

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

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*CHU Caen Côte de Nacre*

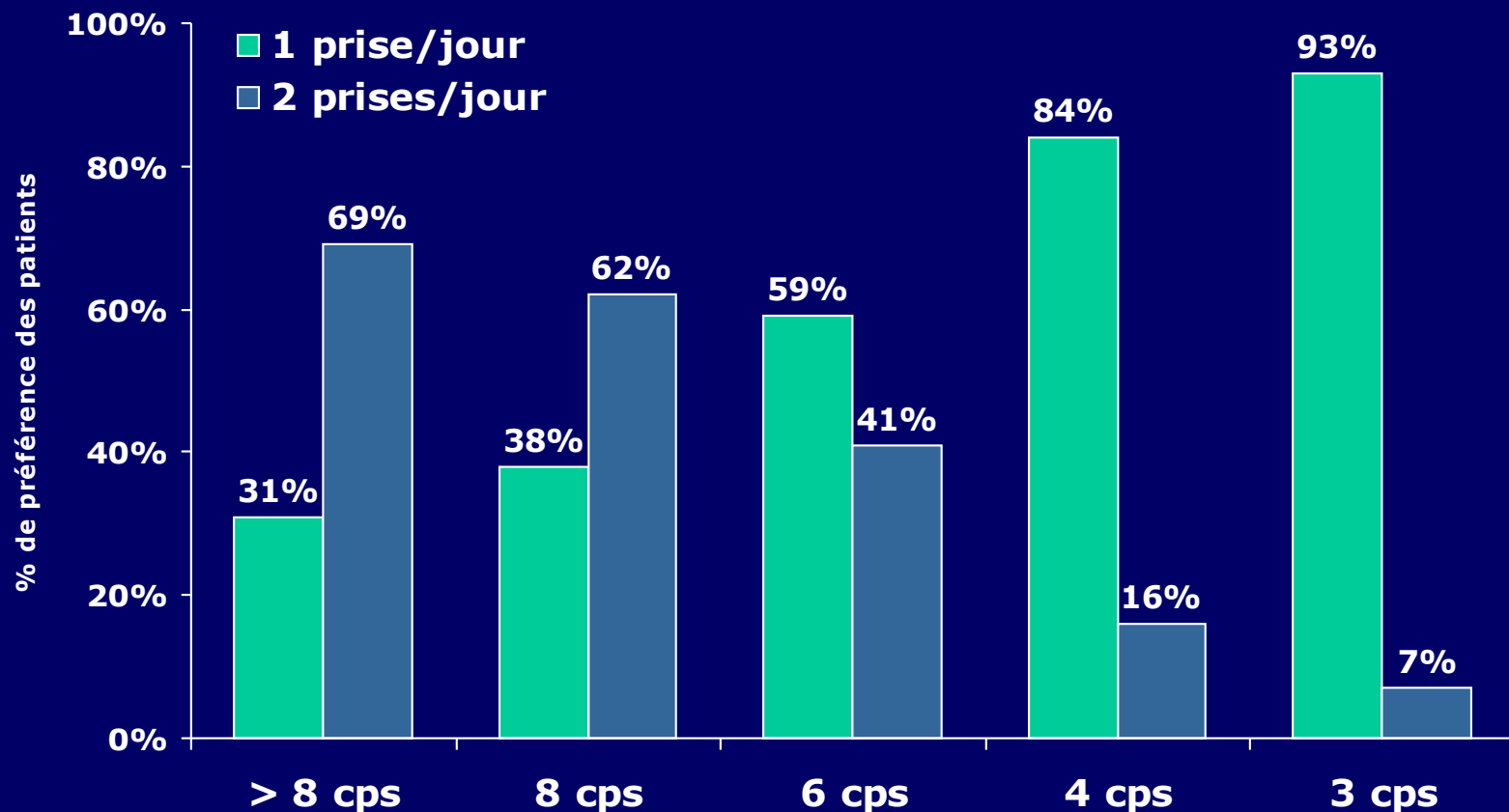
# Plan

- Souhait du patient
- Choix justifié

# Préférences des patients

## Le total des comprimés

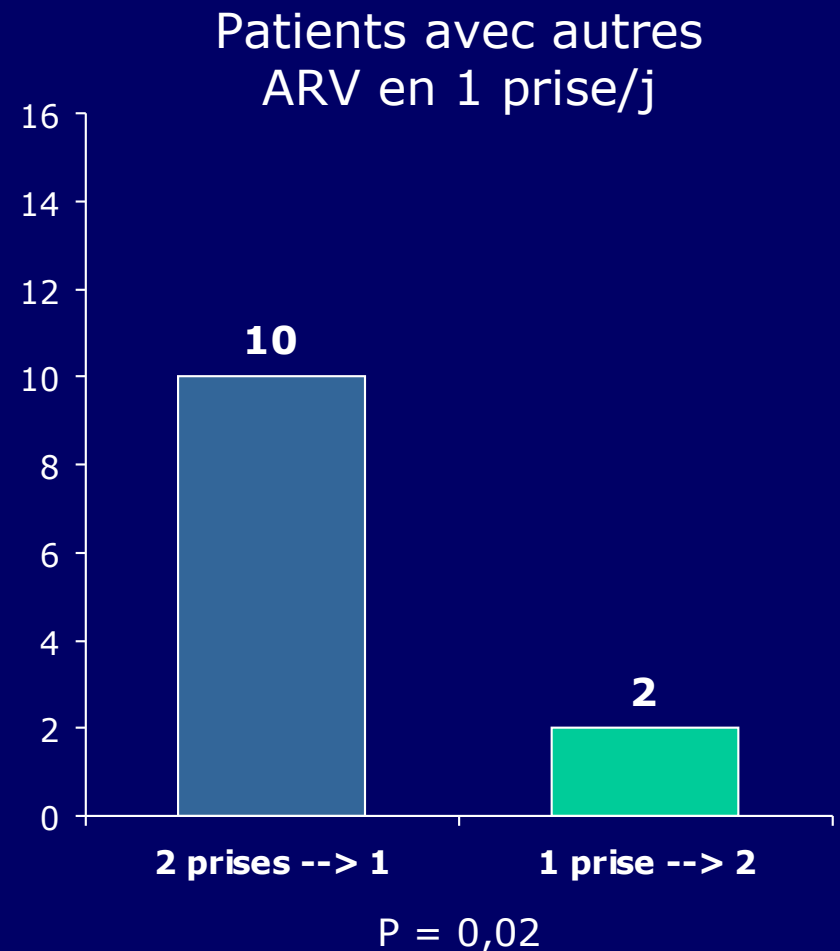
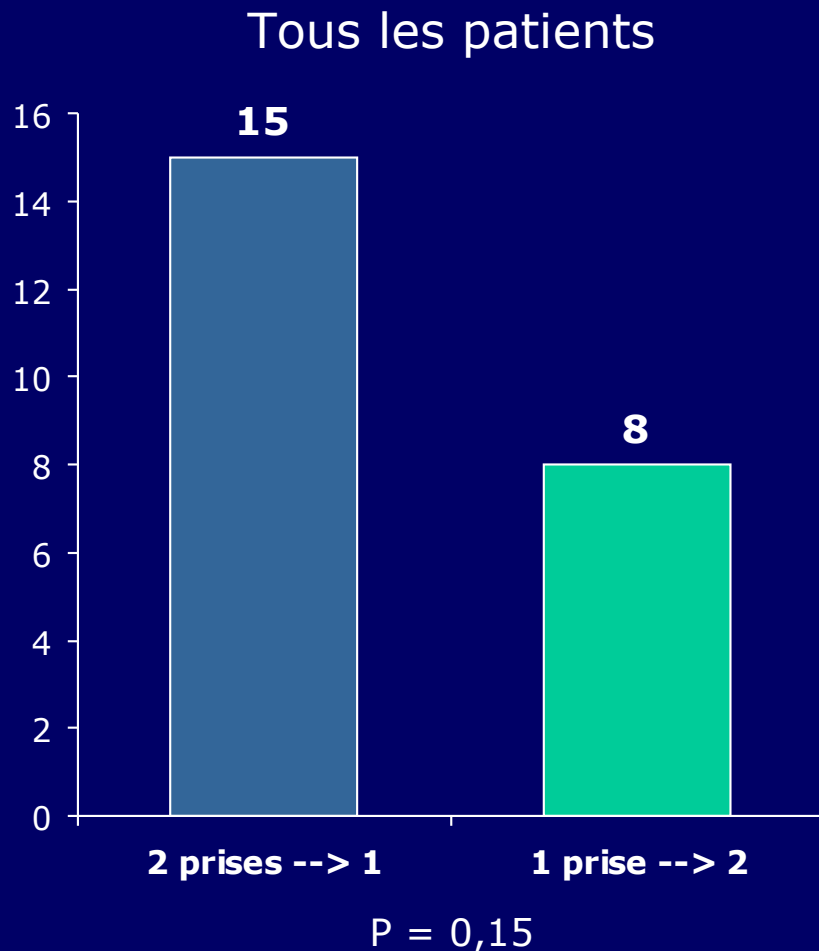
504 patients VIH+ dans 5 grands pays d'Europe



