

# Un exemple : l'essai Monoï

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# Points de réflexion dans la conception d'un protocole

- Question posée
- Justification de la question posée
- Sélection de la population
- Objectifs
- Critères de jugement
- Méthodologie
- Aspect éthique de l'étude
- Faisabilité de l'étude

# Points de réflexion dans la conception d'un protocole

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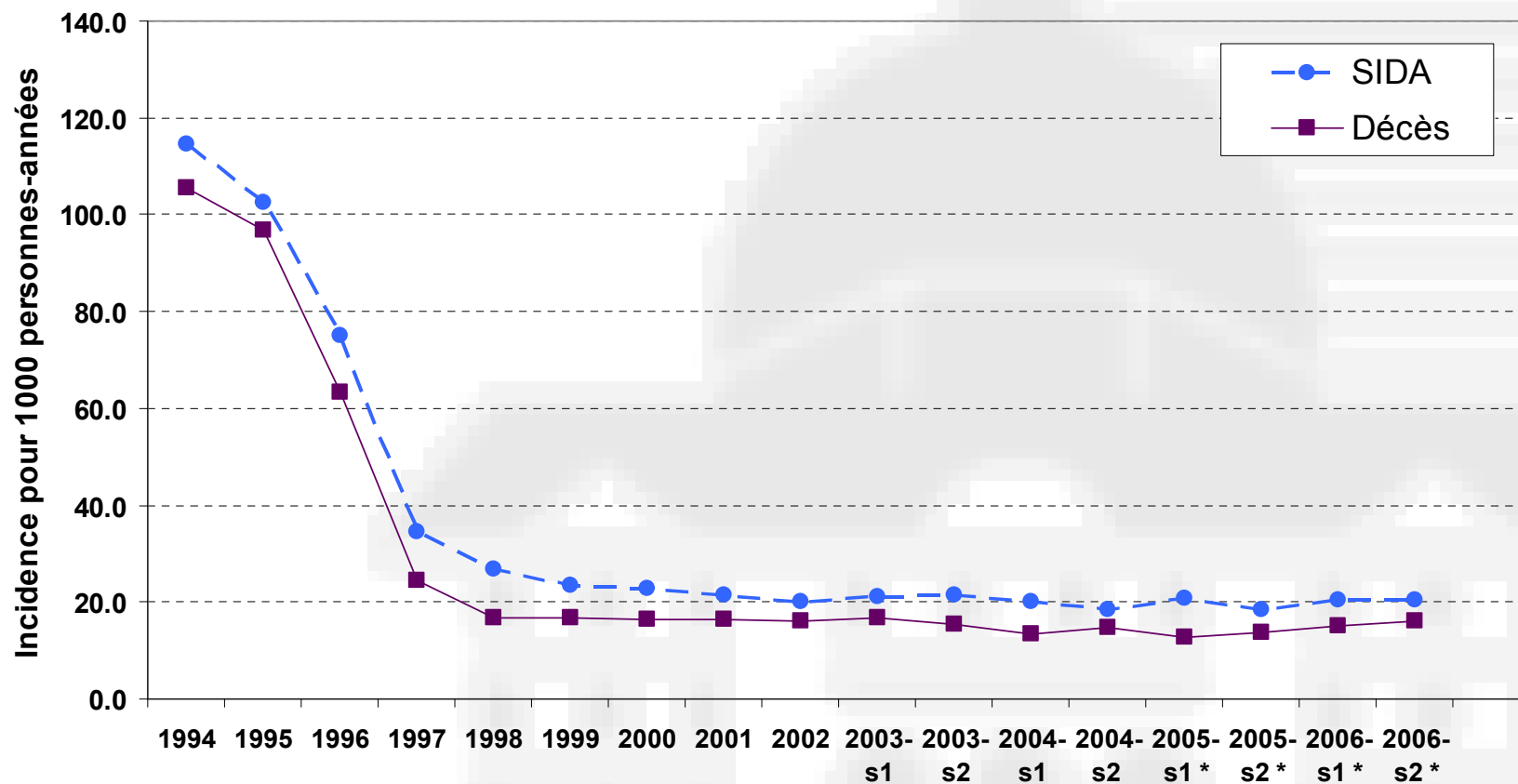
# Question posée

- Peut-on au long cours, tout à la fois maintenir une charge virale indétectable et limiter l'exposition aux molécules, c'est à dire réduire le nombre de molécules utilisées dans chaque classe mais aussi le nombre de classes thérapeutiques chez un patient en situation de contrôle immunovirologique ?

# Points de réflexion dans la conception d'un protocole

- Question posée
- **Justification de la question posée**
- Sélection de la population
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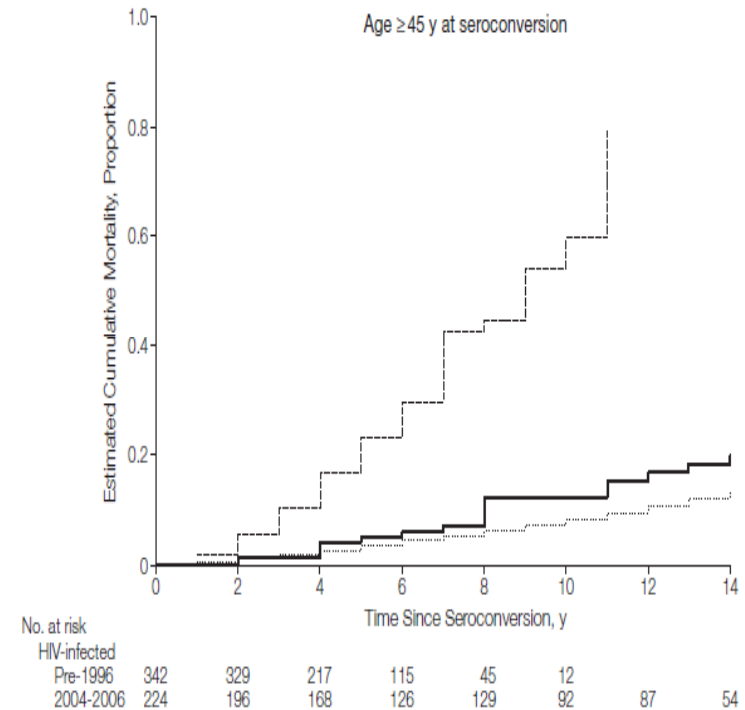
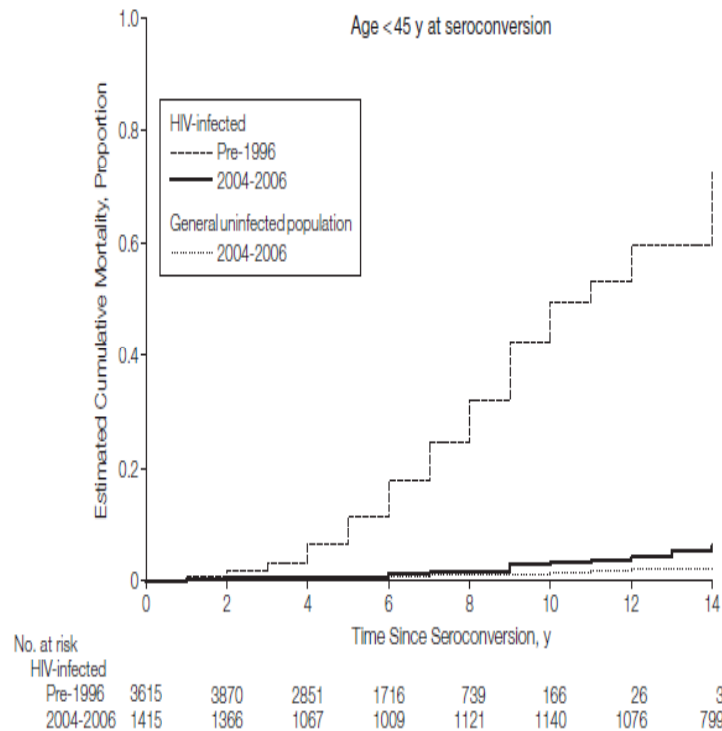
# Incidence des nouveaux cas de SIDA et décès



\* Données corrigées du délai de déclaration

# Changes in the Risk of Death After HIV Seroconversion Compared With Mortality in the General Population

(K. Bhaskaren et al, JAMA, 2008)



- 16 534 patients avec un suivi médian de 6,4 ans [1-24]
- Entre la période pré-1996 et 2004–2006 : diminution de la surmortalité de 94%
- Mortalité équivalente entre population générale et patients séropositifs dans les 5ans qui suivent la séroconversion
- Augmentation de la mortalité dans la période supérieure à 5 ans

# The Challenge of Finding a Cure for HIV Infection

Douglas D. Richman,<sup>1\*</sup> David M. Margolis,<sup>2</sup> Martin Delaney,<sup>3†</sup> Warner C. Greene,<sup>4</sup>  
Daria Hazuda,<sup>5</sup> Roger J. Pomerantz<sup>6</sup>

Although combination therapy for HIV infection represents a triumph for modern medicine, chronic suppressive therapy is required to contain persistent infection in reservoirs such as latently infected CD4<sup>+</sup> lymphocytes and cells of the macrophage-monocyte lineage. Despite its success, chronic suppressive therapy is limited by its cost, the requirement of lifelong adherence, and the unknown effects of long-term treatment. This review discusses our current understanding of suppressive antiretroviral therapy, the latent viral reservoir, and the needs for and challenges of attacking this reservoir to achieve a cure.

6 MARCH 2009 VOL 323 SCIENCE

# HIV Persistence and the Prospect of Long-Term Drug-Free Remissions for HIV-Infected Individuals

Didier Trono,<sup>1\*</sup> Carine Van Lint,<sup>2</sup> Christine Rouzioux,<sup>3</sup> Eric Verdin,<sup>4</sup> Françoise Barré-Sinoussi,<sup>5</sup> Tae-Wook Chun,<sup>6†</sup> Nicolas Chomont<sup>7†</sup>

HIV infection can persist in spite of efficacious antiretroviral therapies. Although incomplete inhibition of viral replication may contribute to this phenomenon, this is largely due to the early establishment of a stable reservoir of latently infected cells. Thus, life-long antiviral therapy may be needed to control HIV. Such therapy is prone to drug resistance and cumulative side effects and is an unbearable financial burden for regions of the world hit hardest by the epidemic. This review discusses our current understanding of HIV persistence and the limitations of potential approaches to eradicate the virus and accordingly pleads for a joint multidisciplinary effort toward two highly related goals: the development of an HIV prophylactic vaccine and the achievement of long-term drug-free remissions in HIV-infected individuals.

# SMART study Design

CD4 cell count > 350 cells/mm<sup>3</sup>  
N=5,472

N=2,752

N=2,720

**Virologic Suppression (VS) Strategy**

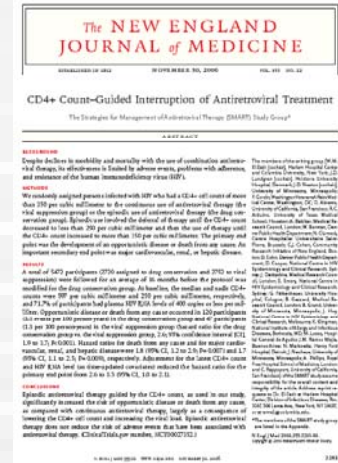
[continuous use of ART to maintain viral load as low as possible]

**Drug Conservation (DC) Strategy**

[defer use of ART until CD4+ <250; then episodic ART Based on CD4+ cell count to increase counts to >350]

