

# VII SESIONES CLÍNICAS GEVIHSS IAPAC

## Iniciándonos en la Investigación Clínica

México, Oaxaca. Marzo 2010

*Héctor Pérez*





Dr. Héctor Pérez  
Médico Servicio Infectología H. Fernández

# Aclaración sobre Conflicto de Intereses

Consultor: Abbott Laboratories Argentina, Gilead (Gador SA), MSD,  
Productos Roche SAQel

Relator: Bristol Myers Squibb Arg, GlaxoSmithKline SA, Janssen Cilag SA,  
Pfizer SRL.

Soporte Material o Financiero en su actividad: No ha tenido



*“Los gobernantes incultos suelen encargar la gestión de la investigación científica de sus países a los médicos. Ignoran que la enorme mayoría de los médicos, aunque aprenden algunos resultados de la investigación científica, no aprenden a hacer ciencia: no se forman como investigadores sino como profesionales de la salud.*

*Si un médico corriente emprende un trabajo de investigación, es raro que lo haga bien. El gobierno del presidente Lyndon Johnson invirtió una millonada en investigación del cáncer. Pero, en lugar de invertir los fondos entre biólogos celulares y moleculares, los asigno entre médicos, en particular cirujanos. El enorme gasto se hizo en vano, porque los cirujanos sólo ven el estado final del proceso de investigación celular...”*

Mario Bunge. Físico y filósofo argentino

*Medicina. Ciencia o técnica? Individual o social?*

## Preguntas que deberíamos responder al concluir esta presentación:

- *¿Que elementos considerar para determinar el tamaño de una muestra?*
- *¿Que es un control?*
- *¿Son los estudios randomizados, mejores que los observacionales?*
- *¿Que podemos decir de superioridad, no inferioridad y equivalencia?*
- *¿Que pacientes serán considerados para el análisis?*
- *¿Quien debe estar enterado de nuestro protocolo de investigación?*

# El camino de la investigación clínica

- **Diseñar un experimento**
  - *Definir hipótesis, preguntas y punto-final*
- **Desarrollo del protocolo de estudio.**
  - *Prever y evitar análisis post-hoc*
- **Ejecución del protocolo.**
  - *Dejarse guiar por el protocolo de trabajo*
- **Análisis de datos**

# Claves para el diseño de un experimento

- Formulación de una pregunta.
- Desarrollo de una hipótesis.
- Factibilidad de la estrategia.
- Cuestiones éticas.
- Recursos disponibles.
- Eficacia.
- Seguridad.



Search Web Site Content

Search IAS Abstract Archive

Now **12274 members** from 187 countries |

[ABOUT IAS](#) | [MEMBERSHIP](#) | [ABSTRACT ARCHIVE](#) | [MEDIA](#)

CONFERENCES: [IAS 2009](#) | [AIDS 2010](#)

- IAS Home Page
- About IAS
- Publications
- Conferences
- Regional Partnerships
- Professional Development
- Journal of IAS
- Industry Liaison Forum
- Membership
- Media/News
- Policy And Advocacy
- Financial Reports/Statements
- Partners
- Awards, Fellowships & Grants
- Requests for Proposals
- Working for IAS
- Contact IAS

## ABSTRACT

### Toxicity profile of non-nucleoside reverse transcriptase inhibitors (NNRTI), and effects on dyslipidemia

Background: Dyslipidemia is usually attributed to protease inhibitors (PI).

Methods: To assess the serum lipid profile of efavirenz (E) and nevirapine (N), a cross-sectional survey was carried out on ~1000 HIV-infected patients (p) treated with antiretrovirals during >12 months.

Results: Among NNRTI-naive p, 246 consecutive p given E were compared with 229 p treated with N, by a multivariate analysis of untoward events, toxicity, and treatment interruptions. The 2 p groups were comparable as to epidemiologic features, disease stage, mean CD4 cell count, HIV viremia, HCV-HBV co-infection rate, antiretroviral therapy background, and pre-existing dysmetabolism and/or lipodystrophy (in pre-treated p). When considering the 132 antiretroviral-naive p, the tolerability measured during the first 3 months did not differ between the 2 NNRTI, but hypersensitivity

### This Abstract

[Email this abstract](#)

[Print this abstract](#)

***Sentido común y conocimiento clínico son requisitos que preceden a los científicos.***

and clinical presentation. P pre-treated with other anti-HIV regimens may show a tendency to cumulative liver toxicity for N, and stable or worsening metabolic-lipid abnormalities for E. Extensive investigation

# SMART Study: Cardiovascular Disease Events

- Planned 8-year open-label study in treatment-experienced patients (n=5472)
  - 95% were treatment-experienced patients and on HAART for 6 years
  - CD4-guided intermittent therapy
    - Stop: CD4 >350 cells/mm<sup>3</sup>
    - Resume: CD4 <250 cells/mm<sup>3</sup>
  - Continuous therapy
- Enrollment stopped January 10, 2006
  - CD4-guided intermittent therapy arm had significantly increased risk of disease progression (relative risk 2.5) versus the continuous-therapy arm
- Retrospective exploratory analysis on cardiovascular disease events

## Baseline Characteristics

CD4 count (cells/mm <sup>3</sup> )	598
Prior CVD (%)	4
Smokers (%)	40
On antihypertensive agents (%)	8.2
On lipid-lowering agents (%)	19
Lipids (mg/dL)	
Total cholesterol	191
HDL-C	41
LDL-C	111
Triglycerides	164

# SMART Study: Cardiovascular Disease Events (cont.)

	CD4-Guided Intermittent Therapy (n=2742)	Continuous Therapy (n=2730)	Relative Hazard (95% CI)
Number of events			
Death from CVD	7	4	
Nonfatal clinical MI	12	12	
Nonfatal silent MI	11	5	
Nonfatal stroke	8	3	
CAD requiring surgery or invasive procedure	22	14	
Clinical MI, silent MI, stroke, death from CVD, CAD requiring invasive procedure	48	31	1.57* (1.00-2.46)
Plus peripheral vascular disease, CHF, CAD requiring therapy	76	52	1.49 <sup>†</sup> (1.04-2.11)
Plus death from unknown causes	84	54	1.58 <sup>‡</sup> (1.12-2.22)

\**P*=0.05.  
<sup>†</sup>*P*=0.03.  
<sup>‡</sup>*P*=0.009.

# Consideraciones a la hora de elegir la estrategia:

- **Factibilidad**

- *PPE en HIV. La prevalencia del evento precluye el uso de ensayos clínicos randomizados.*

- **Aspectos éticos**

- El uso de ramas placebo es muy poderoso para demostrar el efecto de una intervención, pero no es ético en el caso de pacientes con meningitis bacteriana o indicaciones para inicio de tratamiento antirretroviral

- **Recursos disponibles**

- Financieros, personal calificado, aspectos técnicos.

*“Medir todo lo que sea mensurable y hacer mensurable aquello que no se pueda medir”*

# Medicina basada en evidencia: Fuerza y Calidad de la Recomendación

- **Grado A:** Buena evidencia para soportar una recomendación para su uso.
  - **Grado B:** Moderada evidencia para soportar una recomendación para su uso.
  - **Grado C:** Pobre evidencia para soportar una recomendación.
- 
- **Nivel I:** Evidencia de por lo menos 1 estudio randomizado.
  - **Nivel II:** Evidencia obtenida de por lo menos 1 estudio clínico de buen diseño, no randomizado; múltiples series de casos. Resultados dramáticos en ensayos no controlados.
  - **Nivel III:** Opiniones de autoridades respetadas basadas en experiencia clínica, estudios descriptivos o reportes de comités de expertos.

# Los estudios randomizados pueden ser perfectos. Los investigadores no.

- Estudios randomizados = control de variables

## VIEWPOINTS

### Double-Blind Active-Control Trials: Beware the Comparator You Keep

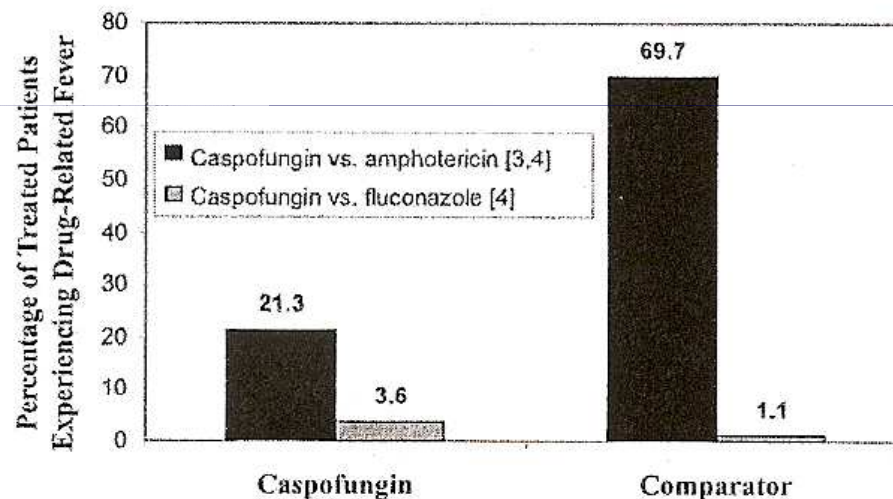
Mark J. DiNubile

Merck Research Laboratories, West Point, Pennsylvania

The indirect impact of the known comparator precipitated, despite its potentially pernicious effect of a comparator (amphotericin) in the evaluation of antifungal drugs. Reported rates of drug-related candidiasis in patients with advanced human immunodeficiency virus (HIV) who received 50 mg of caspofungin plus patients who received the corresponding dosage of amphotericin B deoxycholate were similar with respect to the incidence of drug-related fever, less than the difference between caspofungin and amphotericin B deoxycholate in double-blind active-control trials, the reporting of adverse events was greater by expectations regarding a well-known comparator.

In drug development, comparative trials with an active control group [1] serve to place the new kid on the block in the context of established therapy. However, standards—whether gold or bronze—come with their own baggage. Adverse events may be attributed to a novel agent with a frequency that is, in some part, modulated by the reputation of the comparator drug [2], especially during initial assessment of unconventional compounds in double-blind studies [3, 4]. Consequently, untoward events typically associated with the known comparator may be reflexively reported to the sponsor by site investigators as possibly drug related.

