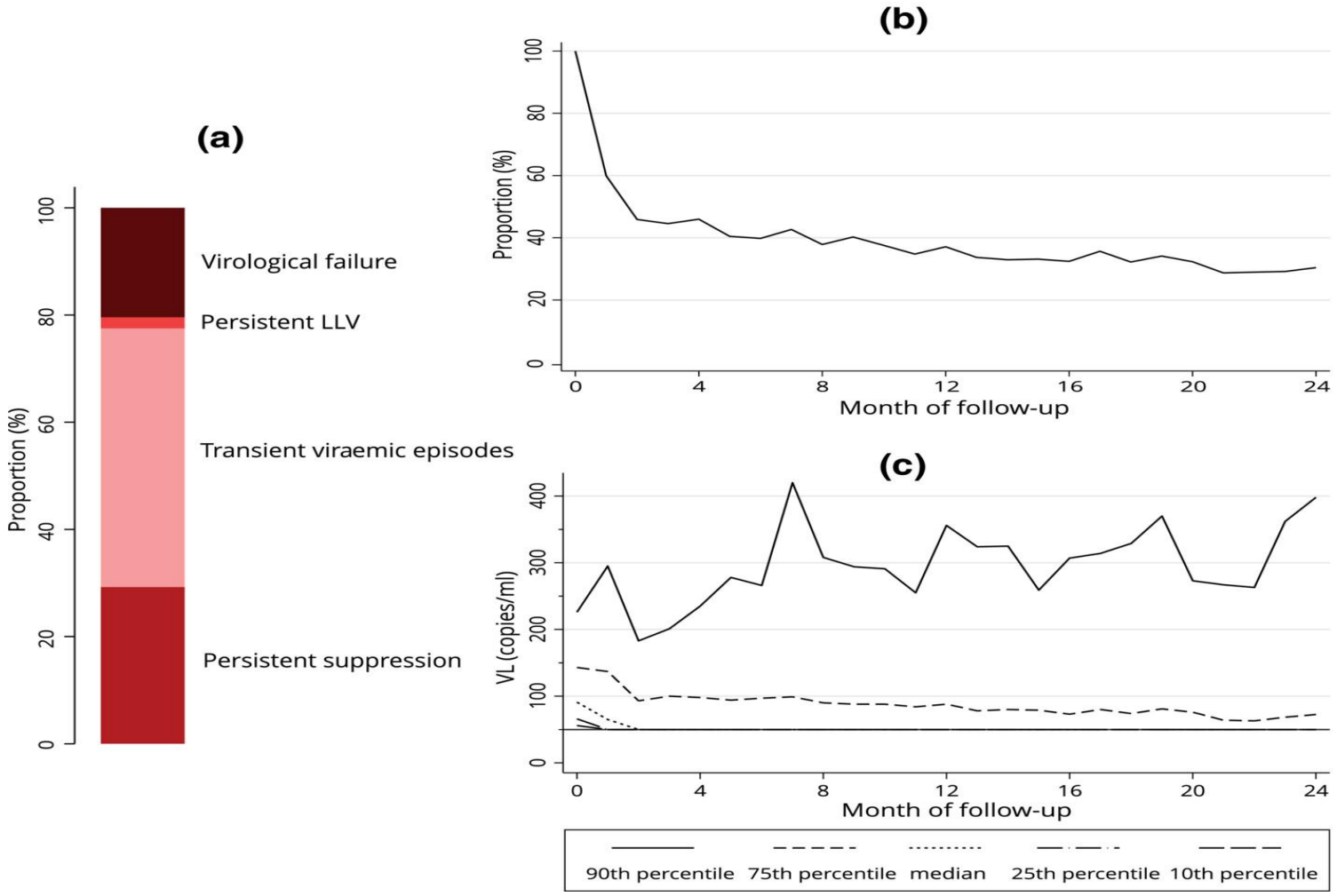
LLV : facteurs de risques

- **Nadir CD4 bas (<200/mm^3)**
- **Zénith de charge virale (>10^6/mL)**
- **Taille des réservoirs**
- Age, durée de l'infection VIH
- Sous-type VIH-1
- Classe thérapeutique (IP/r > NNRTI, INSTI)
- (Mauvaise adhérence)

Elvstam O. et al. CID 2023;76:25-31. Esteban-Cantos A et al. Lancet HIV 2024;11:e333-40.

La LLV est un état instable…

Low-level HIV viraemia during antiretroviral therapy: Longitudinal patterns and predictors of viral suppression



⇒ 2% de LLV « permanente »

⇒ 20% d'échec virologique

Elen S et al. HIV Medicine;25,107-116.

LLV : risque d'échec virologique

Clinical Infectious Diseases

MAJOR ARTICLE

Virologic Failure Following Low-level Viremia and Viral Blips During Antiretroviral Therapy: Results From a European Multicenter Cohort

Olof Elvstam,[1,2] Kasper Malmborn,[1] Sixten Elén,[1] Gaetano Marrone,[3] Federico García,[4] Maurizio Zazzi,[5] Anders Sönnerborg,[6,7] Michael Böhm,[8] Carole Seguin-Devaux,[9] and Per Björkman[1,10]

[1]Department of Translational Medicine, Lund University, Malmö, Sweden; [2]Department of Infectious Diseases, Växjö Central Hospital, Växjö, Sweden; [3]Department of Infectious Diseases and Clinical Virology, Karolinska University Hospital, Stockholm, Sweden; [4]Servicio de Microbiología, Hospital Clínico Universitario San Cecilio, Instituto de Investigación Ibs. Granada, Ciber de Enfermedades Infecciosas, CIBERINFEC, Granada, Spain; [5]Department of Medical Biotechnologies, University of Siena, Siena, Italy; [6]Division of Infectious Diseases, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden; [7]Department of Infecious Diseases, Karolinska University Hospital, Stockholm, Sweden; [8]Institute of Virology, Faculty of Medicine and University Hospital of Cologne, University of Cologne, Cologne, Germany; [9]Department of Infection and Immunity, Luxembourg Institute of Health, Esch sur Alzette, Luxembourg; and [10]Department of Infectious Diseases, Skåne University Hospital, Malmö, Sweden

Table 2. Cox Regression Models for Virological Failure Depending on Viremia Category, Stratified by Origin Database

	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)

Results are hazard ratio with 95% confidence interval.

Abbreviations: ART, antiretroviral therapy; IDU, injecting drug use; LLV, low-level viremia; Ref, reference category; VL, viral load.

[a]Adjusted for age (at outcome event), sex (male/female), CD4 count (modelled linearly, time-updated), pre-ART VL (modelled logarithmically), HIV-1 subtype (B/non-B), transmission group (IDU/non-IDU), type of ART (time-updated) and treatment experience.

Une LLV augmente le risque d'échec virologique de 160%

LLV : risque d'échec virologique

Clinical Infectious Diseases

MAJOR ARTICLE

HIV-1 Low-Level Viremia Predicts Viral Failure in Participants on Antiretroviral Therapy in the Swiss HIV Cohort Study

Caroline Lanz,[1] Jan Meier,[2] Marcel Stöckle,[3,©] Hansjakob Furrer,[4,©] Alexandra Calmy,[5,©] Matthias Cavassini,[6,©] Enos Bernasconi,[7,©] Patrick Schmid,[8,©] Dominique L. Braun,[1,2] Roger D. Kouyos,[1,2] Tom Loosli,[1,2,a] Katharina Kusejko,[1,2,a,©] and Huldrych F. Günthard[1,2,a]; the Swiss HIV Cohort Study[b]

[1]Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, Zurich, Switzerland; [2]Institute of Medical Virology, University of Zurich, Zurich, Switzerland; [3]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, University of Basel, Basel, Switzerland; [4]Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland; [5]Division of Infectious Diseases, HIV/AIDS Unit, University Hospital Geneva, University of Geneva, Geneva, Switzerland; [6]Division of Infectious Diseases, University Hospital Lausanne, University of Lausanne, Lausanne, Switzerland; [7]Division of Infectious Diseases, Ente Ospedaliero Cantonale, University of Geneva and University of Southern Switzerland, Lugano, Switzerland; and [8]Division of Infectious Diseases, Infection Prevention and Travel Medicine, Department General Internal Medicine, Cantonal Hospital St Gallen, St Gallen, Switzerland

Risque d'échec virologique (ajusté sur tous les autres facteurs) augmente avec l'intensité de la LLV

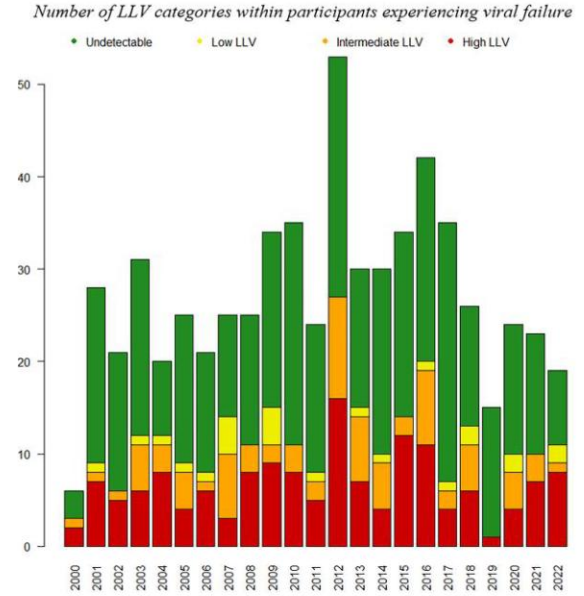
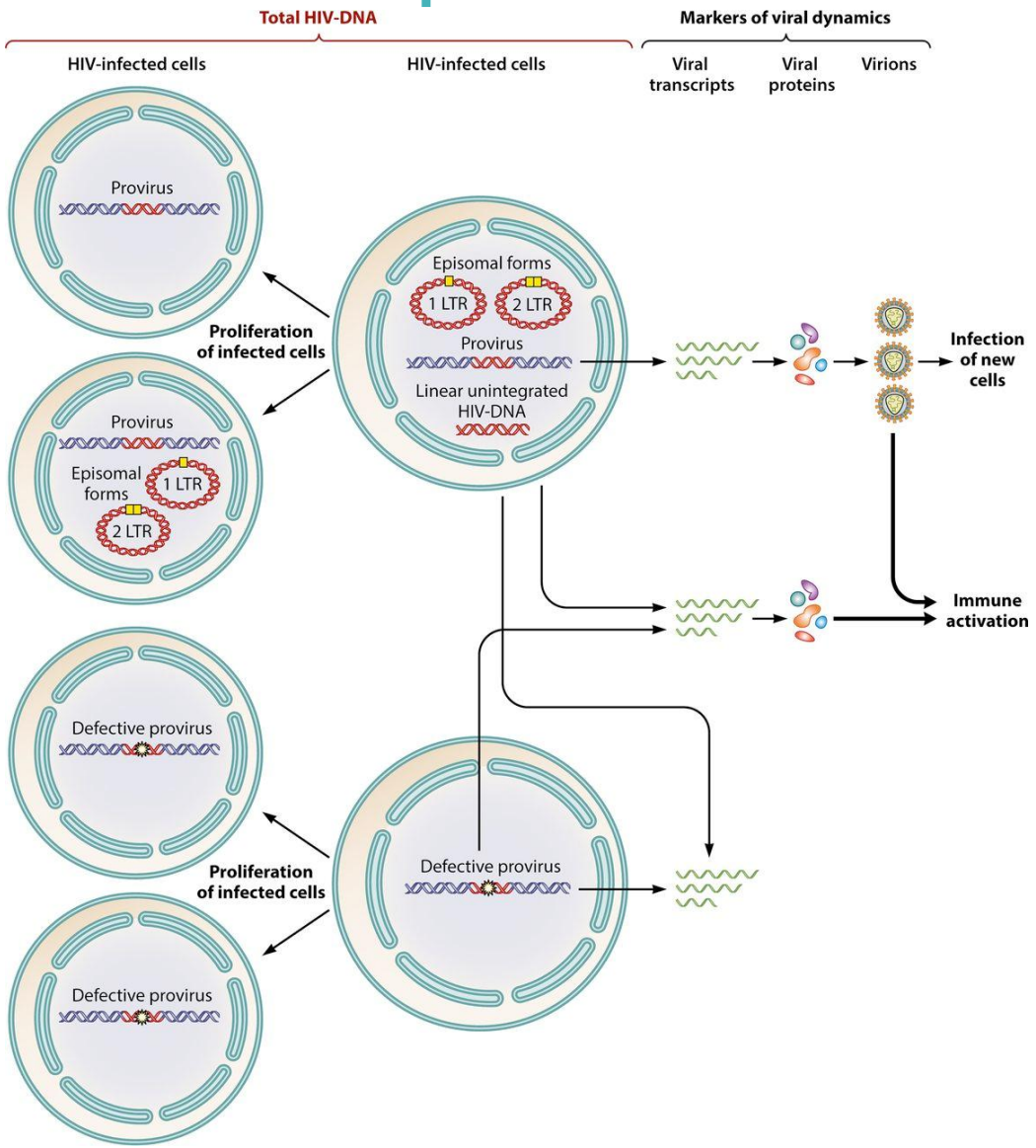


