Pour un traitement efficace à long terme: vers une « Rémission » Pharmacologique ?

Projet ICCARE

Dr P. de Truchis
CHU Raymond Poincaré
UVSQ, Garches 92

stratégies abandonnées

- Traitement tardif
- Combinaisons initiales:
  - En quadrithérapie IN+INN+IP
  - En épargne de nucléosidiques par IP+INN
- Traitements intermittents à cycles longs
- Interruptions programmées
- Initiation et maintenance par nucléosidiques
- Intensification
- Stimulation lymphocytaire par IL2

Allègement:
Stratégies passées et actuelles

- Concept « induction-maintenance »
- Un objectif: réduire la toxicité à long terme
- Un écueil: l'observance
- Stratégies:
  - 2nRTIs+ IP → IP: Trilège…
  - 2nRTIs+ IP → 3 nRTIs
  - Interruptions programmées
  - IP non boostée: ATV
  - Changement classe: INNRT, INI
  - Monothérapies IPr

Letter to the Editor

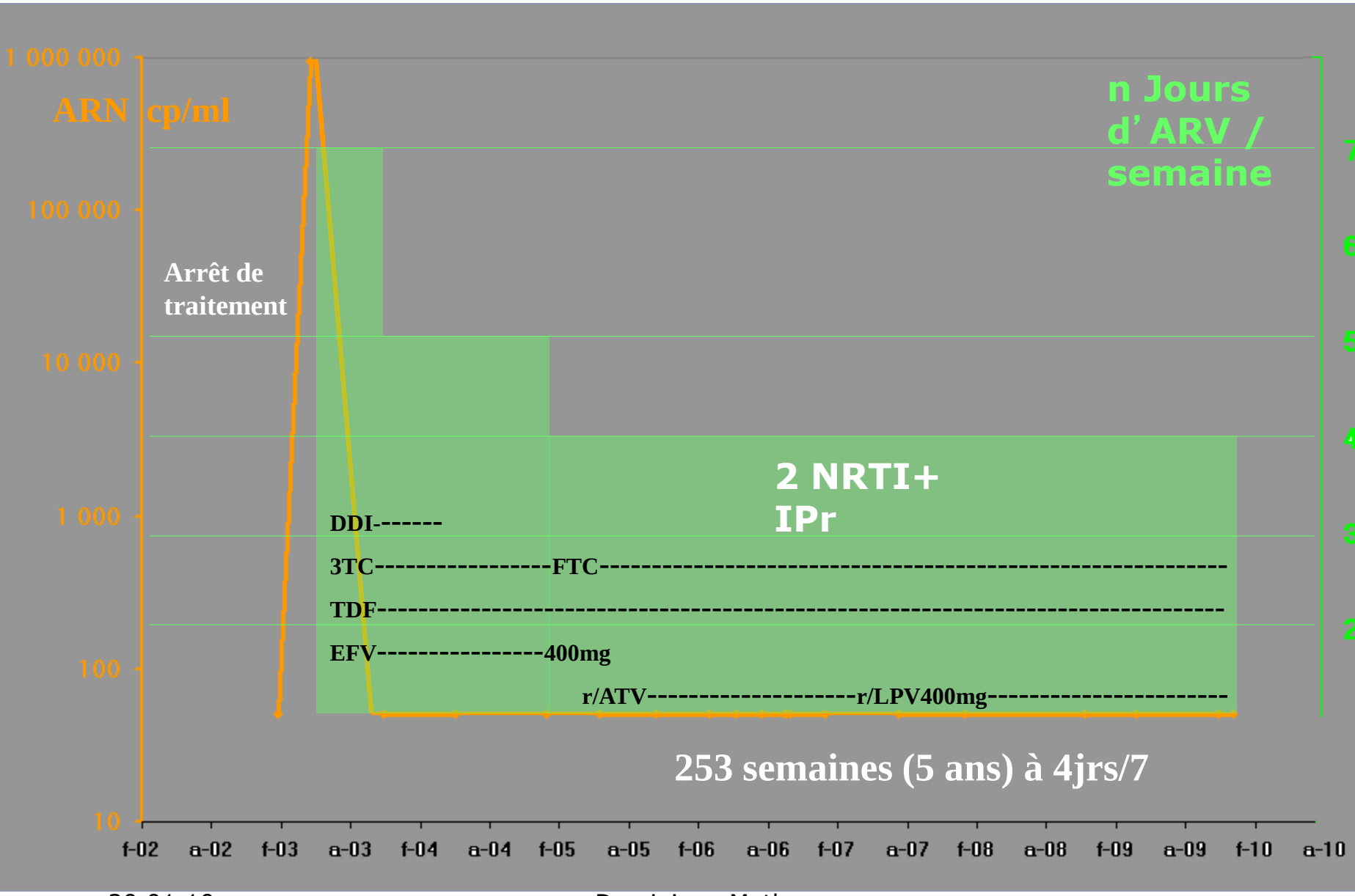
Long-Term Control of Viral Residual Replication Under Maintenance Therapy with Trizivir After a Quadruple Induction Regimen in HIV-1–Infected Adults (Suburbs Trial)

Table 1. Quantification of total cellular viral DNA and HIV infectious cells under maintenance treatment

	Baseline Suburbs	Weeks 24	Weeks 48
HIV infectious cells			
No. patients with detectable cells (>5/10^7 cells)	12/19	12/18	9/14
Cellular viral DNA copies/ 10^6 CD4 cells[a]			
Mean ± *SD*	994 ± 863	1617 ± 1648	1074 ± 1319
Median	1066	1139	441
No. patients with DNA increase	—	4/16	1/13
No. patients with DNA decrease	—	0	4/13
No. patients with stable DNA	—	12/16	8/13

[a]LLD = lower limit of detection of 50 copies/10^6 CD4.

De Truchis, HIV Clin Trials 2007;8(2):102−104


1 000 000
ARN cp/ml
100 000
10 000
1 000
100
10
n Jours d' ARV / semaine
7
6
5
4
3
2
Arrêt de traitement
2 NRTI+ IPr
DDI-------
3TC----------FTC----------
TDF----------
EFV----------400mg
r/ATV----------r/LPV400mg----------
253 semaines (5 ans) à 4jrs/7
f-02
a-02
f-03
a-03
f-04
a-04
f-05
a-05
f-06
a-06
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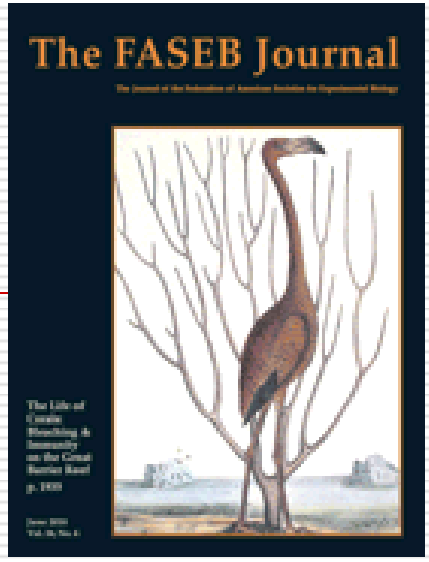
The FASEB Journal article fj.09-148676. Published online January 26, 2010.
The FASEB Journal • Research Communication