# Préférences des patients

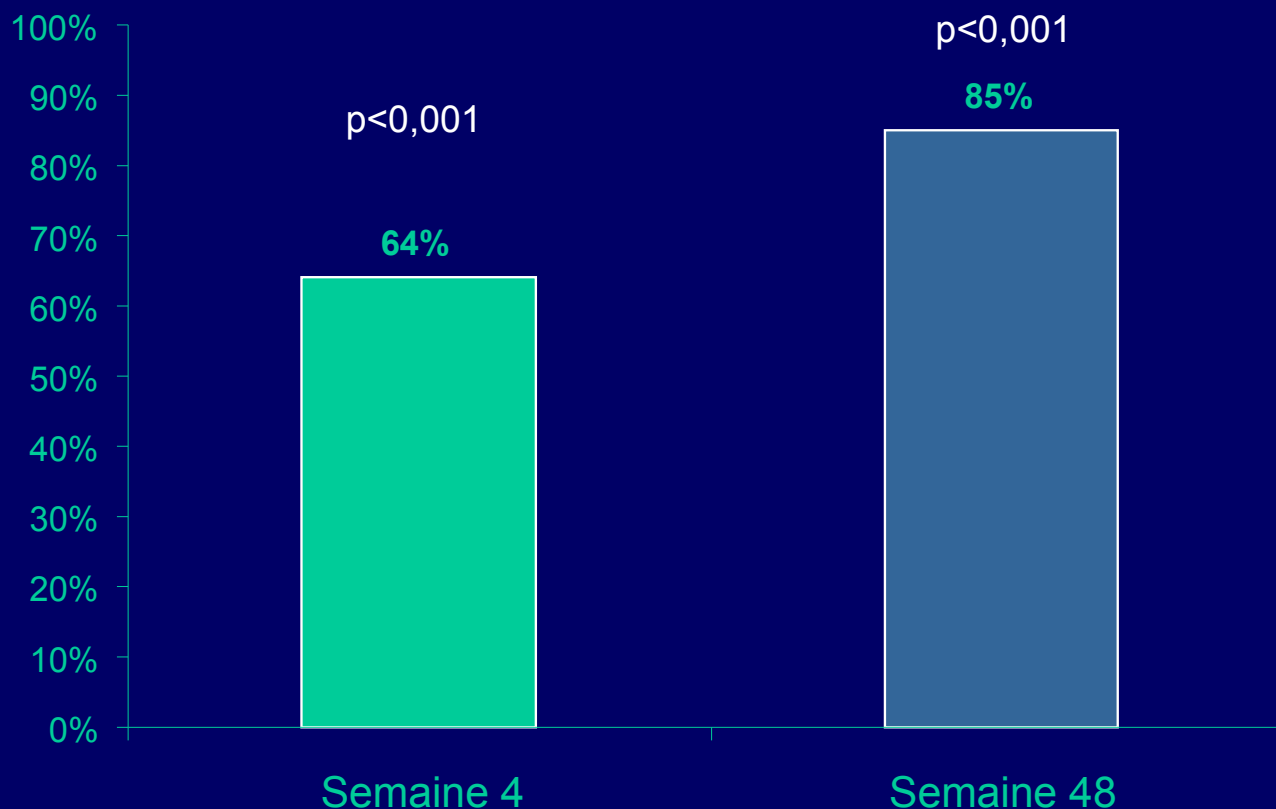
## Les autres comprimés

Essai randomisé multicentrique QD vs BID (n=52)



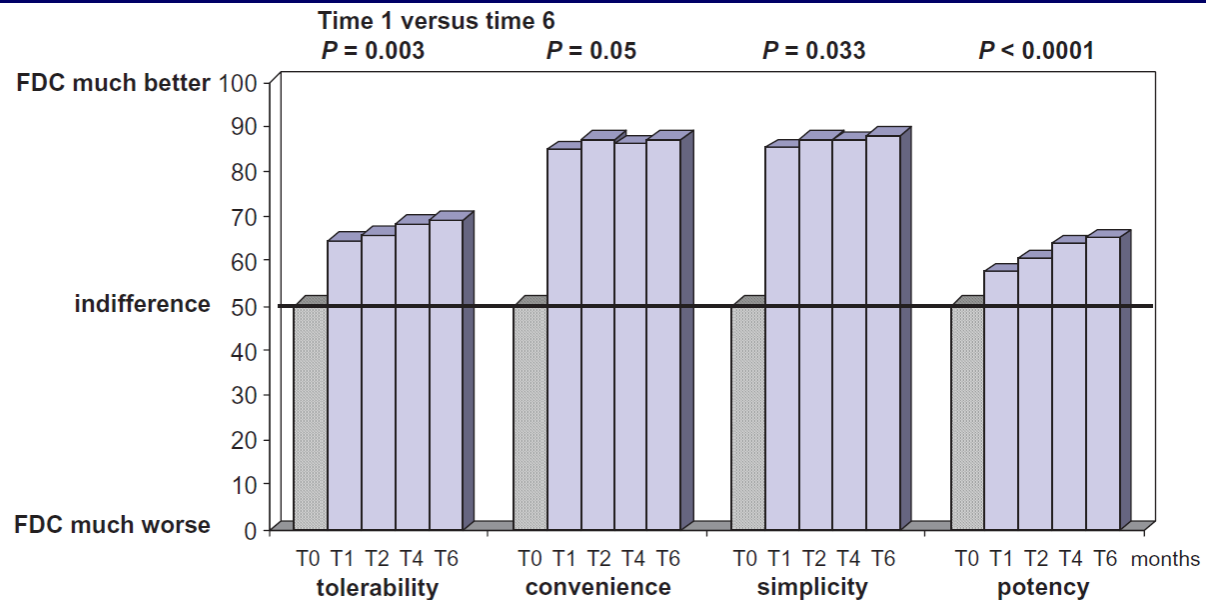