Received 2 June 2008; accepted 30 June 2008; electronically published 9 September 2008.  
Reprints or correspondence: Dr. Mark J. DiNubile, Merck Research Laboratories, US3C-06, PO Box 1000, North Wales, PA 19454-1099 (mark\_dinubile@merck.com).  
**Clinical Infectious Diseases** 2008;47:1064-7  
© 2008 by the Infectious Diseases Society of America. All rights reserved.  
1058-4838/2008/4708-0012\$15.00  
DOI: 10.1093/cid/cin529



**Figure 1.** Reported incidence of drug-related fever in double-blind, active-control trials of caspofungin for treatment of mucosal candidiasis. The frequencies of fever attributed to caspofungin and to the comparator agent were much lower in the 1 trial that used fluconazole [6] than in the combined 2 trials that used amphotericin B deoxycholate [3, 4] as the comparator.

# Randomizado vs observacional

**Conclusions** We found little evidence that estimates of treatment effects in observational studies reported after 1984 are either consistently larger than or qualitatively different from those obtained in randomized, controlled trials. (N Engl J Med 2000;342:1878-86.)

randomized, controlled trials. (N Engl J Med 2000;342:1878-86.)

©2000, Massachusetts Medical Society.

**O**BSERVATIONAL studies have several advantages over randomized, controlled trials, including lower cost, greater timeliness, and a broader range of patients.<sup>1</sup> Concern about inherent bias in these studies, however, has limited their use in comparing treatments.<sup>2,3</sup> Observational studies are used primarily to identify risk factors and prognostic indicators and in situations in

## A COMPARISON OF OBSERVATIONAL STUDIES AND RANDOMIZED, CONTROLLED TRIALS

KJELL BENSON, E.A., AND ARTHUR J. HARTZ, M.D., PH.D.

### ABSTRACT

**Background** For many years it has been claimed that observational studies find stronger treatment effects than randomized, controlled trials. We compared the results of observational studies with those of randomized, controlled trials.

**Methods** We searched the Abridged Index Medicus and Cochrane data bases to identify observational studies reported between 1985 and 1998 that compared two or more treatments or interventions for the same condition. We then searched the Medline and Cochrane data bases to identify all the randomized, controlled trials and observational studies comparing the same treatments for these conditions. For

which randomized, controlled trials would be impossible or unethical.<sup>4</sup>

The empirical assessment of observational studies rests largely on a number of influential comparative studies from the 1970s and 1980s.<sup>5-9</sup> These studies suggested that observational studies inflate positive treatment effects, as compared with randomized, controlled trials. In one major study, Chalmers et al.<sup>6</sup> showed that 56 percent of non-randomized trials yielded favorable treatment effects, as compared with 30 percent of blinded, randomized, controlled trials. Three other studies had similar results.<sup>7-9</sup> According to many experts, these results mean that observational studies should not be used for defining evidence-based medical care: "If you find that [a] study was randomized, we'd suggest that you stop reading and go on to the next article."<sup>10</sup>

Evaluations of observational studies have primarily included studies from the 1960s and 1970s. We evaluated observational studies reported between 1985 and 1998, studies which may be methodologically superior to earlier studies. Possible methodological improvements include a more sophisticated choice of subjects and better statistical methods. Newer methods may have eliminated some systematic bias.

### METHODS

#### Search for Observational Studies

Observational studies were found by systematically searching Medline and the Cochrane Database of Systematic Reviews for articles reported from 1985 through 1998. Although Medline is indexed for highly sensitive searches for randomized, controlled trials, "observational studies" is not an indexable concept in Medline, and there is no search term for observational studies (Wright N, National Library of Medicine: personal communication). Therefore, we used a text-word strategy to search for "observational," "cohort," "retrospective," "cross-sectional," and "non-randomized." We limited the search to journals in the Abridged Index Medicus, which indexes the 120 most widely read, prestigious clinical journals. To restrict the search to studies comparing treatments, we added the Medline tag "comparative study/," defined as a comparison of any two or more concepts from any Medical Subject Heading category.

This strategy identified 3868 articles. We reviewed the abstracts

From the Department of Family Medicine, University of Iowa College of Medicine, Iowa City. Address reprint requests to Dr. Hartz at the Department of Family Medicine, University of Iowa College of Medicine, 01292-D PE, Iowa City, IA 52242-1097, or at arthur-hartz@uiowa.edu.

# Aspectos prácticos a considerar en el diseño experimental

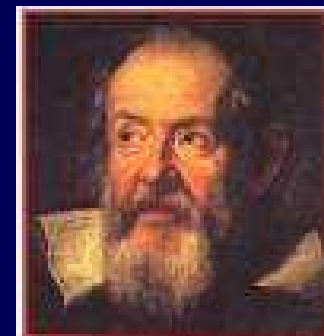
- Error (Bias)
- Controles
- Tamaño muestral
- Eficacia & Seguridad

# Aspectos estadísticos del diseño experimental

- *Valor P*
- Error
- Potencia
- Intervalo de confianza

*“El libro de la naturaleza está escrito en el lenguaje de la matemática”*

**Galileo**



# Tres aproximaciones a la estadística en investigación clínica

- Yo me arreglo solo.
  - *Mejor opción, para los que se animan*
  - *Los programas de Software calculan, raramente analizan*
- Trabajo junto al estadístico.
  - *Enfoque racional y multidisciplinario.*
- Datos empaquetados en el escritorio del estadístico
  - *Asegurarse que el estadístico no conozca sólo de números.*
  - *Tener presente la diferencia entre diferencias clínicas y estadísticas*

*P value = 0.05*

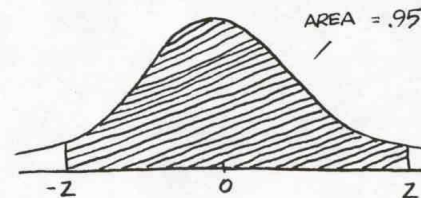
*Hay un 5% de posibilidades que los resultados sean debidos a la casualidad.*

*5% = 1 en 20 = 5 en 100 = 0.05/1*

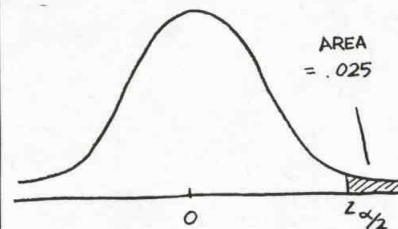
# Qué es un intervalo de confianza?

THE RELEVANT NUMBER HERE WE USUALLY CALL  $\alpha$ . IT MEASURES THE DIFFERENCE BETWEEN THE DESIRED CONFIDENCE LEVEL AND CERTAINTY. FOR EXAMPLE, WHEN THE CONFIDENCE LEVEL IS 95%, OR 0.95,  $\alpha$  IS .05. SO WE SPEAK OF THE  $(1-\alpha)\cdot 100\%$  CONFIDENCE LEVEL.

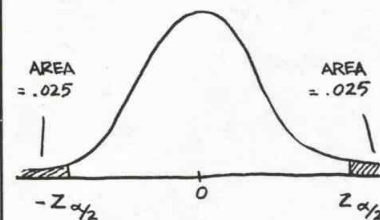
FINDING THE  $(1-\alpha)\cdot 100\%$  CONFIDENCE INTERVAL MEANS: LOOK AT A STANDARD NORMAL CURVE, AND FIND THE POINTS  $\pm Z$  BETWEEN WHICH THE AREA IS  $1-\alpha$ .



THIS POINT, CALLED  $z_{\frac{\alpha}{2}}$ , IS THE Z-VALUE BEYOND WHICH THE AREA IS  $.025 = \frac{\alpha}{2}$ .



THAT'S BECAUSE WE'RE CHOPPING OFF "TAILS" AT BOTH ENDS OF THE CURVE, WHICH HAVE A TOTAL AREA OF  $\frac{\alpha}{2} + \frac{\alpha}{2} = \alpha$ .

