

**Charges virales basses
sous traitement:**
définition
impact virologique

conflits d'intérêts

subventions, honoraires et participation aux frais de formation continue/congrès:

laboratoires pharmaceutiques:

Abbott; Boehringer Ingelheim; Bristol-Myers Squibb; Gilead Sciences; Tibotec Janssen-Cilag; ViiV Healthcare.

ANRS

charges virales basses: définitions

- × **charge virale basse** « *low level viremia* » **LLV**
50 c/ml < CV < 1000 c/ml sous traitement
- × **blips** « *transient viremia* »
une mesure détectable précédée et suivie d'une mesure indétectable
- × **réplication résiduelle** « *residual viremia* »
réplication virale mesurée par PCR ultra-sensible chez des patients dont CV < 50 c/ml de façon durable sous ART stable

charges virales basses: prévalence

Pozniak et al.:

-CV 50 -400
-4,5 à 7,3%

Cohen et al:

-CV 50-500
-4 à 8%

Table 2. Summary data on baseline characteristics, efficacy, and percent HIV RNA 50–400 copies/mL at Week 48 in first-line clinical trials of NNRTI-based HAART (*n* = 4,475)

Trial [Ref]	Antiretrovirals used		Baseline data		Summary 48-week efficacy	
	NRTI + third drug	<i>n</i>	CD4 count (cells/μL)	HIV RNA (log ₁₀ c/mL)	HIV RNA <50 (%)	HIV RNA 50–400 (%)
CNA3021 [28]	ABC/3TC + EFV	386	264	4.9	65%	7%
CNA3024 [29]	ABC/3TC + EFV	324	267	4.8	69%	4%
CNA3021 [28]	ABC/3TC + EFV	384	259	4.9	64%	7%
Gilead 903 [30]	d4T/3TC + EFV	301	283	4.9	81%	6%
FTC 301A [31]	FTC/ddI + EFV	286	318	4.9	78%	3%
ACTG 5095 [24]	ZDV/3TC + EFV	765	238	4.9	83%	6%
CNA3024 [29]	ZDV/3TC + EFV	325	258	4.8	69%	2%
Gilead 934 [32]	TDF/FTC + EFV	254	241	5.0	70%	3%
EPV 2001 [33]	ZDV/3TC + EFV	276	340	4.6	61%	2%
EPV 2001 [33]	ZDV/3TC + EFV	278	386	4.7	59%	5%
MERIT [34]	ZDV/3TC + EFV	361	254	4.9	69%	4%
Gilead 903 [30]	TDF/3TC + EFV	299	276	4.9	82%	5%
Gilead 934 [32]	TDF/FTC + EFV	255	233	5.0	80%	4%
Mean (range)			278 (233–386)	4.9 (4.8–5.0)	71.5% (59–83%)	4.5% (2–7%)

Table 3. Summary data on baseline characteristics, efficacy, and percent HIV RNA 50–400 copies/mL at Week 48 in first-line clinical trials of boosted PI-based HAART (*n* = 3,608)

Trial [Ref]	Antiretrovirals used		Baseline data		Summary 48-week efficacy	
	NRTI + PI	<i>n</i>	CD4 count (cells/μL)	HIV RNA (log ₁₀ c/mL)	HIV RNA <50 (%)	HIV RNA 50–400 (%)
ARTEMIS [35]	TDF/FTC + DRV/r	343	228	4.9	84%	3%
ARTEMIS [35]	TDF/FTC + LPV/r	346	218	4.8	78%	7%
HEAT [36]	TDF/FTC + LPV/r	286	193	4.8	67%	4%
HEAT [36]	ABC/3TC + LPV/r	278	214	4.9	68%	7%
KLEAN [37]	ABC/3TC + LPV/r	444	194	5.1	71%	6%
ABT-863 [38]	d4T/3TC + LPV/r	326	232	5.0	67%	8%
CASTLE [25]	TDF/FTC + LPV/r	443	204	5.0	76%	6%
SOLO [39]	ABC/3TC + FPV/r	173	166	4.8	69%	13%
KLEAN[37]	ABC/3TC + FPV/r	434	188	5.1	73%	7%
CASTLE [25]	TDF/FTC + ATV/r	440	205	5.0	78%	8%
BMS-089 [40]	d4T/3TC + ATV/r	95	201	4.8	75%	11%
Mean (range)			204 (166–228)	4.9 (4.8–5.1)	73.3% (67–84%)	7.3% (3–13%)

Causes and Consequences of Incomplete HIV RNA Suppression in Clinical Trials

Anton Pozniak,¹ Ravindra K. Gupta,² Deenan Pillay,² Jose Arribas,³ and Andrew Hill⁴