Short cycles of antiretroviral drugs provide intermittent yet effective therapy: a pilot study in 48 patients with chronic HIV infection

Jacques Leibowitch,[*,§,1] Dominique Mathez,[*] Pierre de Truchis,[†] Christian Perronne,[†,§] and Jean-Claude Melchior,[‡,§]

*Immunology and Virology Unit, [†]Clinical Infectious Disease Unit, and [‡]Clinical Nutrition and Infectious Disease Unit, Department of Internal Medicine and Infectious Diseases, Raymond Poincaré Hospital, Assistance Publique–Hôpitaux de Paris, Garches, France; and [§]University and Medical School, Paris-Île-de-France-Ouest, Saint Quentin en Yvelines, Versailles, France



Baseline characteristics of the 48 patients

Sex		
Female	11	
Male	37	
Age	51.2 ± 9.5	(35 – 79)
nadir blood TCD4+ cells/µL	154 ± 82	(16 – 313)
nadir blood TCD4+ %	11 ± 6	(1 – 27)
Maximum Viral Load (log_{10})	5.27 ± 0.48	(3.48 – 6.06)
years of follow up prior to study	9.4 ± 4.6	(1.1 – 17.9)
Antecedent AIDS events and/or TCD4+ cell counts <200 µL in:	38 patients (79.2%)	
Antecedent treatments in:	44 patients (91.7%)	
Years of antecedent treatment :	5.5 ± 2.8 (0.2 – 12.7	
Treatment interruption antecedents	from 1 to 5 (median 2)	

Etude Leibowitch et al., FASEB Journal, 2010

Virological and immunological outcomes

	n. patients	Cumulated weeks of effective treatment	**% blips** (number of Viral load determinations)	Number of failure	CD4 /µl ± SD last specimen under each step (range)	% CD4 last specimen under each step (range)
Day 0 of the observational period	**48**				**235 ± 110** (55-599)	**13.1 ± 5.6** (4-26)
treatment 7 days/week	**48**	**3032**	**2.78** (180)	**0**	**420 ± 182** (113-884)	**21.5 ± 7** (6-40)
treatment 5 days/week	**47**	**2626**	**2.25** (222)	**0**	**516 ± 225** (106-1062)	**24.9 ± 7.9** (6-43)
treatment 4 days/week	**48**	**4022**	**2.35** (340)	**0**	**550 ± 204** (159-924)	**28 ± 7.9** (13-46)

Etude Leibowitch et al., FASEB Journal, 2010

Virological and immunological outcomes

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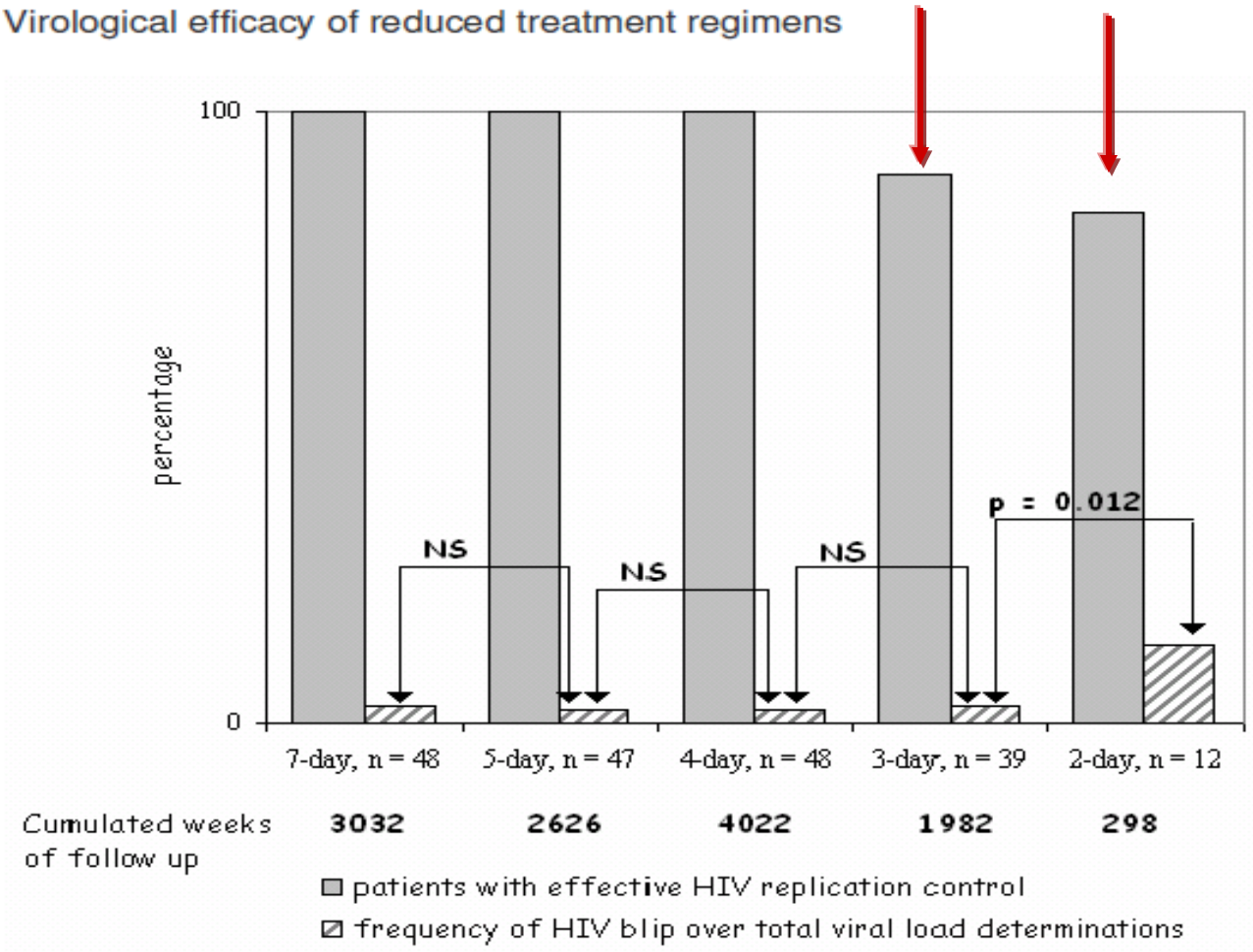
treatment 4 days/week	48	4022	2.35 (340)	0	550 ± 204 (159-924)	28 ± 7.9 (13-46)
treatment 3 days/week	**39**	**1958**	**2.87** (209)	**4**	**656 ± 229** (200-1140)	**30.7 ± 9.2** (12-49)
treatment 2 days/week	**12**	**289**	**12.8** (87)	**2**	No enough data for analysis	

Etude Leibowitch et al., FASEB Journal, 2010

Figure 1

Virological efficacy of reduced treatment regimens



Etude Leibowitch et al., FASEB Journal, 2010

Table IV. Virological failure occured in 6 patients

Weeks of HIV under control (prior to failure)	Under triple ARV combination made of :	During a weekly drug regimen of :
12	FTC, TDF, LPVr	2 days per week
19	FTC, TDF, EFV	"
6	FTC, TDF, RAL	3 days per week
16	ABC, TDF, RAL	"
33	FTC, TDF, RAL	"
72	FTC, TDF, EFV	"