# Préférences des patients 1 comprimé, 1 fois par jour

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



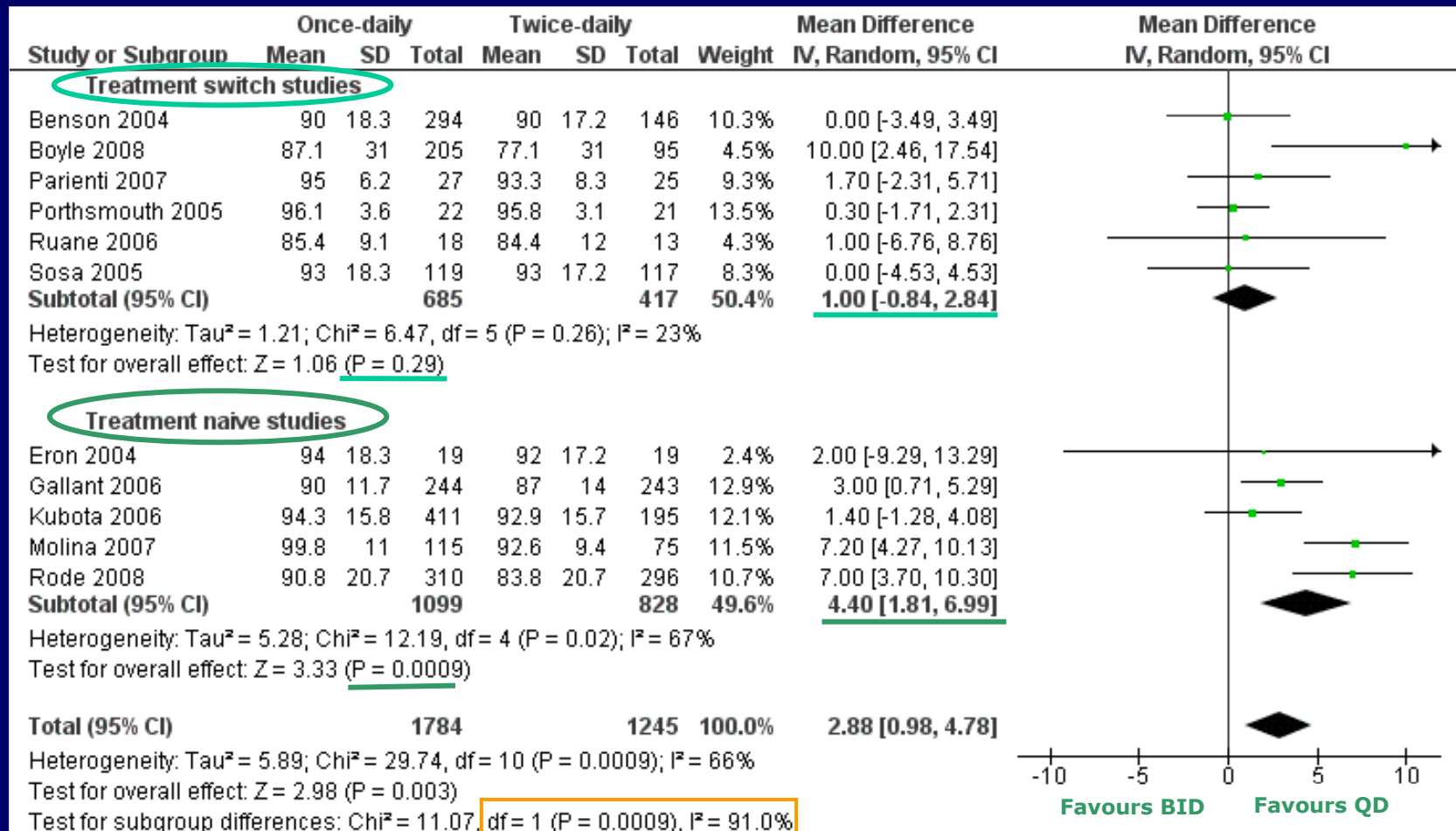
# Préférences des patients 1 comprimé, 1 fois par jour

