Faut-il encore plus simplifier les Traitements ? Pour qui ?

Dr. Jean-Jacques Parienti

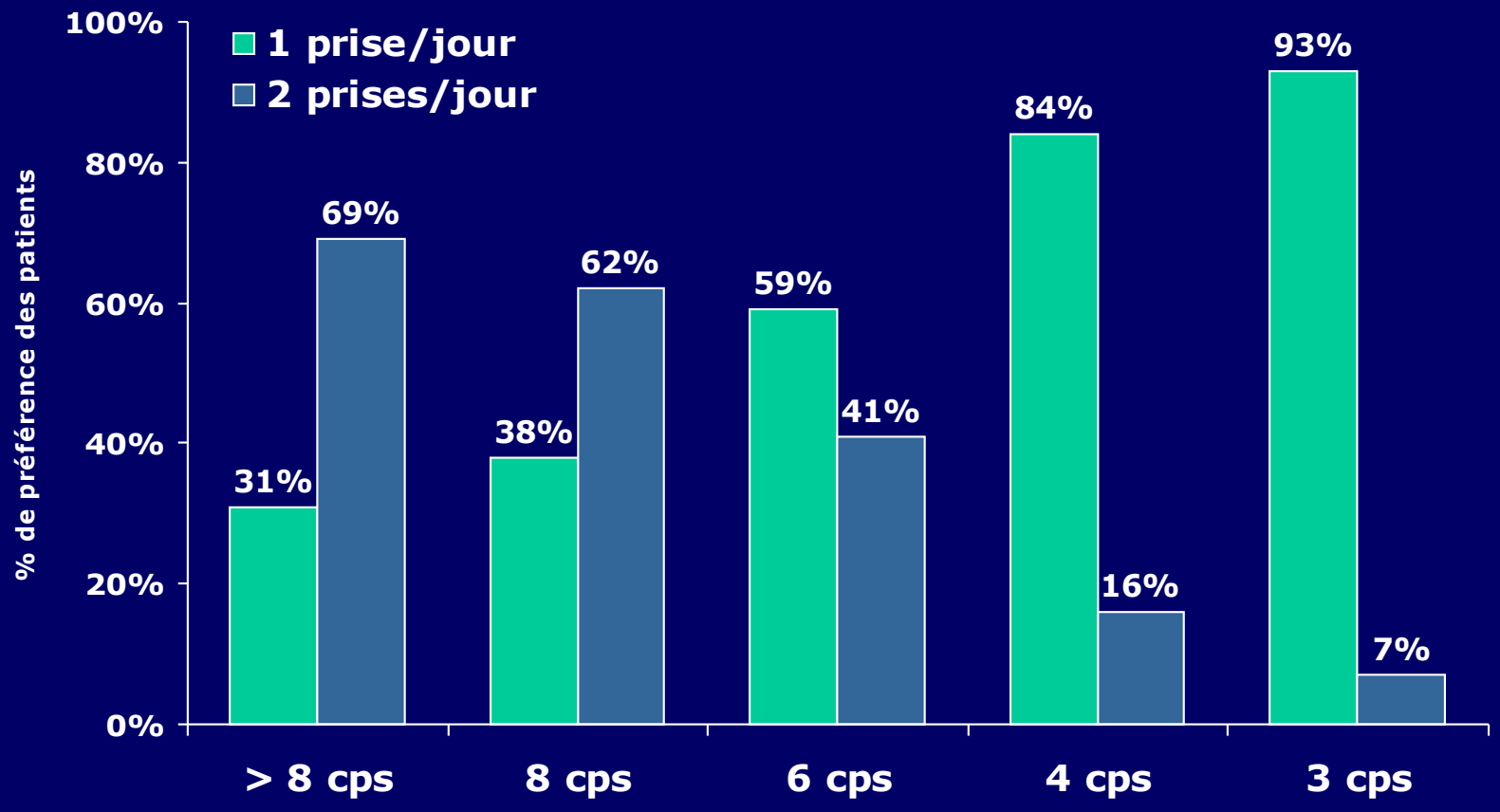
CHU Caen Côte de Nacre

Plan

- Souhait du patient
- Choix justifié

Préférences des patients
Le total des comprimés

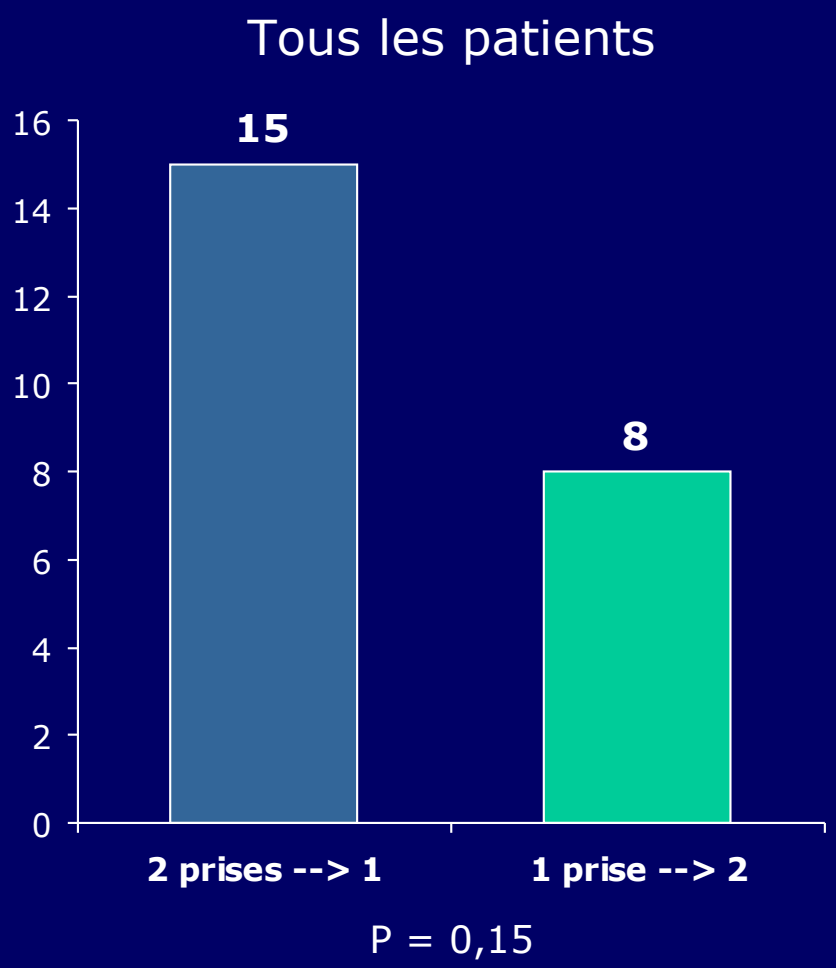
504 patients VIH+ dans 5 grands pays d'Europe