Figure 3. Low-level viremia (LLV) over time. All 90-day observation windows (see Statistical Analysis) with an area under the curve under the human immunodeficiency virus RNA trajectory were divided into tertiles, classified as low, intermediate, and high LLV. *A*, Fraction of LLV over time, with the highest LLV category per year and participant taken into account. *B*, Number of participants experiencing viral failure, by year and LLV category, where the highest LLV category during the whole observation time until failure is taken into account.

LLV : risque inflammatoire



Les produits de la transcription virale, même abortifs, stimulent l'immunité, (monocytaire-macrophagique, cytokines pro-inflammatoire, sgp120 et ADCC des CD4, translocation digestive…)

=> État pro-inflammatoire chronique
=> Morbi-mortalité

Avettand-Fènoël et al. CMR 2016;29:859-80.

LLV : risque inflammatoire

Open Forum Infectious Diseases

MAJOR ARTICLE

Low Level Viremia Is Associated With Serious non-AIDS Events in People With HIV

Anuradha Ganesan,[1,2,3] Hsing-Chuan Hsieh,[1,3] Xiuping Chu,[1,3] Rhonda E. Colombo,[1,3,4] Catherine Berjohn,[1,5] Tahaniyat Lalani,[1,3,6] Joseph Yabes,[1,7] Christie A. Joya,[1,6] Jason Blaylock,[1,2] and Brian K. Agan[1,3]

[1]Infectious Disease Clinical Research Program, Department of Preventive Medicine and Biostatistics, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA, [2]Division of Infectious Diseases, Walter Reed National Military Medical Center, Bethesda, Maryland, USA, [3]Henry M Jackson Foundation for the Advancement of Military Medicine, Inc., Bethesda, Maryland, USA, [4]Infectious Disease Service, Madigan Army Medical Center, Tacoma, Washington, USA, [5]Division of Infe
of Infectious Diseases, Naval Medical Center Portsmouth, Portsmouth, Virginia, USA, and [7]Division of Infec

LLV 50-200 cp/mL
=> évènements non-SIDA : +30 à 57%

Table 3. Univariate and Multivariable Cox Proportional Hazard Model Evaluating Risk Factors for Serious non-AIDS Events (SNAE)

	Unadjusted				Adjusted			
	HR	95% CI		*P*	HR	95% CI		*P*
Time updated viremia categories (referent: VS)								
LLV	1.766	1.653	1.886	<.0001	1.308	1.217	1.405	<.0001
HLLV	2.112	1.970	2.265	<.0001	1.571	1.457	1.695	<.0001
VF	2.711	2.618	2.807	<.0001	1.746	1.671	1.824	<.0001

N = 2283. SNAE cases, n = 387. Adjusted for gender (male, female), race (Caucasian, African-American, Hispanic/Other), time updated age (for every 10-year increase), log viral load at ART initiation, time from HIV diagnosis to ART initiation (for every year increase), time updated CD4 counts (for every 100 cell increase), and time updated ART regimen (integrase strand inhibitors, boosted protease inhibitors, nonnucleoside reverse transcriptase inhibitors, unboosted protease inhibitors, and other combination). SNAE categories: cancers including anal cancer (n = 20), breast cancer (n = 5), colon cancer (n = 1), leukemia (n = 1), lung cancer (n = 3), Hodgkin lymphoma (n = 7), melanoma (n = 11), multiple myeloma (n = 1), prostate cancer (n = 20), other cancers (n = 19); cardiovascular events include cardiomyopathy (n = 7), congestive heart failure (n = 1), pericarditis (n = 5), cerebrovascular disease (n = 16), coronary artery disease without myocardial infarction (n = 45), deep vein thrombosis (n = 17), myocardial infarction (n = 17), peripheral artery disease (n = 3); chronic kidney disease (n = 171); and cirrhosis (n = 17).

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HLLV, higher level of low-level viremia; HR, hazard ratio; LLV, low-level viremia; VF, virologic failure; VS, virologic suppression.

Ganessan A. et al. OFID 2024;11:ofae147.

LLV : risque inflammatoire


Clinical Infectious Diseases

MAJOR ARTICLE

All-Cause Mortality and Serious Non-AIDS Events in Adults With Low-level Human Immunodeficiency Virus Viremia During Combination Antiretroviral Therapy: Results From a Swedish Nationwide Observational Study

Olof Elvstam,[1,6] Gaetano Marrone,[2] Patrik Medstrand,[1] Carl Johan Treutiger,[3] Anders Sönnerborg,[4,5] Magnus

[1]Department of Translational Medicine, Lund University, Malmö, Sweden, [2]Department of Infectious Diseases and Clinical Virology, Kar
[3]Department of Infectious Diseases/Venhälsan, South General Hospital, Stockholm, Sweden, [4]Department of Infectious Diseases, Kar
Infectious Diseases, Department of Medicine Huddinge, Karolinska Institute, Stockholm, Sweden, [5]Department of Infectious Diseases
of Gothenburg, Gothenburg, Sweden, [6]Department of Infectious Diseases, Region Västra Götaland, Sahlgrenska University Hospital,
Skåne University Hospital, Malmö, Sweden

LLV 50-200 cp/mL

=> mortalité (toutes causes) : +120%

Table 4. Cox Regression Models for All-cause Mortality and Serious Non-AIDS Events by Viremia Category, LLV Subdivided Into 50–199 And 200–999 copies/mL

	Unadjusted Model	Unadjusted Model With Time Interaction	Fully Adjusted Model[a]
All-cause mortality, n	6956	6956	4541
Virologic suppression	1 (Ref)	1 (Ref)	1 (Ref)
LLV of 50–199 copies/mL	2.3 (1.5–3.3)	2.9 (1.9–4.3)	2.2 (1.3–3.8)
LLV of 200–999 copies/mL	1.2 (.68–2.0)	2.0 (1.1–3.7)	2.1 (.96–4.7)
Nonsuppressed viremia	2.5 (2.0–3.1)	6.3 (3.9–10.1)	7.7 (3.7–15.8)
Serious non-AIDS events, n	6884	6884	4486
Virologic suppression	1 (Ref)	1 (Ref)	1 (Ref)
LLV of 50–199 copies/mL	1.1 (.76–1.6)	1.3 (.91–2.0)	.86 (.50–1.5)
LLV of 200–999 copies/mL	1.3 (.92–1.9)	2.0 (1.3–3.1)	2.0 (1.2–3.6)
Nonsuppressed viremia	1.5 (1.3–1.8)	3.1 (2.1–4.7)	3.3 (1.8–6.0)

Values are hazard ratios with 95% confidence intervals.

Abbreviations: ART, antiretroviral therapy; LLV, low-level viremia; Ref, reference; VL, viral load.

[a]Adjusted for age, sex, CD4 count and VL before start of ART, injection drug use, born in Sweden, treatment experience, and treatment interruptions. Including, including an interaction term between viremia category and time.

Elvstam O. et al. Clin Infect Dis 2021;72:2079-2086.

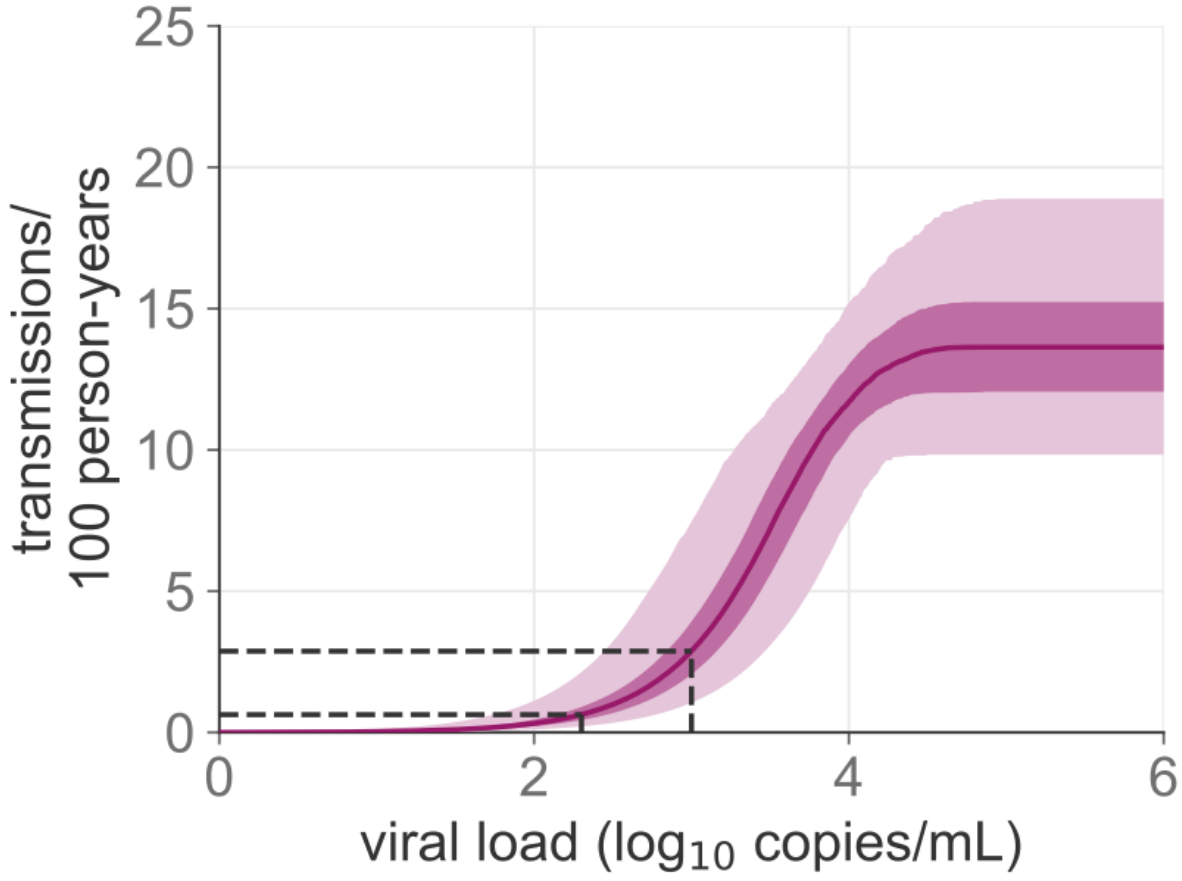
LLV : risque de transmission

Dans un couple séro-différent dont le partenaire infecté est sous ARV :

- Pas de transmission sexuelle en dessous de 200 cp/mL
- Risque très proche de zéro en dessous de 1000 cp/mL, mais pas nul…

Broyles LN et al. Lancet 2023;402:464-71.