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).

# Effet QD sur la MEMS adhérence des ARV



# Adh rence et efficacit  1 comprim , 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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Figure 1. Mean Adherence by Regimen and Month

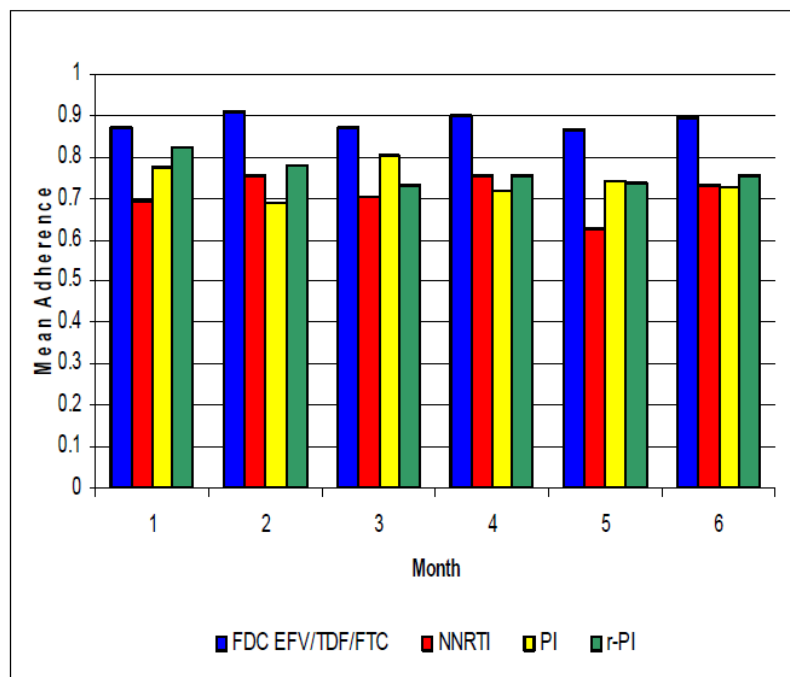
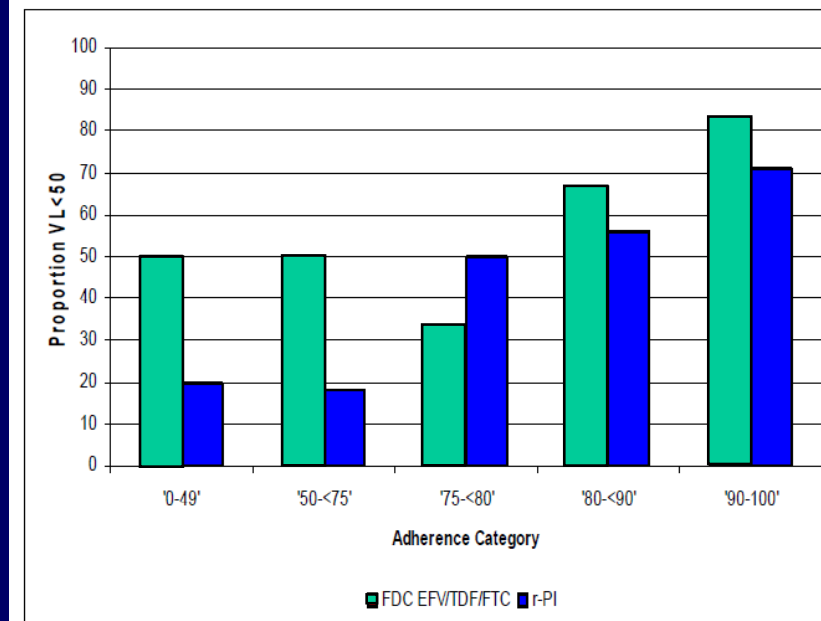