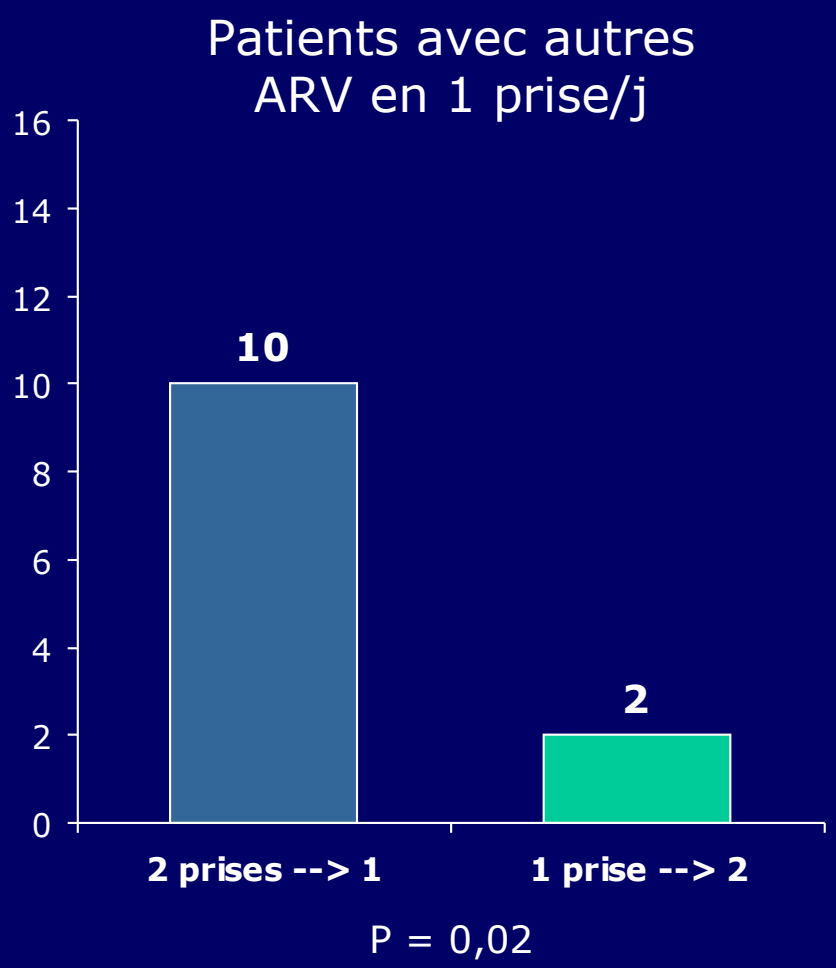


Moyle G. Int J STD AIDS 2003

Préférences des patients
Les autres comprimés

Essai randomisé multicentrique QD vs BID (n=52)

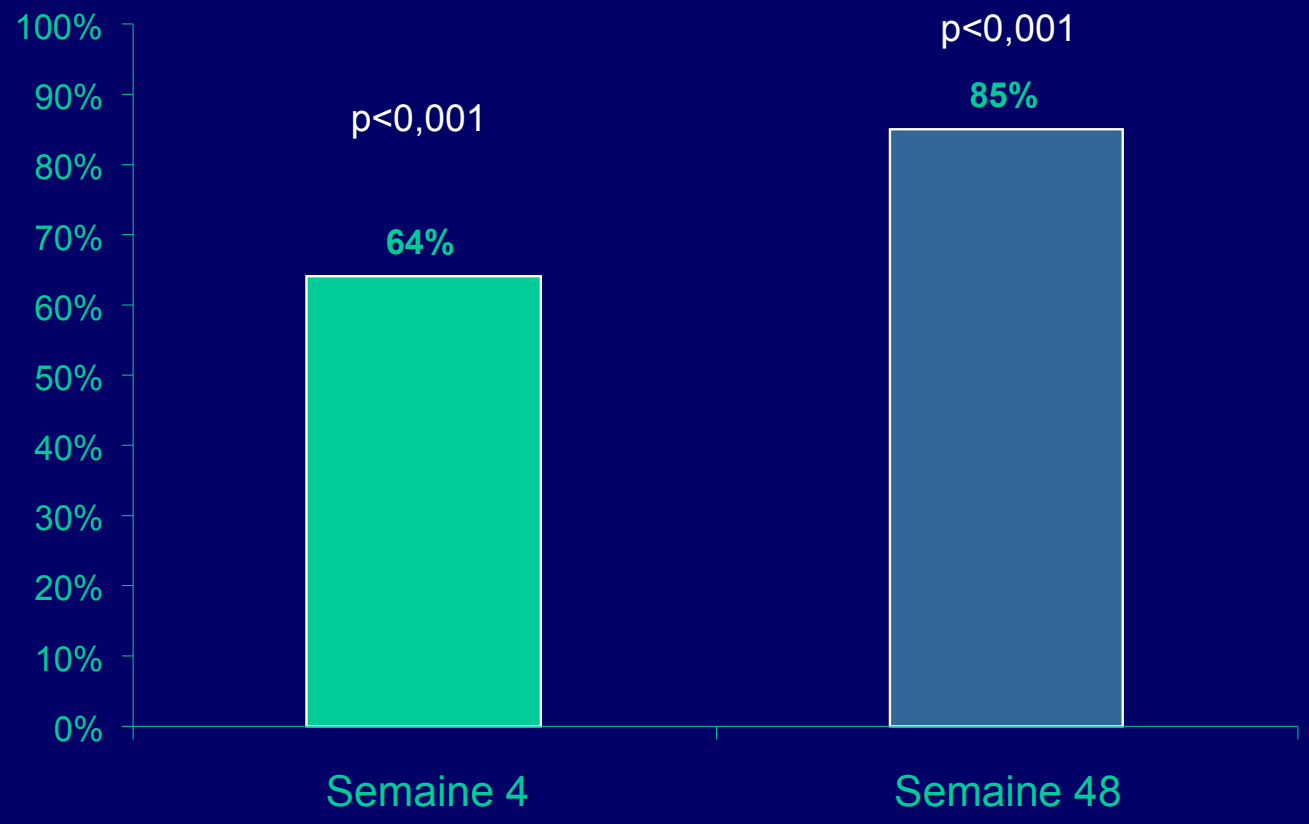




Parienti JJ et al. AIDS 2007

Préférences des patients
1 comprimé, 1 fois par jour

% de patients préférant 1 cp 1 fois par jour à leur traitement antérieur



Étude AI266073 du dossier d'AMM - variation II/19 - module 5, pages 106 à 113 du clinical study report