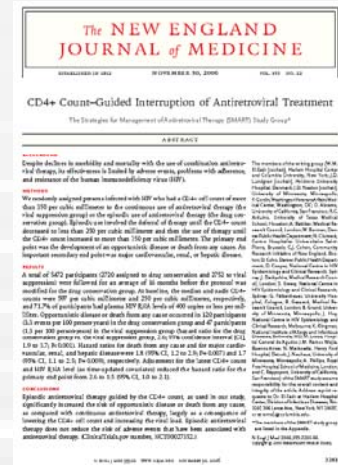
**Findings as of 11 Jan 2006**

**172 primary endpoints (Opportunistic disease/death)  
16 months average follow-up  
1.7% lost to follow-up**

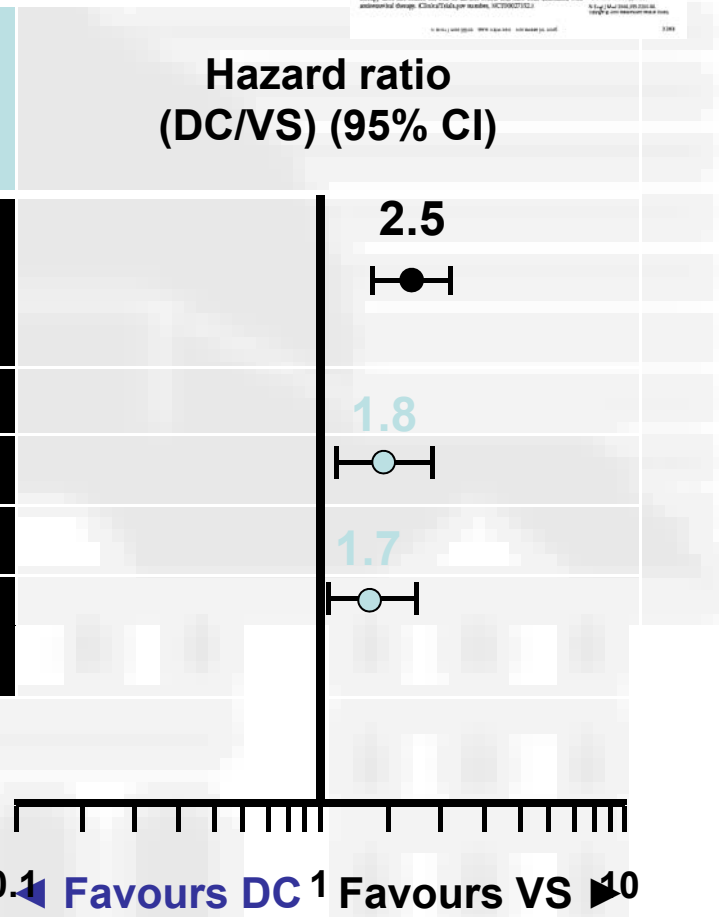


# SMART study

## Main SMART findings: Jan 2006

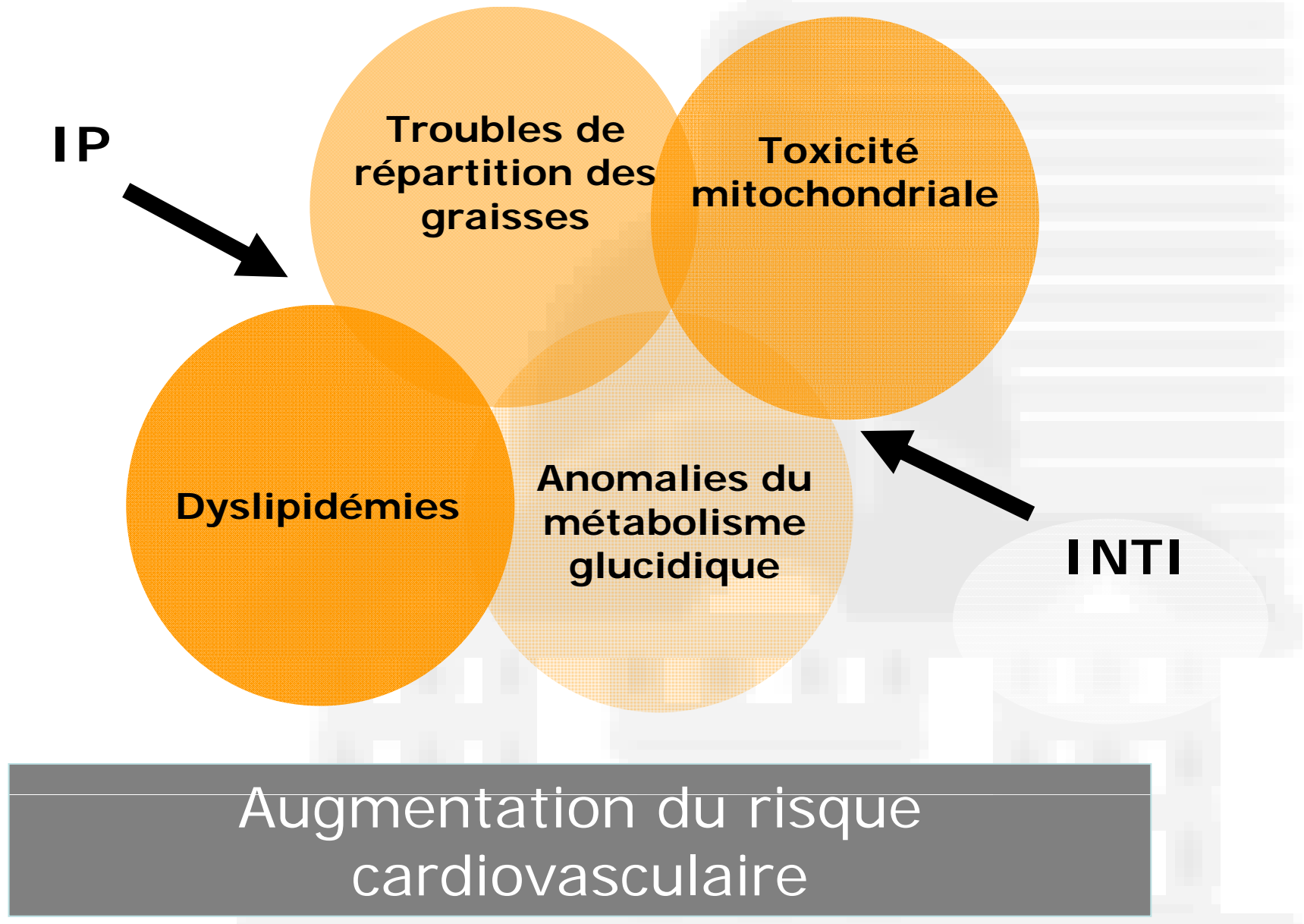


Endpoints	No. of patients with events	Rate* DC VS	
		DC	VS
Opportunistic disease or death (primary endpoint)	172	3.4	1.4
Death from any cause	85	1.5	0.8
CVD, renal, or hepatic disease	104	1.8	1.1



\* Per 100 person-years

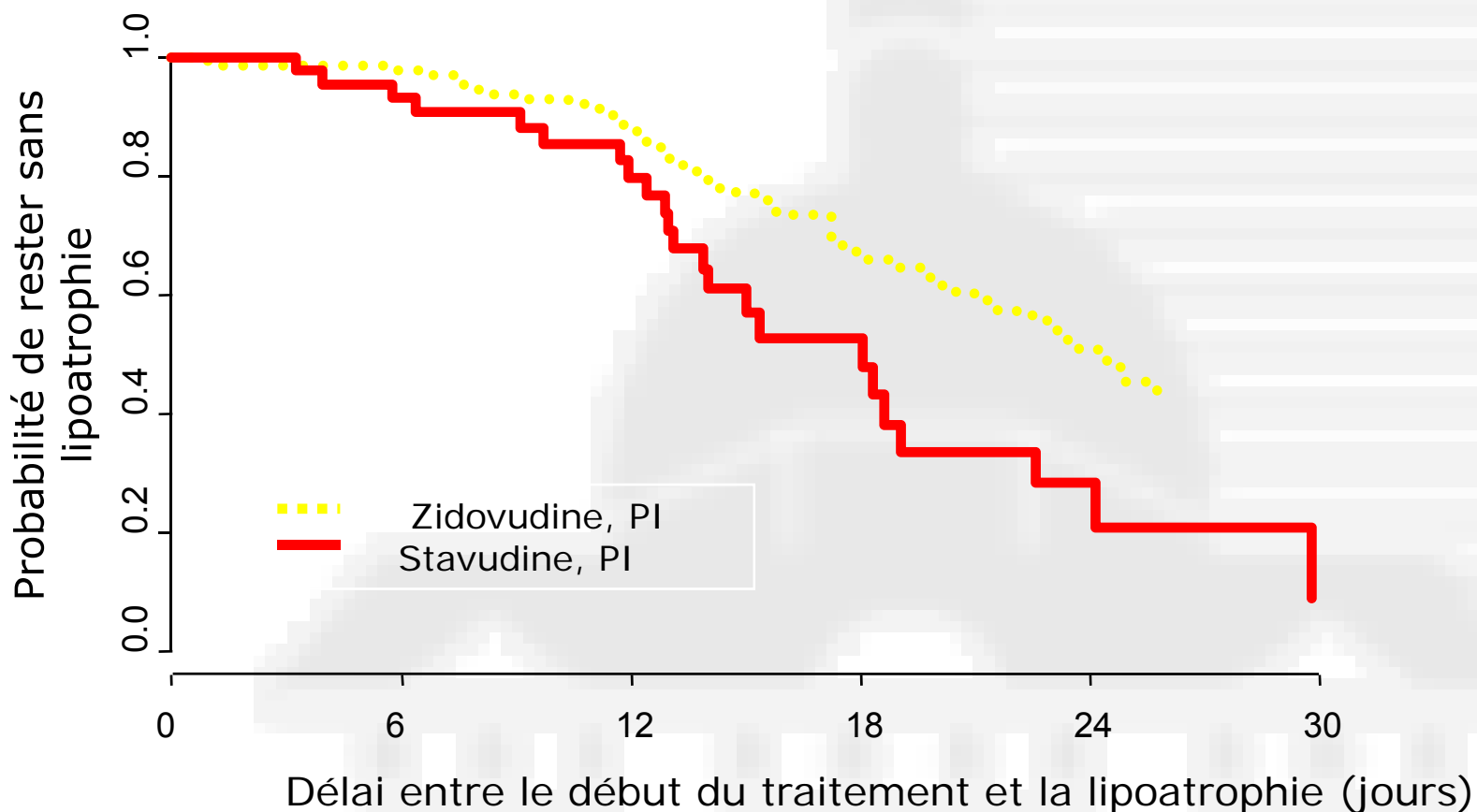
# Complications des traitements antirétroviraux



# Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection

Simon A Mallal, Mina John, Corey B. Moore, Ian R. James and Elizabeth J. McKinnon

*AIDS 2000, 14:1309±1316*



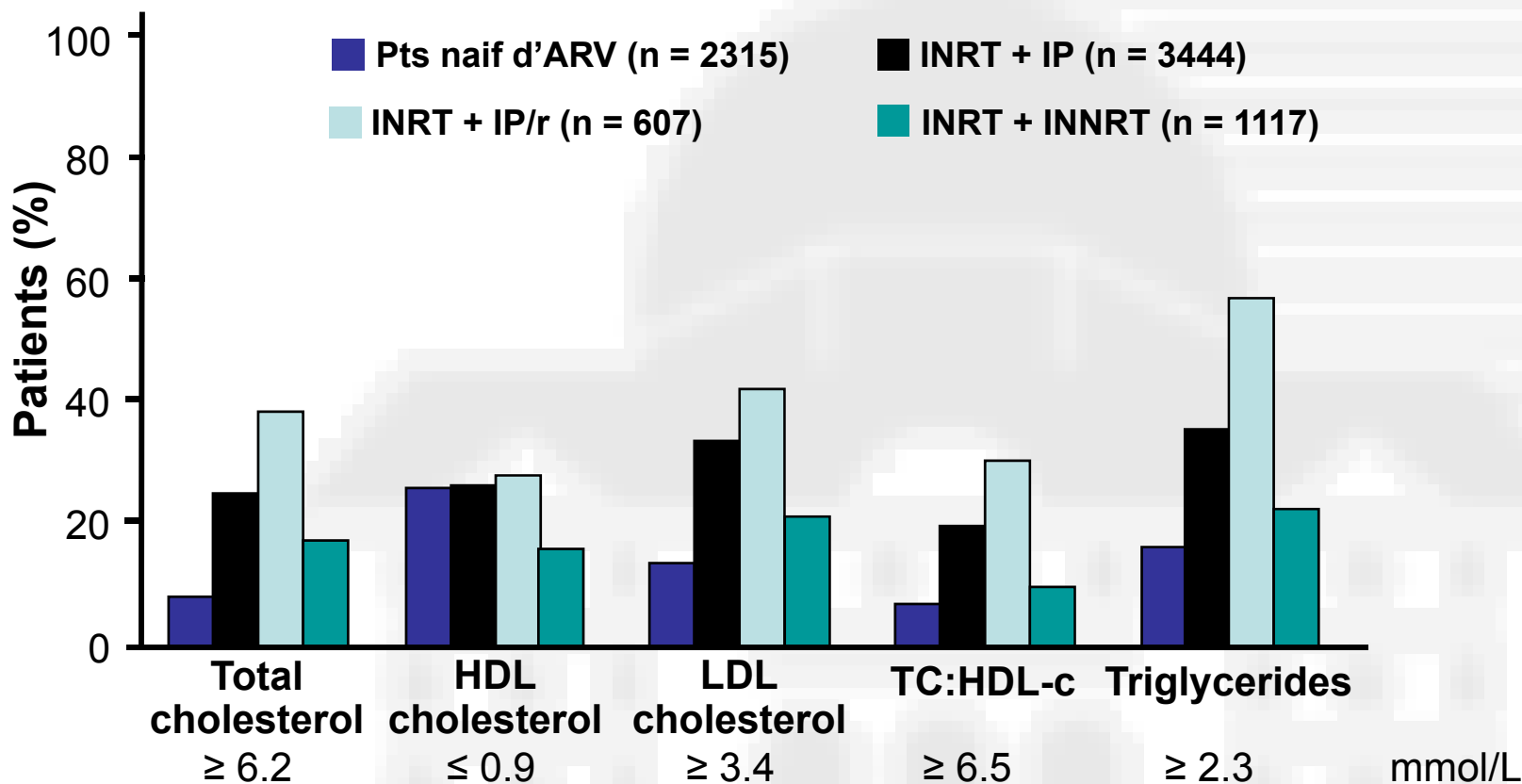
**Augmentation du risque de lipoatrophie avec stavudine / zidovudine : +265 % par an**

# Lipid Profiles in HIV-Infected Patients Receiving Combination Antiretroviral Therapy: Are Different Antiretroviral Drugs Associated with Different Lipid Profiles?

E. Fontas, F. van Leth, C. A. Sabin et col.

Journal of Infectious Diseases 2004; 189:1056–74

Prévalence des dyslipidémies par type de combinaison antirétrovirale (n = 7483)



# Risque cardiovasculaire des antirétroviraux

## Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients The SMART/INSIGHT and the D:A:D Study Groups\*

**Background:** Two nucleoside reverse transcriptase inhibitors (NRTIs) – abacavir and didanosine – may each be associated with excess risk of myocardial infarction. The reproducibility of this finding in an independent dataset was explored and plausible biological mechanisms were sought.

**Methods:** Biomarkers indicative of changes on the electrocardiogram, and rates of various predefined types of cardiovascular disease (CVD) events according to NRTIs used were explored in the Strategies for Management of Antiretroviral Therapy (SMART) study. Patients receiving abacavir and not didanosine were compared with those receiving didanosine, and to those receiving NRTIs other than abacavir or didanosine (other NRTIs). Patients randomly assigned to the continuous antiretroviral therapy arm of the SMART were included in all analyses ( $N=1752$ ); for the study of biomarkers, patients from the antiretroviral therapy interruption arm were also included.

**Results:** Current use of abacavir was associated with an excess risk of CVD compared with other NRTIs. Adjusted hazard ratios for clinical myocardial infarction ( $n=19$ ), major CVD (myocardial infarction, stroke, surgery for coronary artery disease, and CVD death;  $n=70$ ), expanded CVD (major CVD plus congestive heart failure, peripheral vascular disease, coronary artery disease requiring drug treatment, and unwitnessed deaths;  $n=112$ ) were 4.3 (95% confidence interval (CI): 1.4, 13.0), 1.8 (1.0–3.1), and 1.9 (1.3–2.9), respectively, in a subset of patients with biomarker data, high sensitivity-C-reactive protein and insulin-like growth factor-1 ( $n=508$ ). Didanosine was associated neither with altered risk of CVD nor with altered levels of biomarkers.

**Conclusions:** Abacavir was associated with an increased risk of CVD. The drug may cause vascular inflammation, which may precipitate a CVD event.  
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AIDS 2008, 22:517–524

**Keywords:** abacavir, cardiovascular disease, interleukin-6, myocardial infarction

# Risque cardiovasculaire des antirétroviraux

## Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients The SMART/INSIGHT and the D:A:D Study Groups\*

**Background:** Two nucleoside reverse transcriptase inhibitors (NRTIs) – abacavir and didanosine – may each be associated with excess risk of myocardial infarction. The excess risk in an independent dataset was explored and plausible

## Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration

D:A:D Study Group\*

### Summary

**Background** Whether nucleoside reverse transcriptase inhibitors increase the risk of myocardial infarction in HIV-infected individuals is unclear. Our aim was to explore whether exposure to such drugs was associated with an excess risk of myocardial infarction in a large, prospective observational cohort of HIV-infected patients.

**Methods** We used Poisson regression models to quantify the relation between cumulative, recent (currently or within the preceding 6 months), and past use of zidovudine, didanosine, stavudine, lamivudine, and abacavir and development of myocardial infarction in 33 347 patients enrolled in the D:A:D study. We adjusted for cardiovascular risk factors that are unlikely to be affected by antiretroviral therapy, cohort, calendar year, and use of other antiretrovirals.

**Findings** Over 157 912 person-years, 517 patients had a myocardial infarction. We found no associations between the rate of myocardial infarction and cumulative or recent use of zidovudine, stavudine, or lamivudine. By contrast, recent—but not cumulative—use of abacavir or didanosine was associated with an increased rate of myocardial infarction (compared with those with no recent use of the drugs, relative rate 1.90, 95% CI 1.47–2.45 [ $p=0.0001$ ] with abacavir and 1.49, 1.14–1.95 [ $p=0.003$ ] with didanosine); rates were not significantly increased in those who stopped these drugs more than 6 months previously compared with those who had never received these drugs. After adjustment for predicted 10-year risk of coronary heart disease, recent use of both didanosine and abacavir remained associated with increased rates of myocardial infarction (1.49, 1.14–1.95 [ $p=0.004$ ] with didanosine; 1.89, 1.47–2.45 [ $p=0.0001$ ] with abacavir).

**Interpretation** There exists an increased risk of myocardial infarction in patients exposed to abacavir and didanosine within the preceding 6 months. The excess risk does not seem to be explained by underlying established cardiovascular risk factors and was not present beyond 6 months after drug cessation.