Figure 2. Proportion HIV RNA<50c/ml by Adherence Level



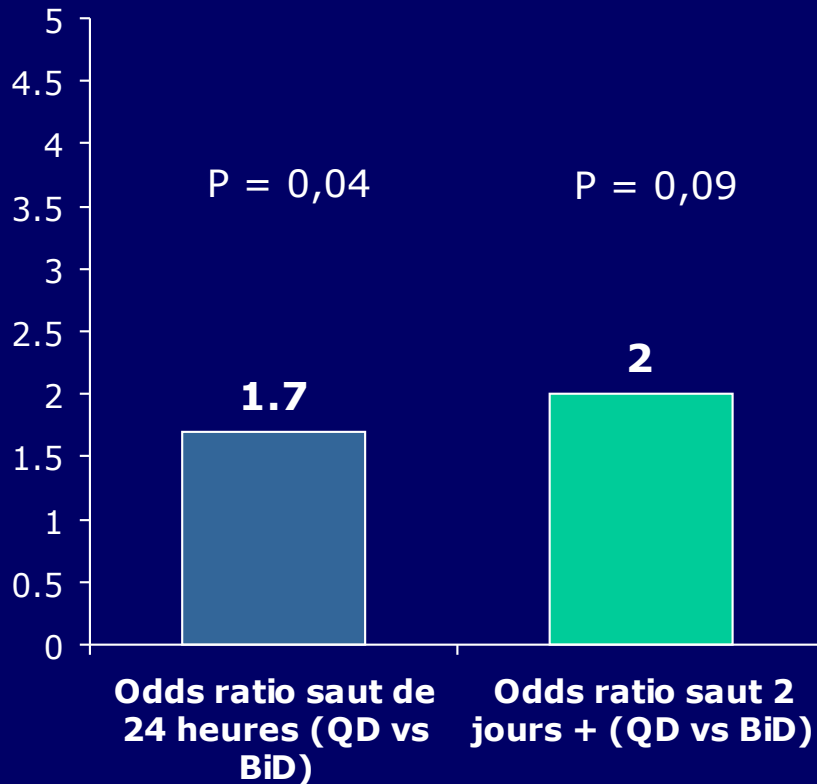
Faut-il encore plus simplifier les  
Traitements ? OUI  
Pour qui ? POUR TOUS

Par quoi??

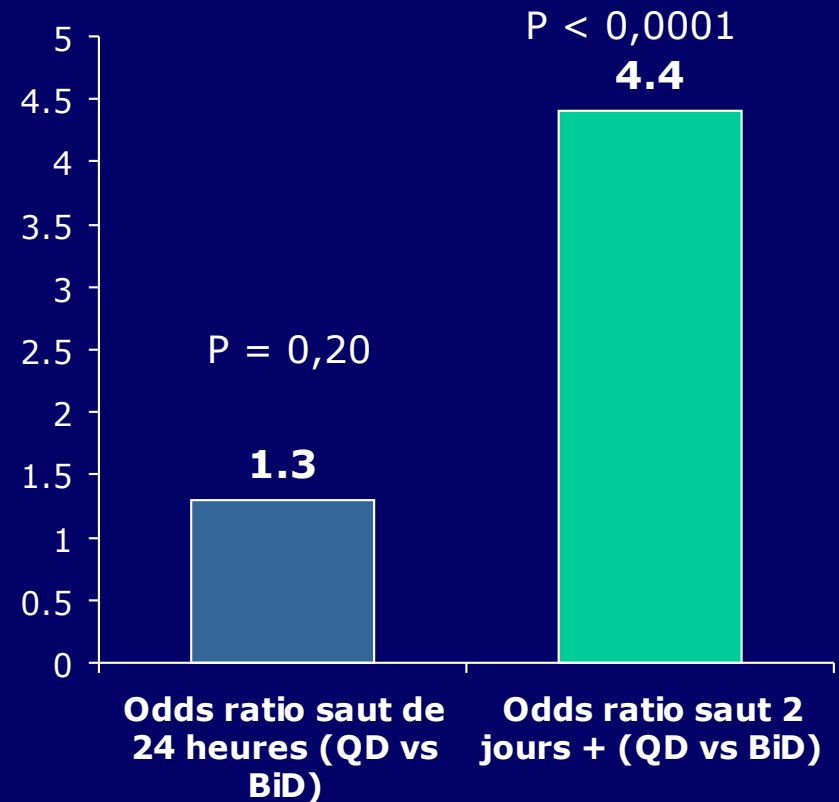
# Impact du QD vs BiD sur les interruptions