Préférences des patients
1 comprimé, 1 fois par jour

One-pill once-a-day HAART: a simplification strategy that improves adherence and quality of life of HIV-infected subjects

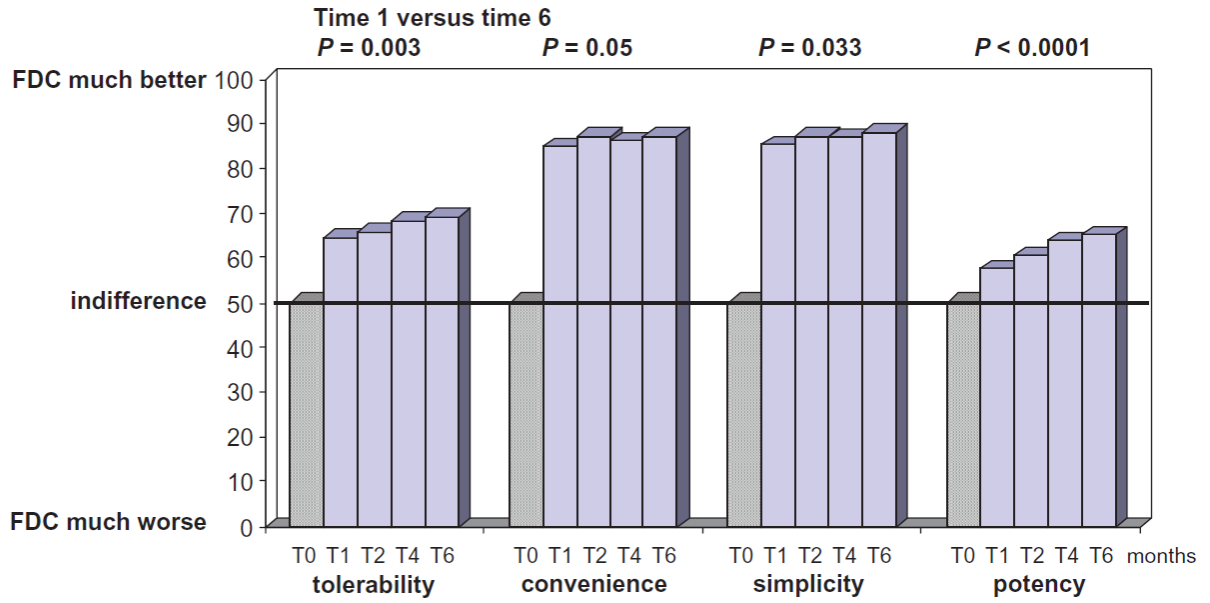
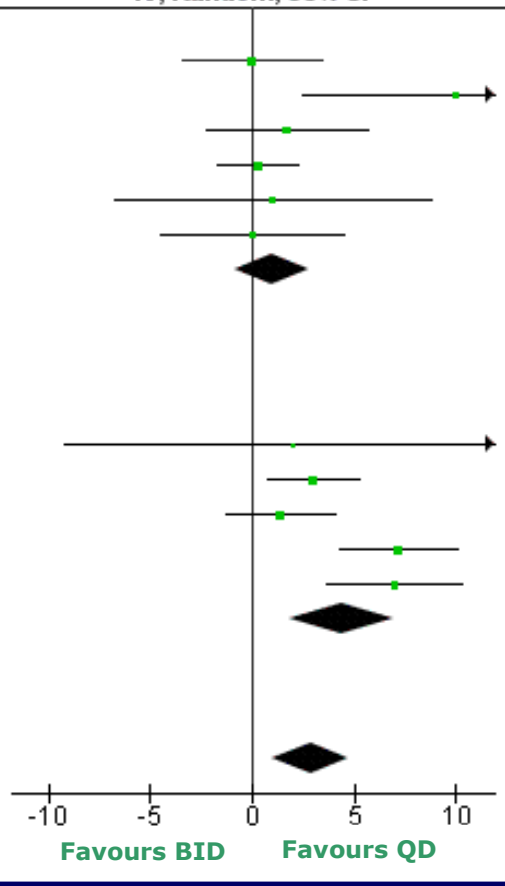


Figure 6 Patients' preferences. Patients' opinion was significantly in favor of the fixed dose combination (FDC) compared to the use of single drug pills (T0).
Note: Statistics refers to differences observed during the FDC use (from 1 month versus 6 months after the switch).

Airoldi M et al. Patient Prefer Adherence 2010

Effet QD sur la MEMS adhérence des ARV

Study or Subgroup	Once-daily Mean	SD	Total	Twice-daily Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Treatment switch studies								
Benson 2004	90	18.3	294	90	17.2	146	10.3%	0.00 [-3.49, 3.49]
Boyle 2008	87.1	31	205	77.1	31	95	4.5%	10.00 [2.46, 17.54]
Parienti 2007	95	6.2	27	93.3	8.3	25	9.3%	1.70 [-2.31, 5.71]
Porthsmouth 2005	96.1	3.6	22	95.8	3.1	21	13.5%	0.30 [-1.71, 2.31]
Ruane 2006	85.4	9.1	18	84.4	12	13	4.3%	1.00 [-6.76, 8.76]
Sosa 2005	93	18.3	119	93	17.2	117	8.3%	0.00 [-4.53, 4.53]
Subtotal (95% CI)			**685**			**417**	**50.4%**	**1.00 [-0.84, 2.84]**
Heterogeneity: Tau² = 1.21; Chi² = 6.47, df = 5 (P = 0.26); I² = 23%								
Test for overall effect: Z = 1.06 (P = 0.29)								
Treatment naive studies								
Eron 2004	94	18.3	19	92	17.2	19	2.4%	2.00 [-9.29, 13.29]
Gallant 2006	90	11.7	244	87	14	243	12.9%	3.00 [0.71, 5.29]
Kubota 2006	94.3	15.8	411	92.9	15.7	195	12.1%	1.40 [-1.28, 4.08]
Molina 2007	99.8	11	115	92.6	9.4	75	11.5%	7.20 [4.27, 10.13]
Rode 2008	90.8	20.7	310	83.8	20.7	296	10.7%	7.00 [3.70, 10.30]
Subtotal (95% CI)			**1099**			**828**	**49.6%**	**4.40 [1.81, 6.99]**
Heterogeneity: Tau² = 5.28; Chi² = 12.19, df = 4 (P = 0.02); I² = 67%								
Test for overall effect: Z = 3.33 (P = 0.0009)								
Total (95% CI)			**1784**			**1245**	**100.0%**	**2.88 [0.98, 4.78]**
Heterogeneity: Tau² = 5.89; Chi² = 29.74, df = 10 (P = 0.0009); I² = 66%								
Test for overall effect: Z = 2.98 (P = 0.003)								
Test for subgroup differences: Chi² = 11.07, df = 1 (P = 0.0009), I² = 91.0%								