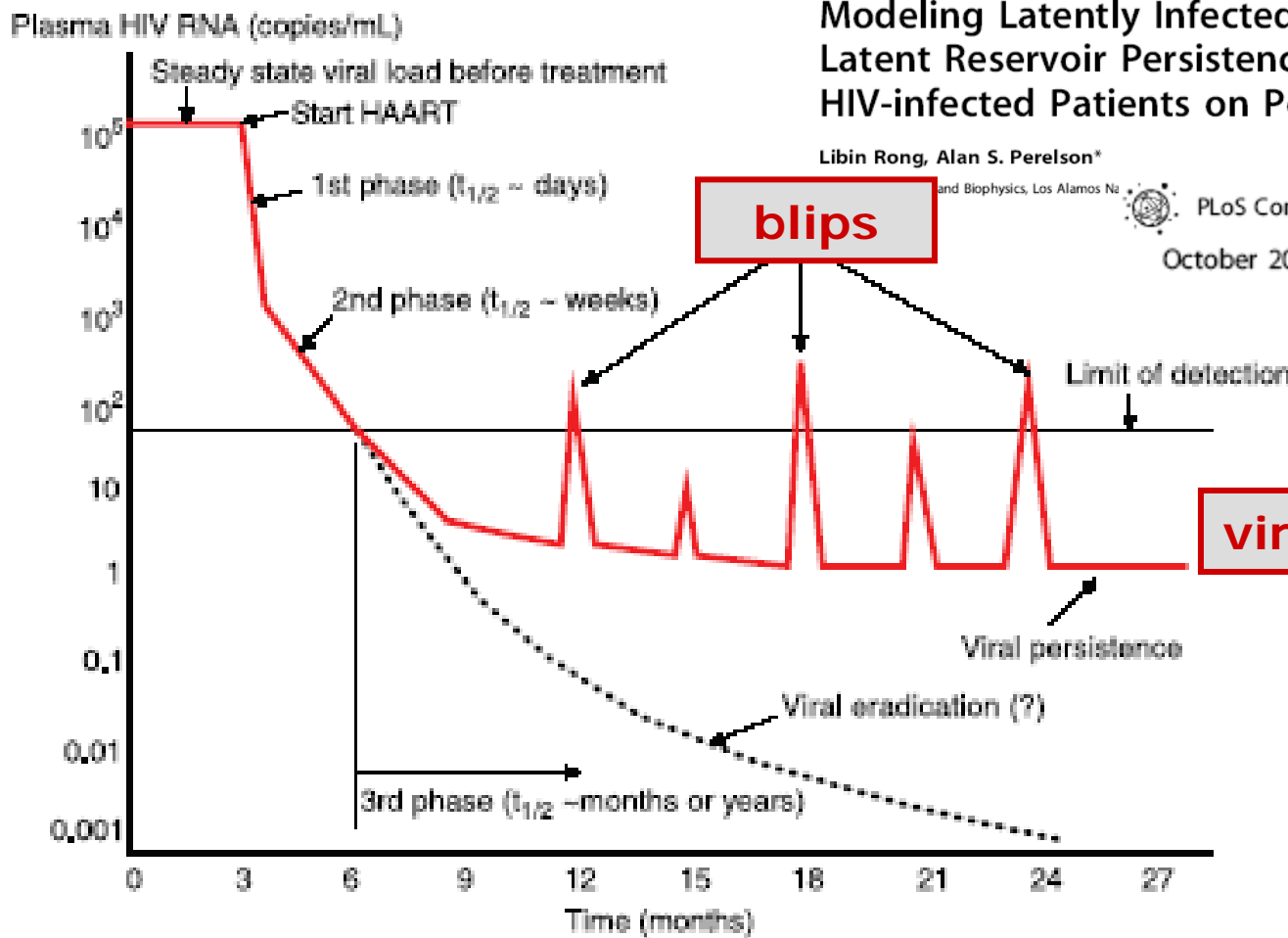


Figure 1. Multiphasic viral decline after potent treatment. After initiation of HAART, the plasma viral load undergoes a multiphasic decay and declines to below the detection limit (e.g., 50 RNA copies/mL) of standard assays after several months. A low level of viremia below 50 copies/mL may persist in patients for many years despite apparently effective antiretroviral treatment. Intermittent viral blips with transient HIV-1 RNA above the limit of detection are usually observed in well-suppressed patients.

charges virales basses: aspects techniques

✗ *distinguer le vrai du faux*

diminution des seuils de détection:

amplicor CA → taqman v1 CTM1 → taqman v2 CTM2
400-200-50 → 40 → 20 copies/ml

emploi de tubes PPTs (plasma preparation tubes)

aléas techniques

charges virales basses: diminution des seuils de détection

× Manavi HIV Clin Trials 2008:

- étude observationnelle 772 patients /ART CV<50 (CA)
- 113 pts (14%) ont 126 épisodes LLV
 - × CV < 50 c/ml CA → détectables >40 c/ml CTM1
 - × 90% des CV détectables < 500 c/ml
 - × durée moyenne 117 jours puis CV < 40 sans modification ARV
 - × génotypes de résistance pour 9 pts CV > 500: pas de mutations
 - × pbs observance et interactions méd. exclus

⇒ redéfinir échecs virologiques et blips / nouveaux seuils

charges virales basses: diminution des seuils de détection

Verhofstede J Clin Virol 2010

181 éch. collectés avril 2007-sept 2009 (pas de PPT)

- spécificité, reproductibilité
- comparaison CA/CTM1/CTM2
- suivi longitudinal : indét. ou blips CA-CTM1 ⇒ LLV en CTM2

		CA	
		<50	>50
CTM1	<40	21 (20.4%)	4 (3.9%)
(n=103)	>40	29 (28.1%)	49 (47.6%)
CTM2	<20	4 (7.5%)	0
(n=53)	>20	32 (60.4%)	17 (32.1%)

? validation clinique du seuil à 20 copies/ml ?

charges virales basses: diminution des seuils de détection

Journal of Clinical Microbiology, May 2010, p. 1911–1912
 0095-1137/10/4812-00 doi:10.1128/JCM.02388-09

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Detection of HIV-1 at between 20 and 49 Copies per Milliliter by the Cobas TaqMan HIV-1 v2.0 Assay Is Associated with Higher Pretherapy Viral Load and Less Time on Antiretroviral Therapy^{†‡}

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TABLE 1. Characteristics of patients who had HIV loads between 20 and 49 cp/ml compared with those of patients whose HIV loads were below 20 cp/ml^a