## Essai randomisé multicentrique QD vs BiD (n=52)

### Analyse randomisée

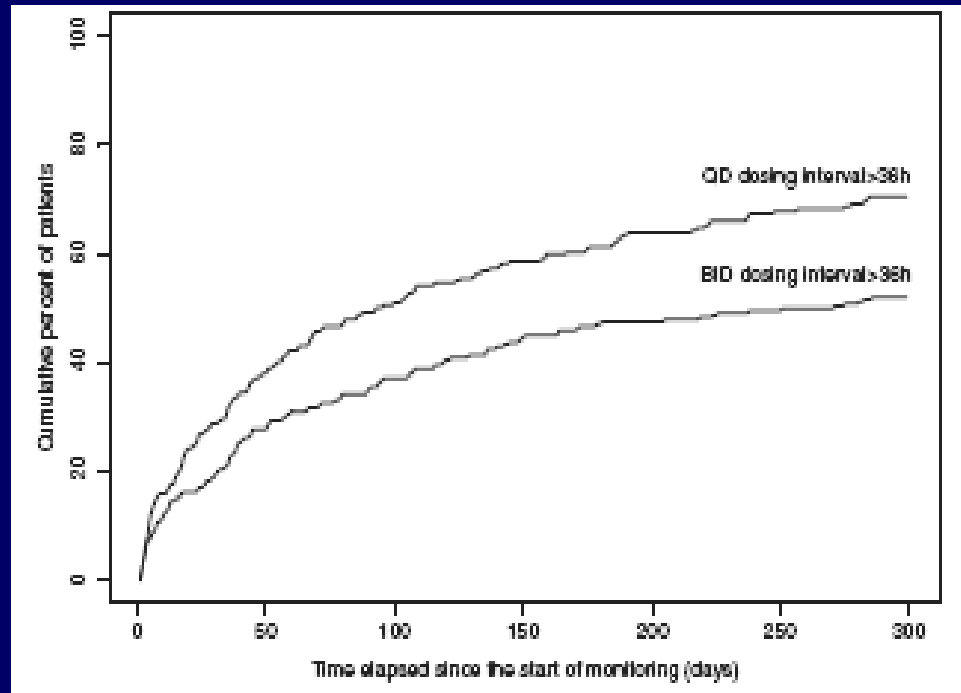


### Analyse longitudinale



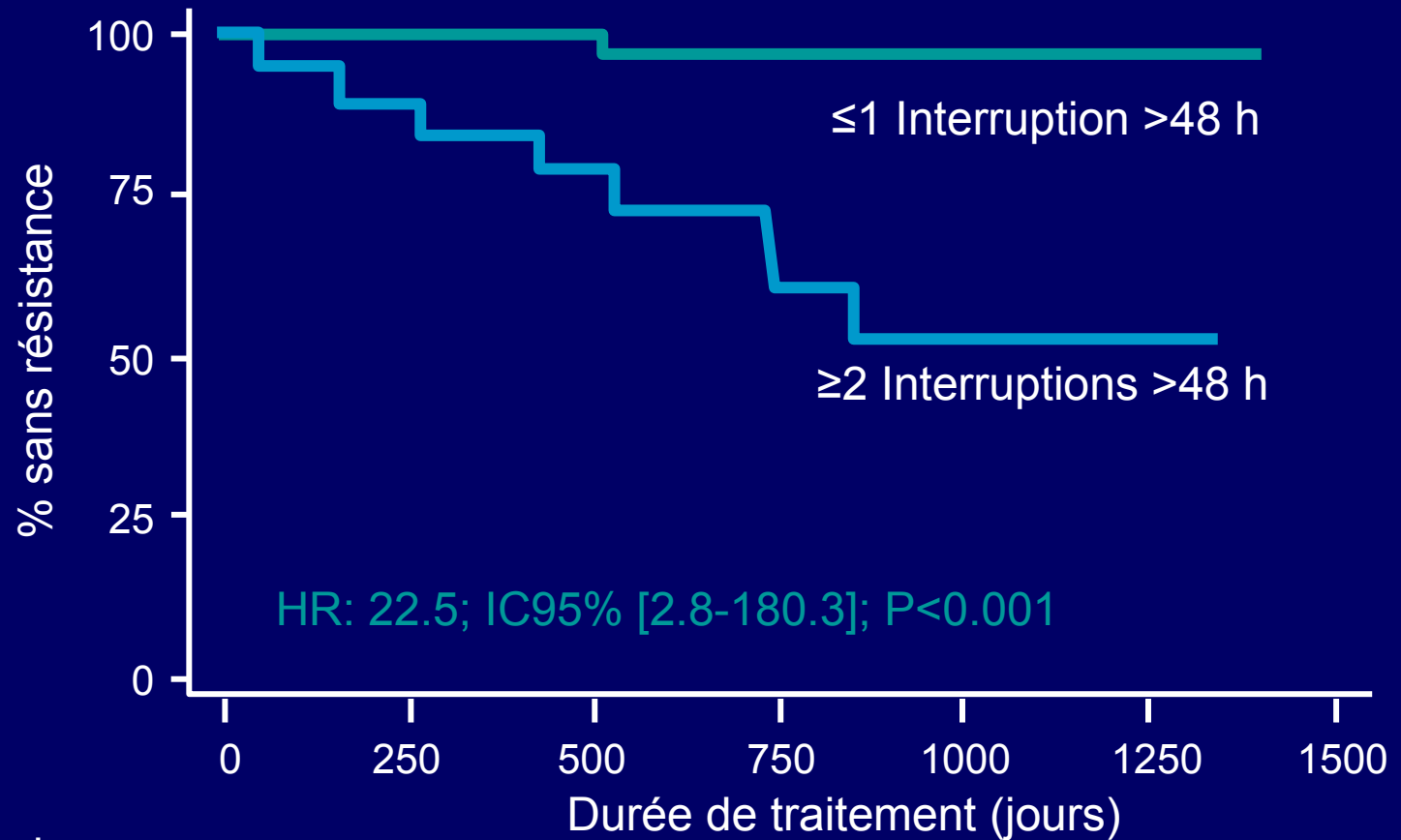
# Impact du QD vs BiD sur les interruptions

Etude de cohorte QD versus BID (n=482)