Adapted from Parienti JJ et al, Clin Infect Dis 2008

Adhérence et efficacité
1 comprimé, 1 fois par jour

A one-pill, once-daily, fixed-dose combination (FDC) of efavirenz, emtricitabine, and tenofovir disoproxil fumarate (EFV/FTC/TDF) regimen is associated with higher unannounced pill count adherence than non-one pill, once-daily

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[1]Massachusetts General Hospital/Harvard Medical School, Boston USA, USA [2]University of California, San Francisco, USA

Figure 1. Mean Adherence by Regimen and Month

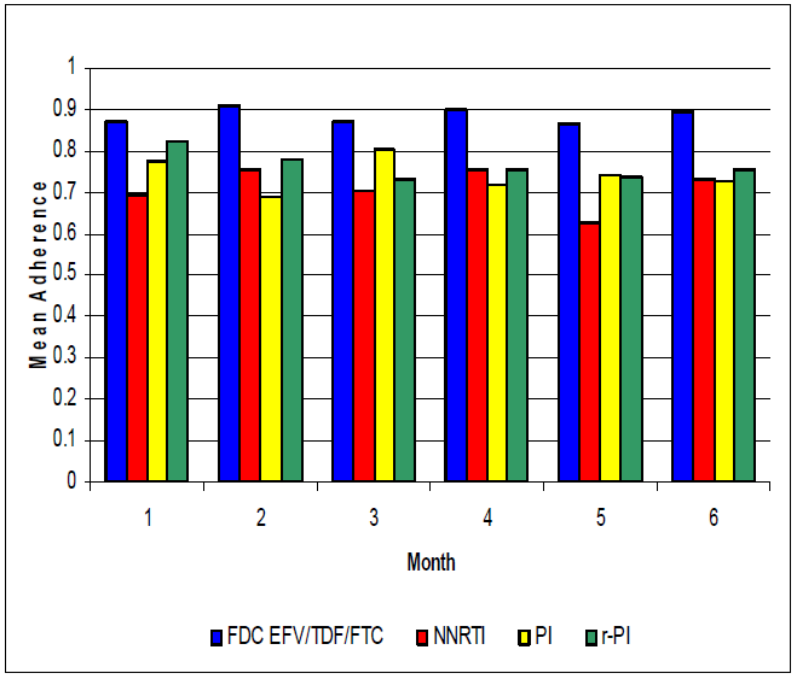
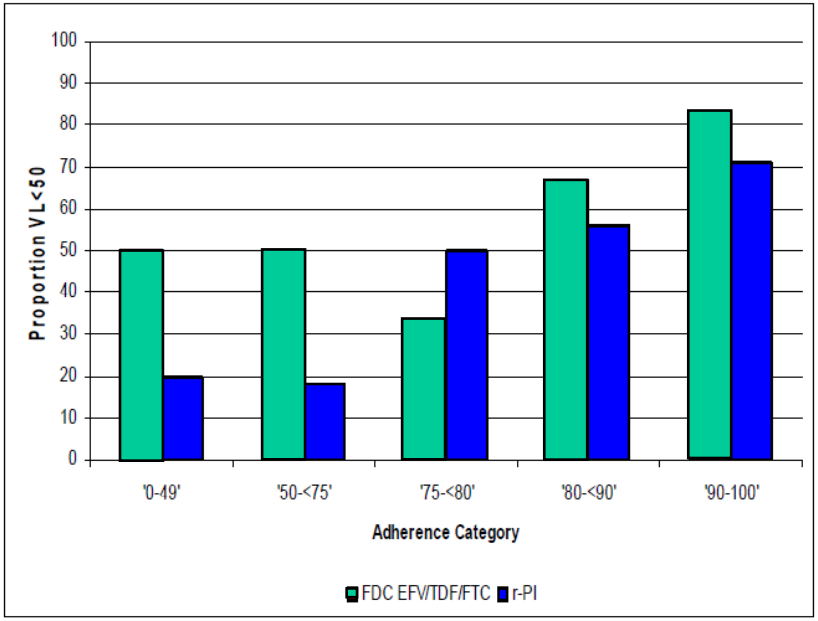