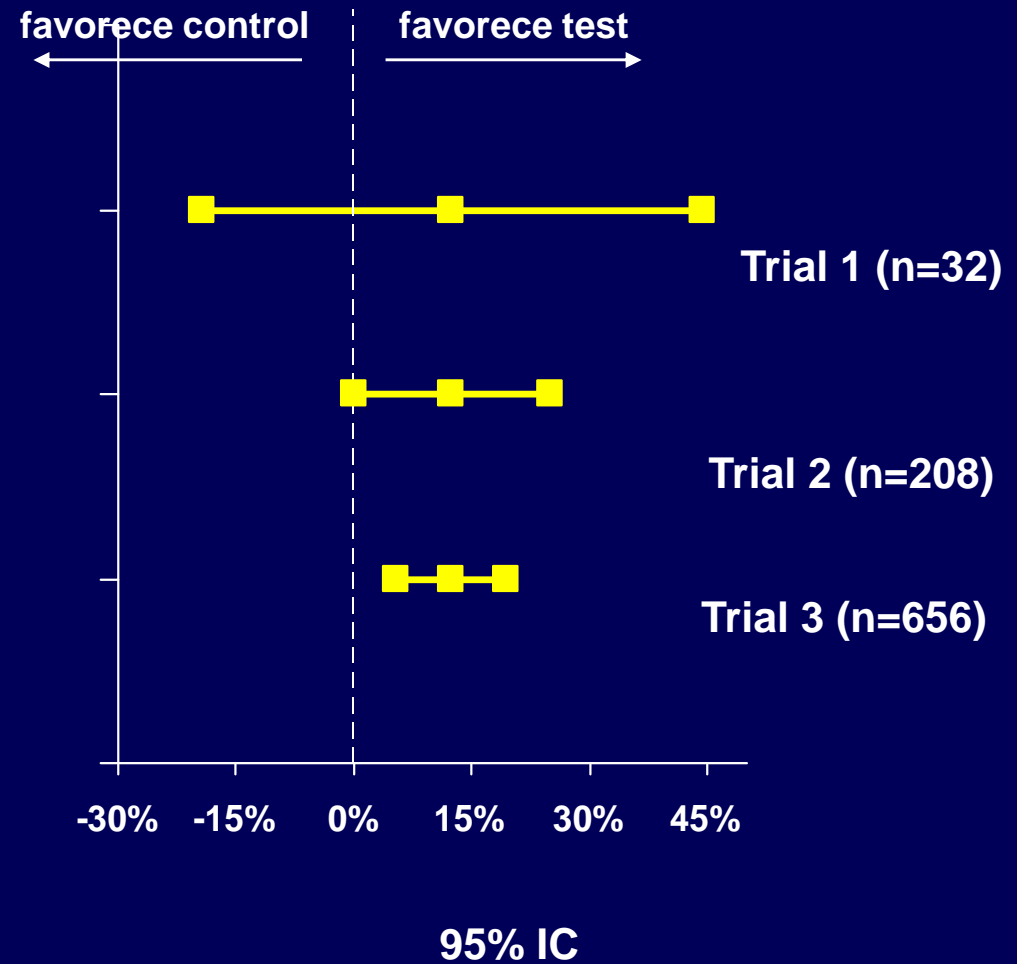
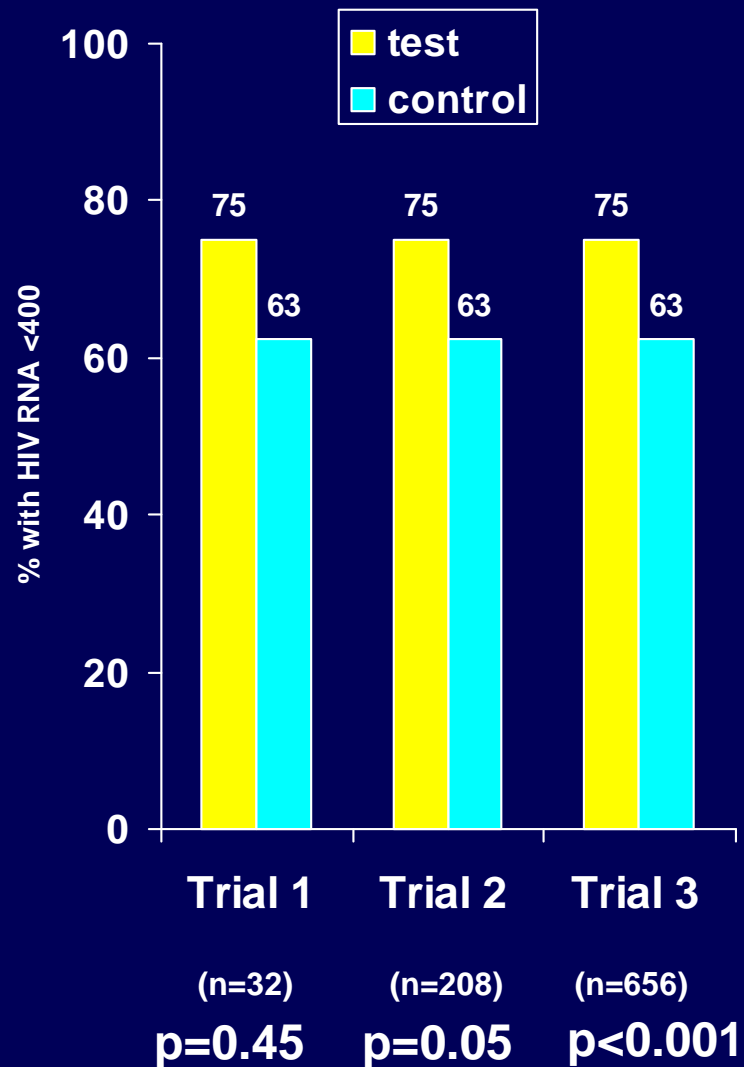


# *Cálculo del tamaño muestral*

- Que requiere el estadístico:
  - Margen de equivalencia y no inferioridad.
  - La diferencia esperada entre el grupo experimental y el control. Expected difference between control group and test group
    - Esta diferencia subraya el valor de los grupos placebo.
  - Poder ( $1-\beta$ ): la probabilidad de rechazar la hipótesis nula cuando la hipótesis alternativa es verdadera; generalmente 80 a 90%



# Relación entre valor $p$ e IC: 3 ejemplos



# Definición de caso

*Es la que establece la población de estudio.*

- En un ensayo clínico va a estar definido por la lista de criterios de inclusión y exclusión.
- Evitar ambigüedades
- Definir con precisión y estrictamente
- Evitar requisitos innecesarios.

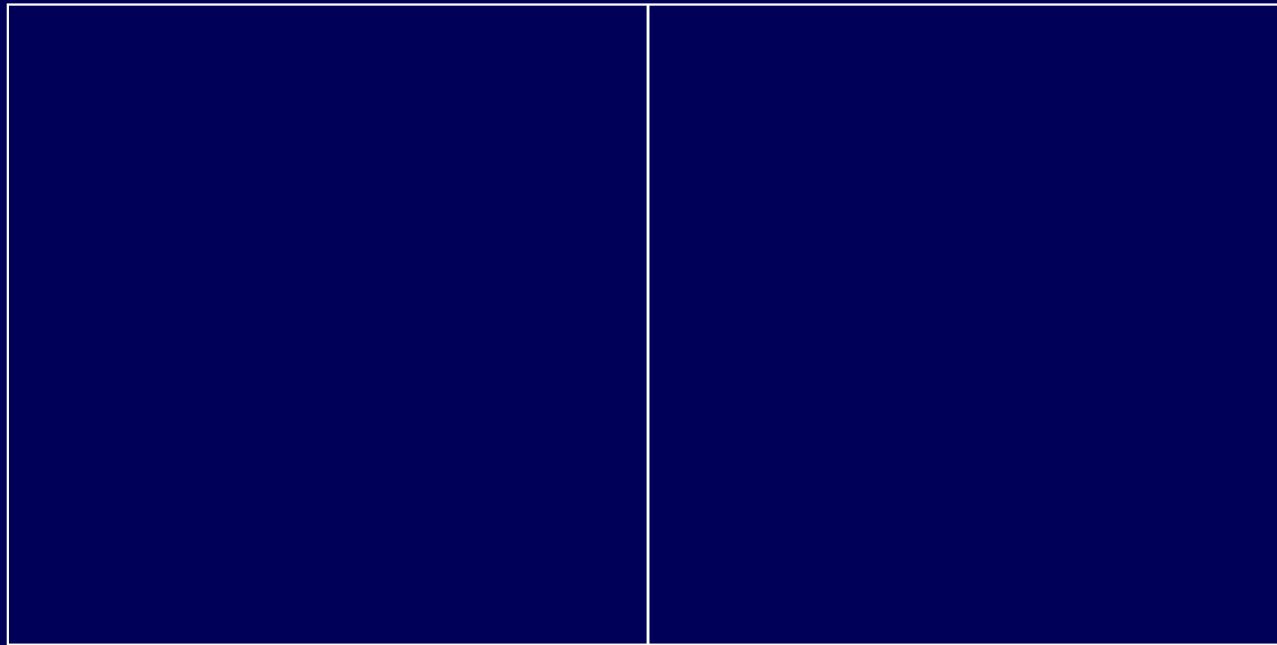
## *¿Cuál es la diferencia entre tests de superioridad, equivalencia y no-inferioridad ?*

- Superioridad: diseñado para detectar una diferencia
- Equivalencia: diseñado para confirmar la ausencia de diferencia (por ej. bioequivalencia)
- No-inferioridad: busca demostrar que una intervención nueva no es peor que una existente (puede ser igual o mejor)

## *¿Cuál es la diferencia entre tests de superioridad, equivalencia y no-inferioridad ?*

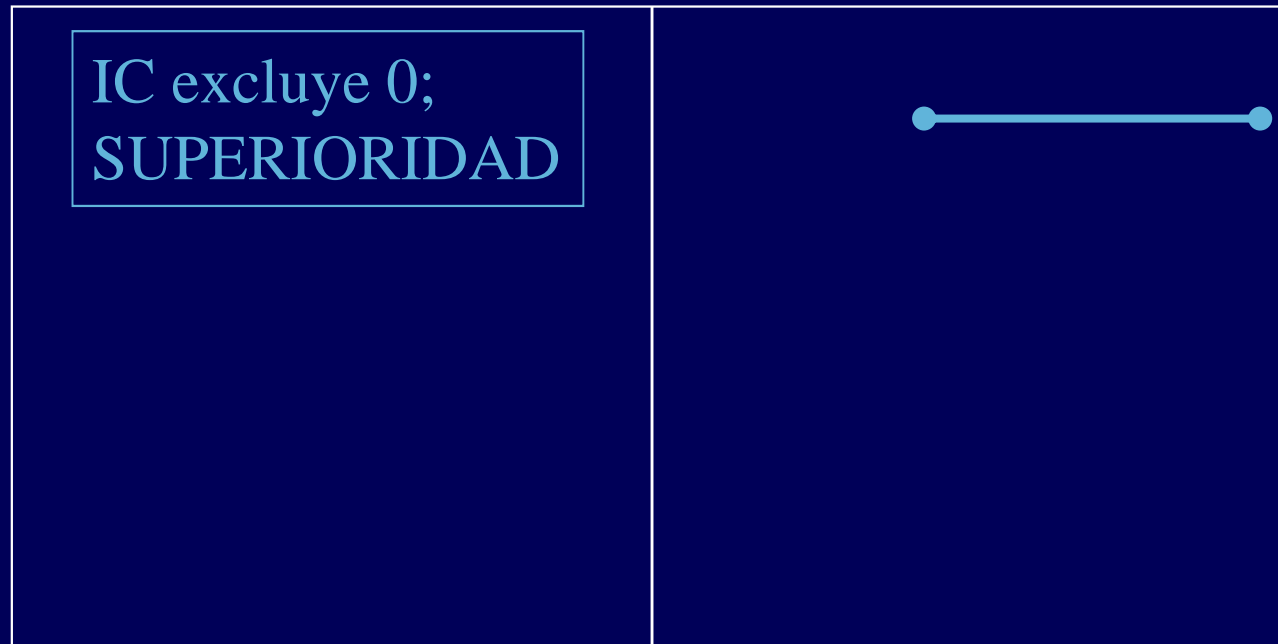
- Superioridad: diseñado para detectar una diferencia
- Equivalencia: diseñado para confirmar la ausencia de diferencia (por ej. bioequivalencia)
- No-inferioridad: busca demostrar que una intervención nueva no es peor que una existente (puede ser igual o mejor)