**Funding** HAART Oversight Committee.

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See Online Correspondence  
S0140-1016/S0140-6736(08)60423-4

\*Members listed at end of report see supplementary for members of the contributing cohorts—ATHENA, Aquitaine, AHOQ, BASS, The British St Pierre Cohort, CPRA, EuroSIDA, HAVENUS, KUNA, Nice Cohort, and SPUS

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# Risque cardiovasculaire des antirétroviraux

## Use of nucleoside reverse transcriptase inhibitor risk of myocardial infarction in HIV-infected The SMART/INSIGHT and the D:A:D Study G

**Background:** Two nucleoside reverse transcriptase inhibitors (NRTIs)—zidovudine and didanosine—may each be associated with excess risk of myocardial infarction. It is unclear whether in an independent dataset was explored.

## Use of nucleoside reverse transcriptase myocardial infarction in HIV-infected the D:A:D study: a multi-cohort coll

D:A:D Study Group\*

### Summary

**Background** Whether nucleoside reverse transcriptase inhibitor HIV-infected individuals is unclear. Our aim was to explore whether excess risk of myocardial infarction in a large, prospective obser

**Methods** We used Poisson regression models to quantify the risk of myocardial infarction in 33 347 patients enrolled in the SMART/INSIGHT and the D:A:D study, who were treated with zidovudine, didanosine, or other NRTIs that are unlikely to be affected by antiretroviral therapy, compared with those with no recent use of these drugs.

**Findings** Over 157 912 person-years, 517 patients had a myocardial infarction and cumulative or recent use of abacavir or didanosine (compared with those with no recent use of these drugs) was associated with an increased risk of myocardial infarction (adjusted relative risk 1.49, 95% CI 1.14–1.95 [ $p=0.003$ ] with didanosine and 1.49, 95% CI 1.14–1.95 [ $p=0.003$ ] with abacavir).

**Interpretation** There exists an increased risk of myocardial infarction in HIV-infected individuals with recent use of abacavir or didanosine, which is not explained by dyslipidaemia. We found no association between use of zidovudine or other NRTIs and myocardial infarction. However, the number of person-years of observation for exposure to these drugs was less than that for exposure to protease inhibitors.

**Funding** HAART Oversight Committee.

## Class of Antiretroviral Drugs and the Risk of Myocardial Infarction

The D:A:D Study Group\*

### ABSTRACT

**BACKGROUND** We have previously demonstrated an association between combination antiretroviral therapy and the risk of myocardial infarction. It is not clear whether this association differs according to the class of antiretroviral drugs. We conducted a study to investigate the association of cumulative exposure to protease inhibitors and nucleoside reverse-transcriptase inhibitors with the risk of myocardial infarction.

### METHODS

We analysed data collected through February 2005 from our prospective observational study of 23 457 patients in the human immunodeficiency virus-1 infection cohort. The incidence rates of myocardial infarction during the follow-up period were calculated, and the associations between myocardial infarction and exposure to protease inhibitors or nucleoside reverse-transcriptase inhibitors were determined.

### RESULTS

Three hundred forty-five patients had a myocardial infarction during 94 469 person-years of observation. The incidence of myocardial infarction increased from 1.55 per 1000 person-years in those not exposed to protease inhibitors to 6.02 per 1000 person-years in those exposed to protease inhibitors for more than 6 years. After adjustment for exposure to the other drug class and established cardiovascular risk factors (including lipid levels), the relative rate of myocardial infarction per year of protease inhibitor exposure was 1.66 (95% confidence interval [CI] 1.38 to 1.95), whereas the relative rate per year of exposure to nucleoside reverse-transcriptase inhibitors was 1.05 (95% CI 0.98 to 1.13). Adjustment for serum lipid levels further reduced the effect of exposure to each drug class to 1.10 (95% CI 1.04 to 1.15) and 1.00 (95% CI 0.95 to 1.05), respectively.

### CONCLUSIONS

Increased exposure to protease inhibitors is associated with an increased risk of myocardial infarction, which is partly explained by dyslipidaemia. We found no evidence of such an association for nucleoside reverse-transcriptase inhibitors; however, the number of person-years of observation for exposure to this class of drug was less than that for exposure to protease inhibitors.

The members of the writing committee (Narcisus-Müller, M.D., Ph.D., University of Copenhagen; Copenhagen Heart Data; M.D., Ph.D., Academic Medical Center, Amsterdam; Caroline, M.D., Ph.D., Royal Albert Walter, M.D., University Hospital Zurich; Zurich, Switzerland; Antonia, M.D., M.P.H., University Hospital of Armauer Weizel, M.D., M.Sc., University of Milan; Milan, Italy; Walter, M.D., M.P.H., Columbia University; New York, N.Y.; Hoggan, M.D., Ph.D., INSERM 0333 and UFR, Victor Segalen-Breton 2 University, Bordeaux France; Scepter, M.D., Ph.D., Centre Hospitalier Universitaire de Montréal, Québec, Canada; M.D., M.Sc., University of Copenhagen, Copenhagen; Dr. Kralj, M.D., Centre for Infectious Diseases, Nijmegen Hospital de Oude, National Centre in HIV Epidemiology and Clinical Research Agency; Aronoff, M.D., Ph.D., Royal Cole and University College London; and Jens, M.D., University of Copenhagen) of the D:A:D Study Group assume responsibility for the accuracy of the data and the content and integrity of the article. Address reprint requests to Dr. Lundgren at the Copenhagen HIV Program, Faculty of Health Sciences, University of Copenhagen, Blegdamsvej 3, Copenhagen N, Denmark or at j.lundgren@hiv.ku.dk.

\*The members of the Data Collection on Adverse Events of Antiretroviral Drugs (DAD) Study Group are listed in the Appendix (N Engl J Med 2007;356:2527-35. Copyright © 2007 Massachusetts Medical Society).

# Risque cardiovasculaire des antirétroviraux

## Use of nucleoside reverse transcriptase inhibitor risk of myocardial infarction in HIV-infected The SMART/INSIGHT and the D:A:D 5

**Background:** Two nucleoside reverse transcriptase inhibitor (NRTI) drugs, zidovudine (ZDV) and zalcitabine (ZC), may each be associated with excess risk of myocardial infarction (MI) in an independent dataset.

## Use of nucleoside reverse transcriptase inhibitor risk of myocardial infarction in HIV-infected the D:A:D study: a multi-cohort

D:A:D Study Group\*

### Summary

**Background:** Whether nucleoside reverse transcriptase inhibitor (NRTI) use is associated with an increased risk of myocardial infarction (MI) in HIV-infected individuals is unclear. Our aim was to assess the risk of MI in a large, multi-cohort study.

**Methods:** We used Poisson regression models to estimate the risk of MI in the preceding 6 months, and past use of zidovudine (ZDV) and zalcitabine (ZC) in 33 347 patients that are unlikely to be affected by antiretroviral therapy.

**Findings:** Over 157 912 person-years, 517 cases of MI were identified. The rate of MI was higher among those exposed to ZDV or ZC in the preceding 6 months—but not cumulative—use of these drugs (compared with those with no exposure) [adjusted relative risk (RR) 1.49, 1.14–1.95 ( $p=0.001$ ) for ZDV; 1.49, 1.14–1.95 ( $p=0.001$ ) for ZC]. These drugs were more than 6 months' exposure for predicted 10-year risk of MI associated with increased rates of MI [ $p=0.0001$ ] with abacavir.

**Interpretation:** There exists an increased risk of MI within the preceding 6 months. The excess risk does not persist beyond 6 months after drug cessation. Risk factors and was not present beyond 6 months after drug cessation.

**Funding:** HAART Oversight Committee.

## Class of Antiretroviral Drugs and the Risk of Myocardial Infarction

The D:A:D Study Group\*

### ABSTRACT

## Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men Murielle Mary-Krause<sup>a</sup>, Laurent Cotte<sup>b</sup>, Anne Simon<sup>c</sup>, Maria Partisan<sup>d</sup>, Dominique Costagliola<sup>a</sup>, and the Clinical Epidemiology Group from the French Hospital Database

**Background:** In the current context of dyslipidaemia, hyperglycaemia and lipodystrophy observed among HIV-seropositive subjects, it is important to study the risk of myocardial infarction (MI) in this population. The French Hospital Database on HIV, which includes a large number of seropositive subjects followed for substantial periods, offers the opportunity to analyse the impact of protease inhibitors (PI) on the risk of MI among men.

**Methods:** Cox model was used to study the risk factors of MI occurrence. Standardized morbidity ratios (SMR) in men exposed to PI were calculated with data from the French general male population (FGMP) of the same age as reference.

**Results:** Between 1996 and 1999, MI was diagnosed in 60 men among 89 029 person-years (PY), including 49 cases among men exposed to PI. The SMR relative to the FGMP was 0.8 (95% CI, 0.5–1.3) for men exposed to PI for  $\leq 18$  months (G1), 1.5 (95% CI, 0.8–2.5) for men exposed for 18–29 months (G2) and 2.9 (95% CI, 1.5–5.0) for men exposed for  $\geq 30$  months (G3). With G1 as reference, the SMR was 1.9 (95% CI, 1.0–3.1) for G2 and 3.6 (95% CI, 1.8–6.2) for G3.

**Conclusion:** Our results point to a duration-related effect relationship between PI and MI, with a higher MI incidence rate among men exposed to PI for 18 months or more.

AIDS 2003, 17:2479–2486

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# Tolérance rénale et osseuse de ténofovir-emtricitabine

## Comparison of Changes in Bone Density and Turnover with Abacavir-Lamivudine versus Tenofovir-Emtricitabine in HIV-Infected Adults: 48-Week Results from the ASSERT Study

Mans-Jürgen Strübenek,<sup>1</sup> Olaf Dicks,<sup>2</sup> Jens Baumert,<sup>3</sup> Julia Geyer,<sup>4</sup> Anja Harhoff,<sup>5</sup> Eric Van Wijngaemont,<sup>6</sup> Adriana Lazzarin,<sup>7</sup> Giuliano Rizzardini,<sup>8</sup> Yvonne S. Sprong,<sup>9</sup> John Lambert,<sup>10</sup> Gunn Viret,<sup>11</sup> David Larder,<sup>12</sup> Sara Higgins,<sup>13</sup> Patrick Zurlo,<sup>14</sup> and Helen Pebody,<sup>15</sup> on behalf of the ASSERT Study Group

<sup>1</sup>Institute for Infectious Diseases, Charité-Universitätsmedizin Berlin, Germany; <sup>2</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>3</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>4</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>5</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>6</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>7</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>8</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>9</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>10</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>11</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>12</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>13</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>14</sup>Charité-Universitätsmedizin Berlin, Germany; <sup>15</sup>Charité-Universitätsmedizin Berlin, Germany

**See the editors' commentary by Peter and Wong on pages 973-974.**

**Background.** Abacavir-lamivudine and tenofovir DF-emtricitabine fixed-dose combinations are commonly used as first-line antiretroviral therapies. However, few studies have prospectively compared their relative safety profiles.

**Methods.** In this European, multicenter, open-label, 48-week study, treatment-naïve adult subjects with human immunodeficiency virus (HIV) infection were randomized to receive either abacavir-lamivudine or tenofovir-emtricitabine with zidovudine. Primary analyses were conducted after 48 weeks of treatment. Bone mineral density (BMD), a proximal secondary end point, was assessed by dual energy X-ray absorptiometry. Bone turnover markers (osteocalcin, procollagen 1-15-terminal propeptide, bone-specific alkaline phosphatase, and type I collagen cross-linked C-telopeptides [CTXs]) were assessed in an exploratory analysis.

**Results.** A total of 385 subjects in the change from baseline in both total hip (abacavir-lamivudine group, -1.9% versus tenofovir-emtricitabine group, -2.4%;  $P = .056$ ), BMD loss of  $\geq 6\%$  was more common in the tenofovir-emtricitabine group (12% versus 5% had a loss of  $\geq 6\%$  in the spine). Bone turnover markers increased in both treatment groups at the first 24 weeks, stabilizing or decreasing thereafter. Increases in all markers were significantly greater in the tenofovir-emtricitabine treatment group than in the abacavir-lamivudine group at week 24. All the CTXs remained significantly different at week 48 (log osteocalcin: abacavir-lamivudine group, +1.67 ng/L; tenofovir-emtricitabine group, +11.32 ng/L;  $P < .001$ ).

**Conclusions.** This study demonstrated the impact of first-line treatment regimens on bone. Greater increases in bone turnover and decrease in BMD were observed in subjects treated with tenofovir-emtricitabine that were observed in subjects treated with abacavir-lamivudine.

Because the treatment of human immunodeficiency virus (HIV) infection is extremely life long, the long-term toxicity profile of antiretroviral therapy (ART) regimens is of major importance. Minimizing long-term toxicity and maximizing the adherence to a treatment regimen and the treatment response are crucial therapy objectives.

At the time of this study, 2 fixed-dose combinations (abacavir/zidovudine [AZV] 300 mg) in combination with lamivudine (300 mg) and tenofovir disoproxil fumarate (300 mg) in combination with emtricitabine (200 mg)

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DOI: 10.1093/cid/cir115

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Mans-Jürgen Strübenek<sup>1</sup>, Olaf Urban<sup>2</sup>, Jens Baumert<sup>3</sup>, Julia Geyrhofer<sup>4</sup>, Jan Hanelt<sup>5</sup>, Eric Van Wijngaert<sup>6</sup>, Adriano Lazzarin<sup>7</sup>, Giuliano Rizzardini<sup>8</sup>, Werner S. Springer<sup>9</sup>, John Lambert<sup>10</sup>, Gunn Viret<sup>11</sup>, David Larder<sup>12</sup>, Sara Hoggan<sup>13</sup>, Pamela Zurbrugg<sup>14</sup> and Helen Pebody<sup>15</sup> on behalf of the ASSERT Study Group

<sup>1</sup>Institute of Infectious Diseases, University of Vienna, Austria; <sup>2</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>3</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>4</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>5</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>6</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>7</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>8</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>9</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>10</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>11</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>12</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>13</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>14</sup>Department of Internal Medicine, University of Vienna, Austria; <sup>15</sup>Department of Internal Medicine, University of Vienna, Austria

See the online commentary by [Gao and Wang](#), on pages 367-371.

**Background:** Abacavir-lamivudine and tenofovir DF-emtricitabine first-line combination are common used as first-line antiretroviral therapies. However, few studies have prospectively compared their relative safety profiles.

**Methods:** In this European, multicenter, open-label, 48-week study, randomized new adult subjects with human immunodeficiency virus (HIV) infection were randomized to receive either abacavir-lamivudine or tenofovir-emtricitabine with stavudine. Primary analyses were conducted after 48 weeks of treatment. Bone density (BMD), a proximal tibia 1.5-tactical propylidone bone specific alkaline phosphatase and osteocalcin (osteocalcin, osteocalcin (OC)) were assessed in an exploratory analysis.

**Results:** A total of 385 subjects were enrolled in the study. BMD loss was observed in both treatment groups. In the change from baseline in both total hip (abacavir-lamivudine group, -1.7% vs. -1.7% in the tenofovir-emtricitabine group,  $P = 0.95$ ) and lumbar spine (abacavir-lamivudine group, -1.7% vs. -1.7% in the tenofovir-emtricitabine group,  $P = 0.95$ ). BMD loss of  $\geq 6\%$  was more common in the tenofovir-emtricitabine group (12% vs. 5% in the abacavir-lamivudine group) and in the tenofovir-emtricitabine group (12% vs. 5% in the abacavir-lamivudine group) at week 48 (log-rank test:  $P = 0.0001$ ). No other significant differences were observed in subjects treated with abacavir-lamivudine or tenofovir-emtricitabine.