Figure 2. Proportion HIV RNA<50c/ml by Adherence Level



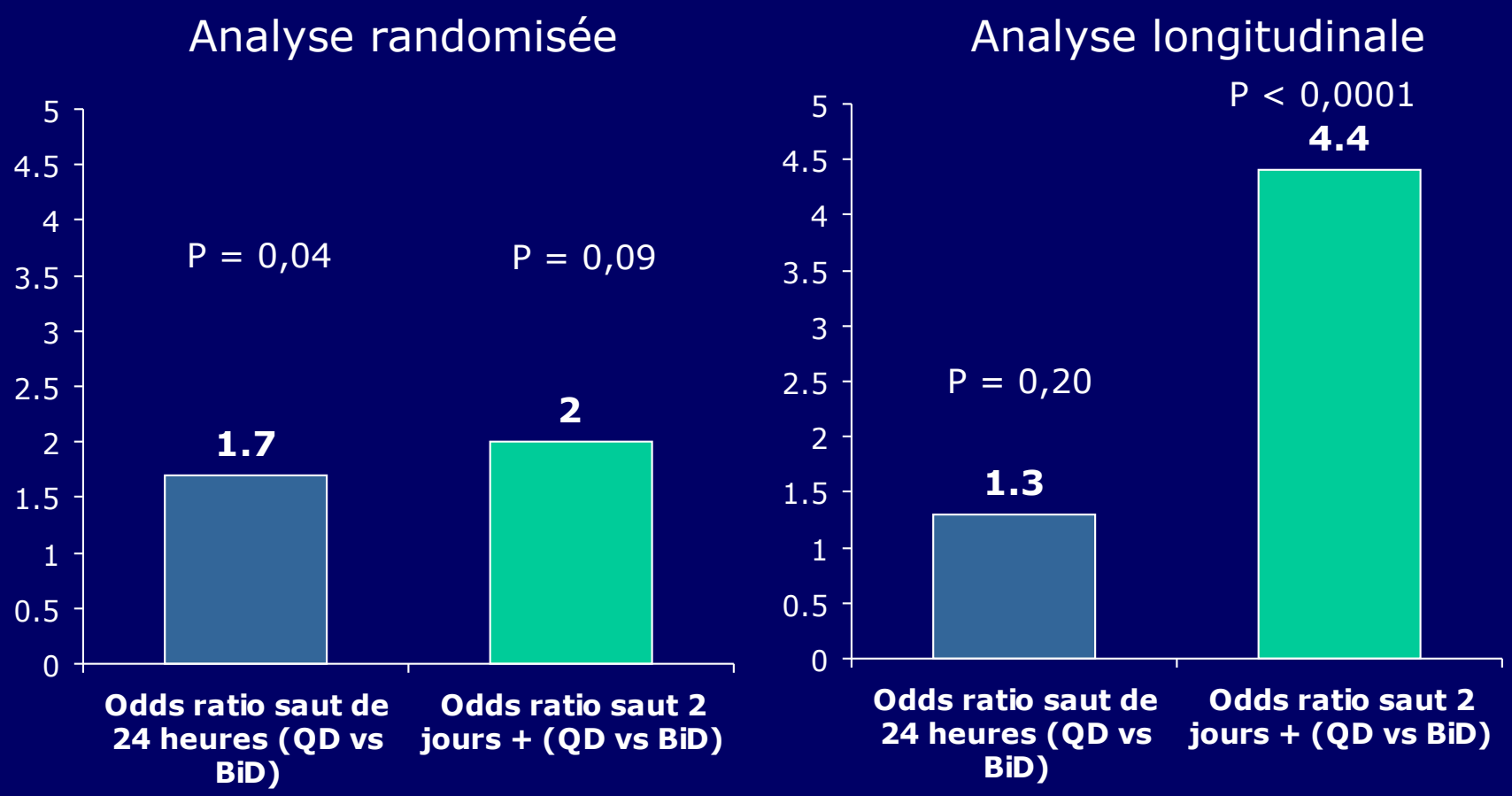
Bangsberg et al. AIDS, 2010

Faut-il encore plus simplifier les Traitements ? OUI
Pour qui ? POUR TOUS

Par quoi??

Impact du QD vs BiD sur les interruptions

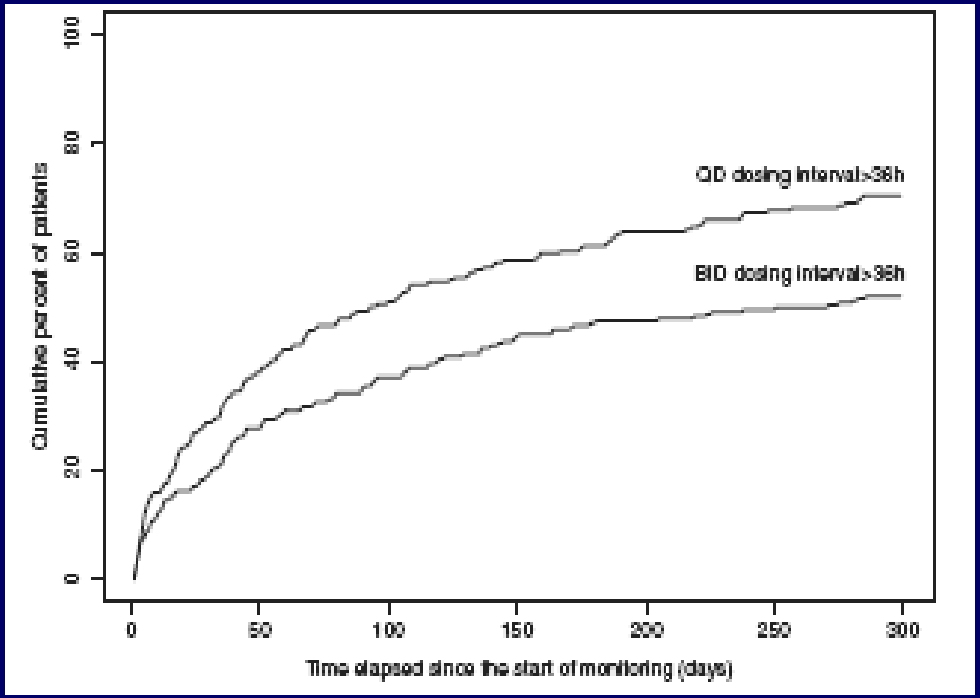
Essai randomisé multicentrique QD vs BID (n=52)