# Interruption et risque de résistance

## N=71, NNRTI



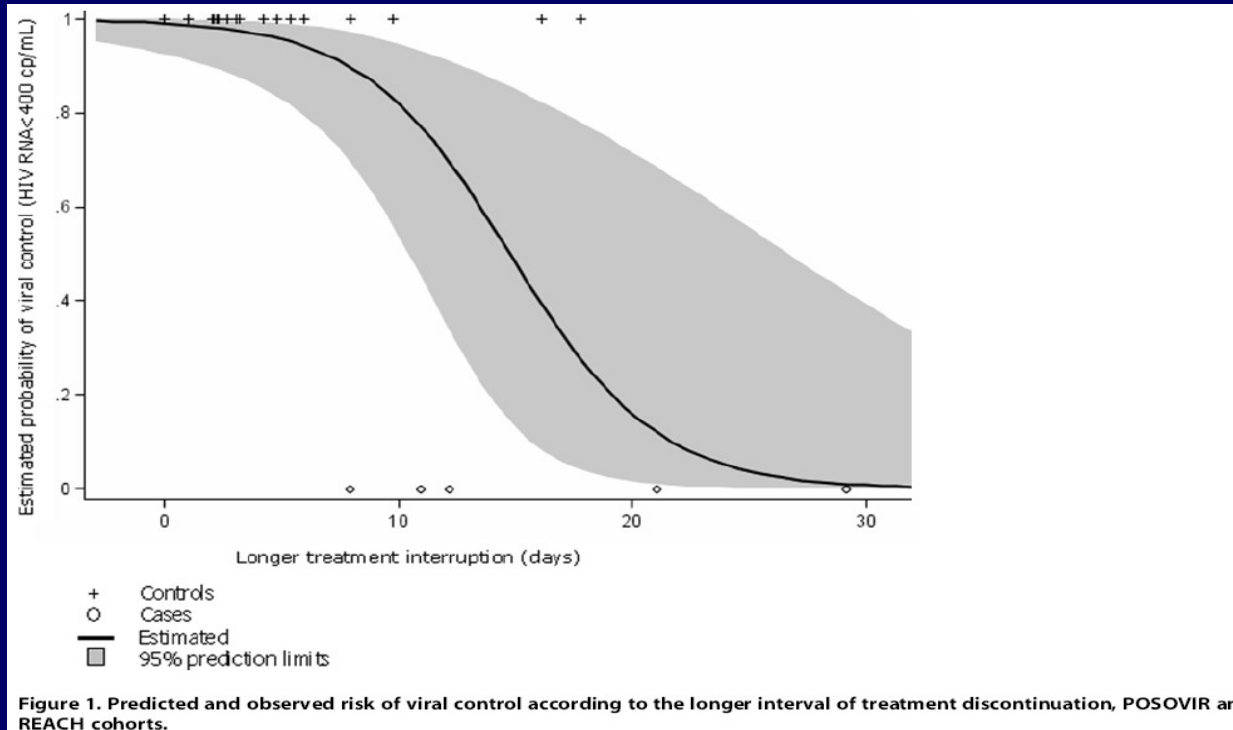
Nb de sujets à risque  
 ≤1 Interruption >48 h  
 ≥2 Interruptions >48 h

52	47	38	30	19	4
19	17	13	10	6	1

# 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

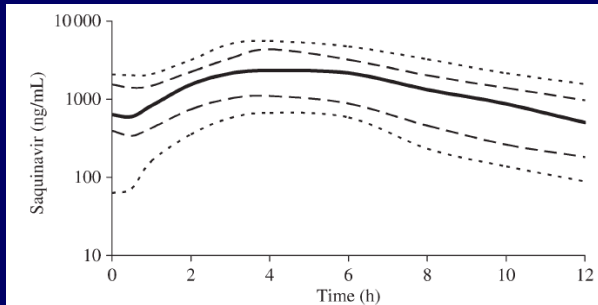
Jean-Jacques Parienti<sup>1,2\*</sup>, Moupali Das-Douglas<sup>3</sup>, Véronique Massari<sup>2</sup>, David Guzman<sup>5</sup>, Steven G. Deeks<sup>3</sup>, Renaud Verdon<sup>1</sup>, David R. Bangsberg<sup>4</sup>



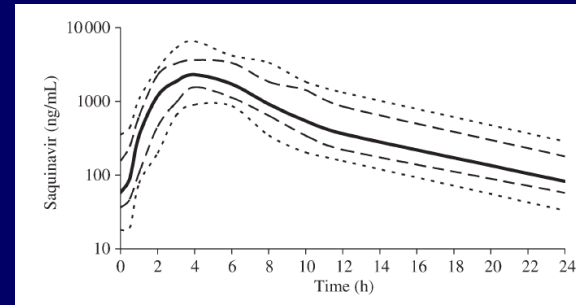
# Interruptions et exposition à des dosages < CMI

## 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

Percentile	1000/100 mg twice daily		1600/100 mg once daily		2000/100 mg once daily	
	$t_{MEC}$ (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):  $t_{last} - t_{MEC}$ .

# Efficacy QD versus BiD

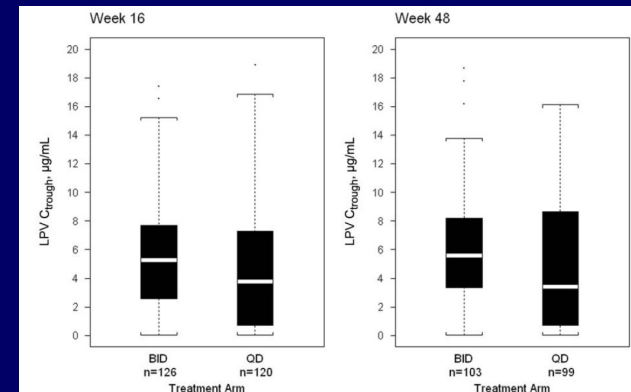
## N=320, lopinavir/ritonavir

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)	<i>P</i>	No. of dosing intervals per subject, median (range)
<b>Weeks 0–24</b>				
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)
<b>Weeks 24–48</b>				
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.



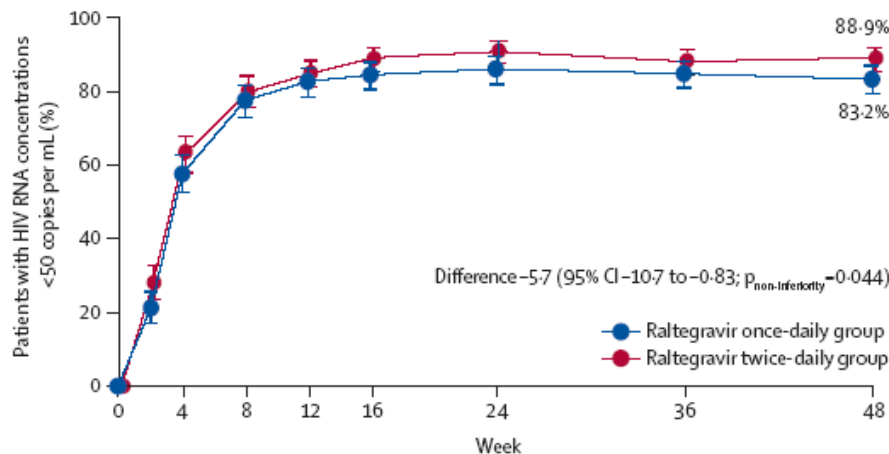
**Table 3. Estimated Probability of Virologic Outcome, by Regimen**