Characteristic	Value for patients with VL of:		Univariate analysis <i>P</i> value	Multivariate analysis OR (95% CI), <i>P</i> value
	<20 cp/ml (<i>n</i> = 62)	20–49 cp/ml (<i>n</i> = 21)		
Age (yr)	39.3 (32.2–44.6)	41.5 (35.7–48.9)	0.2	
Male sex	49 (79)	19 (90.5)	0.239	
AIDS diagnosis	33 (53.2)	12 (57.1)	0.756	
CD4 level (cells/μl) before start of ART	257 (142–385)	207 (127–312)	0.351	
VL (log RNA cp/ml) before start of ART	4.97 (4.65–5.29)	5.13 (4.87–5.70)	0.019	4.24 (1.28–13.97), 0.018
Use of NNRTI/PI in initial ART regimen ^b	24 (38.7)/38 (61.3)	10 (47.6)/11 (52.4)	0.473	
Use of NNRTI/PI in ART regimen at time of VL assessment	27 (43.5)/35 (56.5)	10 (47.6)/11 (52.4)	0.746	
Time on ART (wk)	101 (60–146)	59 (48–112)	0.031	0.987 (0.974–1), 0.044

^a Values are expressed as the median (IQR) for continuous variables and the number (percentage) of patients with the indicated characteristic for categorical variables. NNRTI, nonnucleoside reverse transcriptase inhibitors; PI, ritonavir-boosted protease inhibitor; CI, confidence interval; OR, odds ratio. *P* values in bold indicate statistical significance.

^b Four patients that started with a PI-based regimen switched to an NNRTI-based regimen because of simplification therapy (*n* = 1) or diarrhea (*n* = 3). One patient starting with an NNRTI-based regimen switched to a PI-based regimen because of exanthema.

charges virales basses et tubes PPT

Journal of Clinical Microbiology, July 2009, p. 2170–2174

0095-1137/09/\$08.00+0 doi:10.1128/JCM.02019-09

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Vol. 47, No. 7

Overestimation of Human Immunodeficiency Virus Type 1 Load Caused by the Presence of Cells in Plasma from Plasma Preparation Tubes⁷

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Journal of Clinical Microbiology, June 2010, p. 2186–2190

0095-1137/10/\$12.00 doi:10.1128/JCM.02034-09

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Vol. 48, No. 6

Coamplification of HIV-1 Proviral DNA and Viral RNA in Assays Used for Quantification of HIV-1 RNA⁷

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observations multiples
CV/PPT > CV/EDTA:
élévation artificielle de
la CV liée aux tubes PPT
par co-amplification
d'acides nucléiques
viraux (ADN et ARN)
associés aux cellules



re-centrifugation des
tubes après le transport
avant décantation et
congélation

charges virales basses ≠ blips

Increased frequency of HIV-1 viral load blip rate observed after switching from Roche Cobas Amplicor to Cobas Taqman Assay

TABLE 1. Comparison of Virological Profile of Patients With HIV-1 Viral Load Blips

Platform for HIV-1 Quantitative Polymerase Chain Reaction	Cobas Amplicor	Real-Time Taqman	<i>P</i>
Date	May 04, 2005 to April 27, 2006	May 02, 2006 to April 30, 2007	—
Total no. samples	1735	2333	0.1542 (NS)
No. patients	540	661	
Samples per patient	3.21	3.53	
No. patients on HAART	266	351	
No. blips	18 episodes	113 episodes	< 0.0001
No. patients with blips	18 patients	100 patients	
Blip rate	6.8 episodes per 100 patient-years on HAART	32.2 episodes per 100 patient-years on HAART	
HIV viral load during blips, median (range)	83 (53–390)	90 (40–727)	—
No. PLLV	10 patients	16 patients	0.5554 (NS)
PLLV rate	1.85% of patients (10/540)	2.42% patients (16/661)	

HAART, highly active antiretroviral therapy; PLLV, persistent low level viremia; NS, not statistically significant.

augmentation de la fréquence de blips mais pas de la fréquence des charges virales basses sous ARV (PLLV)

charges virales basses \neq blips

Posadecki JID 2007

études M99-056 et M02-418 (LPV), 223 pts

- valeur médiane 82 c/ml
- pas d'association avec CV et CD4 J0
- association avec \searrow observance

Di Mascio J Virol 2003

8 essais cliniques trithérapie, 123 pts

- valeur médiane 158 ± 152 c/ml, durée estimée 20 à 30 jrs
- corrélation avec CV et CD4 J0
- pas de corrélation avec observance

- retour à l'indétectabilité sans modification thérapeutique
- pas de conséquences en terme d'échec virologique

charges virales basses: causes/origine?

- techniques: erreur, variabilité des mesures, contamination
- observance imparfaite/intermittente
- échappement débutant \pm résistance
- pénétration aléatoire ARV dans les \neq pools cellulaires et sites anatomiques

charges virales basses: causes/origine?