**Conclusions:** This study demonstrated the impact of first-line treatment regimens on changes in bone turnover and decrease in BMD were observed in subjects treated with abacavir-lamivudine or tenofovir-emtricitabine.

Because the treatment of human immunodeficiency virus (HIV) infection is extremely life long, the long-term

toxicity profile of antiretroviral therapy and maintaining the safety and the treatment objectives.

At the time of this study, the following regimens were used: abacavir (300 mg) + lamivudine (150 mg) or tenofovir (300 mg) + emtricitabine (200 mg).

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 Published online in Springerlink: 21 September 2010  
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 DOI: 10.1186/1745-7256-9-367

## Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients

Amanda Mocroft<sup>a</sup>, Ole Kirk<sup>b</sup>, Peter Reiss<sup>c</sup>, Stephane De Wit<sup>d</sup>, Dalibor Sedlacek<sup>e</sup>, Marek Beniowski<sup>f</sup>, Jose Gatell<sup>g</sup>, Andrew N. Phillips<sup>a</sup>, Bruno Ledergerber<sup>b</sup>, Jens D. Lundgren<sup>h,i</sup> for the EuroSIDA Study Group

**Objectives:** Chronic kidney disease (CKD) in HIV-positive persons might be caused by both HIV and traditional or non-HIV-related factors. Our objective was to investigate long-term exposure to specific antiretroviral drugs and CKD.

**Design:** A cohort study including 6643 HIV-positive persons with at least three serum creatinine measurements and corresponding body weight measurements from 2004 onwards.

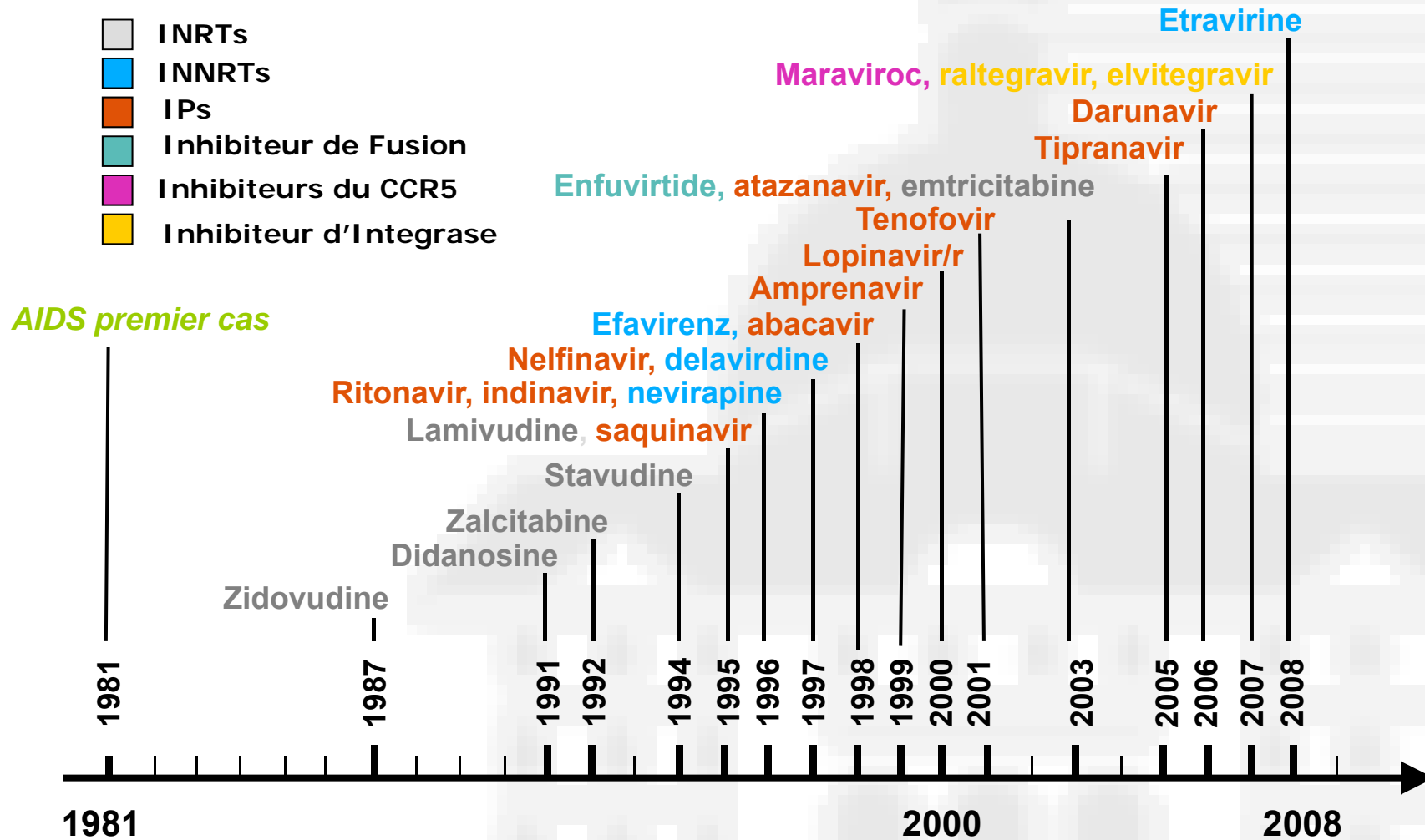
**Methods:** CKD was defined as either confirmed (two measurements  $\geq 2$  months apart) estimated glomerular filtration rate (eGFR) of  $< 60$  mL/min per  $1.73$  m<sup>2</sup> or below for persons with baseline eGFR of above  $60$  mL/min per  $1.73$  m<sup>2</sup> or less, using the Cockcroft-Gault formula. Poisson regression was used to determine factors associated with CKD.

**Results:** Two hundred and twenty-five (3.4%) persons progressed to CKD during 21 482 person-years follow-up, an incidence of 1.05 per 100 person-years follow-up (95% confidence interval (CI) 0.91–1.18); median follow-up was 3.7 years (interquartile range 2.8–5.7). After adjustment for traditional factors associated with CKD and other confounding variables, increasing cumulative exposure to tenofovir (incidence rate ratio (IRR) per year 1.16, 95% CI 1.06–1.25,  $P < 0.0001$ ), indinavir (incidence rate ratio (IRR) 1.05, 95% CI 1.01–1.10,  $P = 0.0001$ ) and zalcitabine (IRR 1.12, 95% CI 1.03–1.24,  $P = 0.0003$ ) and increased rate of CKD. Consistent results were observed in wide-ranging sensitivity analyses, although of marginal statistical significance for lopinavir. No other antiretroviral drugs were associated with increased incidence of CKD.

**Conclusions:** In this nonrandomized large cohort, increasing exposure to tenofovir was associated with a higher incidence of CKD, as was true for indinavir and zalcitabine, whereas the results for lopinavir were less clear.

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 AIDS 2010, 24:1667–1678

# Molécules antirétrovirales disponibles



# Barrières contre la résistance : pharmacologie et génétique

## INRTs

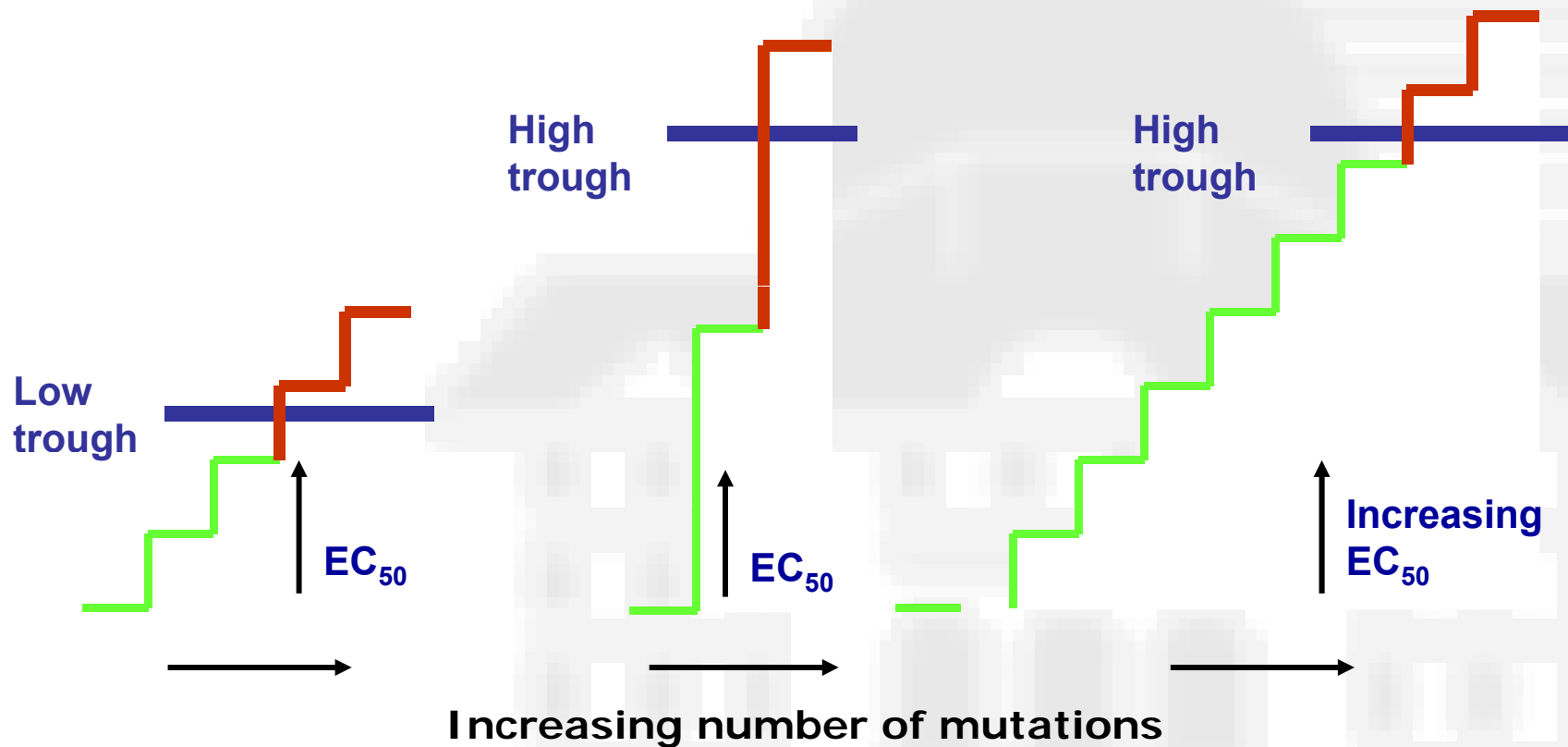
Small change per mutation  
*BUT*  
Low drug levels

## INNRTs

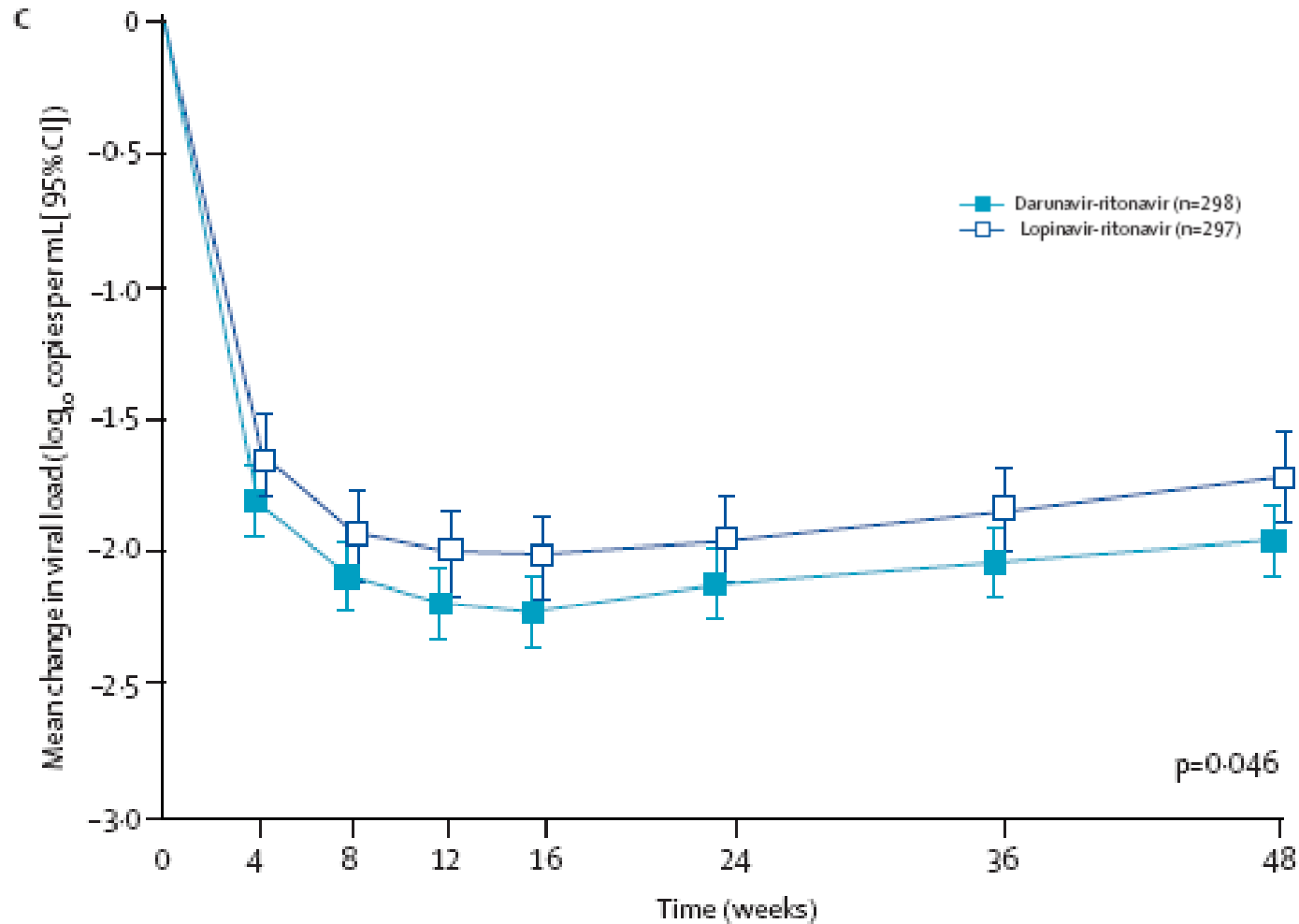
High drug levels  
*BUT*  
Large change per mutation