Outcome <sup>a</sup>	Estimated probability of virologic outcome (95% CI)		
	LPV/r BID	LPV/r QD	Difference
<b>SVR<sup>b</sup></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)

# Efficacy QD versus BiD

## N=770, Raltegravir

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



Number of contributing patients	0	4	8	12	16	24	36	48
Raltegravir once-daily group	382	382	377	381	379	380	381	382
Raltegravir twice-daily group	388	388	386	387	386	387	386	386

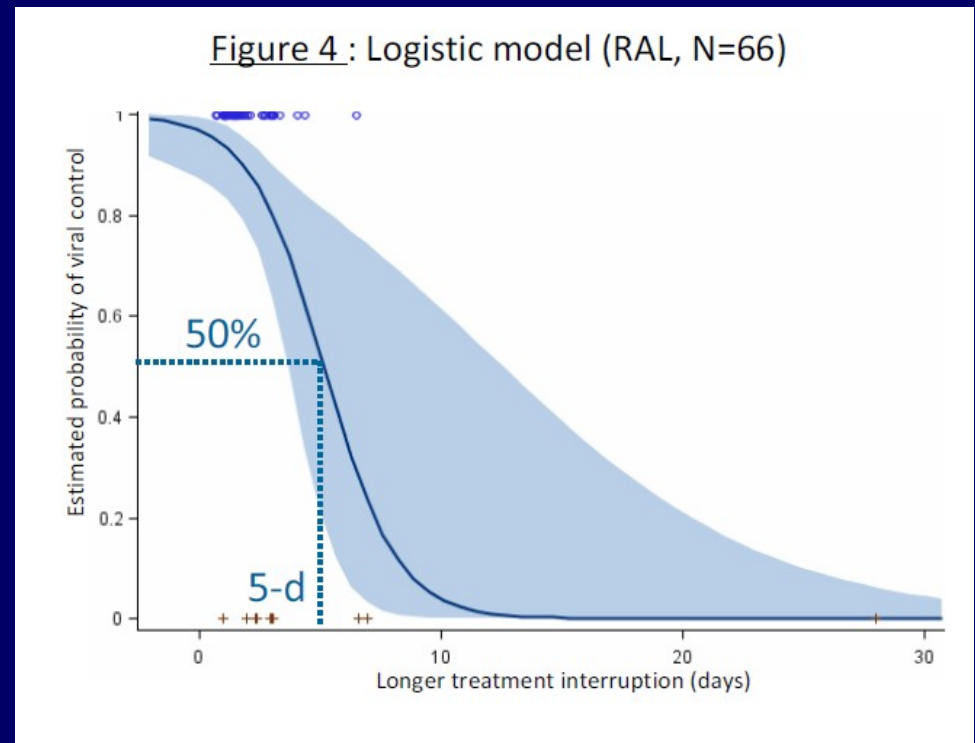
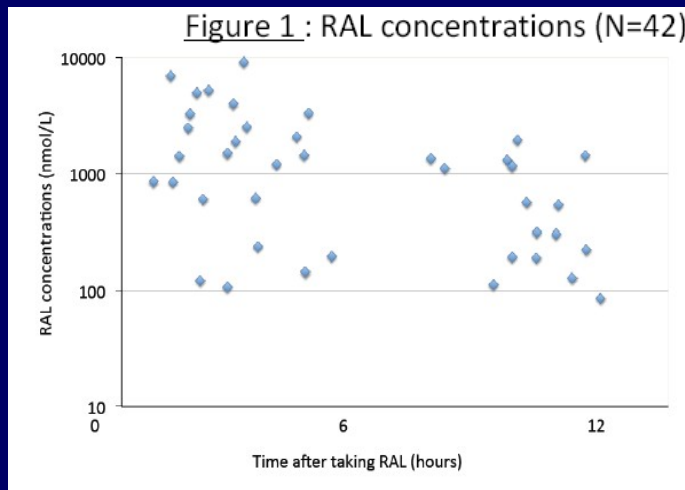
	Raltegravir once-daily group		Raltegravir twice-daily group		Geometric mean ratio (once daily:twice daily; 90% CI)
	Patients	Least-squares mean* (% CV)	Patients	Least-squares mean* (% CV)	
<b>From intensive pharmacokinetic profiles</b>					
AUC <sub>t</sub> (μM·h)	22	30.87 (70)	20	13.14 (99)	1.17 (0.80-1.72)
C <sub>max</sub> (μM)	22	13.46 (69)	20	3.38 (135)	3.98 (2.58-6.16)
C <sub>trough</sub> (nM)‡	22	40 (111)	20	257 (167)	0.15 (0.09-0.26)
<b>From population pharmacokinetic samples</b>					
C <sub>trough</sub> (nM)§	245	83 (140)	304	380 (126)	0.22 (0.19-0.25)
C <sub>11</sub> (nM)	380	196 (176)	384	455 (92)	0.43 (0.38-0.49)
C <sub>24</sub> (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<sub>trough</sub>) in most patients. % CV =  $\sqrt{(\exp(s^2) - 1)} \times 100$ , in which s<sup>2</sup> is the observed variance on the natural log-scale. AUC—area under the curve. \* Back-transformed from log scale. †AUC<sub>0-24</sub> for twice-daily group and AUC<sub>0-12</sub> for the once-daily group; ratio is for 24 h exposure (ie, AUC<sub>0-24</sub> once-daily group / [2 × AUC<sub>0-12</sub> twice-daily group]). ‡C<sub>trough</sub> is C<sub>24</sub> for the twice-daily group and C<sub>11</sub> for the once-daily group. §Geometric mean C<sub>trough</sub> 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

# 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)



# 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