Parienti JJ et al. AIDS 2007

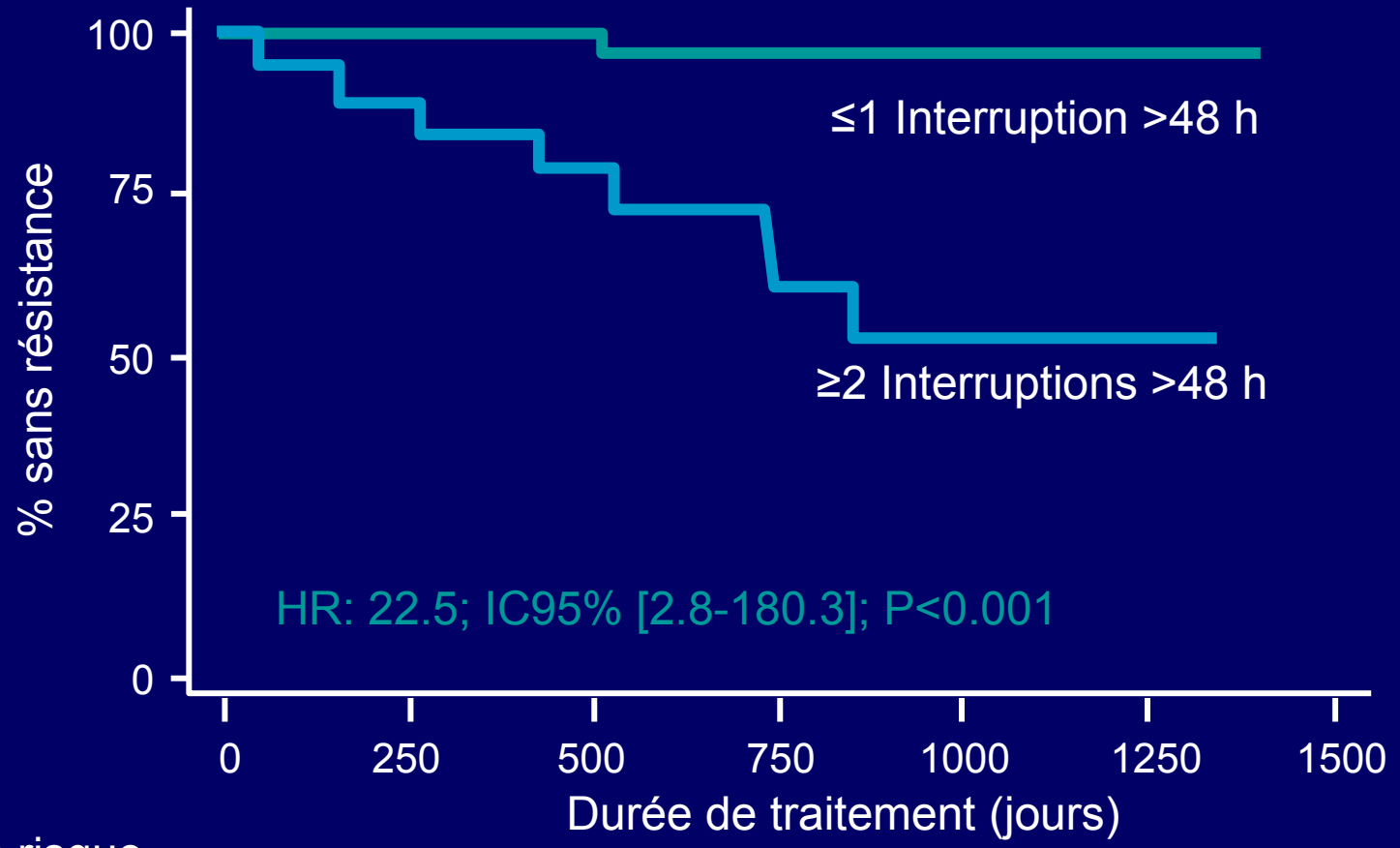
Impact du QD vs BiD sur les interruptions

Etude de cohorte QD versus BID (n=482)



Comté et al. J pharmacokinet pharmacodyn 2007

Interruption et risque de résistance N=71, NNRTI



Nb de sujets à risque						
≤1 Interruption >48 h	52	47	38	30	19	4
≥2 Interruptions >48 h	19	17	13	10	6	1

Parienti JJ et al. Clin Infect Dis 2004

Interruption et risque de réplication N=72, NNRTI

Not All Missed Doses Are the Same: Sustained NNRTI Treatment Interruptions Predict HIV Rebound at Low-to-Moderate Adherence Levels

Jean-Jacques Parienti[1,2*], Moupali Das-Douglas[3], Véronique Massari[2], David Guzman[5], Steven G. Deeks[3], Renaud Verdon[1], David R. Bangsberg[4]

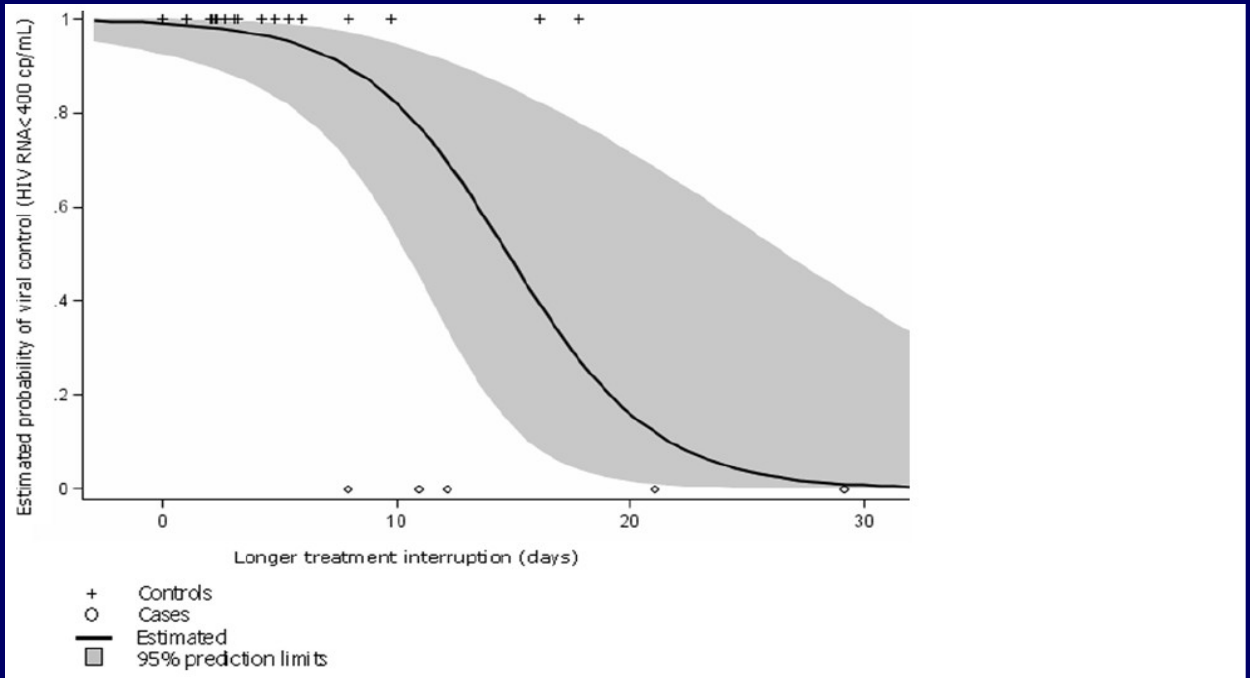
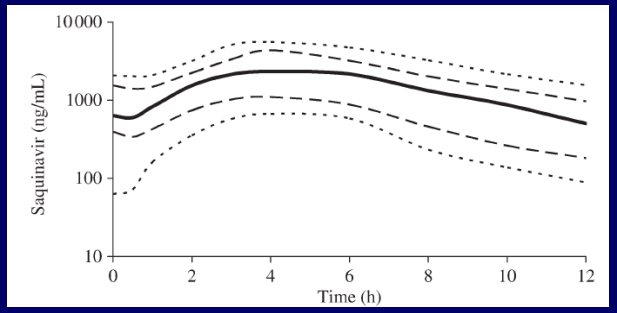


Figure 1. Predicted and observed risk of viral control according to the longer interval of treatment discontinuation, POSOVIR and REACH cohorts.