LLV : risque de transmission



We estimate **2.9 (95% CI 1.1-7.5) transmissions** per 100 person-years at a viral load of **1,000 copies/mL**

We estimate **0.6 (95% CI 0.2-2.1) transmissions** per 100 person-years at a viral load of **200 copies/mL**

Dans une population peu surveillée => suivi CV tous les 3 mois préférable si LLV

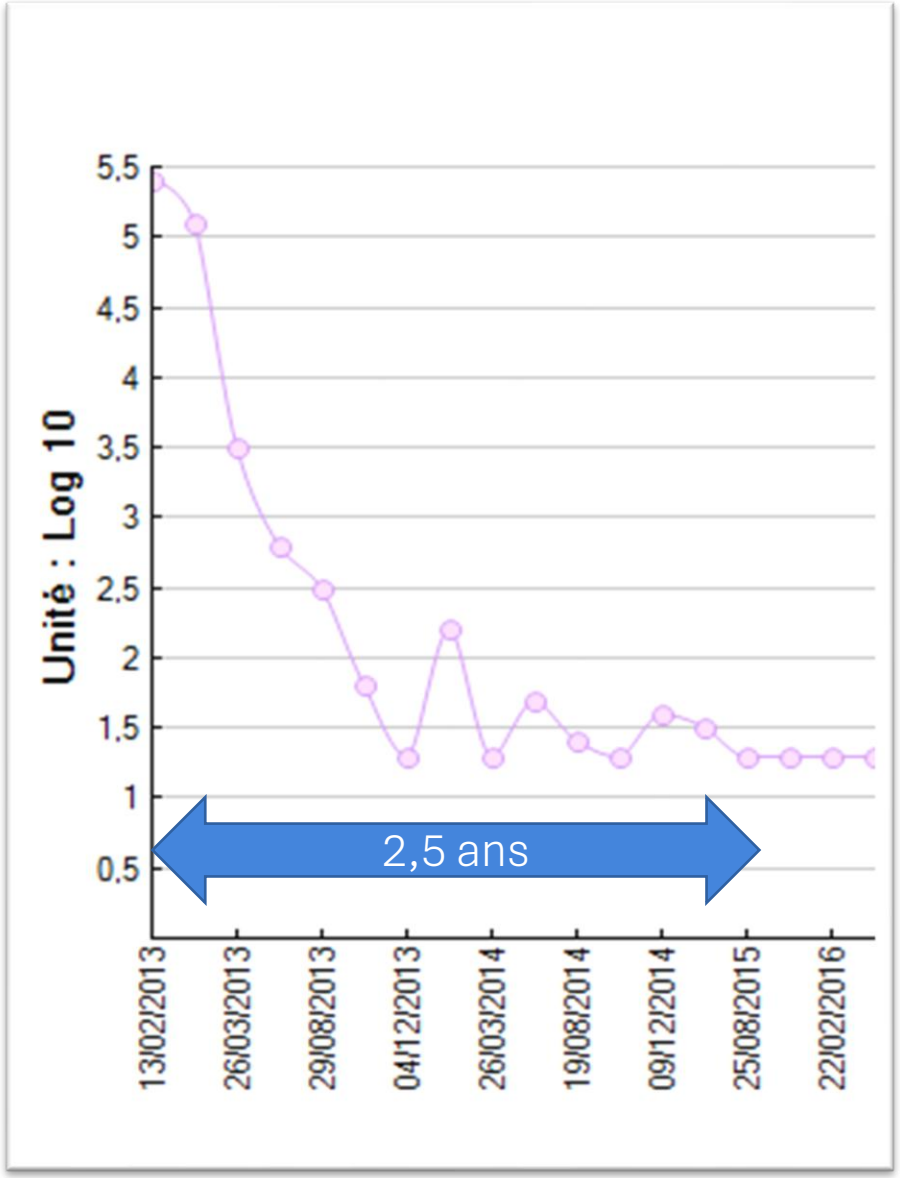
Martin MA et al. CROI 2026 : Poster 903.

Quelques questions devant une LLV

- Primaire / secondaire ?
- Quel niveau de réplication ?
- Quelle durée ?
- Intermittent / permanent ?
- Quelle dynamique ?
- Quel virus (résistance) ?
- Quel patient (CV initiale, adhérence) ?
- Quel traitement (puissance, barrière à la résistance) ?

LLV primaire (d’emblée)

- Patient naïf avec CV très élevée (ex. : primo-infection), le délai acceptable pour CV < 50 cp/mL peut être porté à 12 mois, si baisse >= 2 log10 copies/mL à M1, charge virale <200 copies/mL à M6 et cinétique de décroissance régulière (Rapport Delobel)
- Mauvaise observance pas exclue…
- VNS d’emblée : rare



Principales causes de LLV (secondaires)

Après avoir exclu un traitement inadéquat (cf. génotype cumulé) :

- Problème d'observance (très fréquent)
- Interactions médicamenteuses (très fréquent)
- Maladies intercurrentes (infection, vaccin => plutôt un blip)
- Malabsorption (rare)
- Faux positif du au laboratoire (existe encore ?)

Si persistance : risque d'échec virologique / de mutation de résistance +++

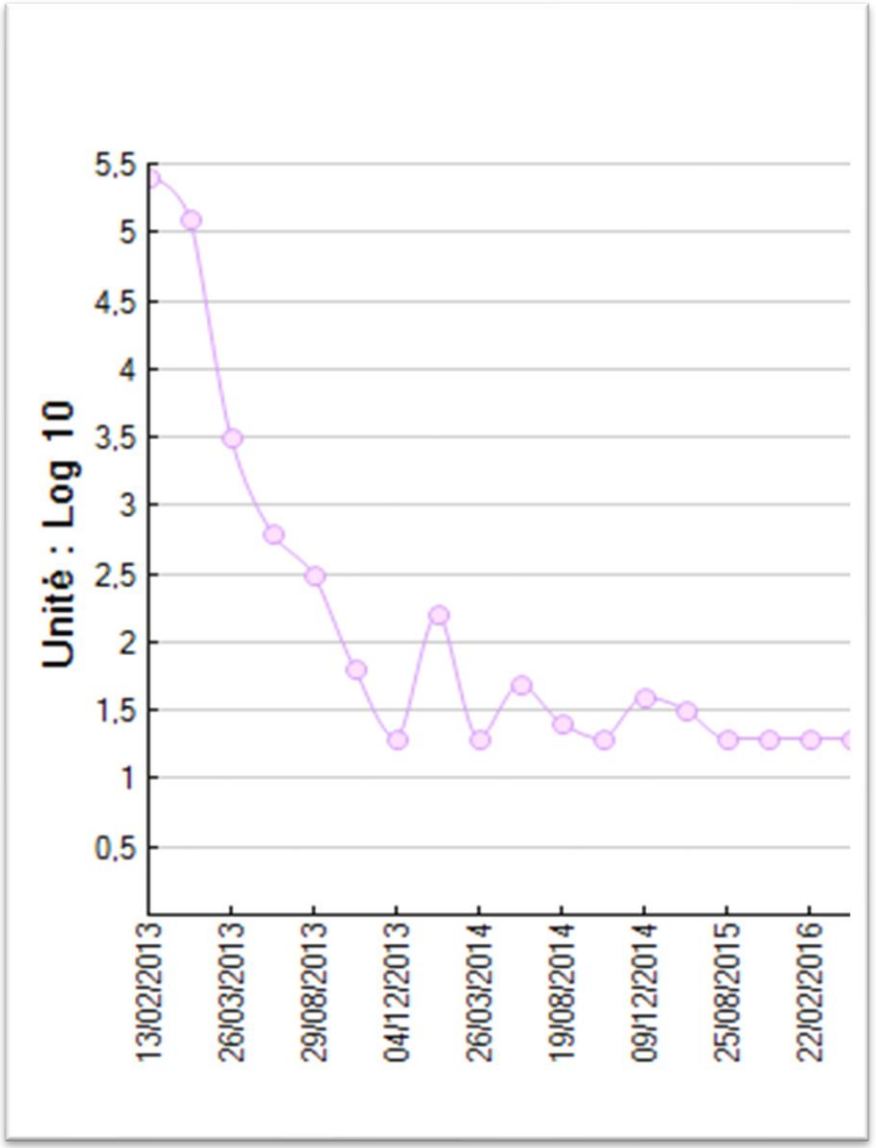
=> Privilégier un traitement simple / bien toléré / haute barrière génétique à la R.

LLV liée à une mauvaise observance

Nous voyons un PVVIH tous les 6 mois : que fait-il entre 2 RDV ?

Pour documenter l'inobservance :

- Dialogue empathique
- Interroger les IDE / pharmacien
- Lecture de la carte Vitale
- MEMS
- Dosage surprise (Cmin)
- Dosage dans les cheveux (?)
- Dried blood Spot (DBS) : ARV intracellulaires (?)



LLV liée à une mauvaise observance

Nous voyons un PVVIH tous les 6 mois : que fait-il entre 2 RDV ?

Pour documenter l'inobservance :