Bonora et al J Med Virol 2009:

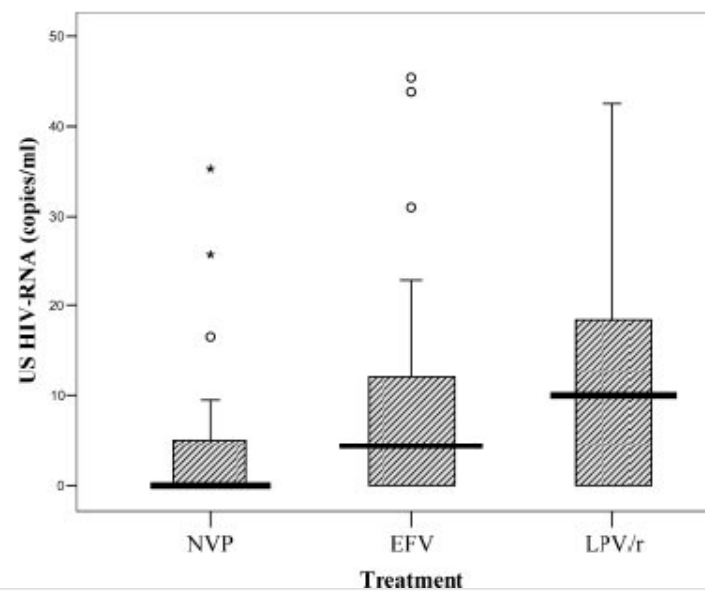


TABLE II. Univariate and Multivariate Analysis of Factors Significantly Associated With Level of Ultrasensitive HIV-RNA

Factors associated with level of US HIV-RNA ^a	Univariate analysis	Multivariate analysis	
	P-value	P-value	95% CI ^b
Gender	0.46		
Thymidine analogue-containing backbone	0.07	0.31	0.262–1.539
On first-line ARV regimen	0.42		
Duration of virological suppression <50 copies/ml (months)	0.03	0.85	0.377–2.240
HAART duration	0.96		
Nadir CD4+ cell count (cells/mm ³)	0.01	0.17	0.303–1.246
Nadir CD4+ cells (%)	0.01	0.27	0.334–1.360
Current CD4+ cell count (cells/mm ³)	0.91		
Gain in CD4+ cell count (cells/mm ³) ^c	0.87		
Third drug of current HAART regimen	0.02 ^d		
Nevirapine		0.013	0.189–0.821
Efavirenz		0.54	0.594–2.909
Lopinavir/ritonavir		0.08	0.911–5.171

ARV, antiretroviral; HAART, highly active ARV therapy.

^aUltrasensitive HIV-RNA measurement (detection limit: 2.5 copies/ml).

^b95% confidence interval.

^cGain in CD4+ cell count from initiation of HAART to time of study sampling.

^dANOVA test.

Haïm et al, antiviral therapy 2010:

165 pts, comparaison EFV (n= 90)/NVP (n=75) sur CV résiduelle,

CV < 1 c/ml: 81.3% pts NVP vs 56.7% des pts EFV

charges virales basses: causes/origine?

1/ persistance de la réplication:

- expression mRNA/PBMC
- évolution séquences virales
- CV faibles ms détectables

2/« relarguage » viral des φ infectées latentes:

- CD4+
- monocytes, φ NK
- φ tissus lymphoïde
intestinal

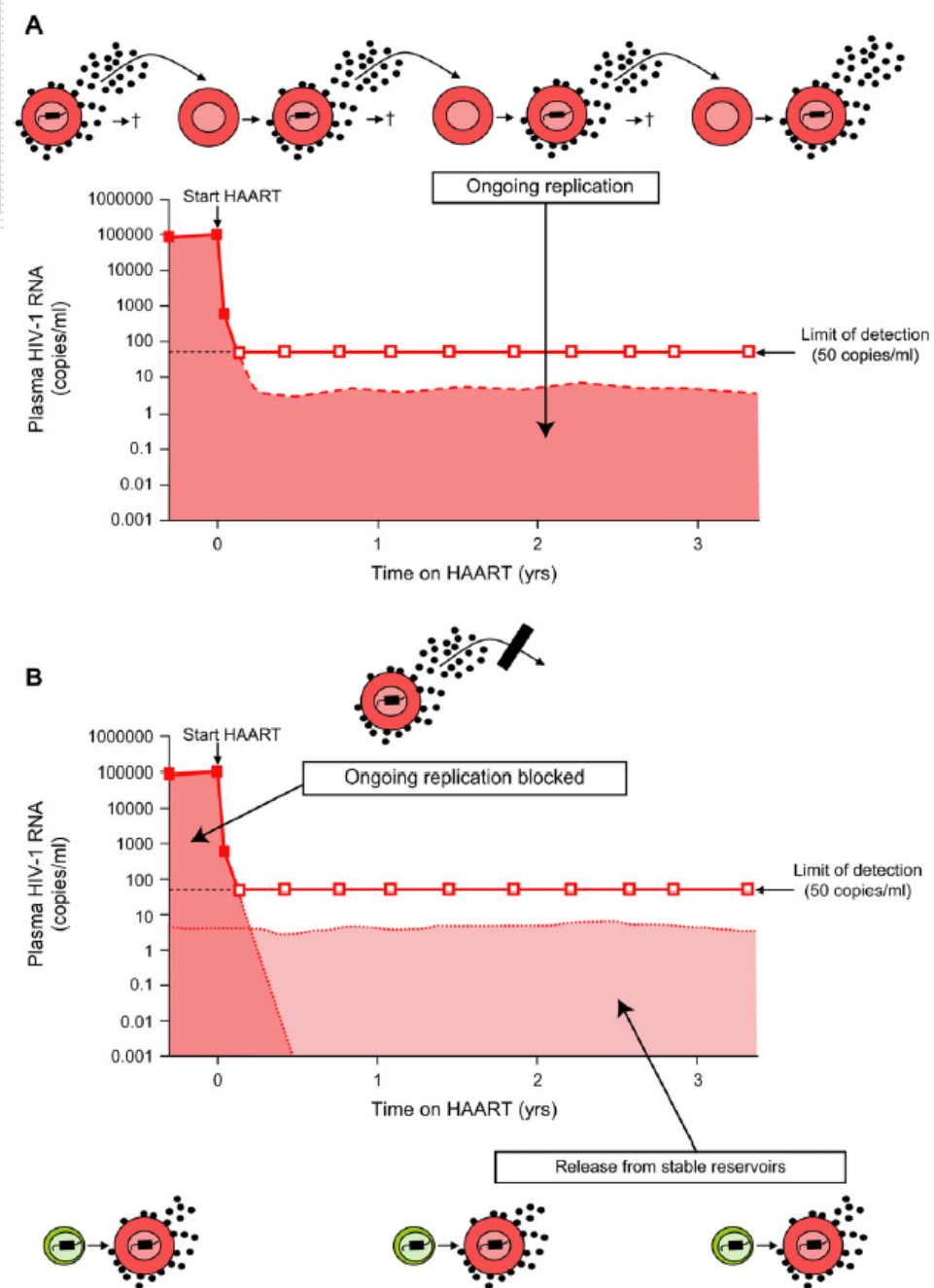


FIG 1. Two theories to explain RV in patients on HAART. A, RV represents ongoing cycles of replication that continue at a lower level because of the suppressive effects of the drugs. B, HAART stops all ongoing cycles replication, and the RV reflects release of virus from stable reservoirs such as the latent reservoir in resting CD4⁺ T cells.

charges virales basses: impacts virologiques

- x « ré-encemensement » des réservoirs
- x résistance
- x échappement

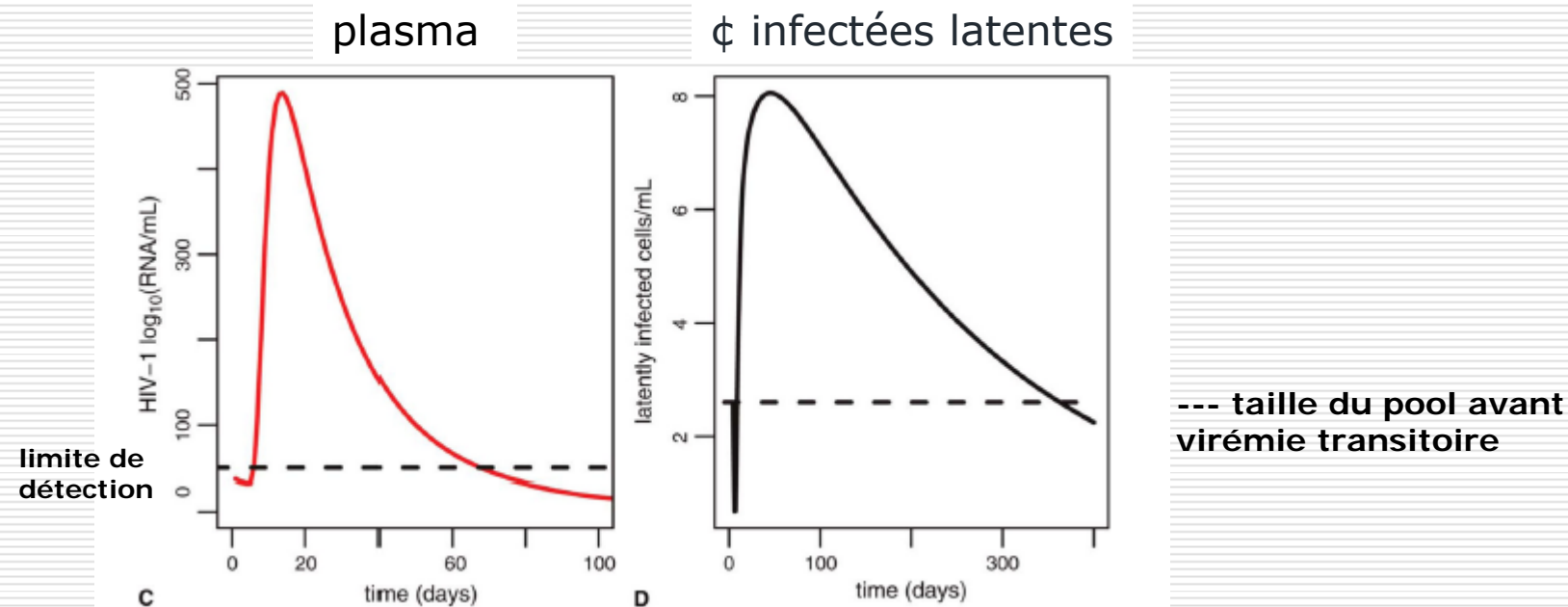
charges virales basses: ré-ensemencement des réservoirs

Transient Viremia, Plasma Viral Load, and Reservoir

Replenishment in HIV-Infected Patients on Antiretroviral Therapy

Laura E. Jones, PhD* and Alan S. Perelson, PhD†

J Acquir Immune Defic Syndr. 2007



pool ϕ infectées latentes \sim HIV-DNA corrélé avec CV J0 et CV sous ARV,
infection croisée entre ϕ latentes et ϕ activées \Rightarrow ré-ensemencement continu
du réservoir latent

charges virales basses: résistance

AM Geretti, IHDRW 2009, abs 56

Mackie et al JID 2010

analyse rétrospective 7861 génotypes:

- ✘ 1001 (12.7%) CV < 1000
- ✘ 65% géno ≥ 1 mutation de résistance
- ✘ détection de mutations de résistance en fonction du niveau de charge virale \Rightarrow présence de mutations (méd. 3) à tous les niveaux de CV y compris < 300
- ✘ détection de ≥ 1 mutation de résistance plus fréquente pour CV 300-10000 que pour CV > 10000

charges virales basses : résistance

AM Geretti, IHDRW 2009, abs 56
Mackie et al JID 2010

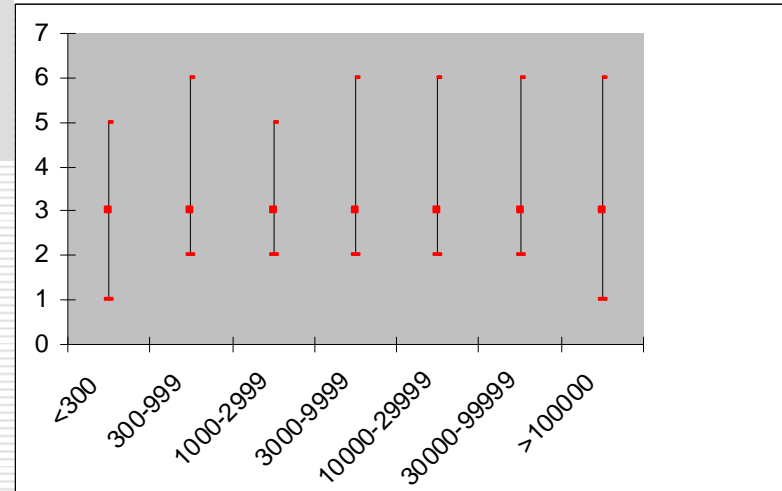


Table 2. Prevalence and Relative Risk (RR) of Detection of Drug Resistance According to Viral Load

Viral load, copies/mL	All patients			Patients receiving NRTIs			Patients receiving NNRTIs			Patients receiving PIs		
	n	Any resistance mutation	RR (95% CI)	n	NRTI resistance mutation	RR (95% CI)	n	NNRTI resistance mutation	RR (95% CI)	n	PI resistance mutation	RR (95% CI)
<300	449	270 (60)	0.94 (0.87–1.01)	410	219 (53)	0.89 (0.81–0.98)	126	61 (48)	0.85 (0.72–1.00)	193	55 (29)	0.85 (0.70–1.04)
300–999	552	399 (72)	0.99 (0.94–1.04)	508	345 (68)	1.01 (0.94–1.07)	161	124 (77)	1.04 (0.94–1.15)	237	90 (38)	1.00 (0.87–1.16)
1000–2999	1119	851 (76)	1	994	712 (72)	1	315	247 (78)	1	423	182 (43)	1
3000–9999	1311	1014 (77)	1.01 (0.97–1.05)	1135	850 (75)	1.01 (0.96–1.06)	363	281 (77)	1.01 (0.94–1.09)	483	224 (46)	0.89 (0.79–1.01)
10,000–29,999	1323	892 (67)	0.91 (0.87–0.95)	1003	700 (70)	0.92 (0.88–0.97)	298	220 (74)	0.96 (0.88–1.04)	454	199 (44)	0.87 (0.77–0.99)
30,000–99,999	1433	862 (60)	0.84 (0.80–0.88)	1014	595 (59)	0.79 (0.74–0.84)	282	170 (60)	0.82 (0.74–0.92)	462	192 (42)	0.85 (0.75–0.96)
≥100,000	1674	811 (48)	0.69 (0.65–0.74)	1076	482 (45)	0.61 (0.57–0.66)	319	155 (49)	0.67 (0.59–0.76)	507	157 (31)	0.64 (0.55–0.75)

⇒ faire génotype dès CV > 50

charges virales basses: résistance

HIV-1 drug resistance evolution during persistent near target viral suppression. Taiwo et al. Antiviral Therapy 2010

× near target viral suppression NTVS = CV 50-1000 (au moins deux fois) après au moins 6 mois d'ARV

× 1234 pts (ACTG 5095 et 5142), 65 NTVS (~ 5%), 58 génotypés:

- présence de mutations de résistance: 20/58
- émergence de nouvelles mutations de résistance: 16/47
- M184V et K103N
- association avec le niveau de CV, même si survenue à des niveaux très bas

NTVS: 5% des pts ⇒ mutations de résistance dans 34% des cas

charges virales basses: échappement

Episodes of low-level viral rebound in HIV-infected patients on antiretroviral therapy: frequency, predictors and outcome

Journal of Antimicrobial Chemotherapy (2008) 61, 699–704

Pilar García-Gascó, Ivana Maida, Francisco Blanco, Pablo Barreiro, Luz Martín-Carbonero, Eugenia Vispo, Juan González-Lahoz and Vincent Soriano*

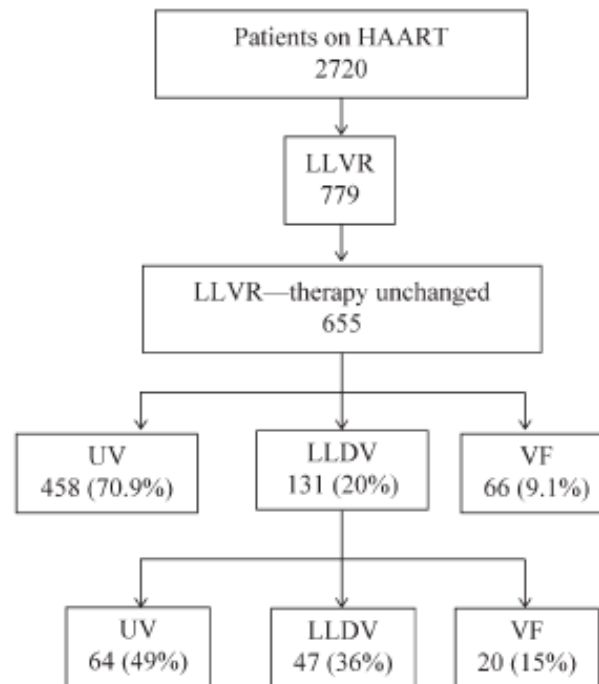


Figure 1. Outcome of patients on antiretroviral therapy who experienced episodes of LLVR. VF, virological failure; LLDV, low-level detectable viraemia without changing therapy; UV, undetectable plasma HIV-RNA.