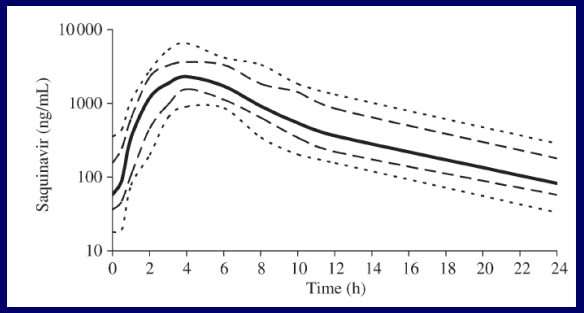
Parienti JJ et al. PLoS ONE 2007

Interruptions et exposition à des dosages < CMI
N=77, saquinavir/ritonavir

Pharmacokinetic analysis to assess forgiveness of boosted saquinavir regimens for missed or late dosing



1000/100 mg twice daily ($n = 34$)



1600/100 mg once daily

Table 1. Interpolated time of reaching the recommended minimum effective concentration (MEC, 100 ng/mL) for saquinavir (t_{MEC}) in the percentiles where concentrations dropped below this threshold, and the length of time that concentrations were likely to be subtherapeutic before the next dosing interval ($t <$ MEC) for the three evaluated saquinavir/ritonavir regimens

	1000/100 mg twice daily		1600/100 mg once daily		2000/100 mg once daily	
Percentile	t_{MEC} (h)	$t <$ MEC (h)	t_{MEC} (h)	$t <$ MEC (h)	t_{MEC} (h)	$t <$ MEC (h)
P10	11.3	0.7	15.4	8.6	17.4	6.6
P25	—	—	18.5	5.5	23.5	0.5
P50	—	—	21.9	2.1	—	—

t_{MEC} determined by rearrangement of standard pharmacokinetic formula: $C = C_0 \times e^{-kt}$.
$t <$ MEC is determined by subtracting t_{MEC} from the last time point (i.e. 12 or 24 h for twice- and once-daily regimens, respectively): $t_{last} - t_{MEC}$.

Dickinson L et al. JAC 2008

Efficacy QD versus BiD N=320, lopinavir/ritonavir

Comparison of Once-Daily versus Twice-Daily Combination Antiretroviral Therapy in Treatment-Naive Patients: Results of AIDS Clinical Trials Group (ACTG) A5073, a 48-Week Randomized Controlled Trial

Table 5. Electronic Monitor-Based Adherence Assessment by Study Week and Treatment Arm

Study weeks, treatment arm	No. of subjects	Percent adherence, median (range)	*P*	No. of dosing intervals per subject, median (range)
Weeks 0–24				
BID arm	151	82.1 (8.9–100.0)	.002	391 (9–393)
QD arm	154	90.8 (5.5–100.0)		195 (4–196)
Weeks 24–48				
BID arm	120	79.9 (0.0–98.6)	<.001	281 (49–281)
QD arm	114	90.6 (0.0–100.0)		140 (19–140)

NOTE. BID, twice daily dosing of lopinavir-ritonavir; QD, once daily dosing of lopinavir-ritonavir.

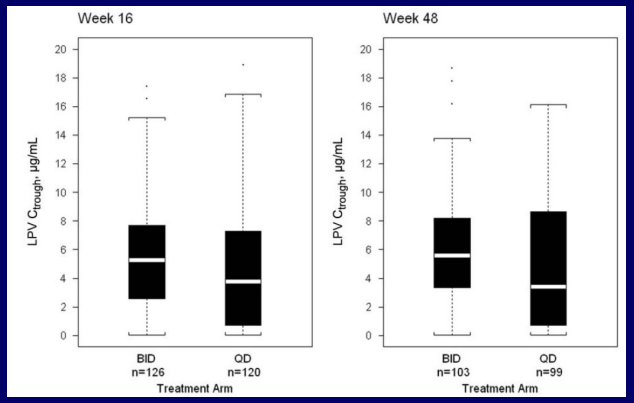


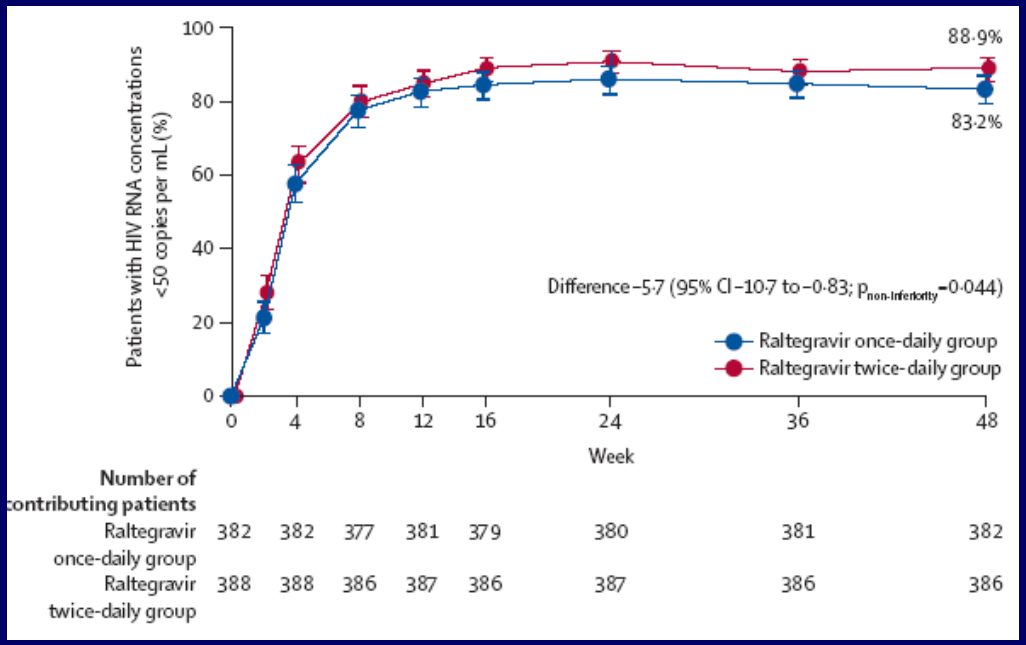
Table 3. Estimated Probability of Virologic Outcome, by Regimen