## IP

Small change per mutation  
*AND*  
High drug levels



# Darunavir/r vs lopinavir

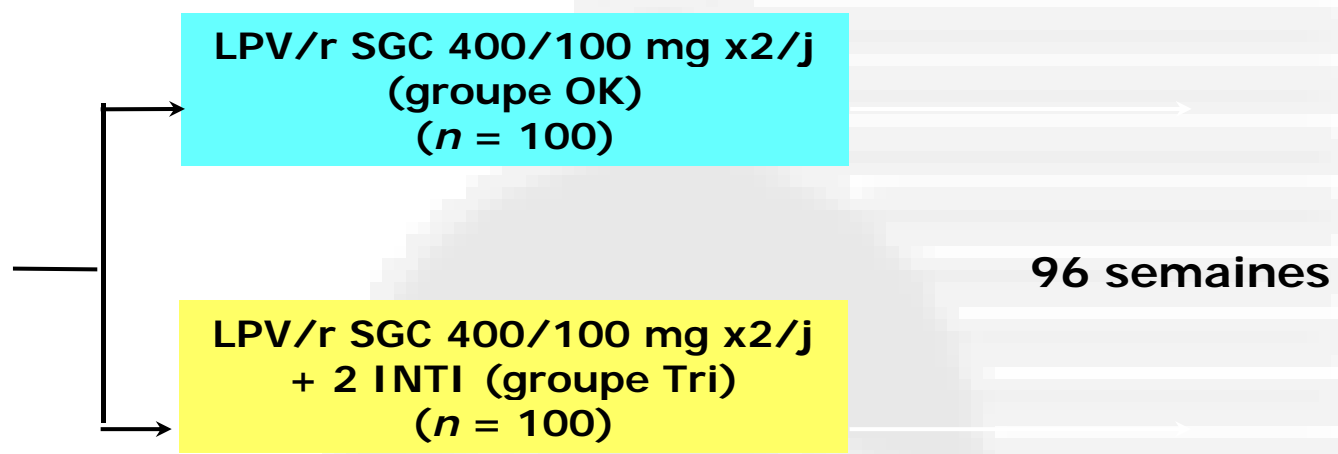


José Valdez Madruga, et al on behalf of the TITAN study group Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial *Lancet* 2007; 370: 49–58

# Simplification par Kalétra en monothérapie vs poursuite de 2 INTI + Kalétra : essai OK04

- Essai randomisé ouvert de non-infériorité

- CV <50 c/ml depuis > 6 mois
- Pas d'ATCD d'échec virologique sous IP
- Sous LPV/r + 2 INTI depuis > 1 mois



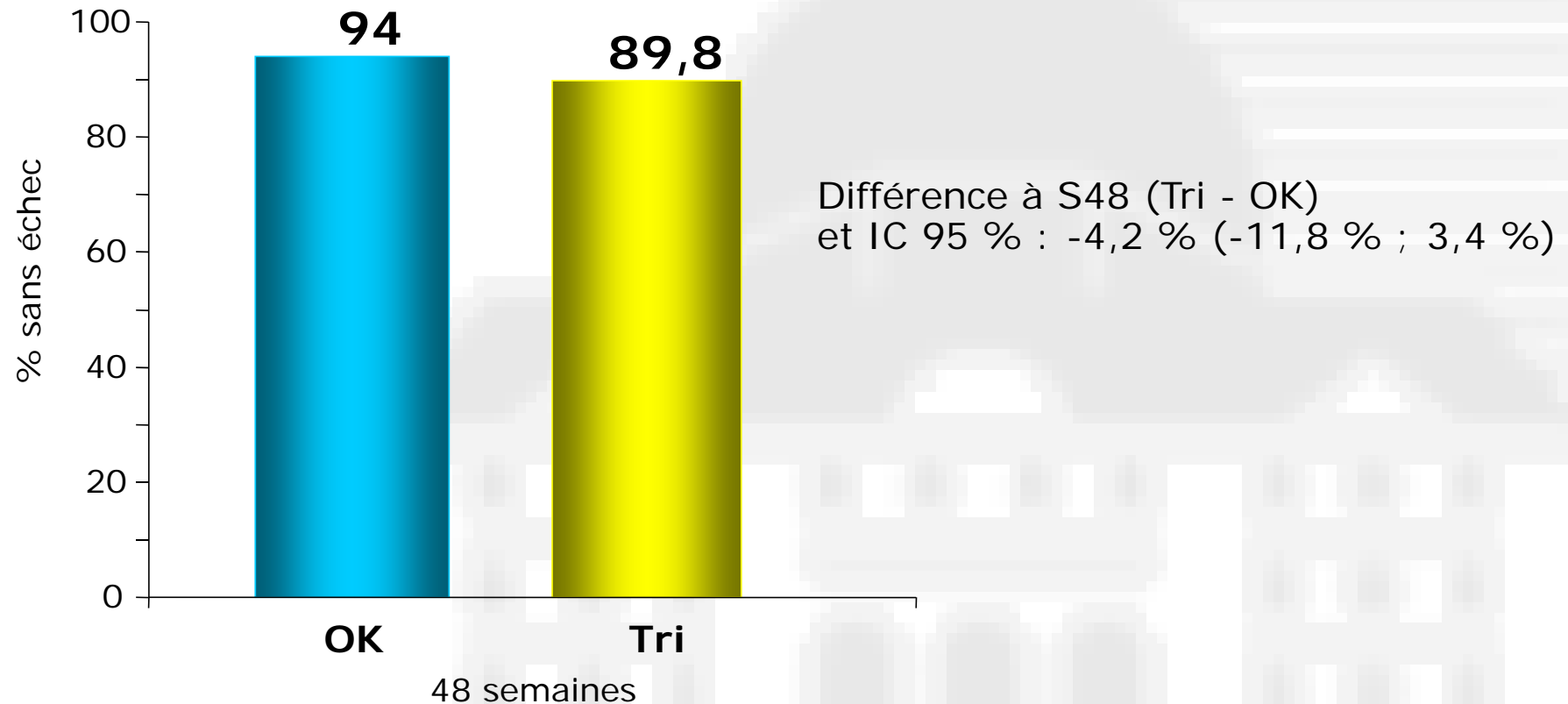
Suivi : sélection, J0, S4, S12, puis toutes les 12 semaines jusqu'à S96

- Critère de jugement principal : absence d'échec à S48
- Définition de l'échec :
  - 2 CV > 500 c/ml espacées de 2 semaines (sans re-négativon de la CV après ré-induction avec 2 INTI dans le groupe OK), OU
  - Modification du traitement alloué pour autre chose qu'une ré-induction, OU
  - Arrêt de traitement, OU
  - Perdu de vue

# Simplification par Kalétra en monothérapie vs poursuite de 2 INTI + Kalétra : essai OK04

Résultats (critère de jugement principal) : % sans échec

- Les patients du groupe OK qui ont maintenu une CV < 50 c/ml après ré-induction par 2 INTIS (n = 4) n'ont pas été considérés comme des échecs



## Simplification par Kalétra en monothérapie vs poursuite de 2 INTI + Kalétra : essai OK04

- Résistance : test génotypique chez tous les patients avec une CV > 500 c/ml, blips > 500 c/ml inclus

	OK (n = 100)	Tri (n = 98)
n	11 (11 %)	4 (4 %)
Souches avec mutations primaires IP	2 [10F, 46I, 82A/V] [54V, 77I, 82A]	1 [54V, 63P, 71V, 82A]
Souches sans mutations primaires IP	9	3

# Points de réflexion dans la conception d'un protocole

- Question posée
- Justification de la question posée
- **Sélection de la population**
- Objectifs
- Critères de jugement
- Méthodologie
- Aspect éthique de l'étude
- Faisabilité de l'étude

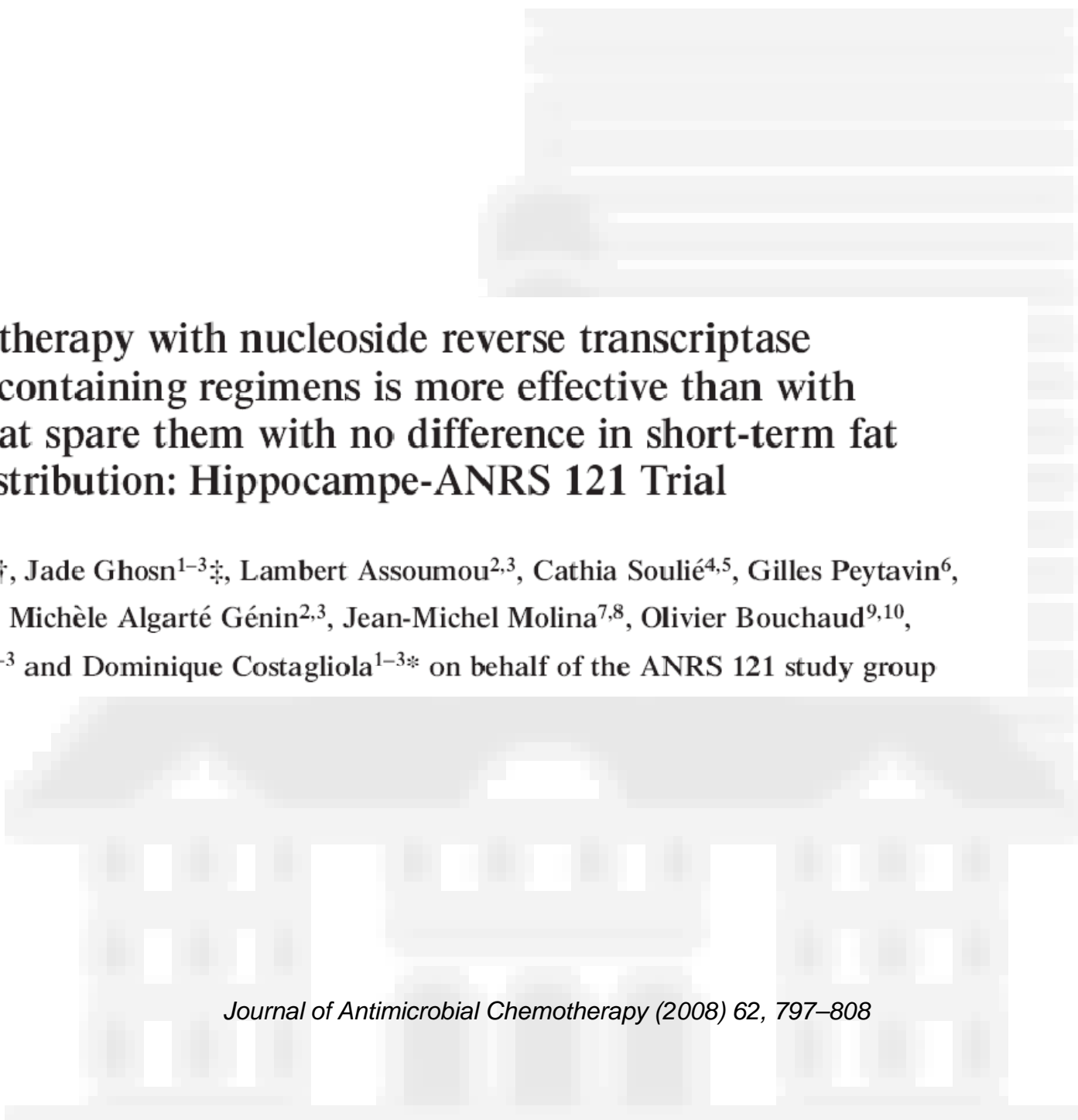
# Sélection de la population

- Patients traités ou non traités ?
- Patients contrôlés ou non contrôlés ?



# Sélection de la population

- Patients traités ou non traités ?
- Patients contrôlés ou non contrôlés ?
- Patients :
  - recevant une trithérapie antirétrovirale
  - présentant une infection VIH contrôlée
  - n'ayant pas d'antécédent d'échec aux IP dans l'histoire thérapeutique
  - n'ayant jamais reçu de darunavir



**Initial therapy with nucleoside reverse transcriptase inhibitor-containing regimens is more effective than with regimens that spare them with no difference in short-term fat distribution: Hippocampe-ANRS 121 Trial**

Claudine Duvivier<sup>1-3†</sup>, Jade Ghosn<sup>1-3‡</sup>, Lambert Assoumou<sup>2,3</sup>, Cathia Soulié<sup>4,5</sup>, Gilles Peytavin<sup>6</sup>, Vincent Calvez<sup>4,5</sup>, Michèle Algarté Génin<sup>2,3</sup>, Jean-Michel Molina<sup>7,8</sup>, Olivier Bouchaud<sup>9,10</sup>, Christine Katlama<sup>1-3</sup> and Dominique Costagliola<sup>1-3\*</sup> on behalf of the ANRS 121 study group

*Journal of Antimicrobial Chemotherapy* (2008) 62, 797–808

# Points de réflexion dans la conception d'un protocole

- Question posée
- Justification de la question posée
- Sélection de la population
- **Objectifs**
- Critères de jugement
- Méthodologie
- Aspect éthique de l'étude
- Faisabilité de l'étude

# Objectifs

- Primaire
  - Evaluer la capacité d'une monothérapie d'IP boosté (darunavir) à maintenir un succès virologique, chez des patients infectés par le VIH-1, ayant une charge virale indétectable de façon prolongée.
- Secondaires
  - Evaluation de la charge virale au sein du compartiment génital masculin
  - Evolution de la répartition des graisses

# Points de réflexion dans la conception d'un protocole

- Question posée
- Justification de la question posée
- Sélection de la population
- Objectifs
- **Critères de jugement**
- Méthodologie
- Aspect éthique de l'étude
- Faisabilité de l'étude

# Critère de jugement

- Critère de jugement
  - Proportion de patients en succès virologique, c'est-à-dire n'ayant pas de **charge virale > 400 copies/ml** sur deux prélèvements consécutifs à 2 semaines d'intervalle, au cours des 48 premières semaines de l'étude.

# Critère de jugement

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# Points de réflexion dans la conception d'un protocole

- Question posée
- Justification de la question posée
- Sélection de la population
- Objectifs
- Critères de jugement
- **Méthodologie**
- Aspect éthique de l'étude
- Faisabilité de l'étude

# Méthodologie

- Etude de **non infériorité** de phase III, multicentrique, prospective, randomisée, sans insu comparant une stratégie de monothérapie d'IP boosté avec le darunavir versus une trithérapie comprenant 2 INTI + darunavir/r.