- Dialogue empathique
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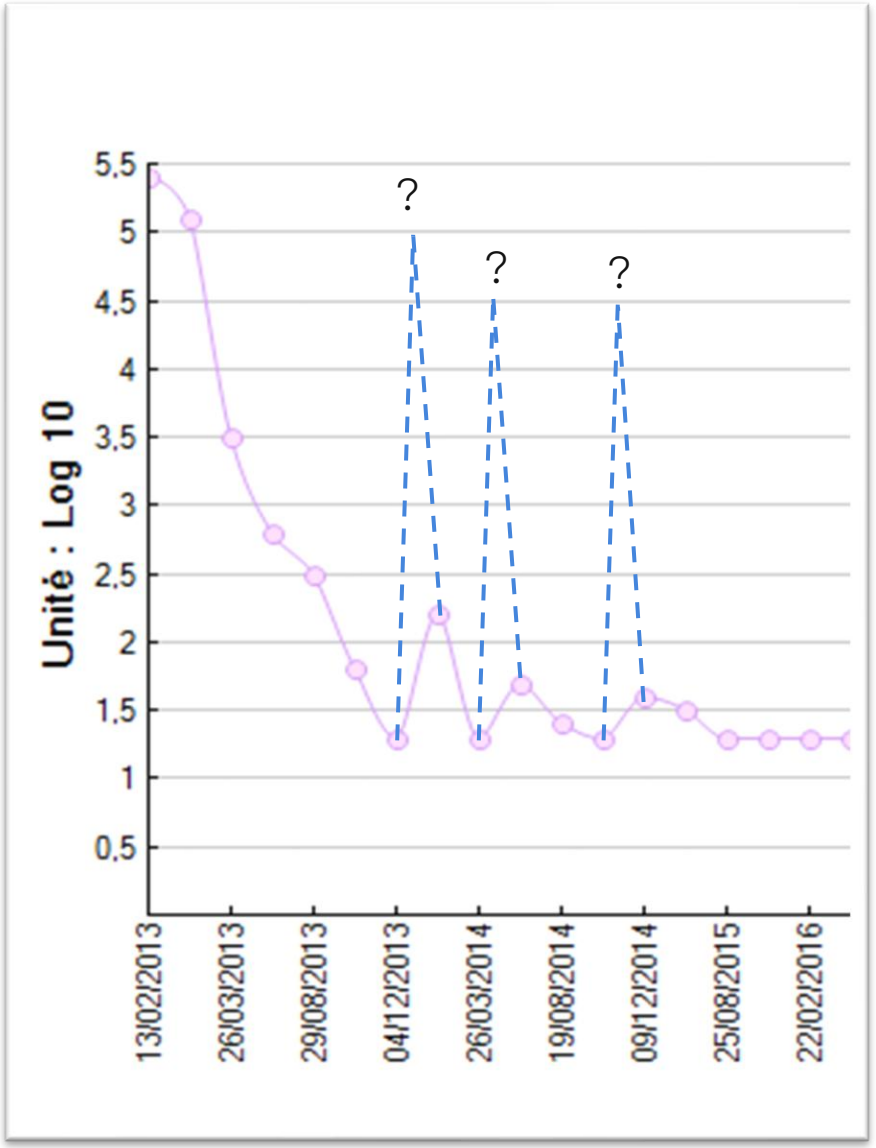
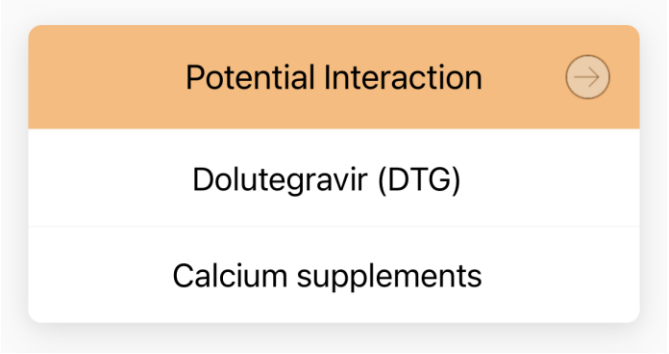
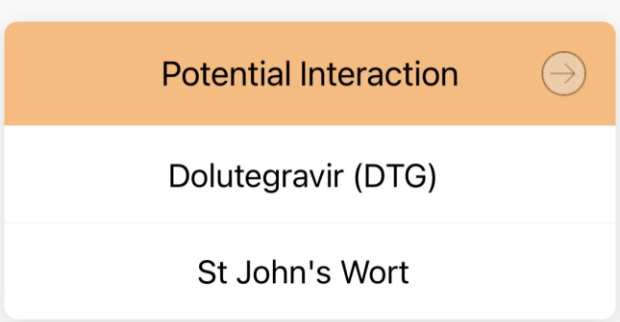


LLV liée à une interaction médicamenteuse

- Les schémas actuels sont essentiellement basés sur NRTI (xTC, TAF/TDF) + INI de 2e génération (DTG, BIC) ou NNRTI (RPV, DOR)
- Les interactions « significatives » se sont raréfiées avec NRTI / INI / DOR…

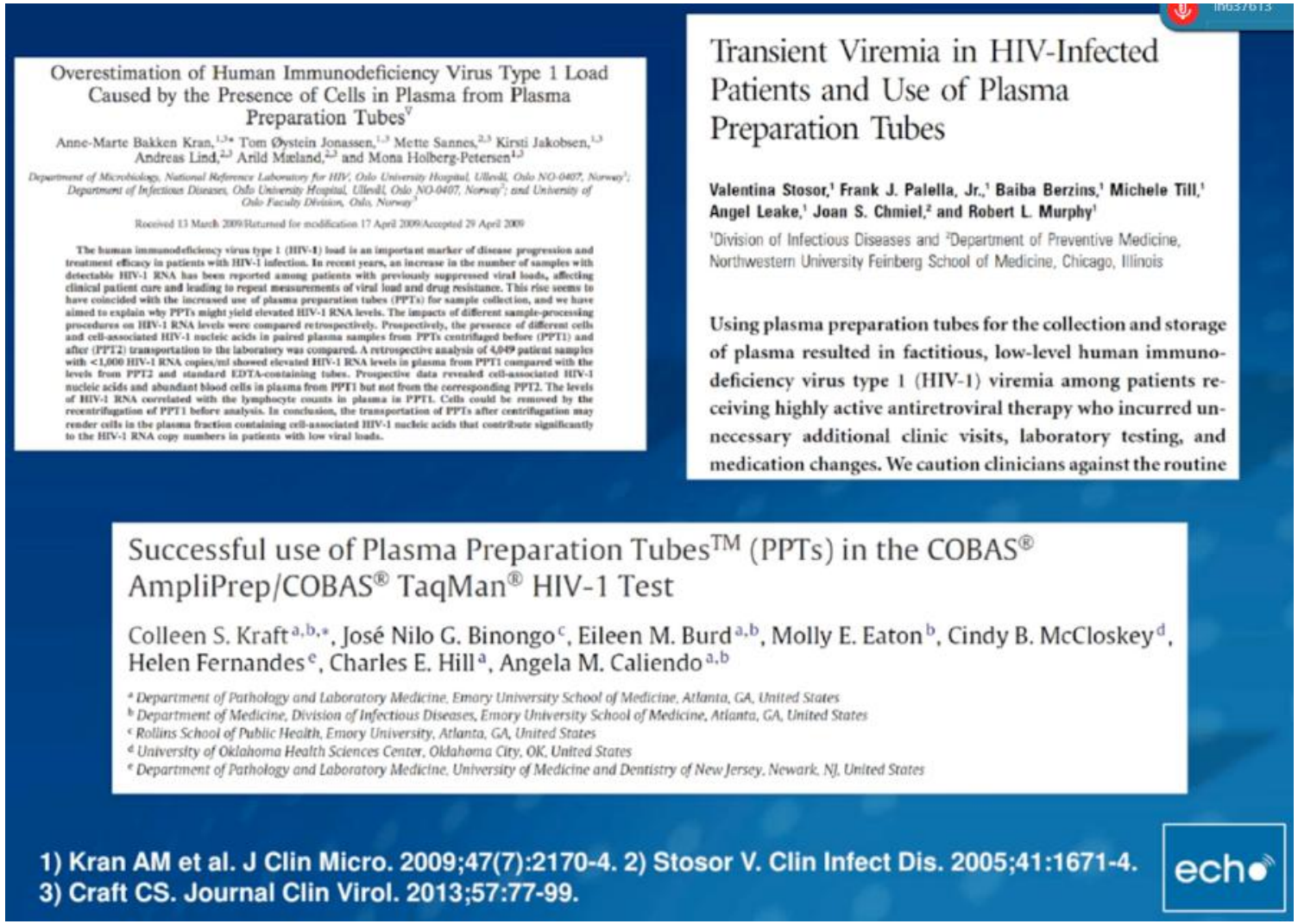




=> Interroger le patient (ordonnance complète, auto-médication, « compléments alimentaires » , « vitamines », « plantes », consommation d'argile…)

=> Dosages (Cmax, Cmin)

Faux positifs « LLV » lié au labo ?



Overestimation of Human Immunodeficiency Virus Type 1 Load Caused by the Presence of Cells in Plasma from Plasma Preparation Tubes[▽]

Anne-Marte Bakken Kran,[1,3]* Tom Øystein Jonassen,[1,3] Mette Sannes,[2,3] Kirsti Jakobsen,[1,3] Andreas Lind,[2,3] Arild Mæland,[2,3] and Mona Holberg-Petersen[1,3]

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Received 13 March 2009/Returned for modification 17 April 2009/Accepted 29 April 2009

The human immunodeficiency virus type 1 (HIV-1) load is an important marker of disease progression and treatment efficacy in patients with HIV-1 infection. In recent years, an increase in the number of samples with detectable HIV-1 RNA has been reported among patients with previously suppressed viral loads, affecting clinical patient care and leading to repeat measurements of viral load and drug resistance. This rise seems to have coincided with the increased use of plasma preparation tubes (PPTs) for sample collection, and we have aimed to explain why PPTs might yield elevated HIV-1 RNA levels. The impacts of different sample-processing procedures on HIV-1 RNA levels were compared retrospectively. Prospectively, the presence of different cells and cell-associated HIV-1 nucleic acids in paired plasma samples from PPTs centrifuged before (PPT1) and after (PPT2) transportation to the laboratory was compared. A retrospective analysis of 4,049 patient samples with <1,000 HIV-1 RNA copies/ml showed elevated HIV-1 RNA levels in plasma from PPT1 compared with the levels from PPT2 and standard EDTA-containing tubes. Prospective data revealed cell-associated HIV-1 nucleic acids and abundant blood cells in plasma from PPT1 but not from the corresponding PPT2. The levels of HIV-1 RNA correlated with the lymphocyte counts in plasma in PPT1. Cells could be removed by the recentrifugation of PPT1 before analysis. In conclusion, the transportation of PPTs after centrifugation may render cells in the plasma fraction containing cell-associated HIV-1 nucleic acids that contribute significantly to the HIV-1 RNA copy numbers in patients with low viral loads.

Transient Viremia in HIV-Infected Patients and Use of Plasma Preparation Tubes

Valentina Stosor,[1] Frank J. Palella, Jr.,[1] Baiba Berzins,[1] Michele Till,[1] Angel Leake,[1] Joan S. Chmiel,[2] and Robert L. Murphy[1]

[1]Division of Infectious Diseases and [2]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Using plasma preparation tubes for the collection and storage of plasma resulted in factitious, low-level human immunodeficiency virus type 1 (HIV-1) viremia among patients receiving highly active antiretroviral therapy who incurred unnecessary additional clinic visits, laboratory testing, and medication changes. We caution clinicians against the routine

Successful use of Plasma Preparation Tubes™ (PPTs) in the COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test

Colleen S. Kraft[a,b,*], José Nilo G. Binongo[c], Eileen M. Burd[a,b], Molly E. Eaton[b], Cindy B. McCloskey[d], Helen Fernandes[e], Charles E. Hill[a], Angela M. Caliendo[a,b]