Outcome[a]	Estimated probability of virologic outcome (95% CI)		
	LPV/r BID	LPV/r QD	Difference
SVR[b]			
Intent-to-treat			
Overall	0.81 (0.73–0.86)	0.78 (0.70–0.84)	0.03 (−0.07 to 0.12)
<100,000 copies/mL	0.72 (0.59–0.81)	0.80 (0.69–0.88)	−0.09 (−0.23 to 0.06)
⩾100,000 copies/mL	0.89 (0.79–0.94)	0.76 (0.64–0.84)	0.13 (0.01 to 0.25)

Flexner C et al. Clin Infect Dis 2010

Efficacy QD versus BiD N=770, Raltégravir

Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomised, active-controlled, phase 3 non-inferiority trial



	Raltegravir once-daily group		Raltegravir twice-daily group		Geometric mean ratio (once daily:twice daily; 90% CI)
	Patients	Least-squares mean* (% CV)	Patients	Least-squares mean* (% CV)	
From intensive pharmacokinetic profiles					
AUC† (μM·h)	22	30·87 (70)	20	13·14 (99)	1·17 (0·80–1·72)
C_{max} (μM)	22	13·46 (69)	20	3·38 (135)	3·98 (2·58–6·16)
C_{trough} (nM)‡	22	40 (111)	20	257 (167)	0·15 (0·09–0·26)
From population pharmacokinetic samples					
C_{trough} (nM)§	245	83 (140)	304	380 (126)	0·22 (0·19–0·25)
C_{ss} (nM)	380	196 (176)	384	455 (92)	0·43 (0·38–0·49)
C_{min} (nM)	380	46 (189)	384	106 (143)	0·43 (0·38–0·50)

Data are results from the intensive pharmacokinetic profiles in a subset of patients and sparse concentration data collected at the end of a dosing interval (C_{trough}) in most patients. % CV=$\sqrt{(\exp[s^2]-1)} \times 100$, in which s^2 is the observed variance on the natural log-scale. AUC=area under the curve. *Back-transformed from log scale. †$AUC_{0\text{-}12\,h}$ for twice-daily group and $AUC_{0\text{-}24\,h}$ for the once-daily group; ratio is for 24 h exposure (ie, $AUC_{0\text{-}24\,h}$ once-daily group / [2 × $AUC_{0\text{-}12\,h}$ twice-daily group]). ‡C_{trough} is $C_{12\,h}$ for the twice-daily group and $C_{24\,h}$ for the once-daily group. §Geometric mean C_{trough} was calculated from sparse pharmacokinetic samples with all concentration measurements 11–13 h after dosing in a patient in the twice-daily group or 22–26 h after dosing in a patient in the once-daily group.

Table 4: Pharmacokinetic profiles for dosing regimens

Eron JJ et al. Lancet Infect Dis 2011

Interruption et risque de réplication N=66, Raltégravir

ADHERENCE PATTERNS TO RALTEGRAVIR-BASED REGIMENS AND THEIR INFLUENCE ON VIROLOGIC OUTCOME:
A PROSPECTIVE COHORT STUDY (RALTECAPS STUDY)

Figure 1 : RAL concentrations (N=42)

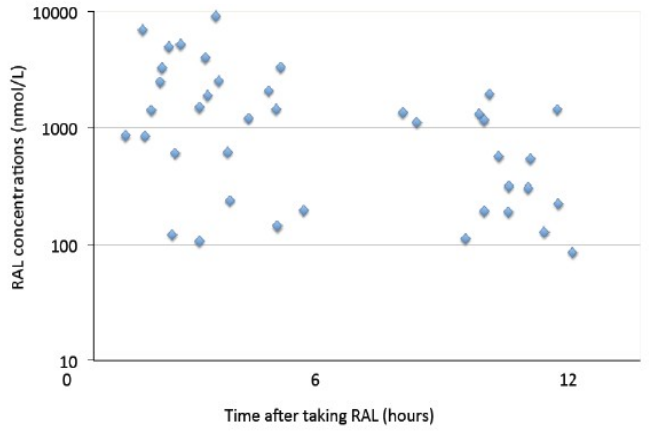
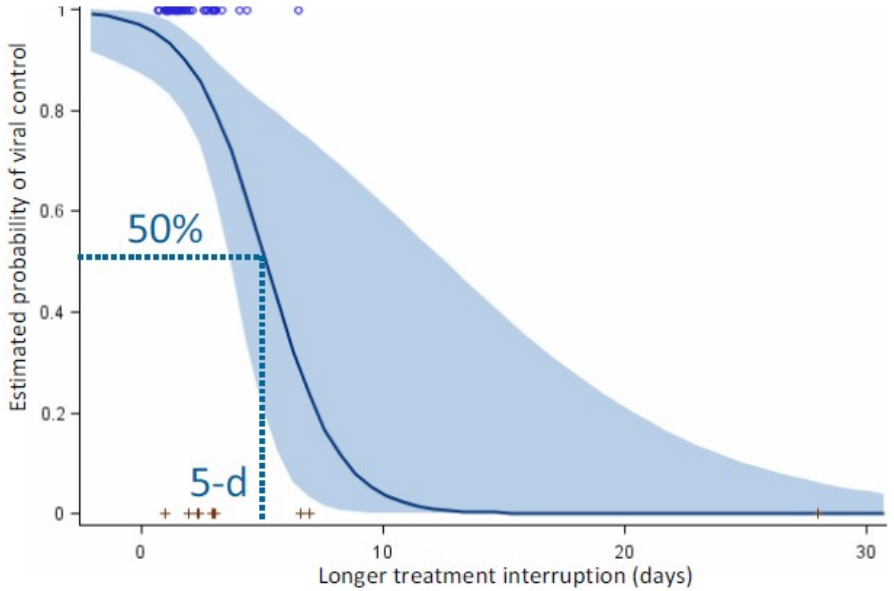


Figure 4 : Logistic model (RAL, N=66)



Gras G et al. IAS Rome 2011

Conclusion (1)

- Préférence des patients !
  - Formes combinées
- Choix justifié ?
  - Profil de tolérance acceptable
  - Validé dans les études cliniques (double aveugle+++)

Conclusion (2)

- Choix justifié?
  - Rationnel pharmacologique
  - Risques en cas d'interruption?
    - Barrière génétique
    - Demi-vie
    - Exposition différentielle