Short-cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: Effects on virologic, immunologic, and toxicity parameters

Mark Dybul*†, Tae-Wook Chun*, Christian Yoder*, Bertha Hidalgo*, Michael Belson*, Kurt Hertogs‡, Brendan Larder‡, Robin L. Dewar§, Cecil H. Fox¶, Claire W. Hallahan*, J. Shawn Justement*, Stephen A. Migueles*, Julia A. Metcalf*, Richard T. Davey*, Marybeth Daucher*, Punita Pandya*, Michael Baseler§, Douglas J. Ward‖, and Anthony S. Fauci*

PNAS | December 18, 2001 | vol. 98 | no. 26 | 15161–15166

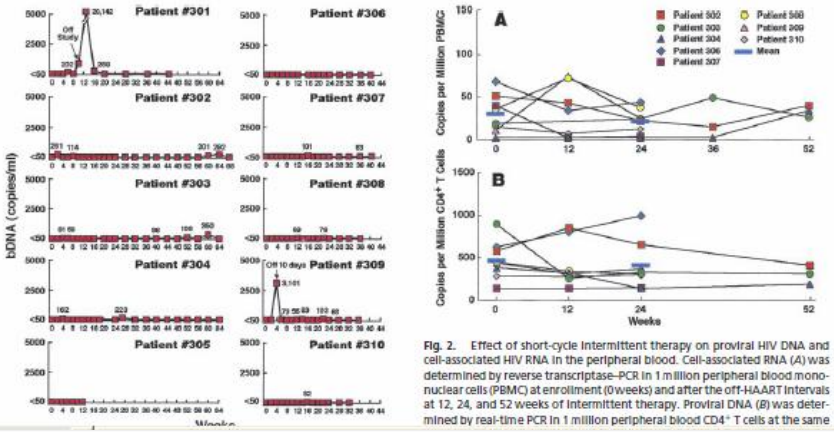


Fig. 2. Effect of short-cycle intermittent therapy on proviral HIV DNA and cell-associated HIV RNA in the peripheral blood. Cell-associated RNA (*A*) was determined by reverse transcriptase–PCR in 1 million peripheral blood mononuclear cells (PBMC) at enrollment (0 weeks) and after the off-HAART intervals at 12, 24, and 52 weeks of intermittent therapy. Proviral DNA (*B*) was determined by real-time PCR in 1 million peripheral blood CD4+ T cells at the same

A Proof-of-Concept Study of Short-Cycle Intermittent Antiretroviral Therapy with a Once-Daily Regimen of Didanosine, Lamivudine, and Efavirenz for the Treatment of Chronic HIV Infection

Mark Dybul,[1] Elizabeth Nies-Kraske,[1] Robin Dewar,[3] Frank Maldarelli,[2] Claire W. Hallahan,[1] Marybeth Daucher,[1] Stephen C. Piscitelli,[5] Linda Ehler,[1] Ann Weigand,[2] Sarah Palmer,[2] Julia A. Metcalf,[1] Richard T. Davey,[1] Diane M. Rock Kress,[1] April Powers,[1] Ingrid Beck,[4] Lisa Frenkel,[4] Michael Baseler,[3] John Coffin,[2] and Anthony S. Fauci[1]

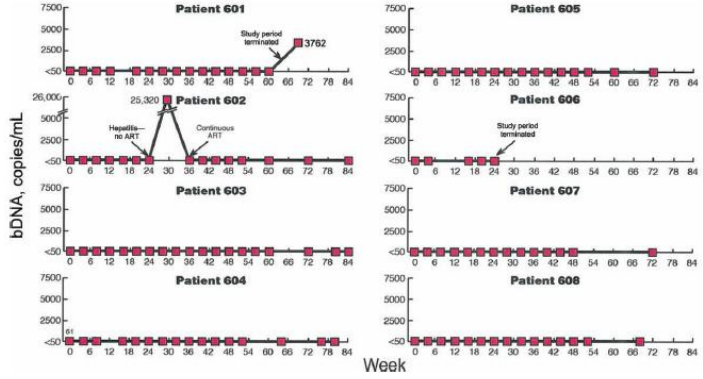


Figure 1. Effects of once-daily short-cycle intermittent therapy on plasma levels of HIV RNA. Eight patients who were receiving cycles of no antiretroviral therapy (ART) for 7 days, followed by ART for 7 days, had plasma levels of HIV RNA measured at the end of periods when ART was not received (i.e., "study period terminated"). The results are shown as the no. of HIV RNA copies per milliliter of plasma, as determined by branched DNA (bDNA) assays. All values of >50 HIV RNA copies/mL of plasma are indicated at the designated time point. Patient 602 received a diagnosis of acute hepatitis, and ART was temporarily discontinued for 12 weeks. Patients 601 and 606 voluntarily withdrew from the study at weeks 64 and 24, respectively.

- **JID 2004:189 (1 June)** • Dybul et al., 1974-82

SSIT: réduction toxicité / dosages

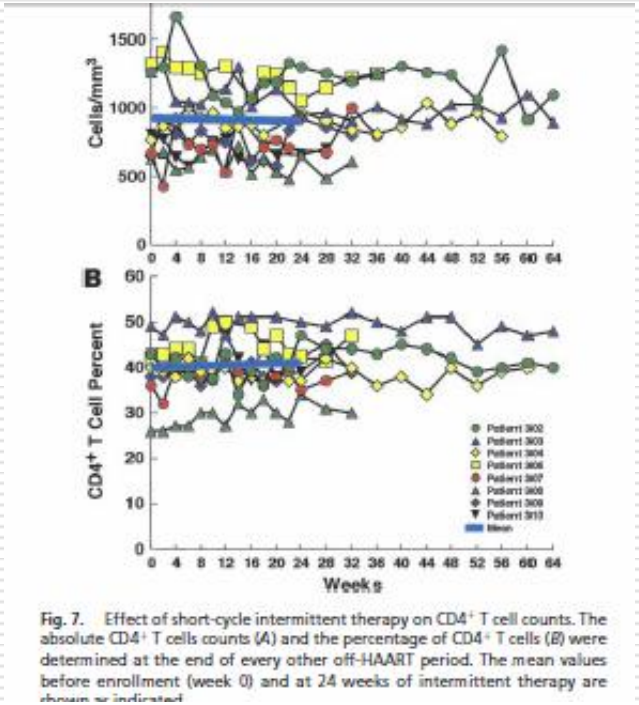


Fig. 7. Effect of short-cycle intermittent therapy on CD4⁺ T cell counts. The absolute CD4⁺ T cells counts (*A*) and the percentage of CD4⁺ T cells (*B*) were determined at the end of every other off-HAART period. The mean values before enrollment (week 0) and at 24 weeks of intermittent therapy are