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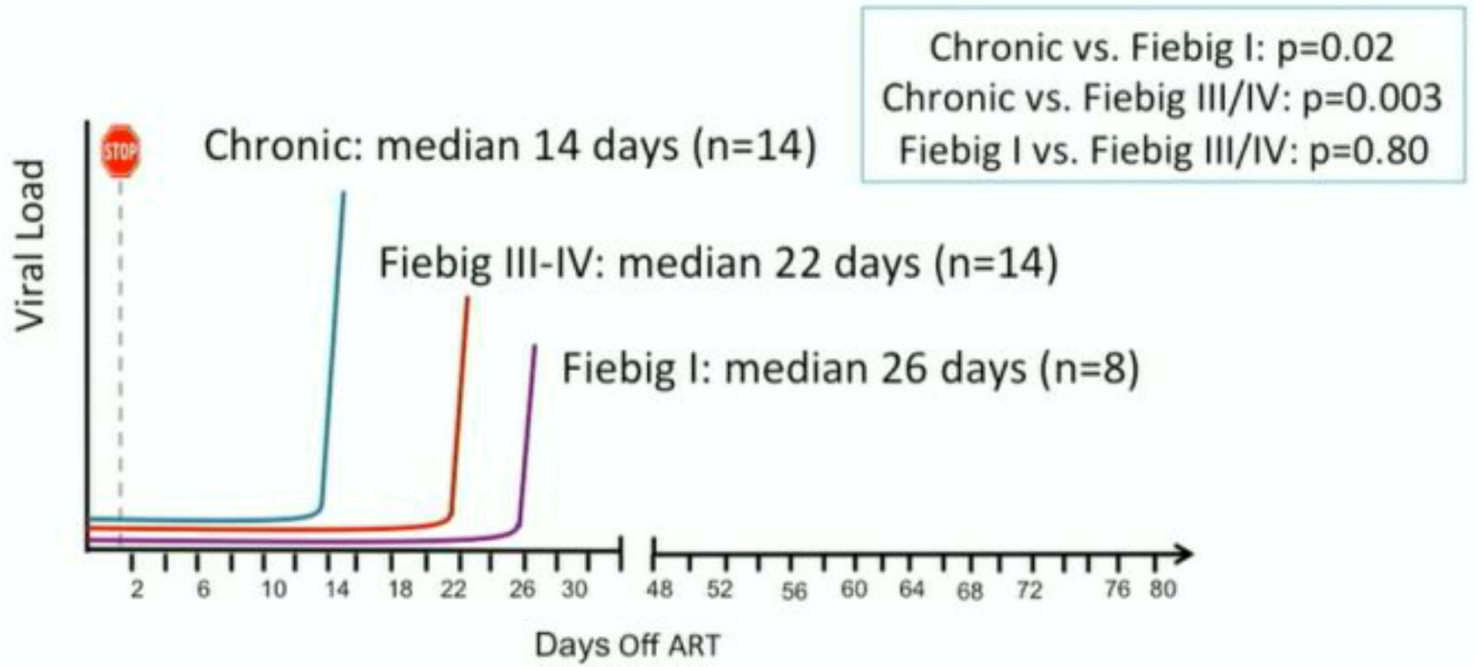
[c] *Rollins School of Public Health, Emory University, Atlanta, GA, United States*
[d] *University of Oklahoma Health Sciences Center, Oklahoma City, OK, United States*
[e] *Department of Pathology and Laboratory Medicine, University of Medicine and Dentistry of New Jersey, Newark, NJ, United States*

1) Kran AM et al. J Clin Micro. 2009;47(7):2170-4. 2) Stosor V. Clin Infect Dis. 2005;41:1671-4.
3) Craft CS. Journal Clin Virol. 2013;57:77-99.

echo

LLV et allègements thérapeutiques ?

- Avec les traitements actuels une adhérence à 95-100% n'est plus nécessaire
- Aucun signal entre LLV (ni virémie résiduelle) et allègements (bithérapies / trithérapies intermittentes) dans de nombreux essais randomisés / cohortes



Ananworanich J. et al. CROI 2017

Intermittent three-drug regimens (i-3DR) as maintenance ART: a meta-analysis including individual participant data

Authors: **Jean-Jacques Parienti**[1], Romain Palich[2], Jessica E. Haberer[3], Lambert Assoumou[4], Anaïs R. Briant[1], R. Calin[5], Dora Luise[6], Massimiliano Lanzafame[7], Karine Amat[8], Laurent Hocqueloux[9], Pierre de Truchis[10], Roland Landman[11]
Institution: [1]Caen University Hospital, Caen, France, [2]Sorbonne University, Pitié-Salpêtrière Hospital, Paris, France, [3]Harvard Medical School, Boston, United States, [4]Sorbonne Université, INSERM, Paris, France, [5]Tenon Hospital, Sorbonne Université, Paris, France, 6Ospedale San Bortolo, Vicenza, Italy, [7]Ospedale Santa Chiara, Trento, Italy, [8]Institut de Médecine et Epidémiologie Appliquée, Hôpital Bichat-Claude Bernard, Paris, France, [9]Orléans University Hospital, Orléans, France, [10]Hôpital Raymond Poincaré APHP, Garches, France, [11]Université de Paris, Hôpital Bichat-Claude Bernard, Paris, France

Intermittent three-drug regimens are non-inferior to continuous therapy at W-48

Figure 2. Meta-analysis of HIV-RNA>50 cp/mL with i-3DR vs continuous ARV at W48

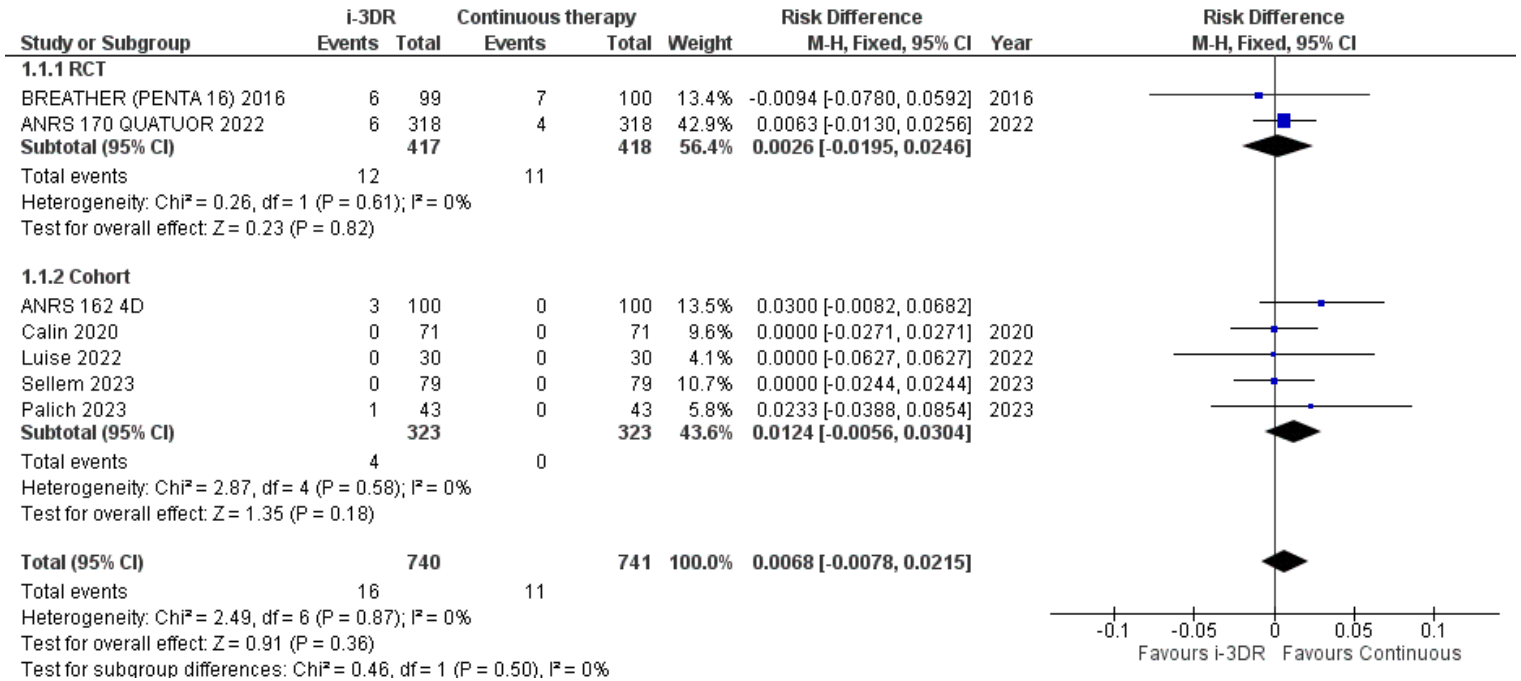
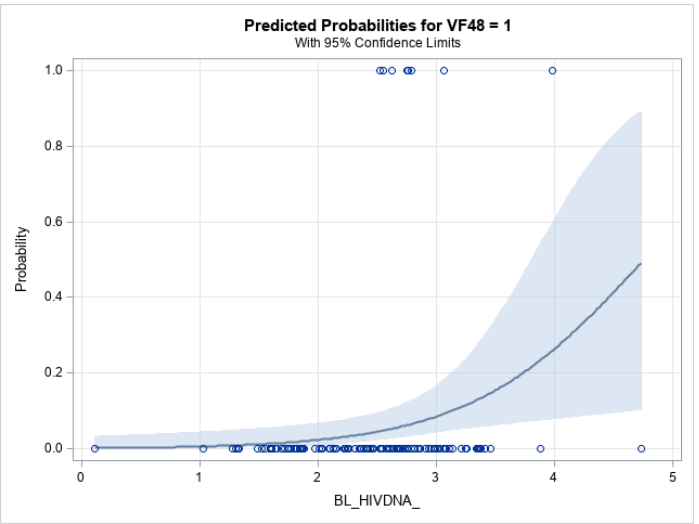


Table 2. Factors associated with HIV-RNA>50 cp/mL with i-3DR at W48

	n	No VF	VF	p-value
Age, mean (SD)	651	49 (11)	45 (9)	0.21
Gender	651			
Men		525 (81)	7 (70)	0.33
Women		116 (18)	3 (30)	
Baseline CD4 cells	630	719 (281)	727 (297)	0.93
Nadir CD4 cells	615	299 (192)	241 (150)	0.35
Baseline HIV-DNA	169	2.23 (0.66)	2.88 (0.48)	*0.007*
ARV combination	651			
BIC or DTG-Based		191 (30)	0	*0.04*
Other		451 (70)	10 (100)	

Figure 3. Probability of HIV-RNA>50 by HIV-DNA at baseline



Conclusion: i-3DR is associated with high virological efficacy at week 48 and meets 4% margin for HIV-RNA>50 cp/mL for non-inferiority compared with continuous therapy. Using INSTI-2G-based i-3DR and low proviral DNA were associated with better virological outcomes. Compared to 4/7, 5/7 i-3DR allows 1-day non-adherence.