charges virales basses: échappement

Episodes of low-level viral rebound in HIV-infected patients on antiretroviral therapy: frequency, predictors and outcome

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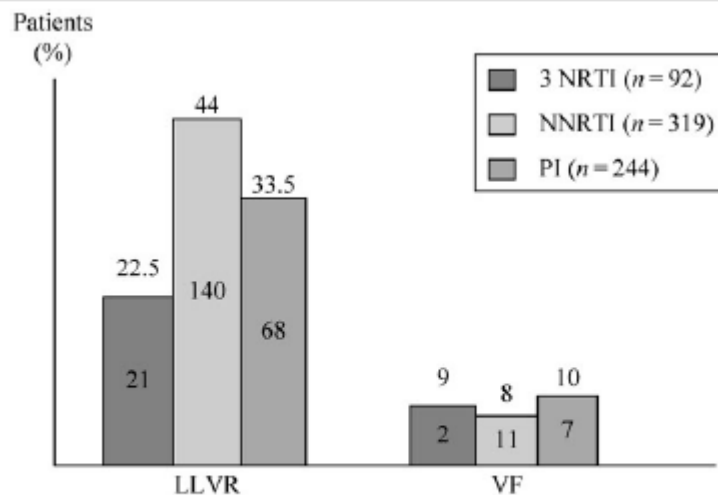


Figure 3. Frequency of LLVR episodes using distinct antiretroviral treatment modalities. Rate of subsequent virological failure (VF).

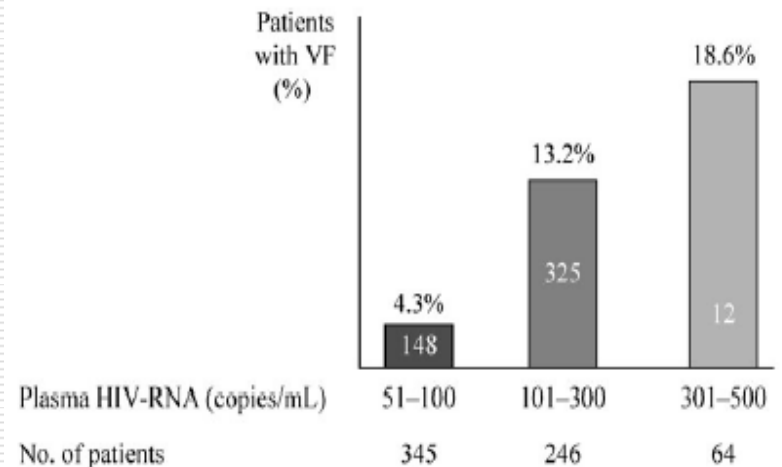


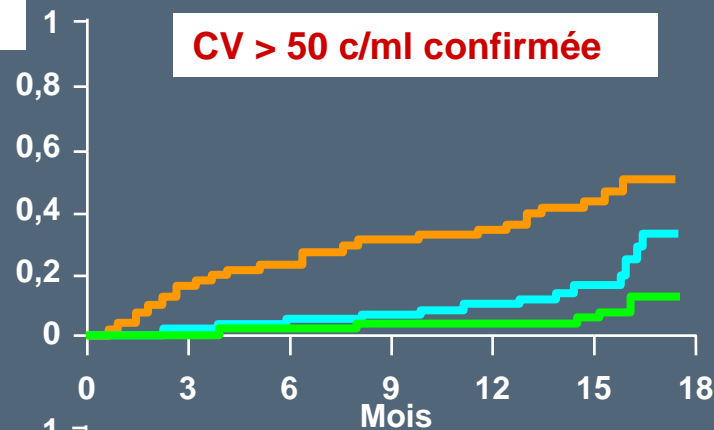
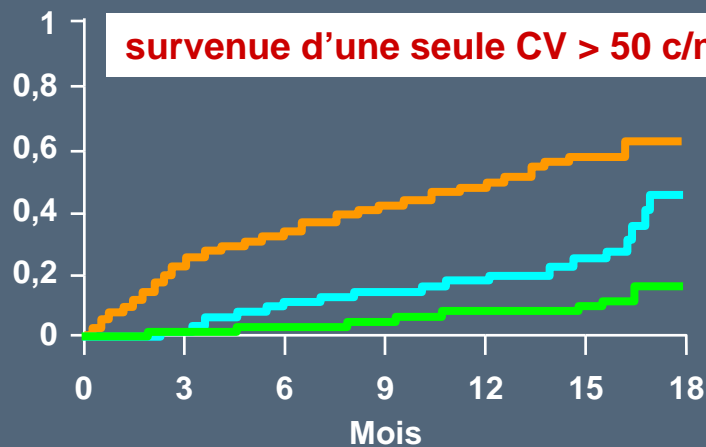
Figure 4. Rates of virological failure (VF) following distinct plasma HIV-RNA levels at the time of LLVR.