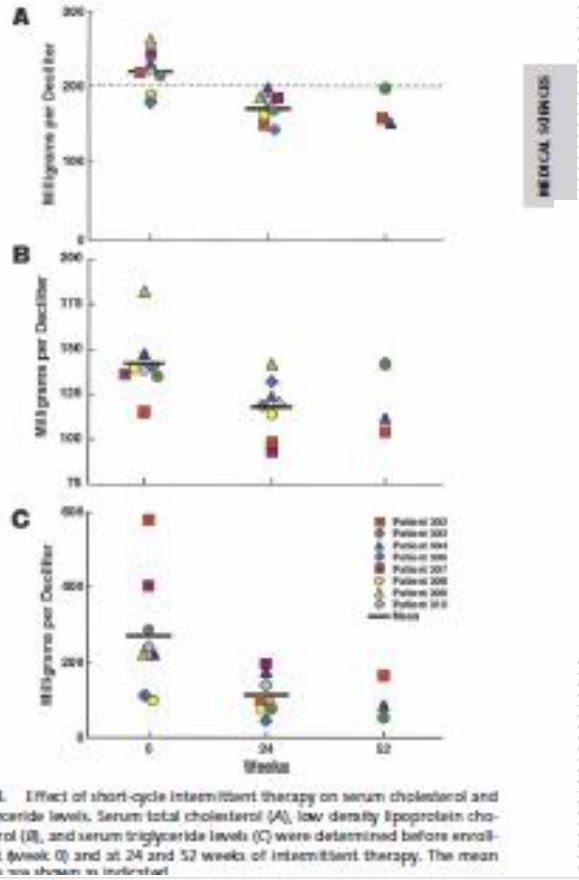


Fig. 8. Effect of short-cycle intermittent therapy on serum cholesterol and triglyceride levels. Serum total cholesterol (*A*), low density lipoprotein cholesterol (*B*), and serum triglyceride levels (*C*) were determined before enrollment (week 0) and at 24 and 52 weeks of intermittent therapy. The mean

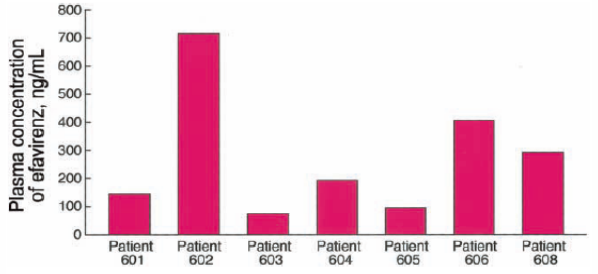


Figure 2. Effect of once-daily short-cycle intermittent therapy on plasma concentrations of efavirenz. Seven patients had trough levels of efavirenz in plasma measured after a 7-day period without antiretroviral therapy. The results are expressed as nanograms per milliliter of plasma. Efavirenz is considered to be therapeutically effective at a concentration of ~1000 ng/mL.

• **JID 2004:189 (1 June)** • Dybul et al., 1974-82

FOTO: 5-Days-On, 2-Days-Off Treatment Strategy With EFV/TDF/FTC

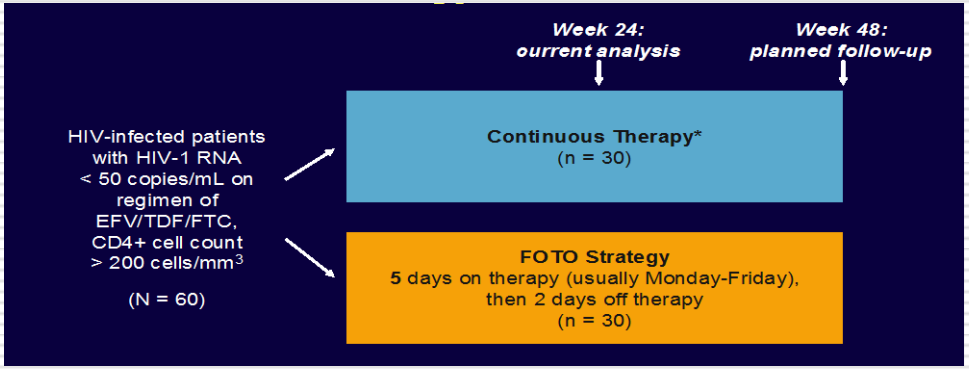
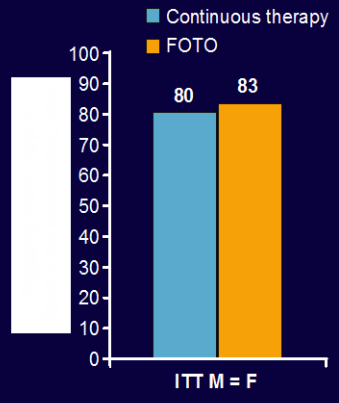


FOTO: Outcomes at Week 24

- No significant difference in virologic response between strategies at Week 24
  - Virologic failures (Confirmed HIV-1 RNA > 400 copies/mL): n = 0
- "Blips" (HIV-1 RNA 50-500 copies/mL between 2 levels at < 50 copies/mL): FOTO (n = 8) vs continuous (n = 10)
- Imperfect adherence to study regimen: 8/30 FOTO patients took > 2 days breaks from therapy; 3/30 took > 5 days therapy
- FOTO = 30% cost savings



FOTO, S48

HIV-1 RNA < 50 copies/mL, % (95% CI)	*FOTO Arm (n = 25)*	*Standard Therapy Arm (n = 28)*
Week 24, as-treated analysis*	**100 (88-100)**	**86 (73-99)**
Extension phase	**Continued FOTO Dosing + Switch From Standard Therapy to FOTO (n = 50)**	
Week 36	**90 (82-98)**	
Week 48	**90 (82-98)**	

CI, confidence interval.