Virémies non-suppressibles

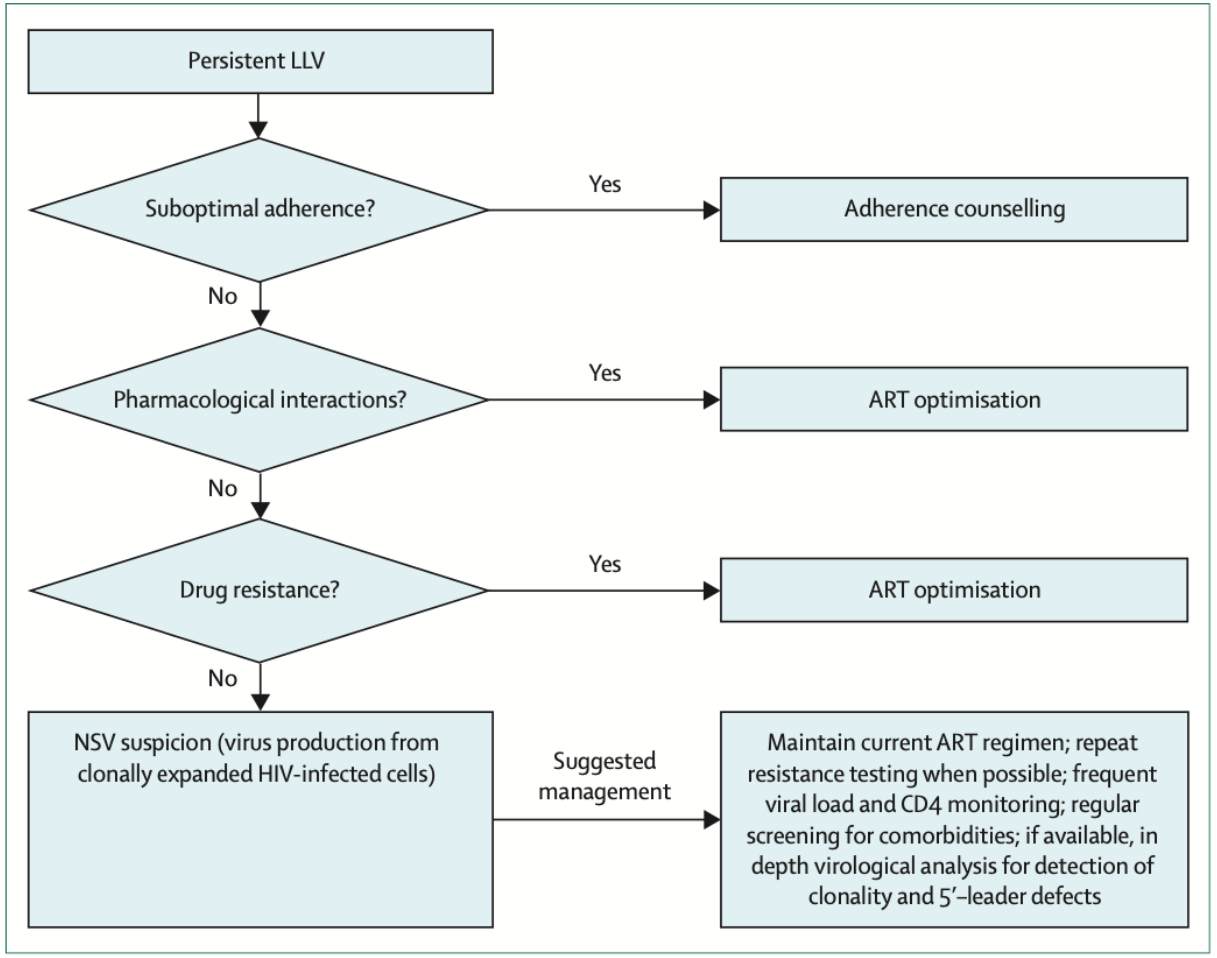


Figure: **Clinical management recommendations for patients with persistent LLV and suspected of NSV**
ART=antiretroviral therapy. LLV=low-level viremia. NSV=non-suppressible viremia.

Esteban-Cantos A et al. Lancet HIV 2024;11:e333-40.

Virémies non-suppressibles

Non-suppressible viraemia during HIV-1 therapy: a challenge for clinicians

Andrés Esteban-Cantos, Rocío Montejano*, Adriana Pinto-Martínez, Javier Rodríguez-Centeno, Federico Pulido†, José R Arribas†*

In individuals receiving antiretroviral therapy (ART), persistent low-level viraemia not attributed to suboptimal ART adherence, detrimental pharmacological interactions, or drug resistance is referred to as non-suppressible viraemia (NSV). This Review presents recent findings in the virological characterisation of NSV, revealing that it consists of one or a few identical populations of plasma viruses without signs of evolution. This finding suggests that NSV originates from virus production by expanded HIV-infected cell clones, reflecting the persistence of the HIV reservoir despite ART. We discuss knowledge gaps regarding the management and the clinical consequences of NSV. The prevalence of NSV remains to be precisely determined and there is very little understanding of its effects on virological failure, HIV transmission, secondary inflammation, morbidity, and mortality. This issue, along with the absence of specific recommendations for the management of NSV in HIV clinical guidelines, underscores the complexities involved in treating individuals with NSV.

- Décrits en 2020
- Virémie faible (<200) persistant des années
- Plutôt secondaire
- Sans inobservance, interaction, résistance
- Fréquence : 1/250 PVVIH sous ARV ?

Hypothèse : exacerbation d'une virémie résiduelle du fait de l'expansion d'un ou plusieurs clones de CD4 infectés par un VIH souvent (mais pas toujours) défectif.

Esteban-Cantos A et al. Lancet HIV 2024;11:e333-40.

Virémies non-suppressibles

- Beaucoup d'hommes
- Avec une longue histoire VIH
- >50 cp/mL depuis des années
- Peu d'inflammation sauf IL6 (risque de morbi-mortalité ?)
- Clone souvent défectif, mais pas toujours (risque de transmission ?)

	Sex	Age*	Ethnicity	Years on ART†	Years with detectable viraemia	Plasma HIV RNA (copies per mL) at study recruitment‡	Nadir CD4+ T cell (cells per µL)	CD4+ T-cell count (cells per µL) at study recruitment
Halvas et al (2020)[16]								
Participant 1	Male	73	White	10	5·2	197	105	380
Participant 2	Male	43	White	9	4·5	62	10	416
Participant 3	Male	62	African American	18	7·4	184	286	1022
Participant 4	Male	59	African American	19	2·1	52	314	1023
Participant 5	Female	55	African American	2	1·3	68	133	533
Participant 6	Male	45	White	10	2·8	106	172	444
Participant 7	Male	59	White	17	5·1	113	299	1105
Participant 8	Male	59	White	12	3·6	43	251	831
White et al (2023)[17]								
Participant 1	Male	63	African American	7·8	5	58	454	828
Participant 2	Male	60	White	26·4	11	20	197	793
Participant 3	Female	58	African American	14·5	5	167	221	803
Participant 4	Male	60	White	27	5	3400	NA	610
Mohammadi et al (2023)[18]								
Participant 1	Male	70–79	Hispanic	NA	8	NA	NA	390
Participant 2	Male	50–59	Native American	NA	2	NA	NA	998
Participant 3	Male	60–69	White	NA	3	NA	NA	531
Participant 4	Male	50–59	White	NA	1	NA	NA	1472
Participant 5	Male	60–69	African American	NA	3	NA	NA	598
Participant 6	Male	60–69	White	NA	5	NA	NA	672
Participant 7	Female	40–49	African American	NA	10	NA	NA	1039
Participant 8	Male	50–59	White	NA	11	NA	NA	923

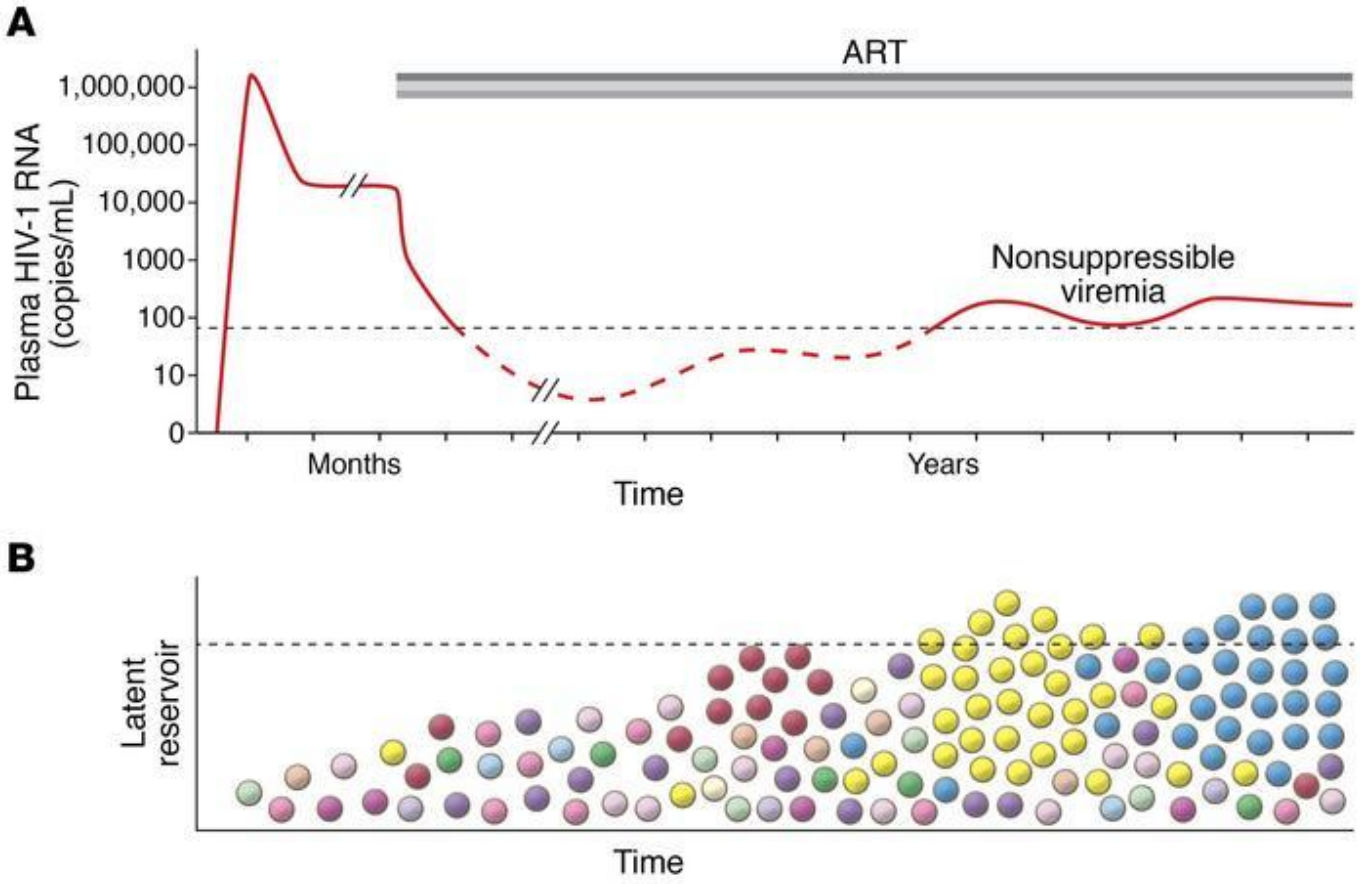
NA=not available. NSV=non-suppressible viremia. *Mohammadi et al report age as a range. †Mohammadi et al report the duration of ART (years) for all participants as a median with interquartile range: 10 (7–14). ‡Mohammadi et al report the last plasma HIV RNA (copies per mL) for all participants as median with interquartile range: 143 (87–536).

Table 2: **Characteristics of individuals with NSV reported in previous studies**

Esteban-Cantos A et al. Lancet HIV 2024;11:e333-40.

Emergence d'un ou plusieurs clones de CD4 activés (par quoi ?)