Conclusions: Episodes of LLVR in HIV patients on successful HAART are relatively common and represent transient events (*blips*) in most cases (71%). Keeping the same treatment regimen, virological failure follows in <10% of the cases. Plasma HIV-RNA level at the time of LLVR is the best predictor of subsequent failure.

charges virales basses: échappement

étude de 1 247 patients traités par ARV avec CV < 50 c/ml

analyse rétrospective de l'échec virologique selon le niveau des virémies: risque de survenue de l'échec virologique selon ≠définitions

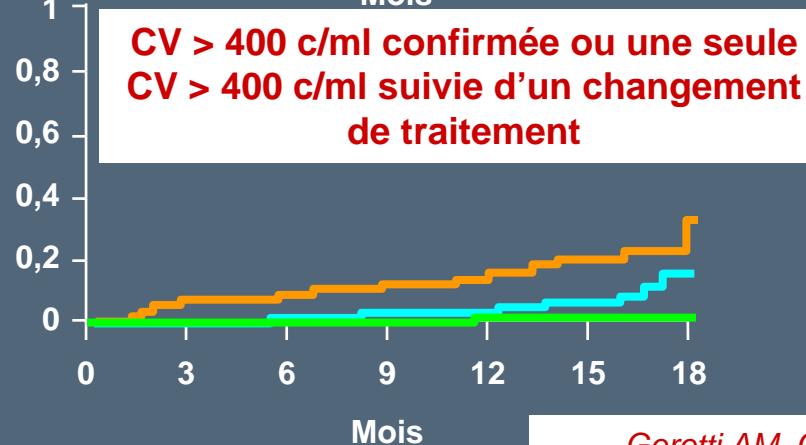
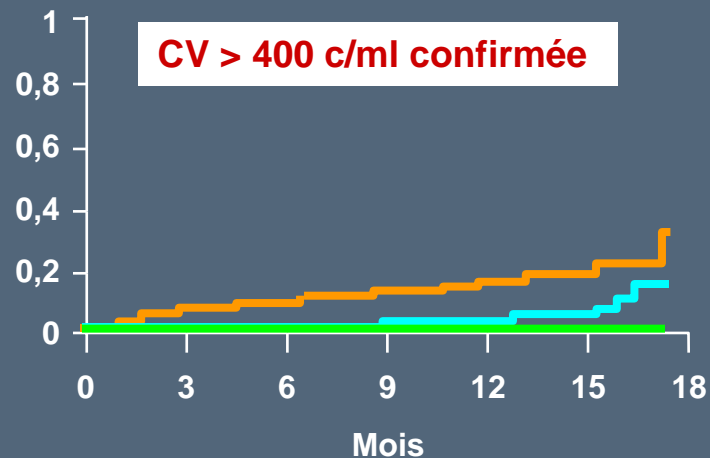


mesure initiale

— CV : 40-49 c/ml

— ARN détectable < 40 c/ml

— ARN non détectable



conclusion (1)

Review

Low-Level Viremia in HIV-1 Infection: Consequences and Implications for Switching to a New Regimen

Calvin Cohen¹

HIV Clin Trials 2009;10(2):116–124

LLV ne restent pas LL éternellement

LLV avec CD4 maintenus \Rightarrow CD4 finissent par \searrow

LLV \Rightarrow mutations de résistance, progression clinique et compromission des options futures

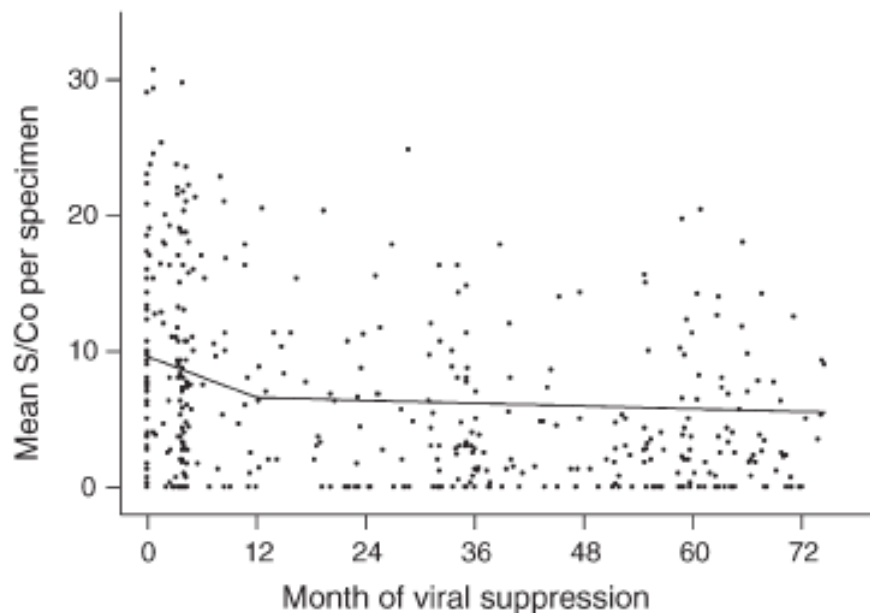
conclusion (2)

- ✘ **impact immunologique:**
hyperstimulation lymphocytaire
chronique, non restauration ...
- ✘ **conséquences:**
système cardiovasculaire, survenue des
cancers, système osseux, système
nerveux central, vieillissement...

conclusion (3)

Evidence of persistent low-level viremia in long-term HAART-suppressed, HIV-infected individuals

Hiroyu Hatano^a, Eric L. Delwart^{b,c}, Philip J. Norris^{a,b,c},
Tzong-Hae Lee^b, Torsten B. Neilands^d, Colleen F. Kelley^e,
Peter W. Hunt^a, Rebecca Hoh^a, Jeffrey M. Linnen^f, Jeffrey N. Martin^a,
Michael P. Busch^{b,c} and Steven G. Deeks^a



« nouvelles » techniques
de mesures de la CV :
seuils 1-3 copies/ml