**P* < .001 for noninferiority of FOTO arm vs standard-therapy arm.

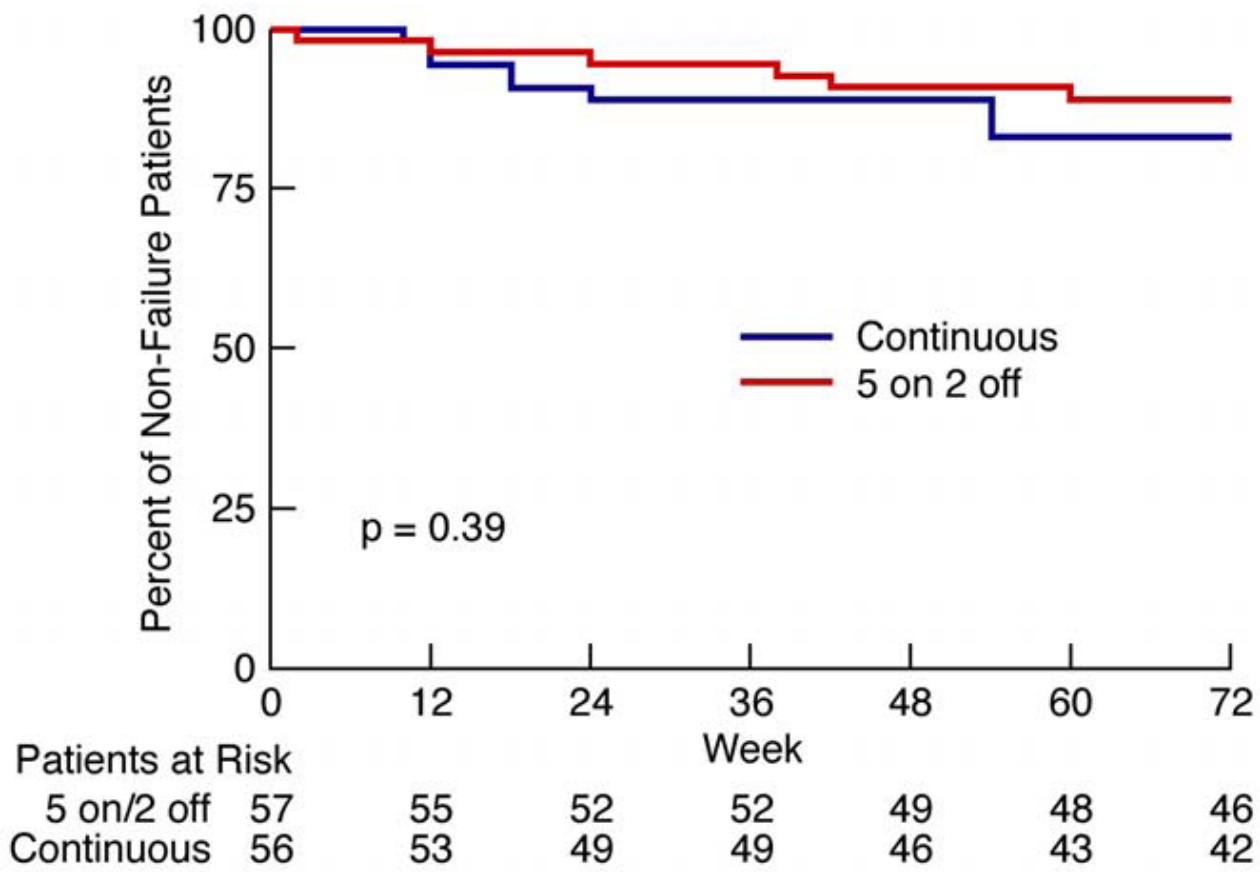
Cohen, Glasgow 2008; IAS 2009

OPEN ACCESS Freely available online

PLoS one

A Randomized, Controlled, Trial of Short Cycle Intermittent Compared to Continuous Antiretroviral Therapy for the Treatment of HIV Infection in Uganda

Steven J. Reynolds[1,2*], Cissy Kityo[3], Claire W. Hallahan[1], Geoffrey Kabuye[3], Diana Atwiine[3], Frank Mbamanya[3], Francis Ssali[3], Robin Dewar[4], Marybeth Daucher[1], Richard T. Davey, Jr.[1], Peter Mugyenyi[3], Anthony S. Fauci[1], Thomas C. Quinn[1,2], Mark R. Dybul[5,6]



Actualisation des données Garches:
63 patients

Weekly Treatment Schedule ANTI VIRAL COM BIN ATI ONS	Nb patients	Nb treatment attempts	Weeks on Intermittent Treatment MEAN	Weeks on Intermittent Treatment MEDIAN	RANGE	Weekly Treatment Cycles CUMULATED	FAILURES
Four days a week							
➢24 weeks							
2 NRTI + b PI	28	31	71, 5	52, 5	3.6 –321	2220	-
2 NRTI + NNRTI	24	28	61, 5	58	7- 194	1718	-
3 NRTI + 1 NNRTI	30	31	43	30	5 – 172	1327	-
Other	10	-	44, 5	40	13, 5 – 84	446	-
All combinations	63	78	73	57, 5	24 - 321	5711	None
Three days a week >12 weeks							
2 NRTI+ b PI	15	Id		37	7 – 152	746	None
2 NRT I+ 1 NNRTI	18	20	50	47	10 - 200	1349	1*
3 NRTI + 1 NNRTI	32	35	67, 5	28, 5	10. 5 - 126. 5	1311	2**
Other	8	8	37, 5	14, 5		149	3 ***
All combinations	52	61	18, 5	39	15462	3555	6 total
			58		12. 5 – 200		

Et ensuite…: 33 patients à 2 jours/sem, 12 patients en quadrithérapie 1 jour/sem

Weekly Treatment Schedule ANTI VIRAL COM BIN ATI ONS	Nb patients	Nb treatment attempts	Weeks on Intermittent Treatment MEAN	Weeks on Intermittent Treatment MEDIAN	RANGE	Weekly Treatment Cycles CUMULATED	FAILURES
Two days a week							
2 NRTI + b IP	3	-	15	13, 5	11, 5 – 19, 5	45	1**
2 NRTI + 1 NNRTI	7	-	25	26, 5	7 – 50	176	1 **
3 NRTI + 1 NNRTI	31	33	34, 5	33, 5	5 - 80	1142	2**
All combinations	33	40	34	32	5 - 80	1363	4 total
One day a week							
3 NRTI + 1 NNRTI	12	-	35	31	10 - 61	41	1 *

J. Leibowitch et al., IAS Rome, 2011

Conditions du succès de la « réduction » pharmacologique

- Réplication virale contrôlée avant la réduction pharmacologique
- Traitement combiné synergique nécessaire
- Pas de résistance aux ARV utilisés, barrière génétique à la résistance
- propriétés pharmacologiques des ARV?
  - ½ vie plasmatique des INNRT
  - liaison intracellulaire prolongée des INRT, de certaines IP, à leur cible
- Absence d' augmentation attendue du réservoir (stabilité DNA viral)
- Réduction de l'activation CD4 sous traitement ARV efficace permet une moindre 'infectivité' cellulaire

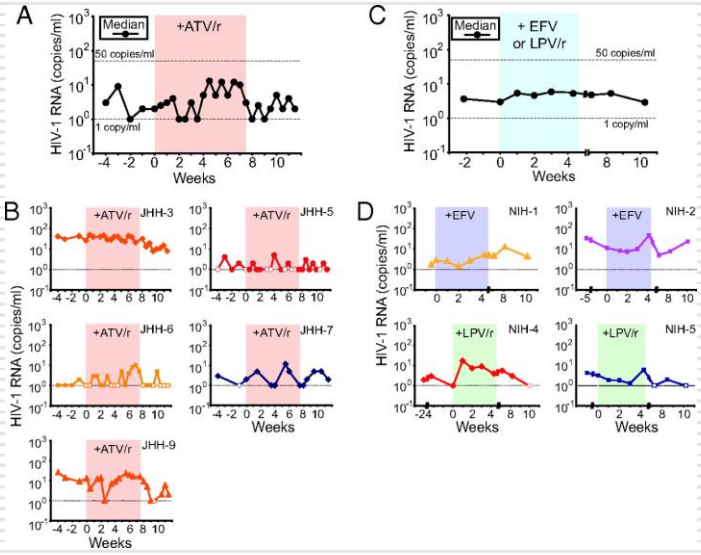
SCIENCE • VOL. 277 • 4 JULY 1997 • www.sciencemag.org

Positive Effects of Combined Antiretroviral Therapy on CD4$^+$ T Cell Homeostasis and Function in Advanced HIV Disease