Figure 1: Nonsuppressible HIV-1 viremia: a reflection of how the reservoir persists

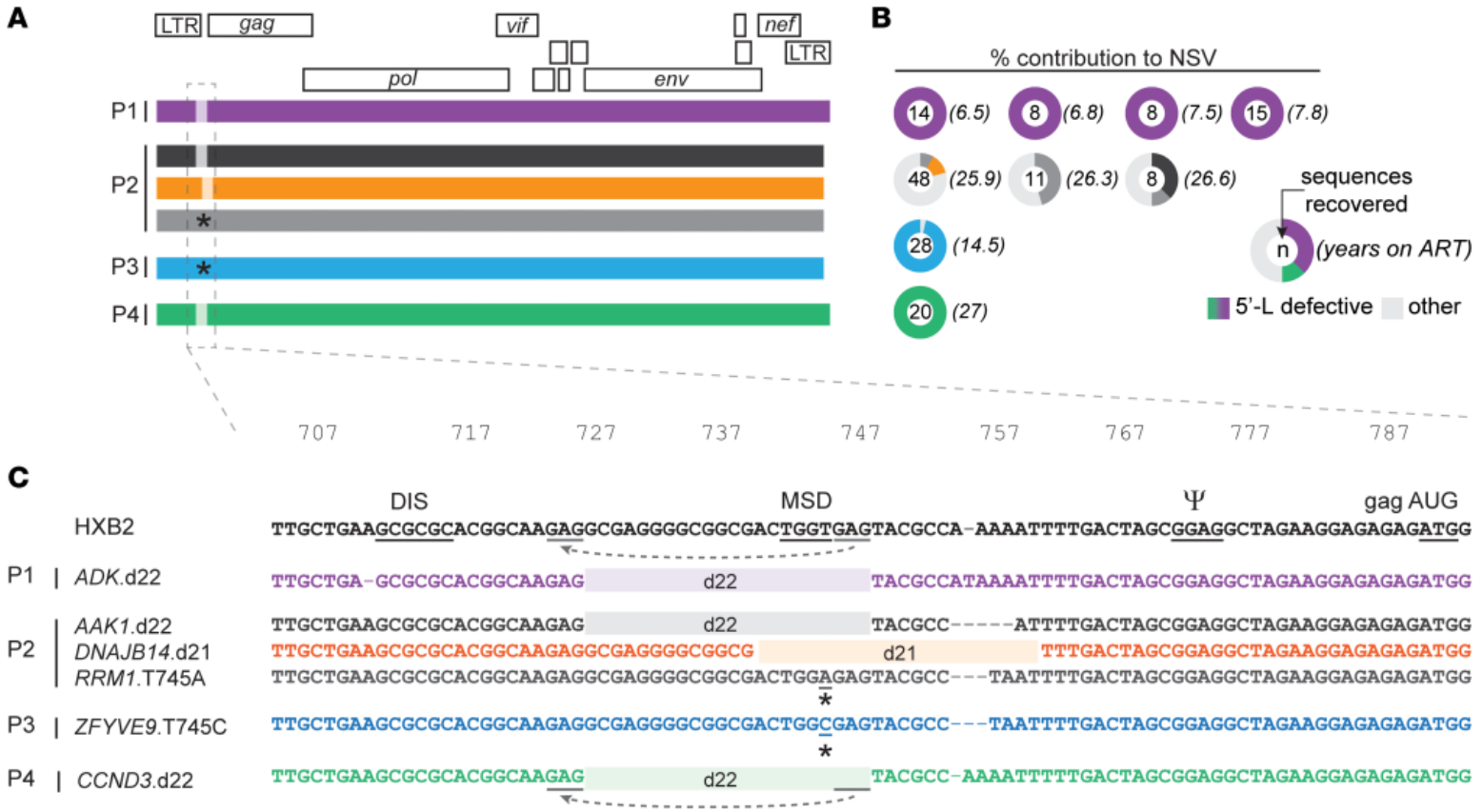


- Dans la NSV, le génome défectif donnerait un avantage sélectif au virus (persistance, échappement au système immunitaire)
- Aucune évolution du virus clonal
- Dans un cas bien documenté le trigger semble être un Ag tumoral

Siliciano J et R. J Clin Invest 2020;130:5665-7.
Simonetti FR et al. PNAS 2016;113:1883-88.

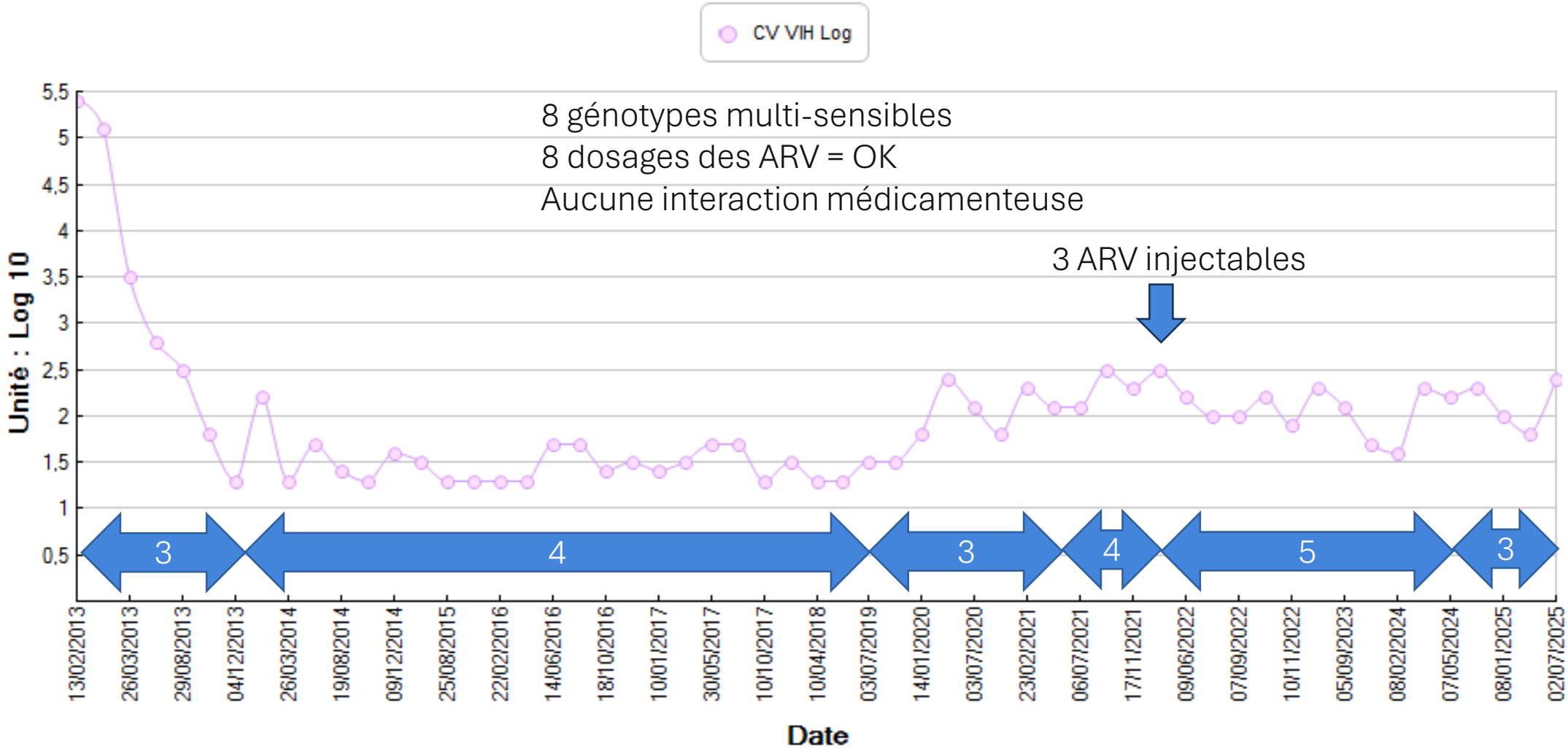
VNS : mutations en 5’-leader

- Mutations dans la région 5’-leader (région en amont de *gag*) impliquée dans la dimérisation et l’empaquetage du génome viral, la rétrotranscription, l’épissage et la traduction des ARN viraux



White et al. J Clin Invest 2023; Mohammadi et al. Nature Med 2023

VNS : aucune efficacité d'une intensification



Dépistage des VNS par une technique rapide?

414

CLAWS

JOHNS HOPKINS MEDICINE

Novel dPCR Assay Confirms 5'Leader-Defective RNA as the Main Source of Nonsuppressible Viremia

Julia R. Box[1], Angelica Camilo-Contreras[1], Filippo Dragoni[1], FengYun Yue[2], Jesper D. Gunst[3,4], Frank Maldarelli[5], Mario Ostrowski[2], Colin Kovacs[6], Francesco R. Simonetti[1]

[1] Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2] University of Toronto, Toronto, Ontario Canada; [3] Aarhus University, Department of Clinical Medicine, Aarhus, Denmark; [4] Aarhus University Hospital, Department of Infectious Diseases, Aarhus, Denmark ; [5] National Cancer Institute, Frederick, MD, USA; [6] Maple Leaf Medical Clinic, Toronto, Ontario, Canada

ONTARIO HIV TREATMENT NETWORK

CENTER FOR AIDS RESEARCH JOHNS HOPKINS UNIVERSITY

W.W. SMITH CHARITABLE TRUST

Background

Despite effective therapy, residual viremia persists in a large fraction of people with HIV (PWH). In some PHW, HIV RNA remains above the limit of detection (LOD) of clinical assays, a condition referred to as nonsuppressible viremia (NSV), which raises concerns about treatment failure, pathogenesis, and transmission. We and others have shown that NSV may contain 5'Leader (5'L)-defective RNA. The frequency of 5'L defects is unknown, and identifying 5'L integrity by sequencing is labor-intensive. ***To enable feasible profiling of 5'L intact and defective NSV, we developed a new quantitative approach: Capture 5'L Anomalies Without Sequencing (CLAWS).***

Methods

We recovered 532 5'L RNA sequences from a training set of plasma from PWH with NSV (N=31, **Fig. 1**); 91 unique variants were used to design a dPCR assay based on a single amplicon and two probes annealing to highly conserved regions: a reference probe targeting the *gag* ORF (required for virus production), and a "drop off" probe binding to 10 nucleotides affected by 96% of 5'L defects (**Fig. 2 A-B**). Among the 91 unique 5'L RNA variants recovered, 26% harbored deletions and 30% contained single-nucleotide mutations within the MSD site (**Fig. 1A-B**). Only double-positive HIV RNA molecules are scored as intact (**Fig. 2 C**). Assay performance was validated using intact and defective dsDNA and virus standards, and its agreement was tested against a set of 27 plasma samples from NSV. We also applied the assay to 10 PWH before and post ART introduction and NSV in a PWH from the TITAN clinical trial.

Results

CLAWS correctly scored as defective 18/18 dsDNA standards with single mutations or deletions in the 5'L, and accurately quantified levels of intact RNA in mixtures of wildtype and defective NL4-3 virus (**Fig. 2D-F**). CLAWS is linear (Spearman r=1, p=0.0028) with 95% LOD of 9 copies/ml plasma (**Fig 3G**).

In samples from PWH with NSV, estimates were comparable between single genome sequencing (SGS) and CLAWS (n=27, 4.5% vs. 8.0%, p=0.28; **Fig. 3A**), confirming that most NSV virus is defective. SGS and CLAWS were highly correlated (Spearman r = 0.84, p<0.0001; **Fig. 3B**) with a mean bias of 2.4% (95% CI, ±19.3%; **Fig. 3C**), confirming strong agreement and supporting CLAWS as an alternative to SGS.

Studying pairs of longitudinal plasma samples from 10 participants who were highly monitored from ART initiation to sustained suppression (**Fig. 3D**) with CLAWS denoted low-level defective RNA during the second phase decay of viremia (35 days on ART) in 6/10 individuals and revealed a progressive enrichment of 5'L defects in plasma during long-term ART (98%, 22/23, **Fig. 3F**). The percentage of 5'L defective RNA measured by CLAWS is shown in **Fig. 3E**.

In a TITAN trial participant with NSV, CLAWS revealed that HIV RNA was defective at baseline, but new intact variants were present in rebound viremia and fueled persistent NSV for years after ART reintroduction, in agreement with sequencing data (r=0.96, p<0.0001, **Fig. 6 A-F**).

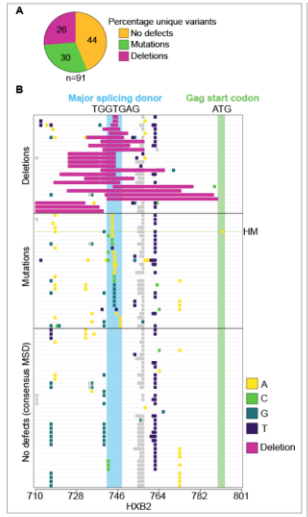


Figure 1 – Deletions and single nucleotide mutations are narrowly focused on the MSD, affecting HIV-1 RNA splicing.