# Méthodologie

- Etude de **non infériorité** de phase III, multicentrique, prospective, randomisée, sans insu comparant une stratégie de monothérapie d'IP boosté avec le darunavir versus une trithérapie comprenant 2 INTI + darunavir/r.
- Principe de l'essai de non infériorité
  - Accepter une nouvelle stratégie même si elle n'est pas plus efficace que le traitement standard
  - Avantage sur d'autres points
  - A condition qu'il n'entraîne pas une perte d'efficacité supérieure à une certaine limite

# Méthodologie

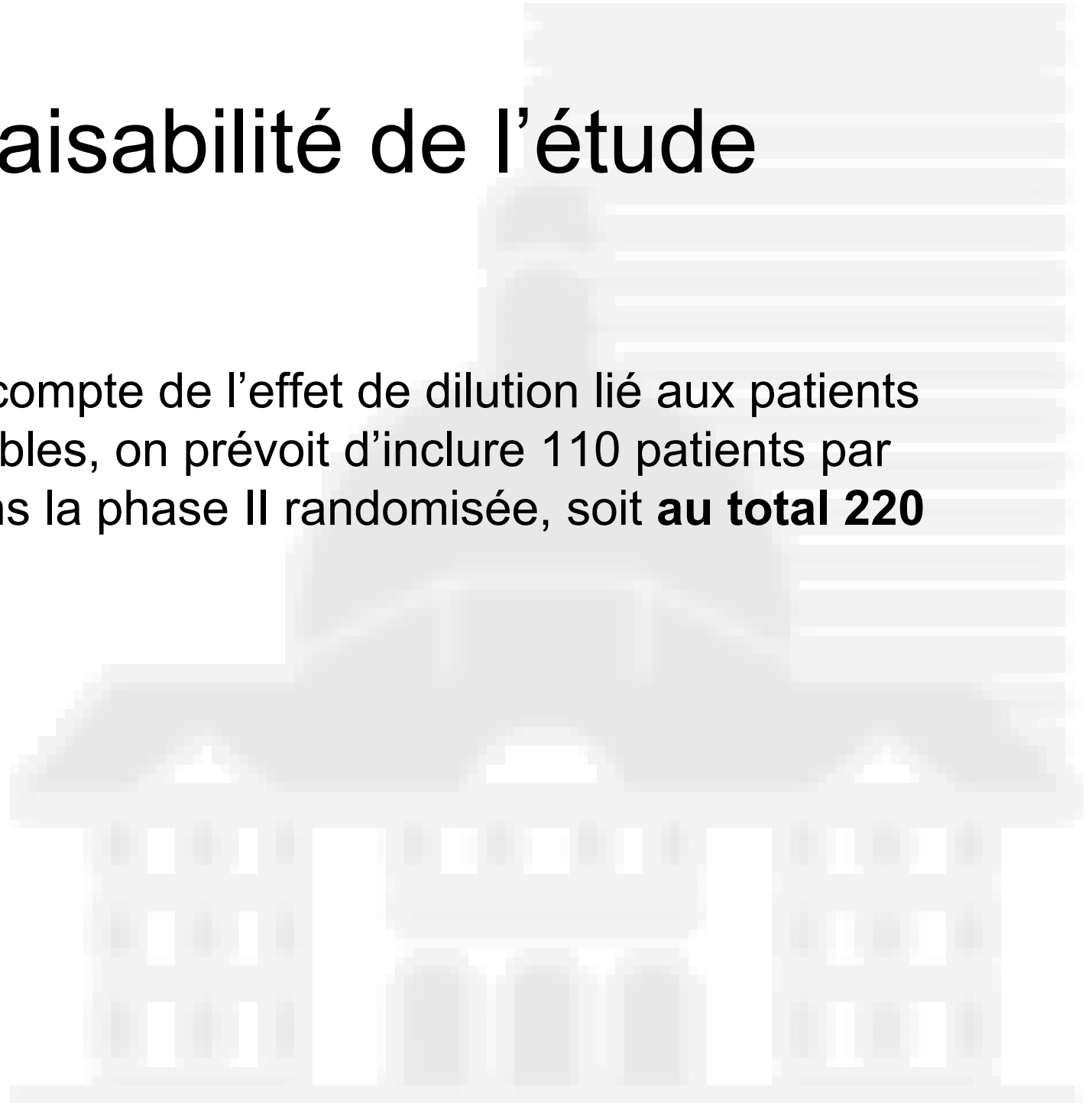
- Hypothèse du maintien de succès à 95 % dans le bras trithérapie et hypothèse de succès dans le bras IP boosté seul allant de 95% à 90%.
- Pour la non-infériorité virologique :
  - calcul de l'intervalle de confiance unilatérale à 95% de la différence du pourcentage de patients ne développant pas d'échec virologique entre le bras monothérapie de darunavir et le bras maintien de la trithérapie.
  - comparaison entre la borne inférieure de l'intervalle de confiance et la borne de non-infériorité prédéfinie, 10%.

# Points de réflexion dans la conception d'un protocole

- Question posée
- Justification de la question posée
- Sélection de la population
- Objectifs
- Critères de jugement
- Méthodologie
- **Faisabilité de l'étude**
- Aspect éthique de l'étude

# Faisabilité de l'étude

- Pour tenir compte de l'effet de dilution lié aux patients non évaluables, on prévoit d'inclure 110 patients par groupe dans la phase II randomisée, soit **au total 220 patients**.



# Points de réflexion dans la conception d'un protocole

- Question posée
- Justification de la question posée
- Sélection de la population
- Objectifs
- Critères de jugement
- Méthodologie
- Faisabilité de l'étude
- Aspect éthique de l'étude

# Aspect éthique

- Assurer au patient un traitement antirétroviral efficace
- Assurer un suivi virologique stricte et établir la conduite à tenir en cas d'échappement virologique
- Etablir la conduite à tenir en cas d'événement indésirable



# MONOI ANRS 136

A randomized multicenter study to compare the efficacy of a monotherapy of darunavir to a triple therapy with 2 nucleosides analogues combined to darunavir/r in HIV infected patients with full viral suppression.

C Katlama, MA Valantin, M Algarte-Genin, C Duvivier, S Lambert-Niclot, PM Girard, JM Molina, B Hosten, S Pakianather, G Peytavin, AG Marcelin, P Flandre.

**Abstract WELBB102**



**5th IAS**

Conference on HIV Pathogenesis, Treatment & Prevention

19-22 July 2009 • cape town • south africa

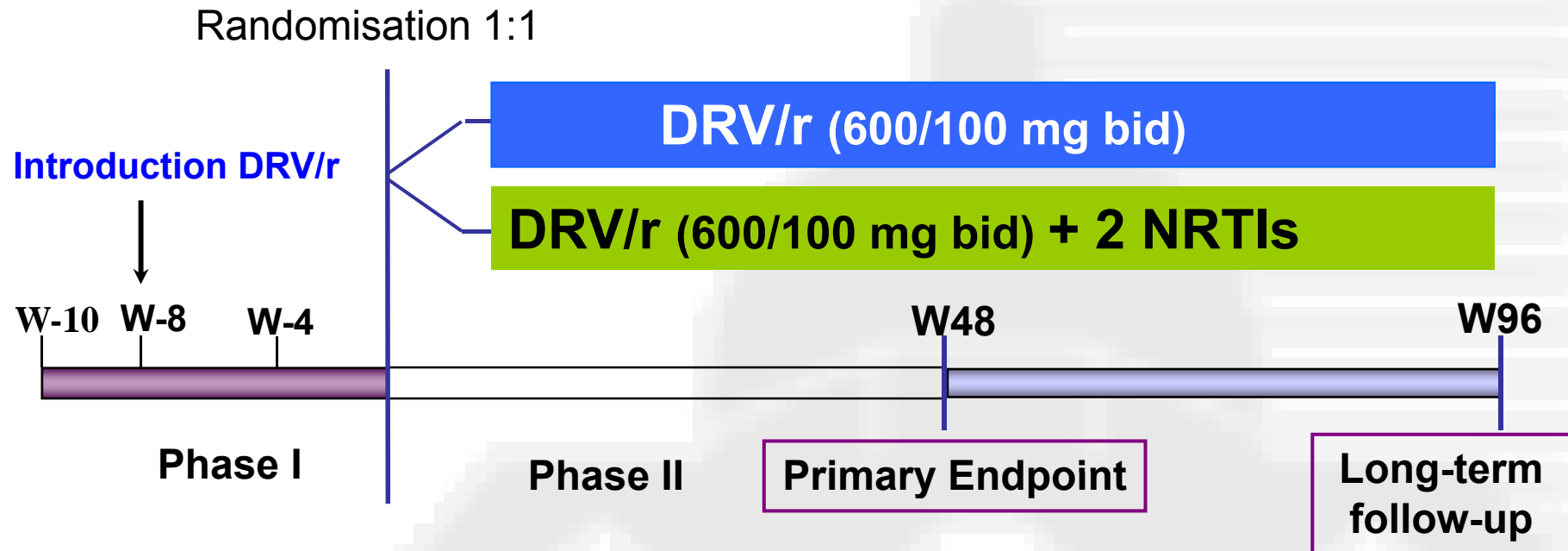
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# MONOI Study Design 1

- Multicenter open label randomized study



## Main inclusion criteria

- cART  $\geq$  18 months
- CD4 count  $\geq$  200 cells/mm<sup>3</sup>
- HIV RNA  $<$ 400 copies/ml in the last 18 months and  $<$ 50 copies/ml at entry
- No history of PI failure and naïve to darunavir



# MONOI Study Design 2

- **Primary objective**

To demonstrate non-inferiority of DRV/r monotherapy versus 2 NRTIs + DRV/r in patients with viral suppression ( per protocol population )

- **Primary endpoint** : virological success until W48

Virological failure is defined as

- 2 consecutive HIV-1 RNA > 400 copies/ml within 2 weeks
- Any ART modification or study withdrawal

- **Study power**

Power = 80% Non-inferiority margin of 10% ( 90% CI )  
assuming success rates in both arms at W48 of 90%

- **ITT population**

All patients receiving drug at D0 (ITT exposed)

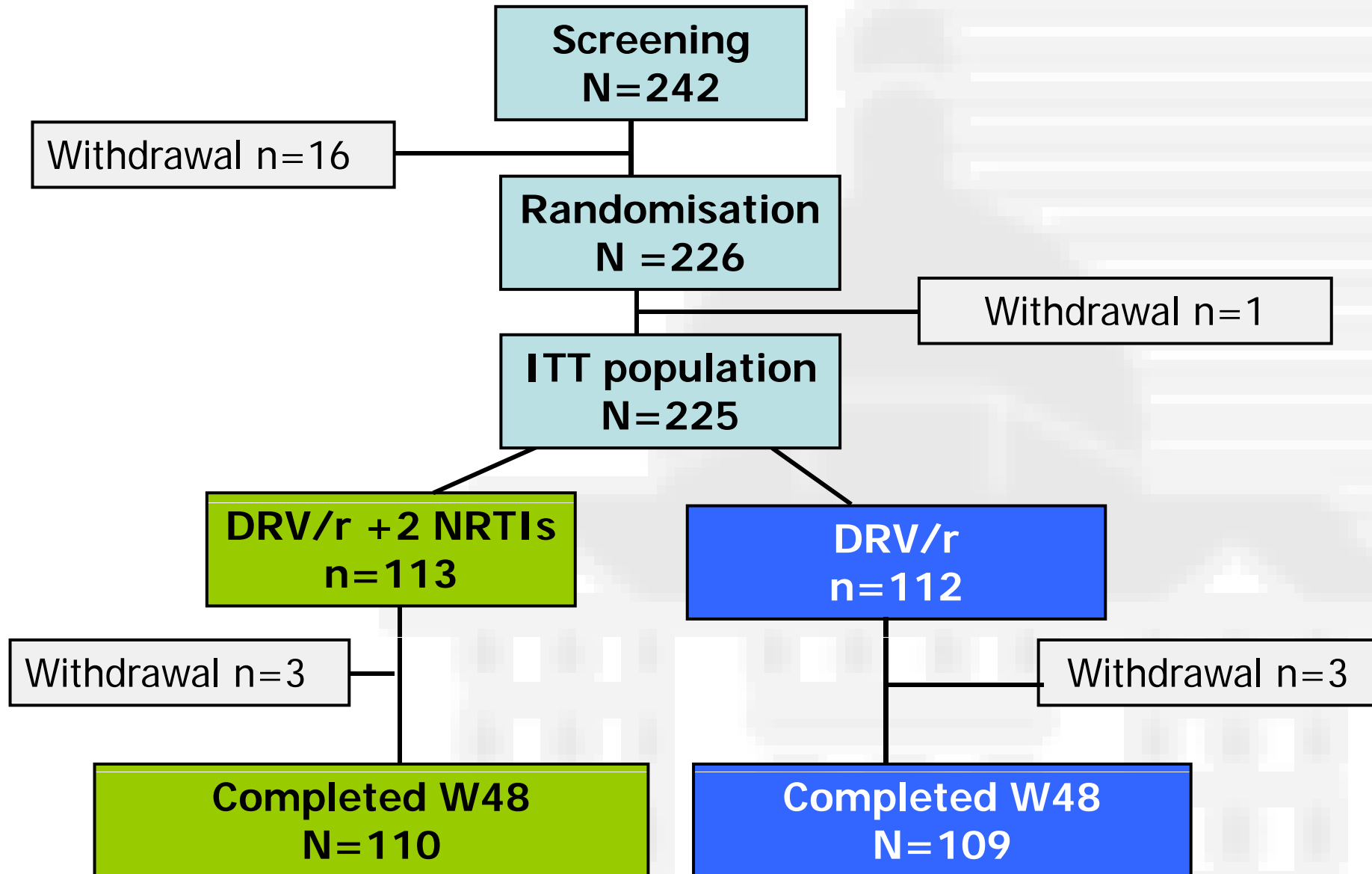
- **Per protocol (PP) population** excluded

Patients who withdrew (n=6) or discontinued Rx without VF or SAE (n=10)

Patients who did not fulfill the inclusion criteria (n=5)



# Patients Disposition



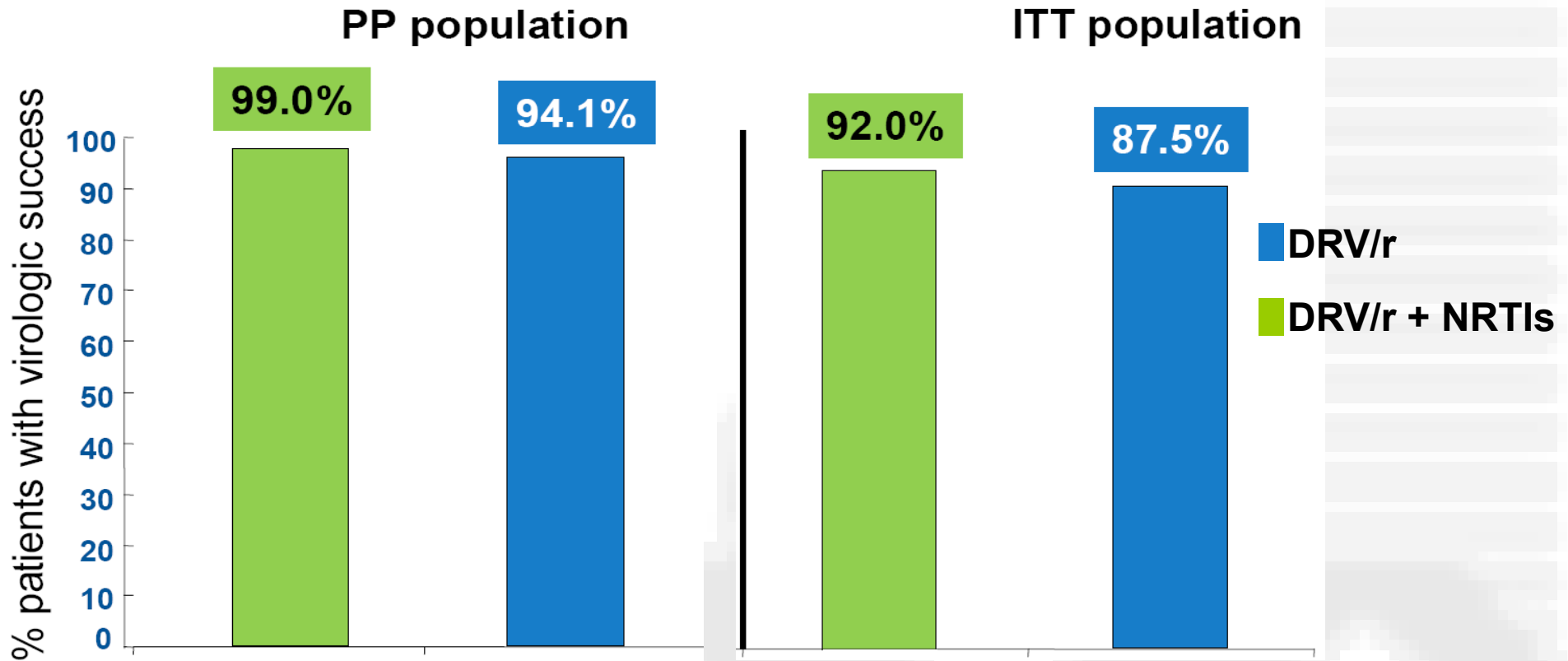


# Patient Characteristics

median value (IQR)	DRV/r + 2 NRTIs N=113	DRV/r N=112
<b>Age</b>	45.4 (39–56)	45.8 (41 – 52)
<b>HIV-RNA before Rx initiation log<sub>10</sub> (n=153)</b>	4.9 (4.4– 5.3)	4.9 (4.4 – 5.3)
<b>Baseline CD4 count</b>	582 (390–780)	585 (457–757)
<b>Duration of HIV infection, years</b>	8.9 (4.2–15.6)	11.7 (6.6–15.9)
<b>Duration of ART, years</b>	<b>7.8 (3–11.3)</b>	<b>8.7 (4.7-11.3)</b>
<b>N with 3 class experience (%)</b>	<b>49 (43%)</b>	<b>43 (38%)</b>
<b>ART at screening (W-10)</b>		
<b>2 NRTIs + PI</b>	73%	64%
<b>2 NRTIs + NNRTI</b>	19%	20%
<b>3 NRTIs</b>	6%	14%