B. Autran,* G. Carcelain, T. S. Li,† C. Blanc,† D. Mathez, R. Tubiana, C. Katlama, P. Debré, J. Leibowitch

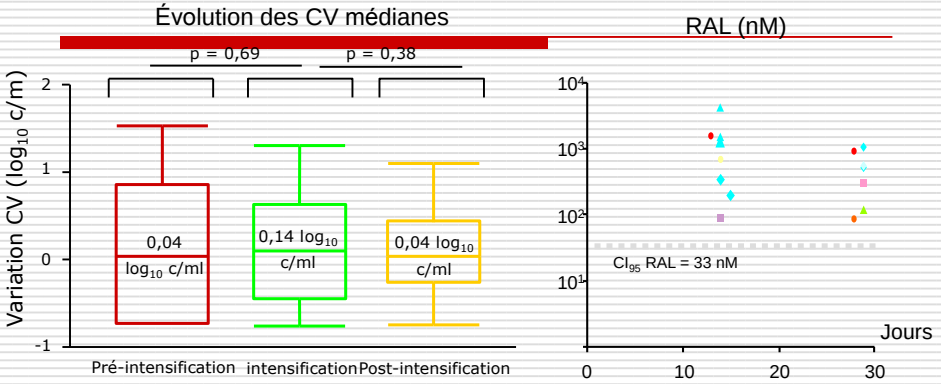
Intensification chez des patients avec réplication virale indétectable: pas d'effet sur la réplication résiduelle….

Intensification par PI ou NNRTI ne réduit pas la virémie résiduelle



Dinoso J B et al. PNAS 2009

Intensification par RAL ne réduit pas la virémie résiduelle



Les virémies résiduelles ne proviennent donc probablement pas de cycles réplicatifs complets

Le traitement ARV seul, même avec intensification par RAL, ne peut pas aboutir à l'élimination des réservoirs

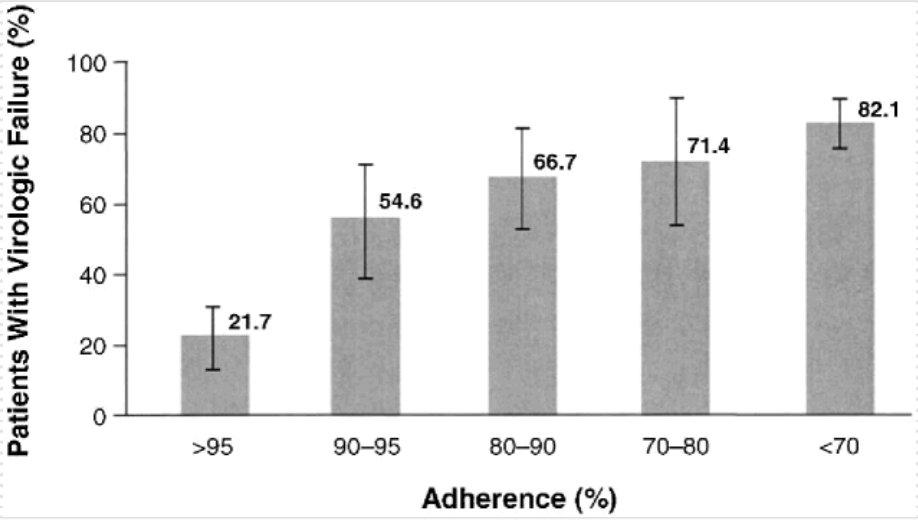
Moyenne C_{min} RAL : 1001 nM (extrêmes : 79-3847)

McMahon et al. CID 2010

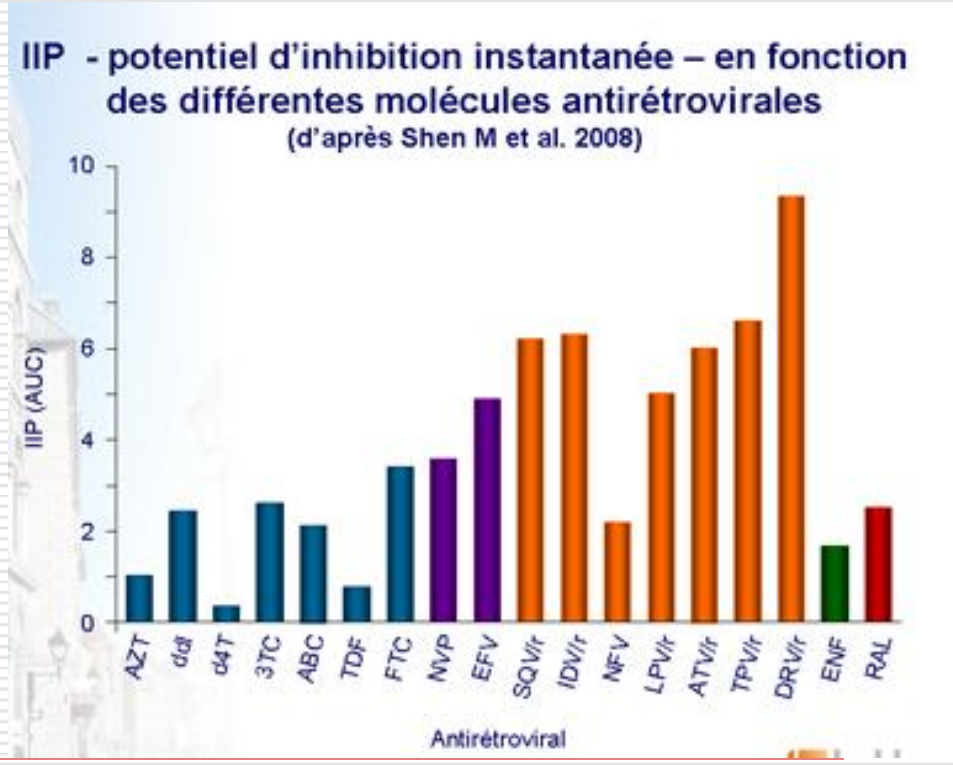
… un traitement maximaliste chez un patient avec CV contrôlée aurait peu d'avantage virologique