# *Un test de superioridad, no-inferioridad o equivalencia?*



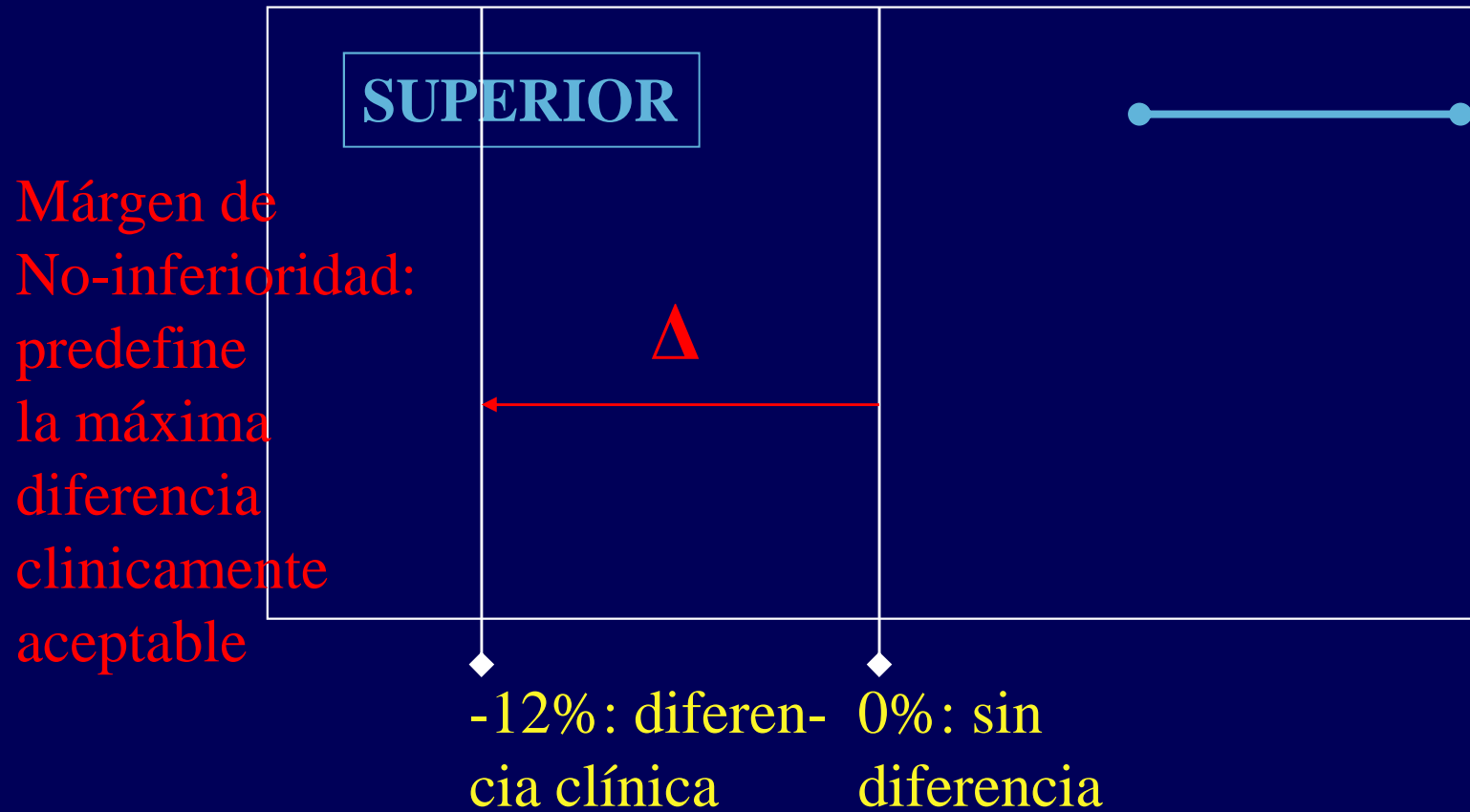
0%: sin  
diferencia

# Un test de superioridad, no-inferioridad o equivalencia? - cont



0%: sin  
diferencia

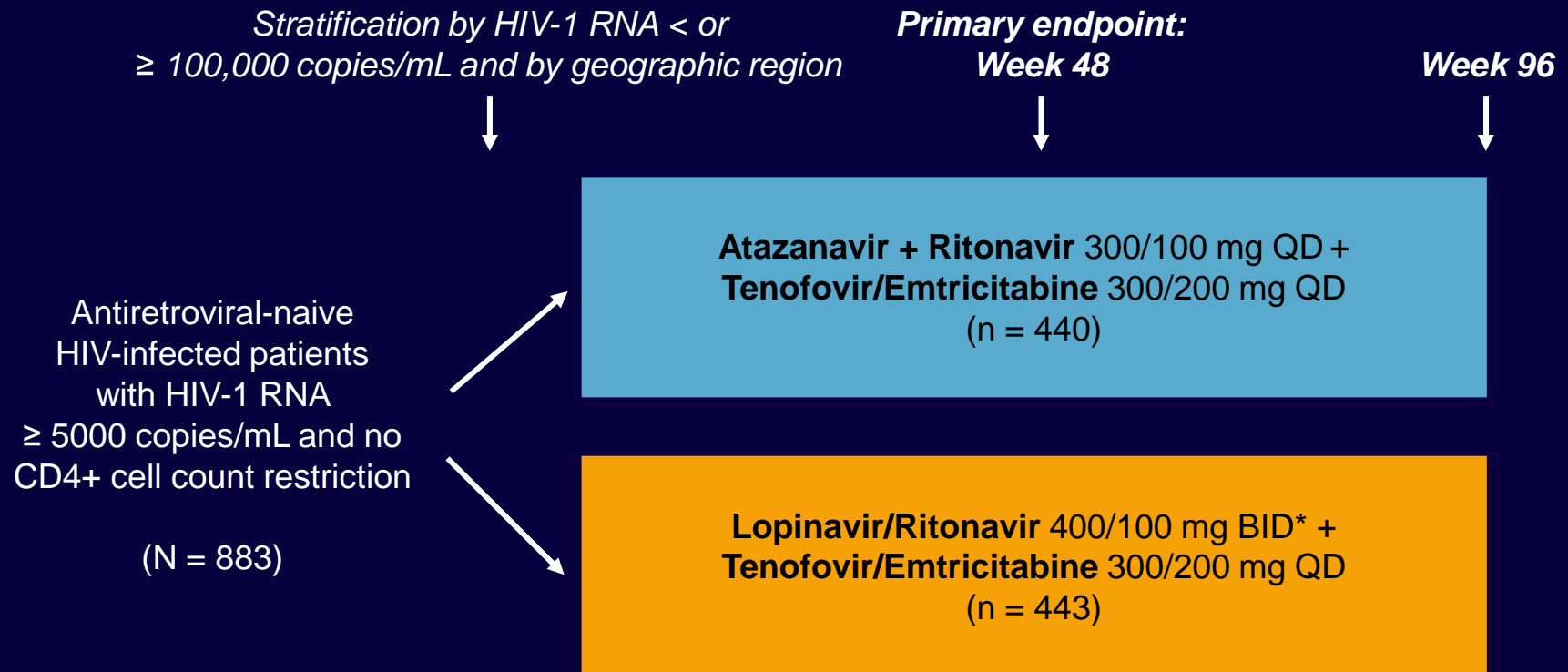
# Un test de superioridad, no-inferioridad o equivalencia? - cont



## *¿Cuál es la diferencia entre tests de superioridad, equivalencia y no-inferioridad ?*

- Superioridad: diseñado para detectar una diferencia
- Equivalencia: diseñado para confirmar la ausencia de diferencia (por ej. bioequivalencia)
- No-inferioridad: busca demostrar que una intervención nueva no es peor que una existente (puede ser igual o mejor)

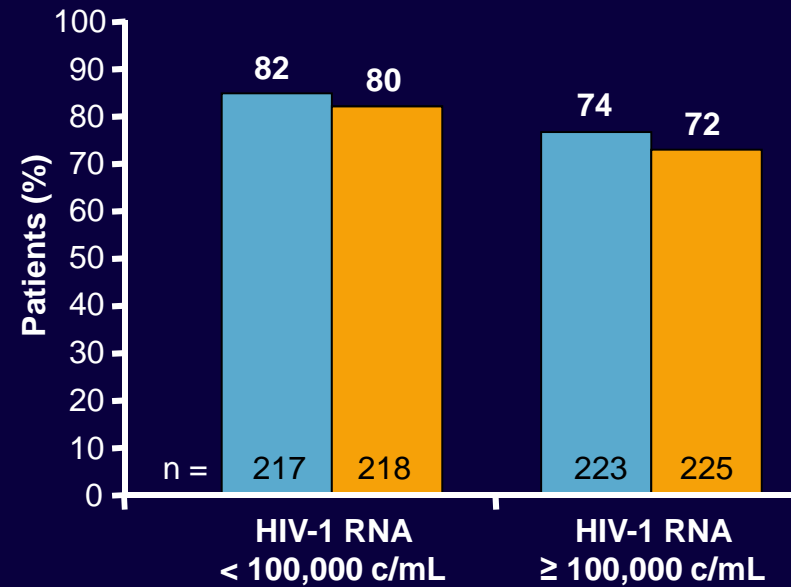
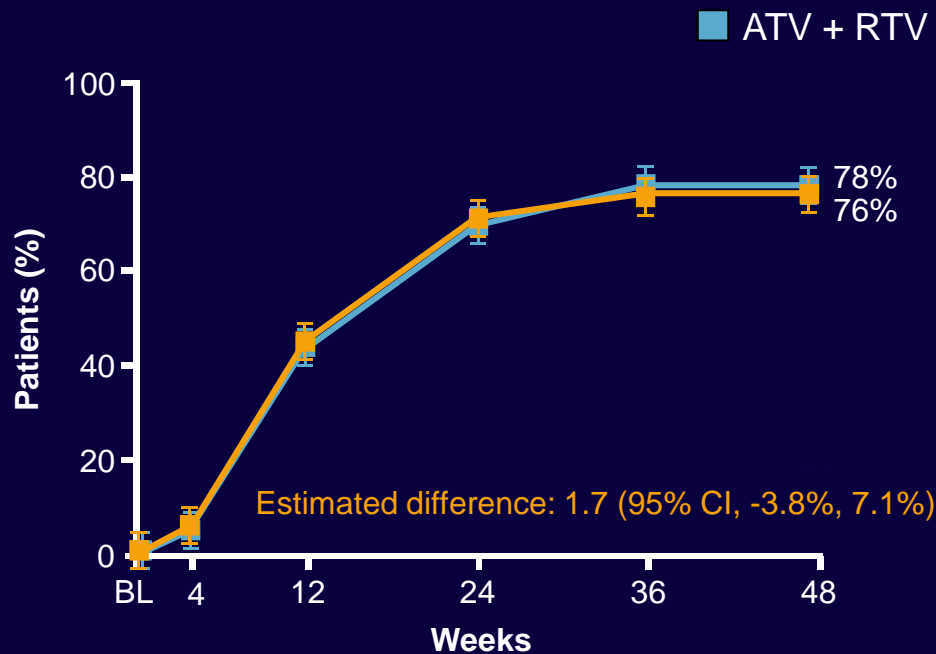
# CASTLE: ATV/RTV vs LPV/RTV in Treatment-Naive Patients



\*Lopinavir/ritonavir administered as soft-gel capsules through Week 48; tablet formulation administered after Week 48 where available.