# MONOI Primary Endpoint W48



Response	Difference (Lower limit CI)
Rx success (PP, n=204)	- 4.9% ( - 9% )
Rx success (ITT, n=225)	- 4.5% (-11% )

-9% > -10% → mono DRV/r non inferior to DRV/r + 2 NRTIs

-11% < -10% → failure to demonstrate non-inferiority



# MONOI Reasons for failure

ITT population	DRV/r + 2 NRTIs N = 113	DRV/r N = 112
Rx modification	6 (5.3%)	8 (7.1%)
Study withdrawal	3 (2.7%)	3 (2.7%)
Virological failure	0	3 (2.7%)

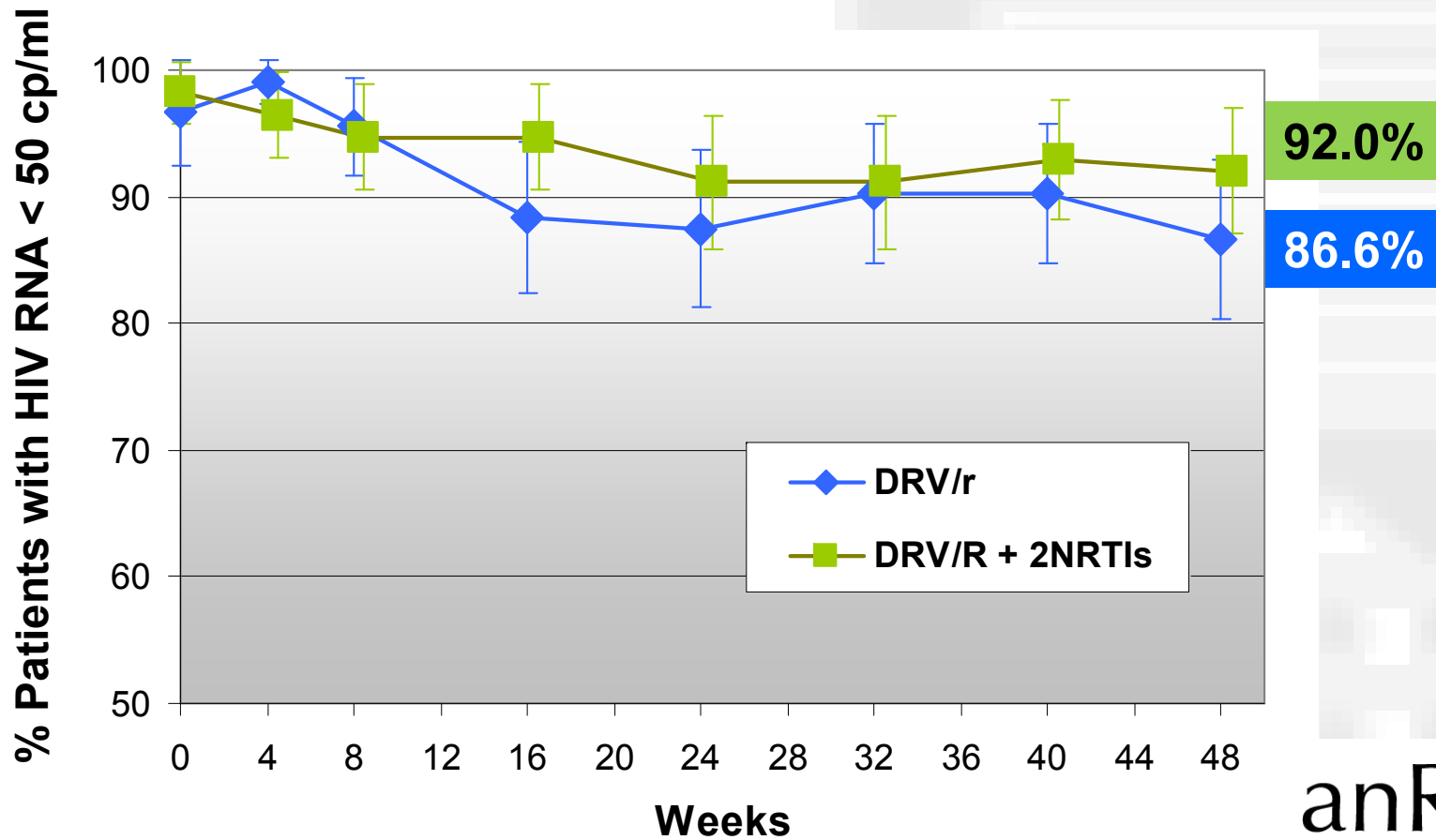


# Virological Failures in DRV/r arm

- HIV RNA and DRV PK data at time of failure
  - pt # 1 : W8 **2722 cp/ml**      **Low C<sub>24h</sub>**      **1120 ng/ml**
  - pt # 2 : W24 **411cp/ml**      **Adequate C<sub>24h</sub>** **3480 ng/ml**
  - pt # 3 : W32 **484.569 cp/ml**      **Treatment discontinuation**
- No new DRV resistance mutations in the 3 patients
- In all 3 patients, intensification with 2 NRTIs added to DRV/r, led to HIV RNA <50 copies/ml



# Proportion of patients with HIV RNA < 50 copies /ml : ITT population

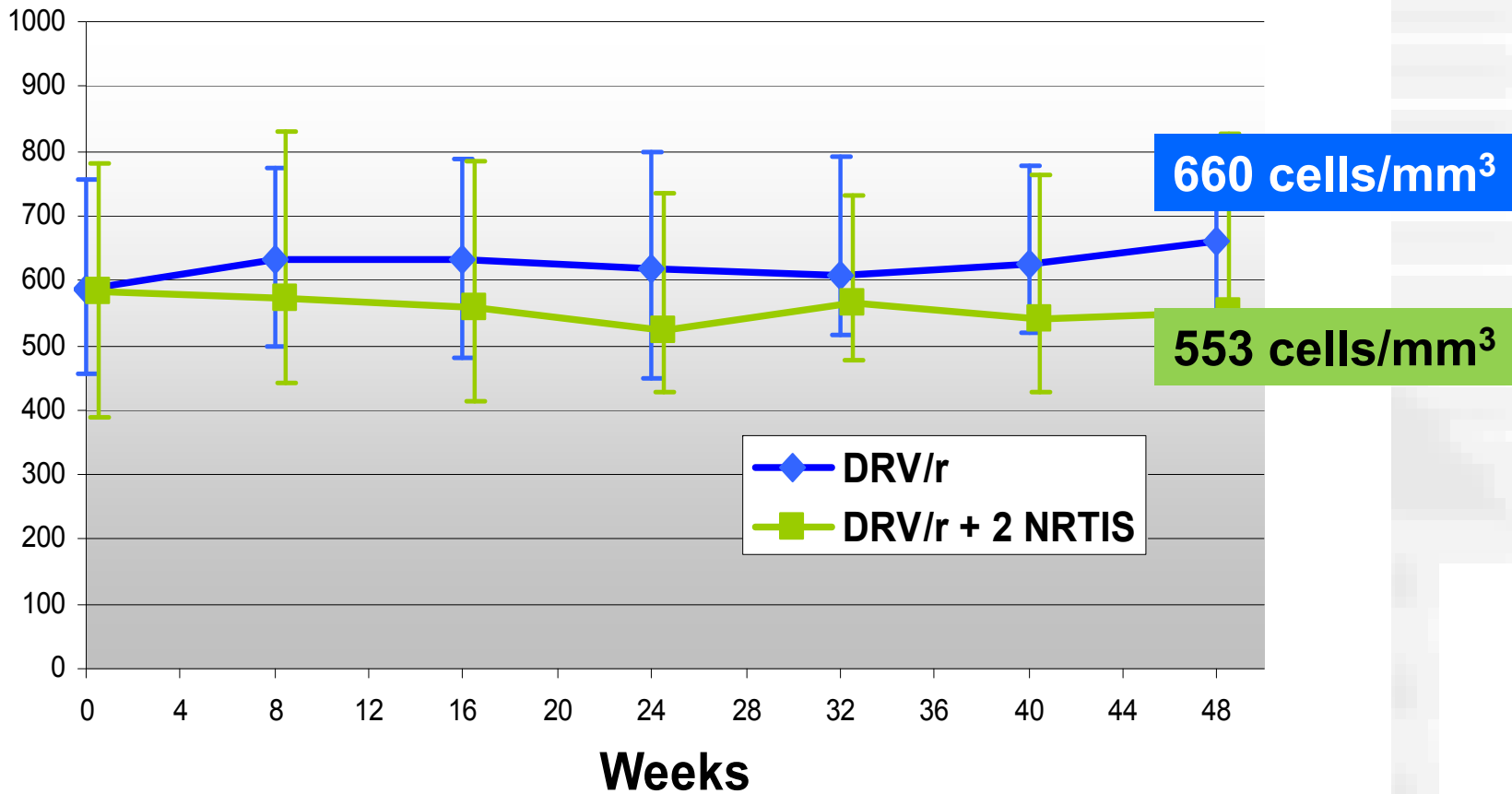




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# CD4 cell count response ITT population

Median CD4 cell count and IQR





# MONOI Serious Adverse events

Number of events	DRV/r + 2 NRTIs n=15	DRV/r n=14
Infections	2	2
Psychiatric events	1	0
CNS disorders	1	3*
Cardiovascular	2	1
Cancer	0	3
Lipodystrophy	0	1
Surgery	6	3
GI disorders	1	0
Hepatic transaminases increase	1	1
CPK	1	0

\*one HIV encephalitis and one neurological symptoms possibly related to HIV, both possibly related to study treatments

HIV RNA CSF:580 cp/ml and 330 cp/ml



# Summary

- DRV/r monotherapy showed non-inferior efficacy versus 2 NRTI + DRV/r at W48 in the primary analysis :  
**94.1% vs 99.0%** (Per Protocol population)
- The efficacy rates in ITT were very concordant and close to non-inferiority : **87.5% vs 92%**
- Three virological failures (>400 cp/ml ) were observed in DRV/r monotherapy with no induced resistance to DRV and subsequent viremia suppression after resuming 2 NRTIs
- Discordant Plasma/CNS symptomatic HIV replication in 2 pts on DRV/r with subsequent viral suppression