Quelques données pour repenser l' « adhésion » aux traitements ARV

- Propriétés pharmacologiques et antivirales modifiées des « nouveaux » ARV

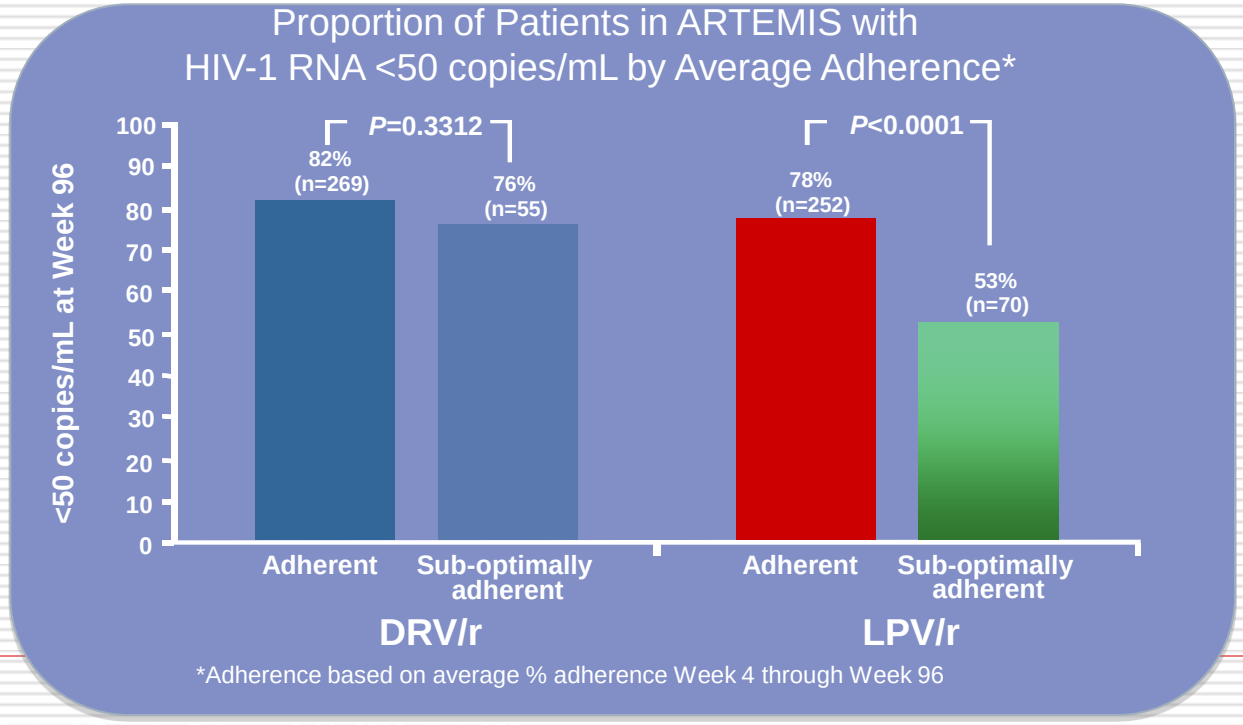


Paterson, 2000



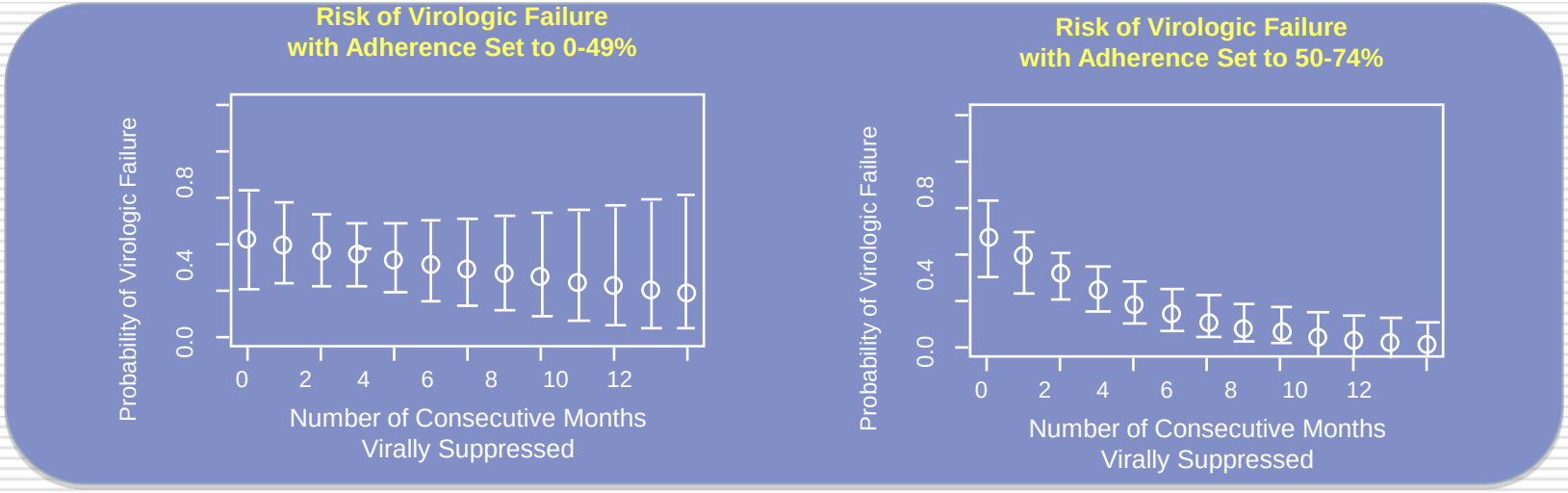
ARTEMIS: Predictors of Success

- Comparison of DRV/r/TDF/FTC and LPV/r/TDF/FTC in ARV-naïve pts
  - ITT-TLOVR HIV RNA <50 c/mL at 96 wks: DRV/r 79% vs. LPV/r 71% (*P*=0.012 for superiority)
- Sub-analysis of factors associated with successful virologic response demonstrated non-adherent pts did significantly better on DRV/r than LPV/r



REACH cohort: risque d'échec virologique réduit avec le temps si observance > 50%

- Relationship between adherence and maintenance of virologic suppression evaluated in subset of REACH cohort: homeless or marginally housed with HIV RNA <50 c/mL (n=221)
  - VL and adherence by unannounced pill counts measured monthly
  - ART: NNRTI (38%); Boosted PI (32%)



- With longer duration of viral suppression, adherence >50% becomes more likely to maintain viral suppression

Adhesion, durée arrêt ARV, et risque de rebond virologique sous INNRT

- 72 patients sous NNRTI >3mois, VL<50, Observance mesurée par MEMS, définition rebond = VL>400

Table 2. Effect of adherence rates and patterns on the risk of virologic rebound.

	Controls (n = 67)	Cases (n = 5)	OR* [95% CI]	P value
Percentage adherence rate[§], mean (SD)	88.5 (2.2)	53.1 (7.3)	0.56 [0.37–0.81]	<0.002
No. of days without dose[$], mean (SD)	2.1 (0.4)	5.0 (1.4)	1.15 [0.94–1.40]	0.16
No. of TI[&], mean (SD)	1.2 (0.2)	8.0 (2.7)	1.38 [1.13–1.77]	<0.002
Longest interval w/o dose, mean in days (SD)	1.5 (0.4)	16.2 (3.9)	1.34 [1.15–1.68]	<0.0001

*OR [95% CI]: Odds Ratio [95% confidence interval] computed by conditional exact logistic regression. OR>1 means an increased probability of viral rebound.
§OR and 95% CI are provided for a 10% increase in adherence rate.
$Days without dose defined as drug discontinuations for more than 24 hours and less than 48 hours.
&TI: Treatment interruptions defined as drug discontinuations for more than 48 hours.
doi:10.1371/journal.pone.0002783.t002

Risque VF:

- +10%adherence: OR=0,56[0,37-0,81]
- +1 interruption>2d: OR=1,34 [1,15-1,68]
- durée interruption+1d: OR=1,38