# CASTLE: Patients With VL < 50 c/mL at Week 48 (ITT-CVR, NC = F)

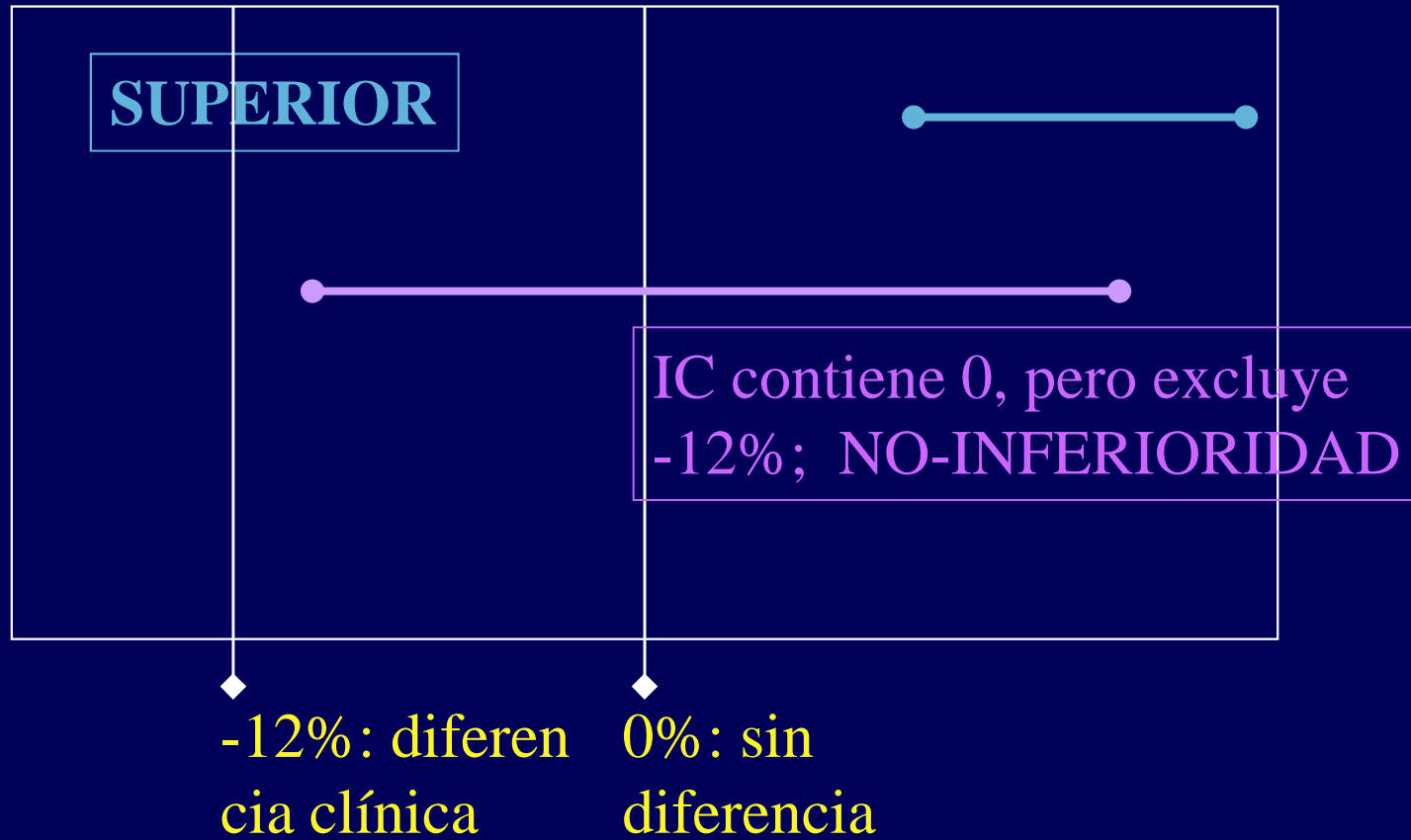
- ATV + RTV QD met virologic efficacy criteria for noninferiority to LPV/RTV BID
- Mean increase in CD4+ cell count lower with use of ATV + RTV vs LPV/RTV
  - 203 cells/mm<sup>3</sup> vs 219 cells/mm<sup>3</sup>; difference: -16.4 (95% CI: -35.9 to 3.1)



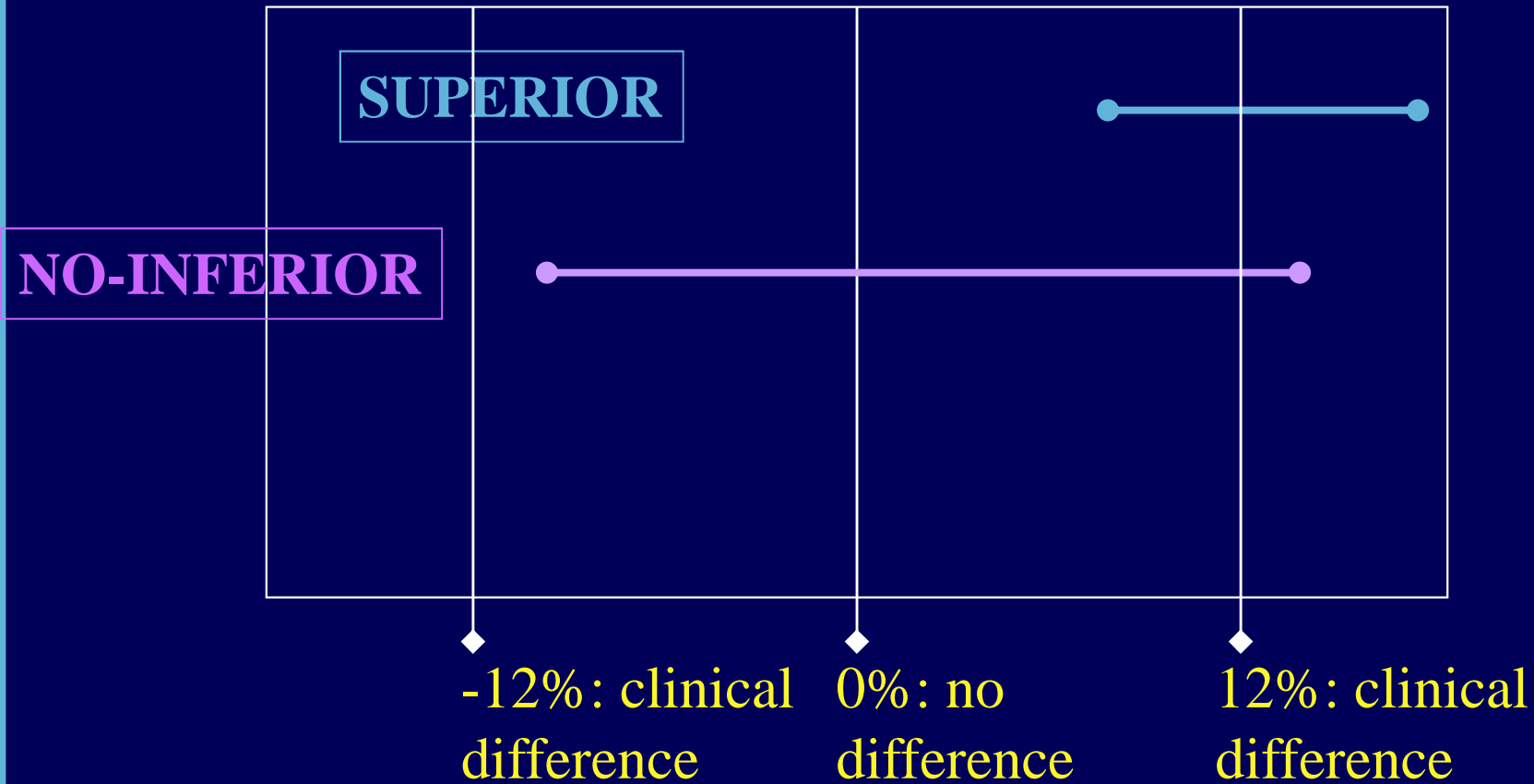
Molina JM, et al. CROI 2008. Abstract 37.

[clinicaloptions.com/hiv](http://clinicaloptions.com/hiv)