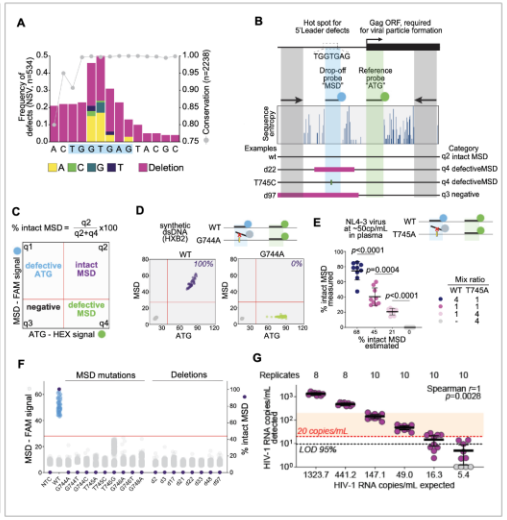


Figure 2 – A single digital PCR assay allows to distinguish intact and defective 5'L RNA.

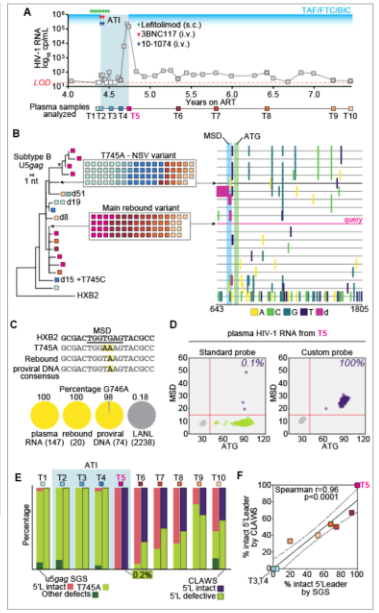


Figure 4 – 5'L defective RNA contributes to NSV in a participant of the TITAN trial. Viral rebound affected viral populations cvausing NSV after ART re-introduction.

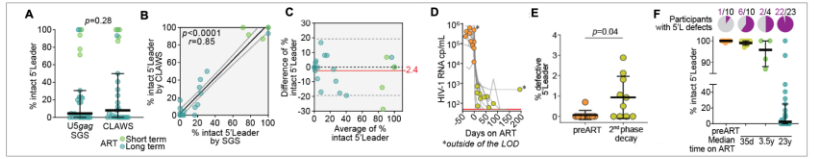


Figure 3 – CLAWS strongly correlates with 5'L sequencing data, detects rare 5'L defective RNA during 2nd phace decay of viremia, and reveals a progressive increase of 5'L-defective RNA in plasma over time on ART.

Conclusion

5'L-defective proviruses are a major source of NSV. CLAWS is a feasible, high-throughput assay that accurately quantifies intact 5'L RNA, which will be useful for investigating persistent viremia and HIV cure clinical trials.

Additional Key Information

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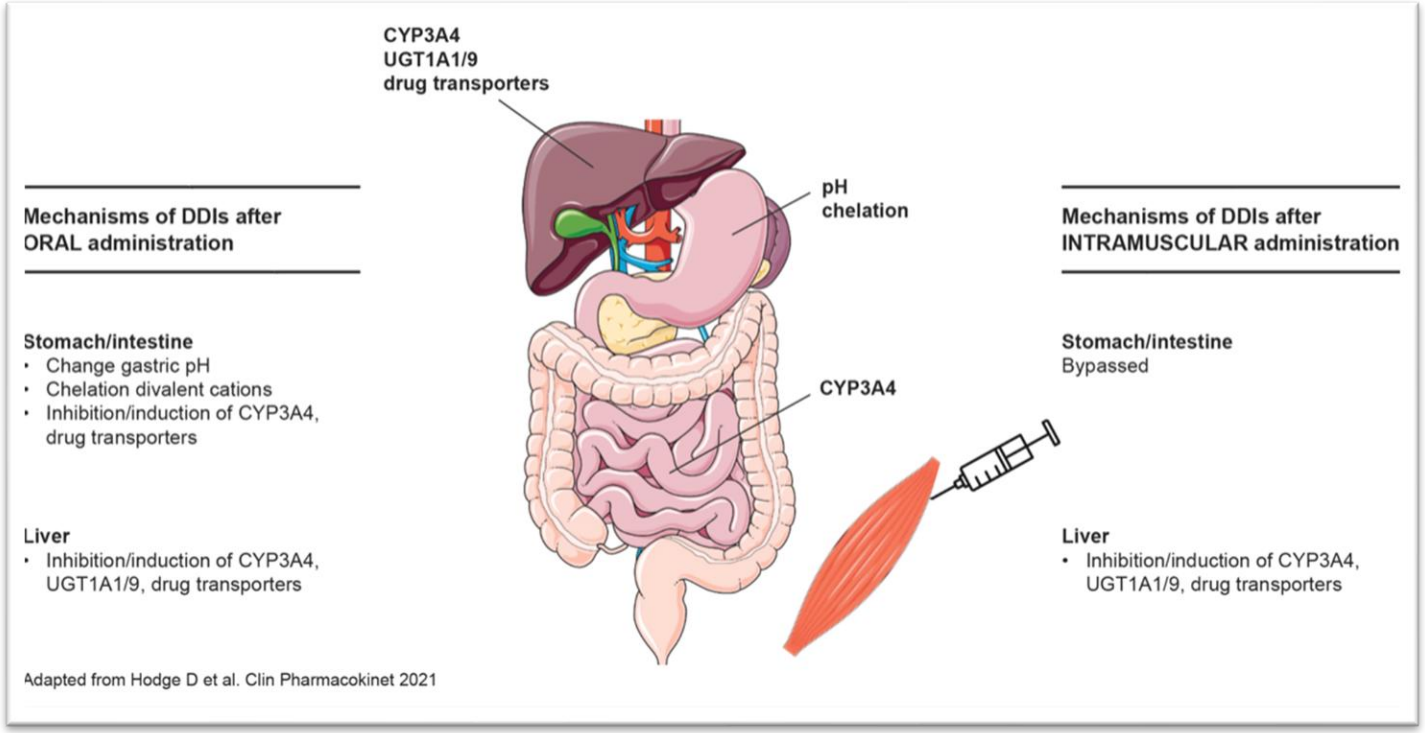
Plain Language Summary

We developed a simpler, cheaper method to quantify HIV-1 RNA in plasma and distinguish intact from defective viral RNA, called CLAWS. This novel approach can be used to better understand persistent viremia in both clinical practice and HIV-1 cure-focused trials.

LLV sous injectable de longue durée d'action

- Observance optimale (si respect des dates d'injections)
- Moindre risque d'interaction médicamenteuse (mais pas nul)



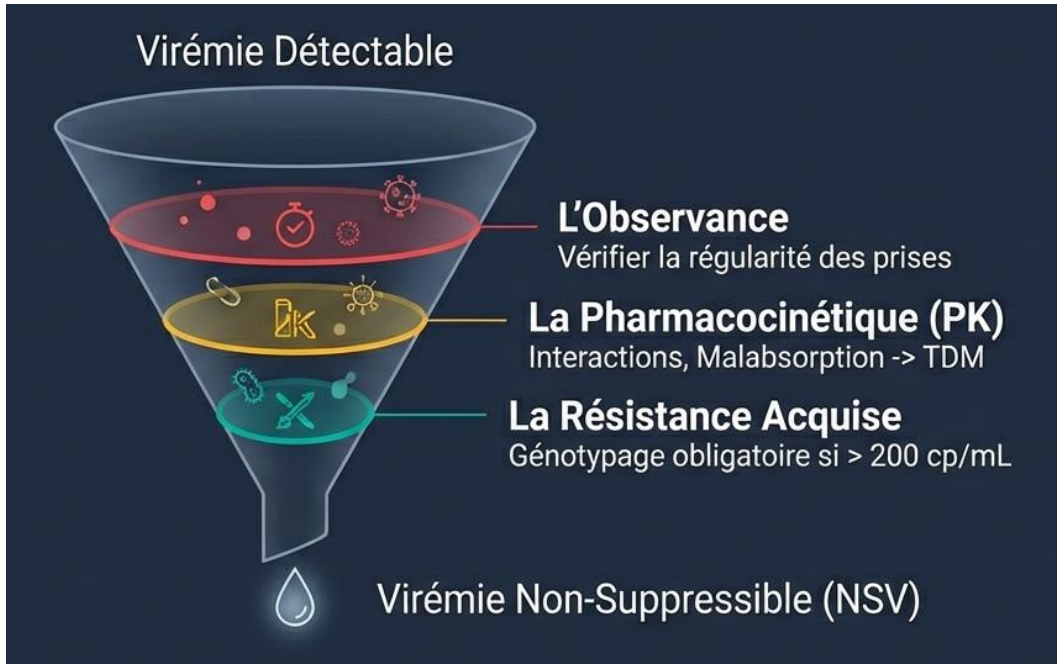
Examples of medications interacting with the oral but not the intramuscular administration of RPV	Examples of medications interacting with the oral but not the intramuscular administration of CAB
• Antacids • famotidine • lansoprazole • liraglutide • omeprazole • orlistat • pantoprazole • rabeprazole • ranitidine	• Antacids • calcium • iron • magnesium • multivitamins containing divalent cations • orlistat • strontium ranelate

LLV sous injectable de longue durée d'action

- Virémie très fréquente : ≥50 copies/mL = 15-16%, LLV persistante = 4%
- LLV liée aux paramètres pré-thérapeutiques (CD4 nadir, zénith CV, réservoirs) et au fait d'avoir une LLV avant (sous traitement oral)

CAT devant une LLV

- On ne change pas le traitement à la première CV > 50 cp/mL !
  - On contrôle
  - On cherche à expliquer
- En pratique :
  - ❑ < 50 copies/mL : on surveille uniquement
  - ❑ 50-200 copies/mL : « vraie » LLV
  - ❑ >200-1000 copies/mL : échec virologique jusqu'à preuve du contraire



2 grands cadres de LLV

LLV incidente / période limitée

Il est possible de retrouver une cause sur laquelle agir (avant l'échec / résistance) :

- Observance inadéquate
- Interaction médicamenteuse
- Evènement intercurrent
- Résistance archivée lors d'un switch

LLV prévalente / durée prolongée

RIEN n'explique une virémie faible, assez stable, prolongée (géno sensible, dosages corrects, etc)

- Virémie Non-Suppressible ?

CAT devant une LLV persistante

- Renforcement de l'observance, correction d'une interaction médicamenteuse, adaptation du schéma posologique guidée par le suivi thérapeutique pharmacologique. (AE)
- La simplification du traitement (nombre de prises quotidiennes, nombre de comprimés par jour, taille des comprimés) peut permettre d'améliorer l'observance. (AE)
- Si barrière génétique faible ou intermédiaire (3TC, FTC, INNTI, INI de 1re génération), le risque de sélection de mutations de résistance augmente avec le niveau de réplication virale et sa durée. (Grade A)
- Faire génotype ARN (ou ADN à défaut), changer le traitement vers un INI de 2e génération (BIC ou DTG) ou DRV/r associé à deux INTI. (Grade A)
- Penser aux complications inflammatoires / au risque de contamination (>>200 cp/mL)

Rapport Delobel

Remerciements

- Quentin Le Hingrat (Bichat)
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Bibliographie indispensable

- Elvstam O. et al. CID 2023;76:25-31.
- Esteban-Cantos A et al. Lancet HIV 2024;11:e333-40.