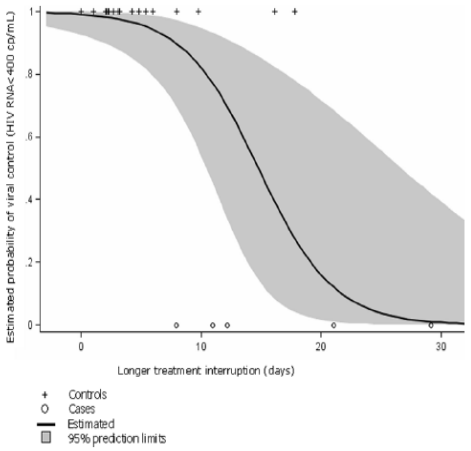
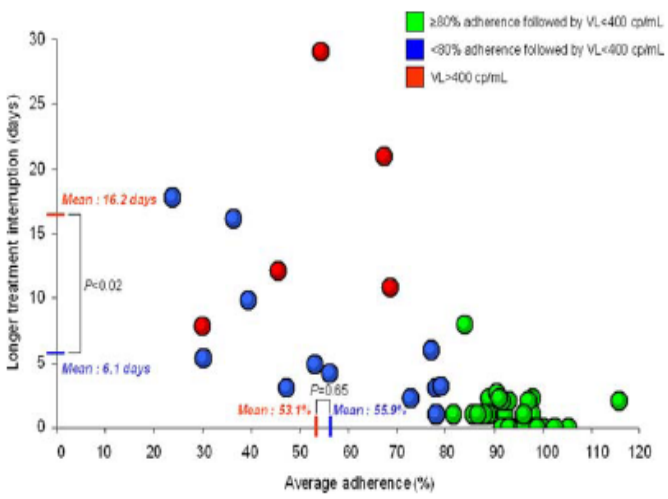


Figure 1. Predicted and observed risk of viral control according to the longer interval of treatment discontinuation, POSOVIR and REACH cohorts.
doi:10.1371/journal.pone.0002783.g001



Parienti JJ, PLoS One, 2008, 3 (7), e2783

Essai Clinique Probatoire Etablissant la Non Infériorité de Combinaisons Antivirales Listées Prises 4 jours sur 7 Versus 7 jours sur 7

Intermittents,

en **C**ycles **C**ourts,

les **A**nti rétroviraux

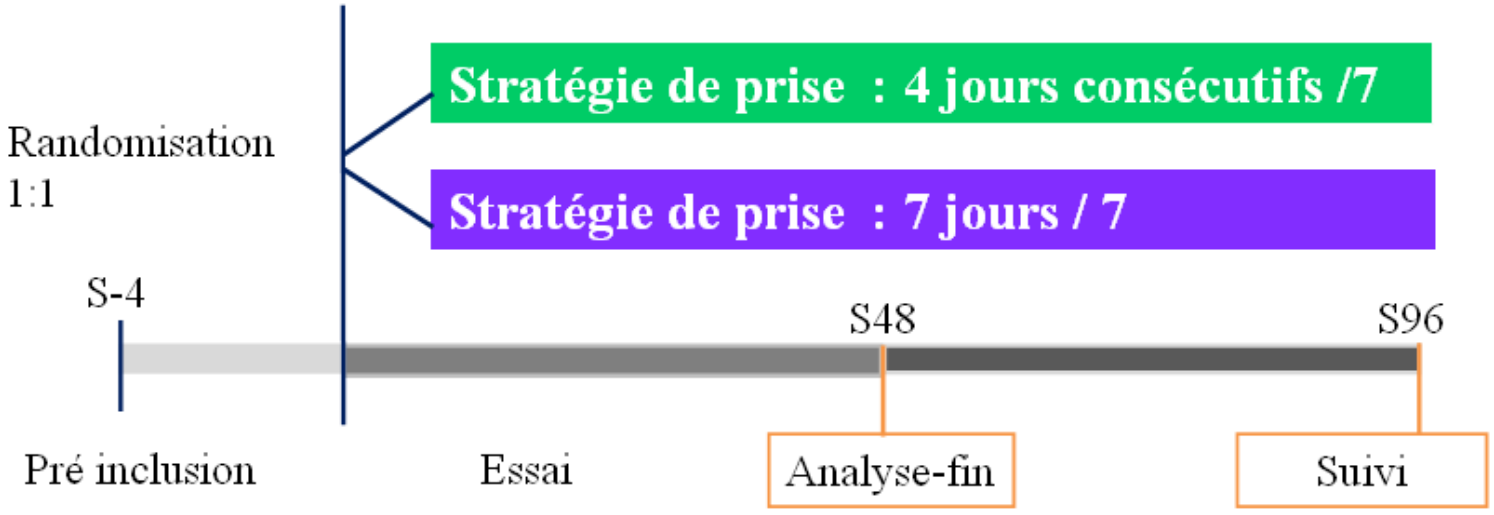
Restent **E**fficaces

Essai I.C.C.A.R.E

20.01.10

Essai I.C.C.A.R.E

Essai randomisé, contrôlé, ouvert, multicentrique



Objectif principal de l'essai :

maintien d'une charge virale <50 cp/ml à 48 semaines

Mesure de référence : incidence des échecs virologiques définis comme **deux CV > 50 cp consécutives** à 2 - 4 semaines d'intervalle

Principaux critères d'inclusion

- CD4 ≥ 200 /mm^3 depuis ≥ 6 mois
- HIV ARN <50 copies/ml depuis ≥ 12 mois (1seul blip autorisé)
- Virus sensibles aux ARV de la combinaison au début du traitement 7j/7

(à défaut de génotype, pas d'antécédent d'échec virologique)

- traitement stable depuis au moins 4 mois comprenant les ARV de la liste

INTI = *sauf AZT et d4T*

IP/boostée = *lopinavir, darunavir, telzir, atazanavir* ;

INNTI = *efavirenz, etravirine, nevirapine*

Principaux critères d'exclusion

- Infection VIH2
- Hépatite B chronique active avec Hbs +
- Hépatite C chronique active nécessitant une mise au ttt dans les 48 semaines
- Traitement d'attaque d'une infection opportuniste
- Toutes conditions compromettant manifestement l'observance

Critères de jugement

- **Critère principal:** CV à S48
- **Critères secondaires:**

- évolution de l'observance et de la qualité de vie
- tolérance clinique et biologique au traitement
- % de blips
- délais de survenue et profil des mutations de résistance si échec
- évolution des lymphocytes CD4 de l'inclusion à S48
- mesure activation immunitaire/inflammatoire
- motifs d'arrêt de la stratégie thérapeutique
- analyse coût-efficacité
- analyse pharmacocinétique plasmatique et intracellulaire
- évolution S96

Statistiques: taux de succès attendu à 48 semaines : 85 %, Risque bilatéral : 5 % limite de non infériorité pour une différence entre les deux groupes de 10 % puissance : 80 %, perdus de vue évalués à 10%: **220 patients :110 / groupe**

Conclusion: ICCARE: une autre conception du traitement

- Une autre vision de l' observance thérapeutique: adhésion à une stratégie « allégée », implication personnelle du patient pour son traitement
- Une perception de mini- « vacances » thérapeutiques hebdomadaires
- L'exigence d'un contrôle virologique maintenu
- Une évaluation scientifique indispensable, et des questions sur:
  - le type de patients volontaires
  - les différentes molécules
  - la tolérance de l' intermittence
  - l' absence de réplication a minima
  - l' activation immunitaire/ inflammatoire
  - …
- Et la question du coût..