# Acknowledgment



Agence nationale de recherches  
sur le sida et les hépatites virales

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F RAFFI

**Partnership** A.CHERET Tibotec / Janssen- Cilag



# MONOI ANRS 136

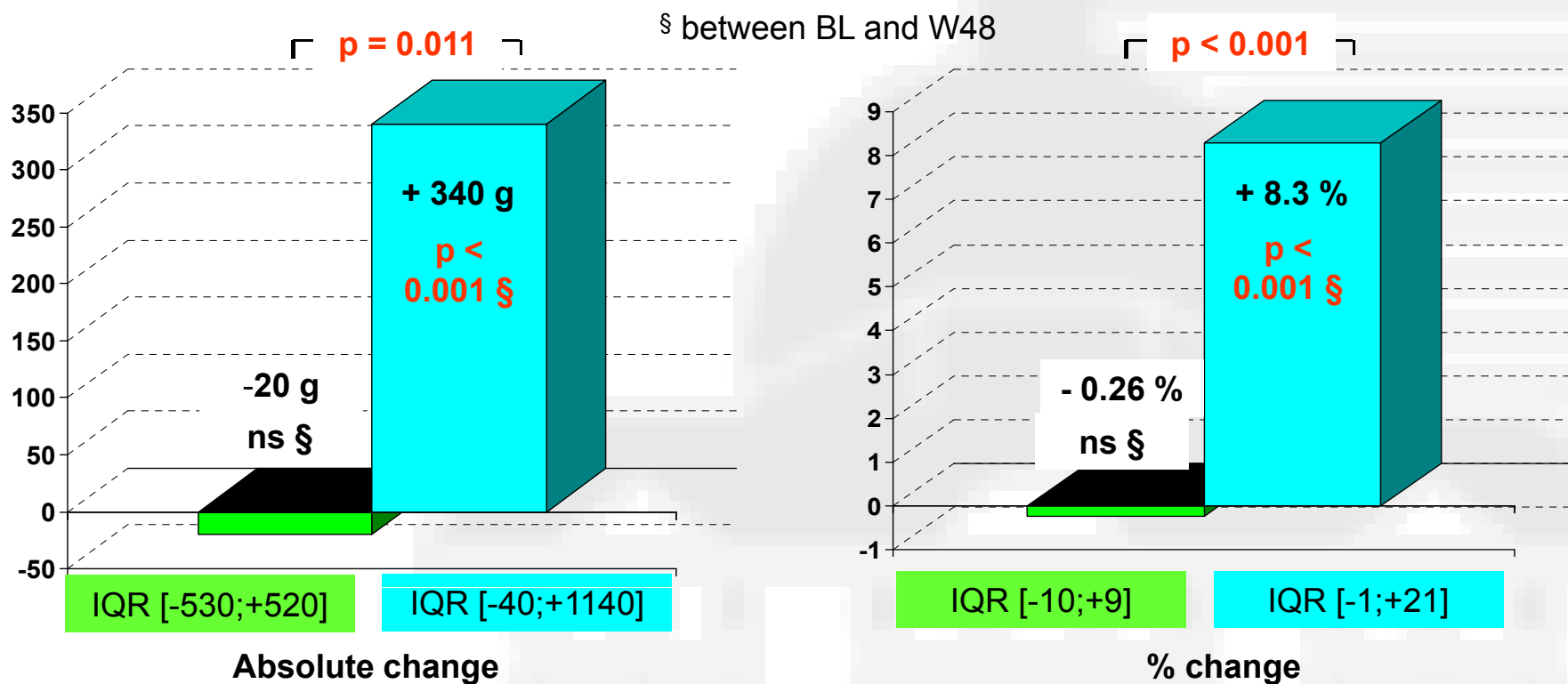
## Etude Dexa



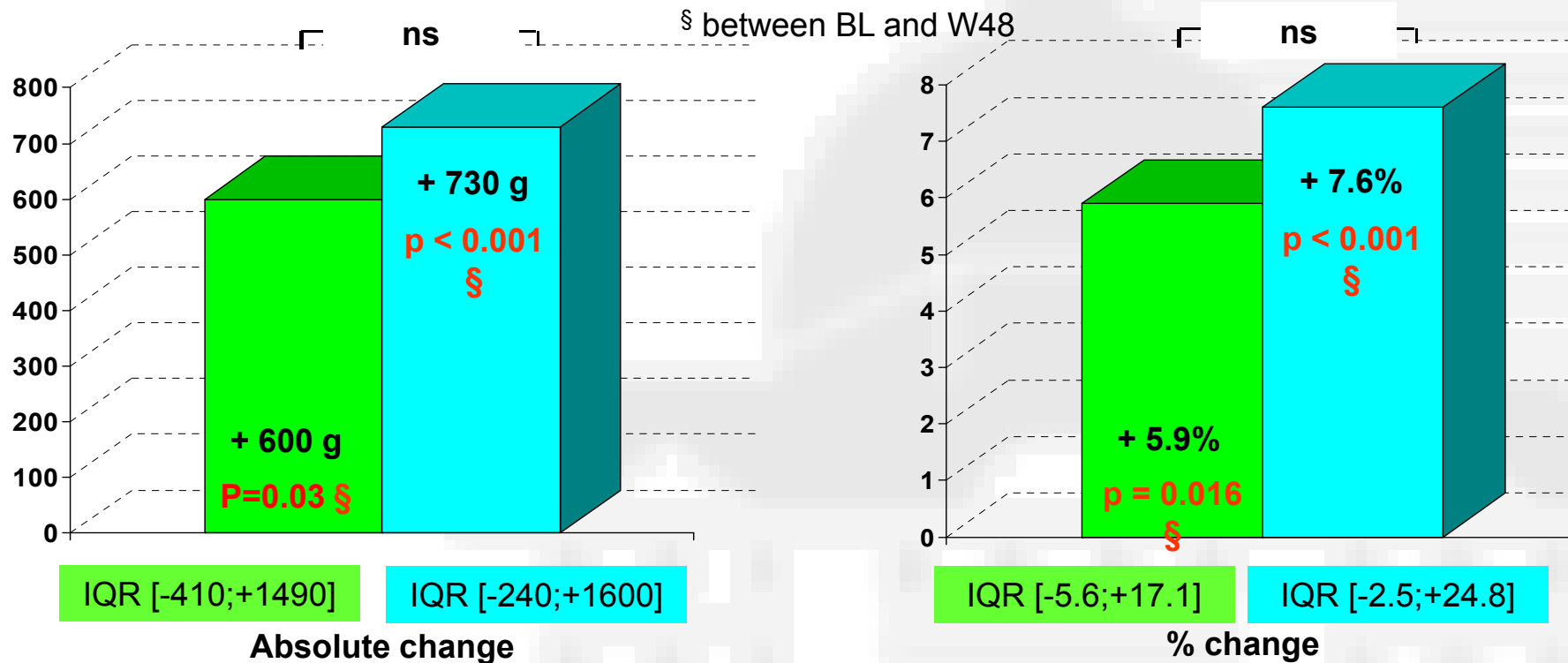
# Methods

- Body composition was measured by whole body scan using dual x-ray absorptiometry (DEXA) at study entry, week 48 and week 96.
- All DEXA evaluations were performed according to a standardized protocol and data were centrally analyzed blinded to treatment group. Results at week 48 are presented.
- At baseline and week 48 : 141 patients (DRV/r + 2 NRTIs n=74; DRV/r n=77) of the 225 patients MONOI subjects.

# Median change in limb fat from baseline to week 48



# Median change in trunk fat from baseline to week 48



# Sensitivity analysis of lipoatrophy and lipohypertrophy occurrence at week 48

	DRV/r + 2 NRTIs N=74	DRV/r N=67	p
<b>Lipoatrophy</b>			
>10% loss in limb fat n (%)	17/74 (22.9%)	4/67 (5.9%)	<b>p=0.005</b>
>20% loss in limb fat n (%)	8/74 (10.8%)	1/67 (1.5%)	<b>p=0.035</b>
>30% loss in limb fat n (%)	2/74 (2.7%)	0/67	ns
<b>Lipohypertrophy</b>			
>10% gain in trunk fat n (%)	25/74 (33.8%)	32/67 (47.8%)	ns
>20% gain in trunk fat n (%)	17/74 (23.0%)	18/67 (26.9%)	ns
>30% gain in total fat n (%)	9/74 (12.2%)	13/67 (19.4%)	ns

# Serum lipid change from baseline to week 48

	DRV/r + 2 NRTIs	DRV/r	p
Total cholesterol (mg/dl) (median [IQR])	2.3 [-27.1-17.4]	6.4 [-15.5-30.9]	ns
LDL cholesterol (mg/dl) (median [IQR])	2.3 [-26.0-24.8]	5.8 [-23.3-21.8]	ns
HDL cholesterol (mg/dl) (median [IQR])	-0.6 [-6.0-8.1]	0.4 [-5.4-6.6]	ns
Triglycerides (mg/dl) (median [IQR])	-4.2 [-35.9-36.0]	4.4 [-37.0-51.7]	ns
Glucose (mg/dl) (median [IQR])	-1.8 [-5.4-3.6]	3.6 [-3.6-7.20]	<b>0.012</b>

# Conclusion

- Moins de lipoatrophie dans le bras darunavir/r monothérapie
  - Impact des INRT en particulier le ténofovir ou l'abacavir ?
- Augmentation de volume abdominal dans les deux bras
  - Lien avec les inhibiteurs de la protéase ?
    - Equilibre entre INRT et IP ?
  - Influence du mode de vie ?
  - Evolution naturelle ?
    - Vieillesse accélérée ?
- Augmentation de la glycémie dans le bras monothérapie
- Pas d'impact sur les lipides

Poster N-131

17th Conference on Retroviruses and  
Opportunistic Infections  
San Francisco - February 16-19, 2010

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# Darunavir Concentrations in Seminal Plasma in patients receiving Darunavir/ritonavir (DRV/r) monotherapy: a MONOI-ANRS 136 substudy

Lambert-Niclot S<sup>1</sup>, Duvivier C<sup>2</sup>, Algarte-Genin M<sup>3</sup>,  
Pakianather S<sup>3</sup>, Meynard JL<sup>4</sup>, Valantin MA<sup>5</sup>, Molina JM<sup>6</sup>,  
Marcelin AG<sup>1</sup>, Katlama C<sup>5</sup>, Peytavin G<sup>7</sup>

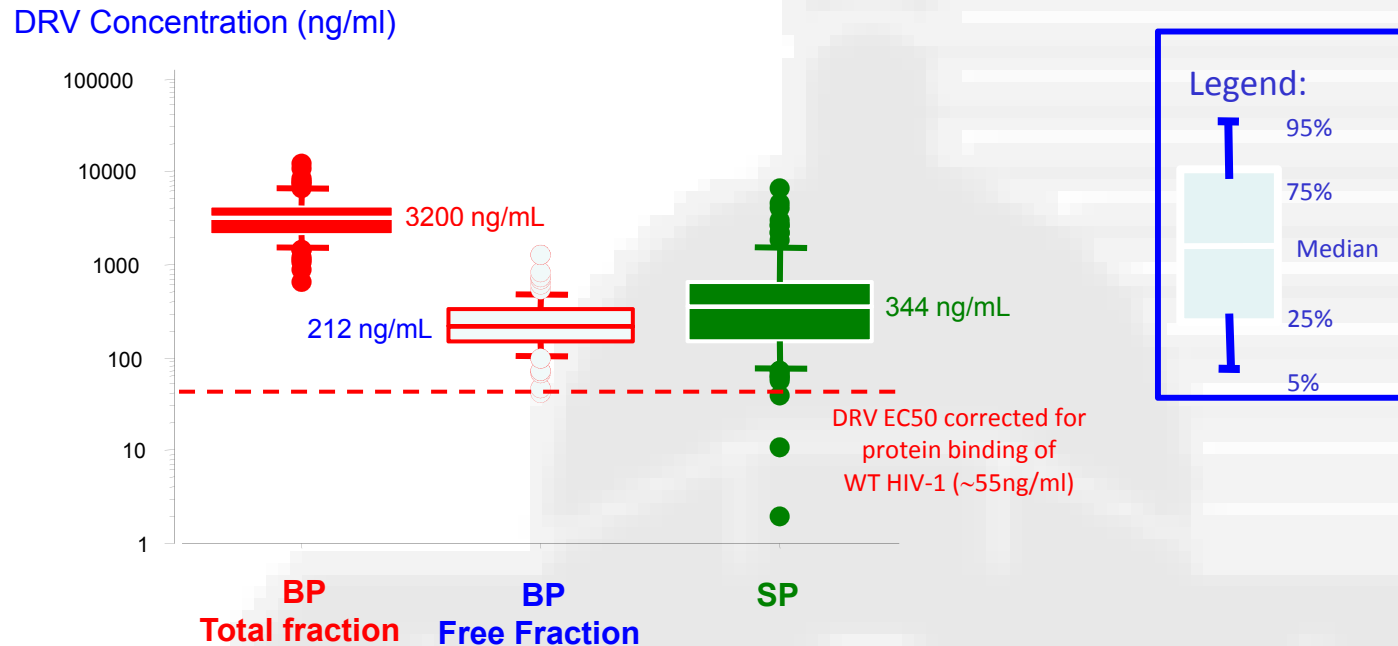
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# DRV Concentrations in Blood Plasma (free and total protein binding) and in Seminal Plasma



	Interval last intake/Sampling		DRV Concentrations (ng/mL)			DRV Ratio (%)	
	BP (Hours)	SP (Hours)	BP Total Fraction	BP Free Fraction	SP	BP Free/ Total Fraction	SP/BP Total fraction
<b>N</b>	69	87	70	70	95	70	70
<b>Median</b>	12.0	15.9	3200	212	344	7,2%	8,6%
<b>IQR25%-75%</b>	10.8-13.5	13.3-17.3	2127-4179	154-326	149-652	5,9-9,0%	5,7-22,2%

DRV results from tritherapy and monotherapy were merged for this analysis,

# Virological results

- Among the 45 patients tested for HIV-1 RNA in both samples, HIV-1 RNA was detectable (> 200 c/mL) in 6 SP samples in 6 different patients:

Patients N°	D0		W48		Arm
	BP	SP	BP	SP	
1	<40	<200	<40	270	Mono
2	<40	1345	<40	<200	Mono
3	<40	345	<40	<200	Mono
4	<40	385	<40	NA	Triple
5	<40	<200	<40	345	Triple
6	<40	<200	<40	475	Triple

- Whatever the biological matrix, no relationship between DRV concentrations and HIV-RNA was evidenced.

# Communications dans les congrès & Publications

- IAS conference on HIV Pathogenesis, Treatment and Prevention 2009 (Cape Town) communication orale. Premiers résultats virologiques (S48)
- Conference on Retroviruses and Opportunistic Infections 2010 (San Francisco) poster. Résultats sur le tissu adipeux.
- Conference on Retroviruses and Opportunistic Infections 2010 (San Francisco) communication orale. Etude sperme.
- Soumission à la Conference on Retroviruses and Opportunistic Infections 2011:
  - Résultats virologiques à S96
  - Facteurs prédictifs
  - Etudes pharmacologiques

# Communications dans les congrès & Publications

- IAS 2009 virology  
 Low frequency of intermittent HIV-1 semen excretion in patients treated by darunavir/ritonavir (600/100 mg BID) + 2 nucleoside reverse transcriptase inhibitors or monotherapy  
 Darunavir diffusion in seminal plasma  
 Sidonie Lambert-Niclot,<sup>1</sup> Gilles Peytavin,<sup>2</sup> Claudine Duvivier,<sup>3,4</sup> Catherine Poirot,<sup>5</sup> Michèle Algarte-Genin,<sup>6</sup> Sophie Pakianather,<sup>6</sup> Jean-Luc Meynard,<sup>7</sup> Marc-Antoine Valantin,<sup>8</sup> Jean-Michel Molina,<sup>9</sup> Philippe Flandre,<sup>10</sup> Christine Katlama,<sup>8</sup> Vincent Calvez,<sup>1</sup> Anne-Geneviève Marcelin,<sup>14</sup>
- Conférence Francophone d'Infectiologie  
 Virology Department, AP-HP, Pitié-Salpêtrière Hospital, UPMC Université Paris 06 et INSERM U943, Paris, France<sup>1</sup>; Clinical Pharmacy Department, AP-HP, Bichat-Clau Bernard Hospital and EA 449 Paris 7 University, Paris, France<sup>2</sup>; Centre d'Infectiologie Necker-Pasteur, AP-HP, Hôpital Necker-Enfants malades, Université René Descartes I Paris, France<sup>3</sup>; Institut Pasteur, Centre Médical de l'Institut Pasteur, UPMC Université Paris, France<sup>4</sup>; Institut Pasteur, Centre Médical de l'Institut Pasteur, UPMC Université Paris, France<sup>5</sup>; Institut Pasteur, Centre Médical de l'Institut Pasteur, UPMC Université Paris, France<sup>6</sup>; Institut Pasteur, Centre Médical de l'Institut Pasteur, UPMC Université Paris, France<sup>7</sup>; INSERM UMR-S 943 and UPMC Université Paris 06, Paris, France<sup>8</sup>; Infectious Diseases Department, AP-HP, Saint Antoine Hospital, Paris, France<sup>9</sup>; Infectious Diseases Department, AP-HP, Pitié-Salpêtrière Hospital and INSERM U943, Paris, France<sup>10</sup>; Infectious Diseases Department, AP-HP, Saint Louis Hospital, Paris, France<sup>11</sup>
- Soumis Infectious Diseases  
 – Résultat  
 – Facteur  
 – Etude

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Key words: darunavir, semen, monotherapy, HIV, shedding

## Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136

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**Background:** Darunavir/ritonavir (darunavir/r) maintenance strategy, in patients with suppressed HIV RNA viremia, is a potential long-term strategy to avoid nucleoside analogue toxicities and to reduce costs.

**Methods:** MONOI-ANRS 136 is a prospective, open-label, noninferiority, 96-week safety and efficacy trial in virologically suppressed patients on triple therapy who were randomized to a darunavir/r triple drug regimen or darunavir/r monotherapy. The primary endpoint was the proportion of patients with HIV RNA less than 400 copies/ml at week 48; treatment failure was defined as two consecutive HIV RNA more than 400 copies/ml (time to loss of virologic response) or any change in treatment. The trial had 80% power to show noninferiority for the monotherapy arm ( $\delta = -10\%$ , 90% confidence interval).

**Results:** A total of 242 patients were screened, 225 of whom were randomized. In the per protocol efficacy analysis, treatment success was 99% on darunavir/r triple drug versus 98% on darunavir/r monotherapy ( $\delta = -4.9\%$ , 90% confidence interval, from -9.1 to -0.8). Similar results were found in intent-to-treat population (92 versus 87.5%,  $\delta = -4.5\%$ , 90% confidence interval from -11.2 to 2.1). Three patients experienced virologic failure on darunavir/r monotherapy and none on darunavir/r triple drug. No resistance to protease inhibitor emerged in patients with plasma viral load above 50 copies/ml. The two groups did not differ in the number of serious adverse events.

**Conclusions:** Darunavir/r monotherapy exhibited efficacy rate over 85% with concordant results in the magnitude of difference with darunavir/r triple drug regimen in both intent-to-treat and per protocol analyses, but discordant conclusions with respect to the noninferiority margin. Patients failing on darunavir/r monotherapy had no emergence of new darunavir resistance mutations preserving future treatment options.

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**Keywords:** darunavir, HIV suppressed viremia, maintenance therapy, protease inhibitor monotherapy

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