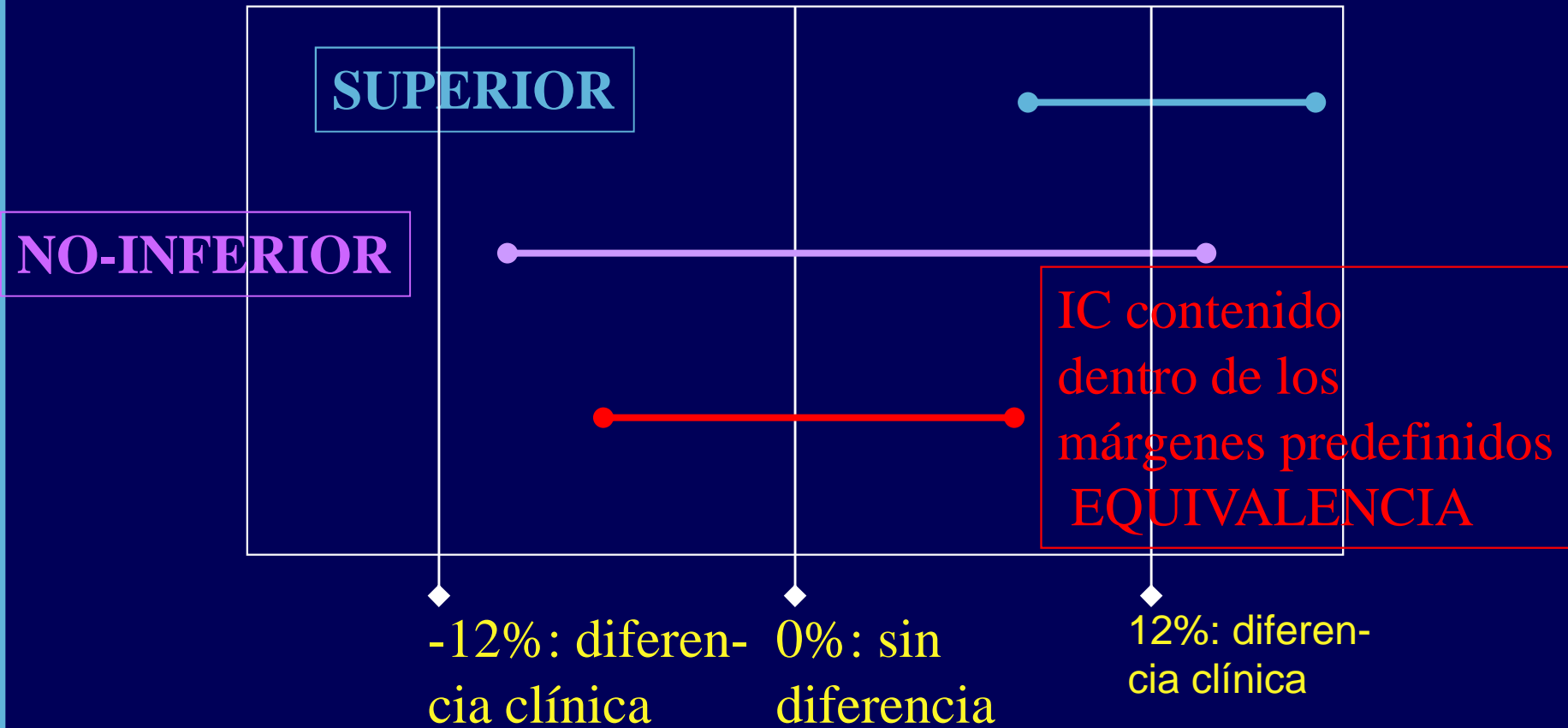
# Un test de superioridad, no-inferioridad o equivalencia? - cont



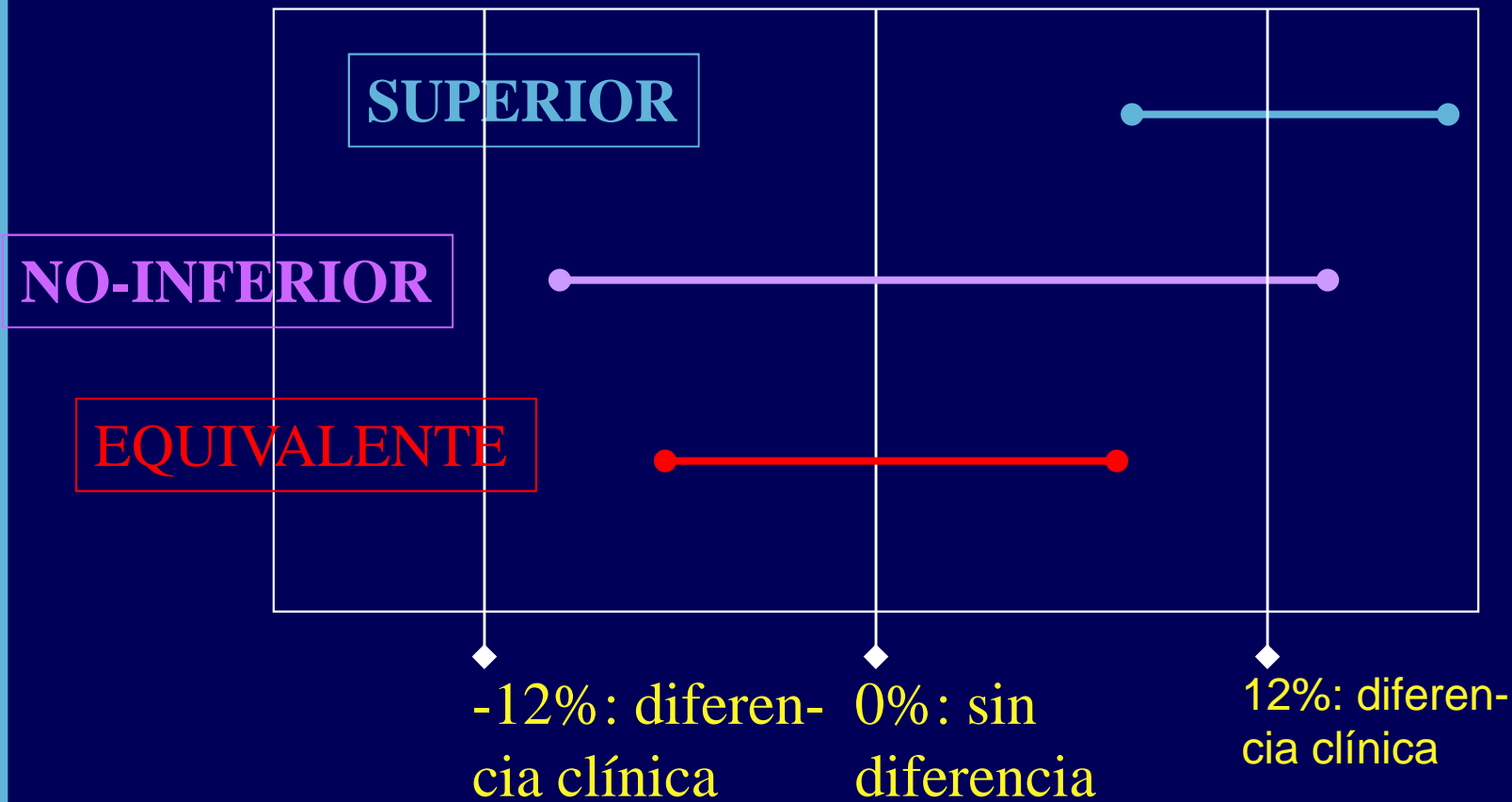
# *A superiority test, a non-inferiority test and an equivalence test? – cont'd*



# Un test de superioridad, no-inferioridad o equivalencia? - cont



# Un test de superioridad, no-inferioridad o equivalencia? - cont



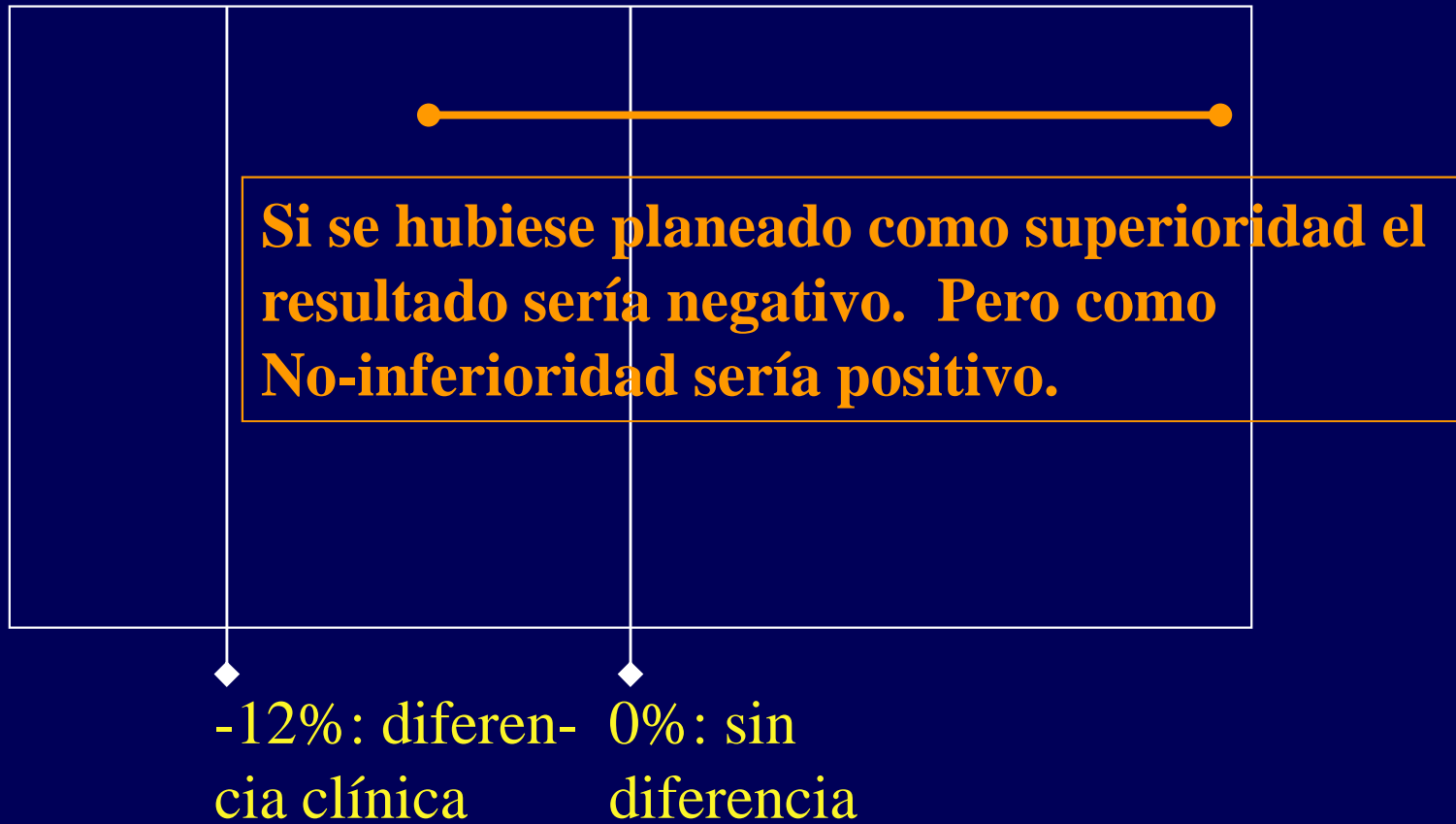
Outcomes of multidrug-resistant patients switched  
from enfuvirtide to raltegravir within a  
virologically suppressive regimen

Marianne Harris<sup>a</sup>, Gerene Larsen<sup>a</sup> and Julio S.G.  
Montaner<sup>a,b</sup>

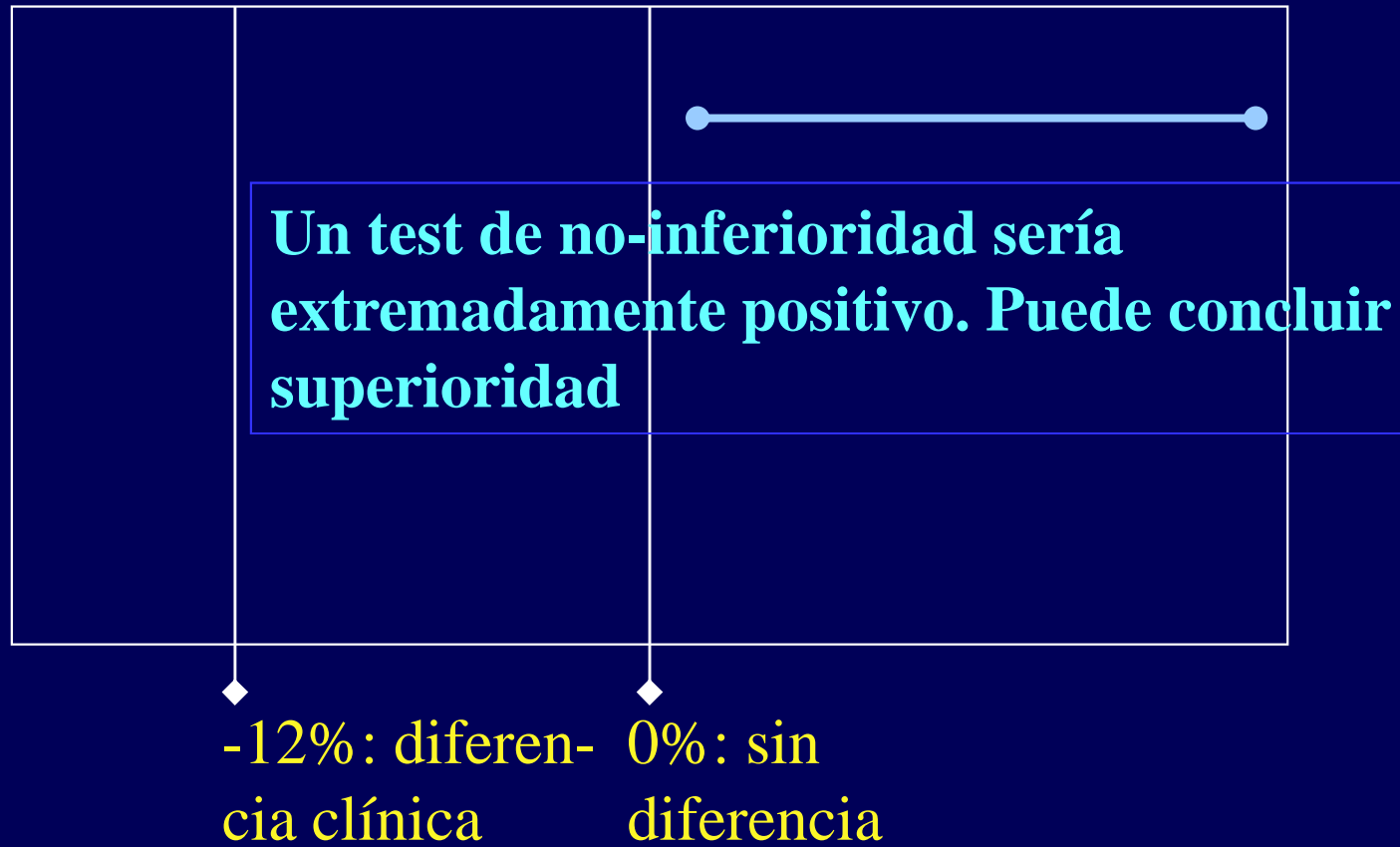
**Median follow-up: 7 months (1-13)**

**All 35 patients remain on raltegravir, with VL < 50 copies  
(1 case had blips at month 1 and 2)**

# Un test de superioridad, no-inferioridad o equivalencia? - cont



# Un test de superioridad, no-inferioridad o equivalencia? - cont

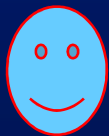
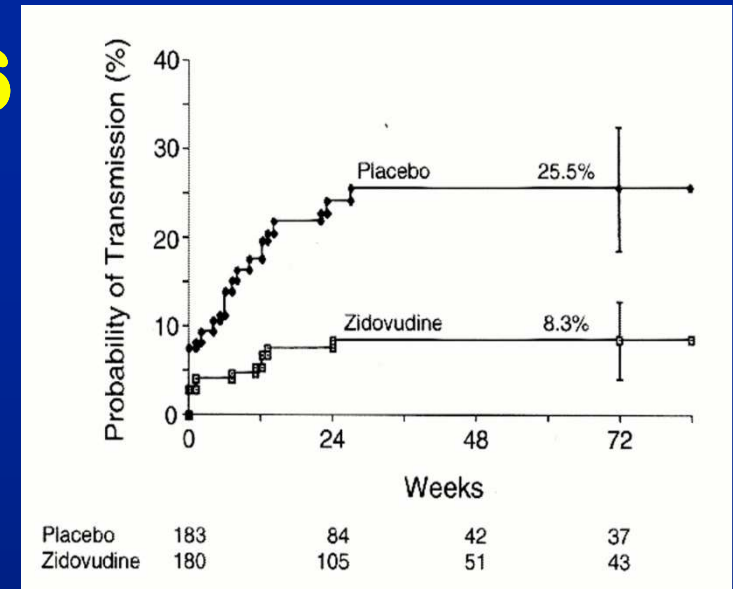


## *¿Cuál es la diferencia entre tests de superioridad, equivalencia y no-inferioridad ?*

- Superioridad: diseñado para detectar una diferencia
- Equivalencia: diseñado para confirmar la ausencia de diferencia (por ej. bioequivalencia)
- No-inferioridad: busca demostrar que una intervención nueva no es peor que una existente (puede ser igual o mejor)

# HIV PERINATAL: ACTG 076

- 14-34 semanas
- Naive, CD4 > 200
- AZT 500 mg/día
- AZT intraparto 2mg/kg dosis de carga, 1mg/kg hora
- AZT jarabe 2mg/kg/dosis cada 6 horas por 6 semanas
- Controlado contra placebo



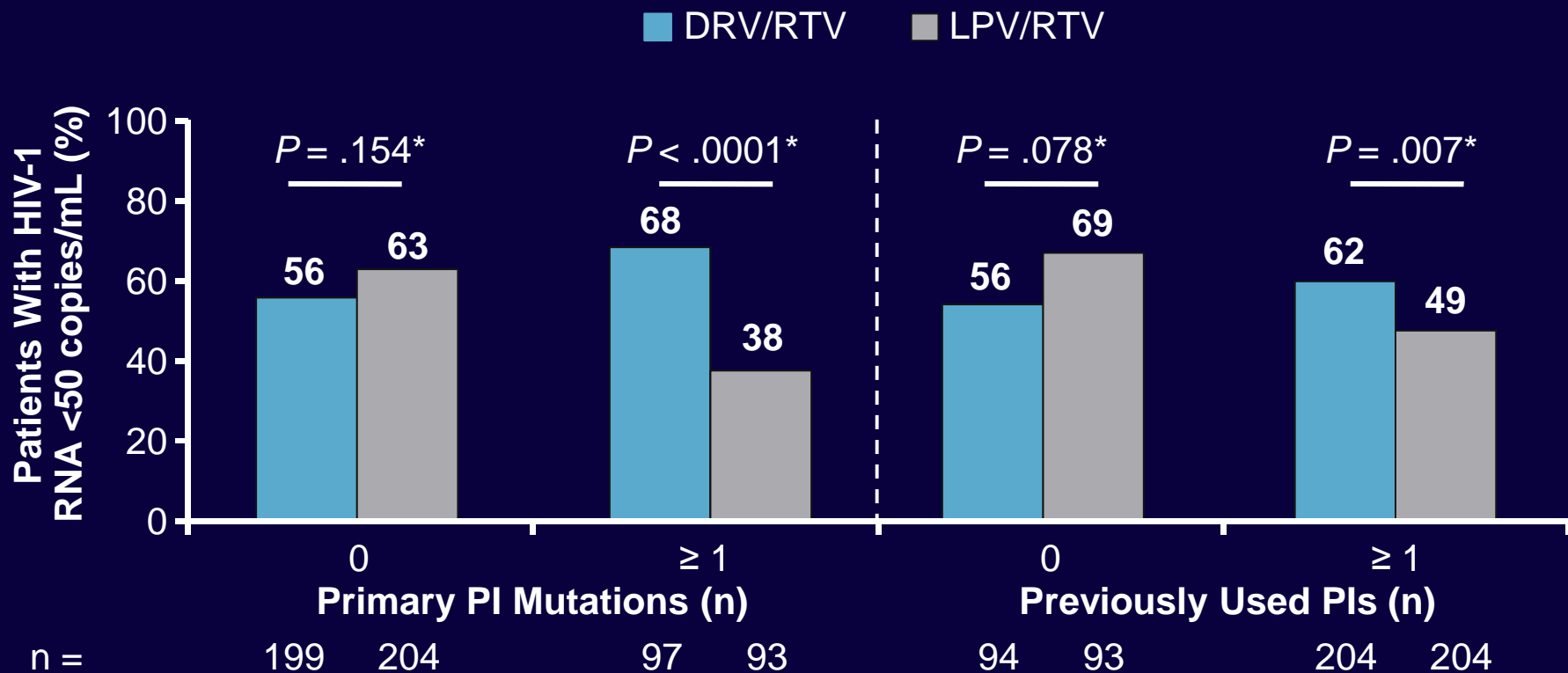
**Transmisión: 22.6% vs**  
**7.6%**

*Sperling et al: N Engl J Med 1996;335:1621*

# TITAN: DRV/RTV vs LPV/RTV in Treatment-Experienced Patients

- Patients with HIV-1 RNA > 1000 c/mL and on current regimen for ≥ 12 weeks randomized to
  - DRV/RTV 600/100 mg BID plus OBR or LPV/RTV 400/100 mg BID plus OBR
- DRV/RTV noninferior to LPV/RTV based on proportion of patients with HIV-1 RNA < 400 c/mL at Week 48 by per-protocol-TLOVR analysis
- DRV/RTV met criteria for superiority to LPV/RTV in proportions with HIV-1 RNA < 400 c/mL and < 50 c/mL at Week 48 by ITT-TLOVR analysis
- Safety and tolerability of DRV/RTV similar to LPV/RTV except less grade 2-4 diarrhea and TG elevations, more rash
- More patients in LPV/RTV arm experienced VF; among patients with VF, DRV/RTV associated with lower rates of new PI and NRTI resistance mutations

# TITAN: Week 96 Virologic Outcomes by BL PI Mutations and Prior PI Use



\*Chi-square test.

# Riesgo Relativo

Incidencia de un efecto  
en aquellos expuestos a un factor

---

Incidencia de un efecto  
en aquellos **no** expuestos a un factor

# Riesgo relativo y fuerza de impacto

Caso 1:

$$RR = 1 : 100,000 / 2 : 100,000 = 2$$

Caso 2:

$$RR = 40,000 : 100,000 / 80,000 : 100,000 = 2$$

¿Quién debe saber acerca del proyecto antes de iniciar la fase experimental?

- Comités institucionales (I&D, biética)
- Autoridades regulatorias locales
- Registros de ensayos clínicos

# Registros de ensayos clínicos

***Consultelos con su hipótesis***

***Aliméntelos con su proyecto***

1. <http://www.actr.org.au>
2. <http://www.clinicaltrials.gov>
3. <http://www.ISRCTN.org>
4. <http://www.umin.ac.jp/ctr/index/htm>
5. <http://www.trialregister.nl>

# Estrategias para optimizar los (limitados) recursos

- Dominar lenguaje científico.
- Establecer colaboraciones sin ser sólo un “exportador de muestras”
- Buscar nichos no explorados
- Focalizar
- Buscar el plus que lo diferencie
- Entrenamiento en búsqueda de recursos
- Publicar

**Nunca desestime la calidad de investigación de sitios de escasos recursos en procura de resolver sus propios problemas sanitarios.**



1. What specific question is being asked?

2. How does the design of the study address the question posed?

3. What are the controls for each experiment?

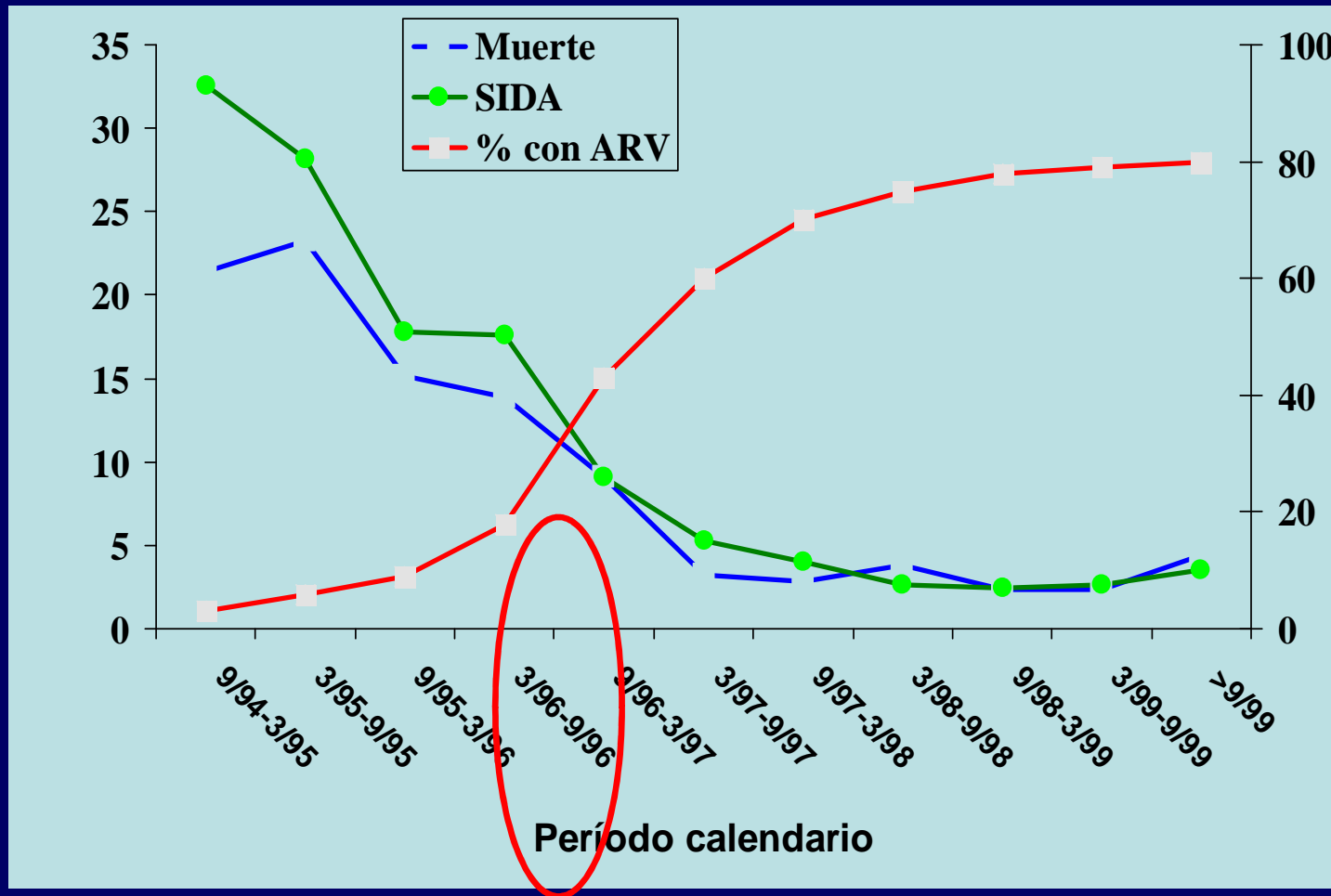
4. How convincing are the results?

Are any of the results surprising?

5. What contribution does this study make towards answering the original question?

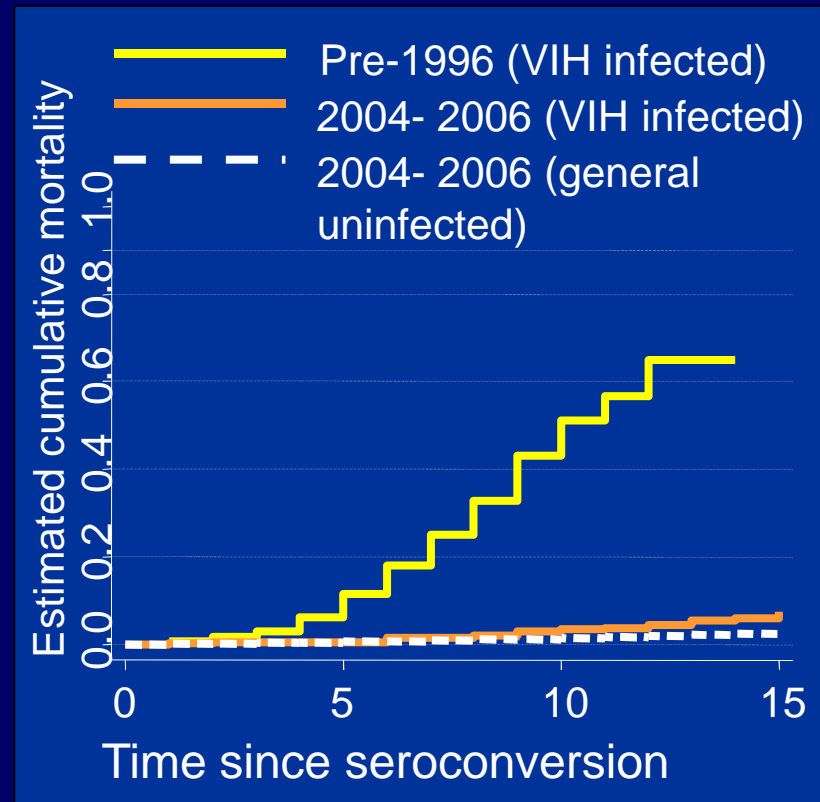
6. What aspects of the original question remain unanswered?

# Impacto del HAART en sobrevida



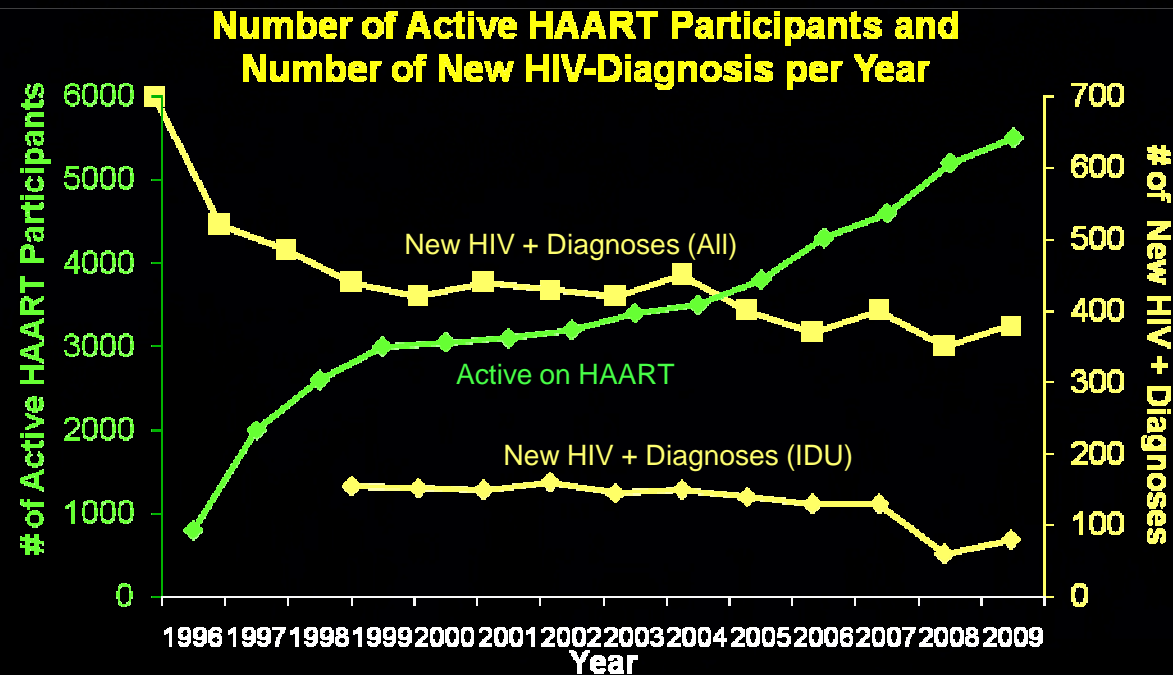
# Drogas ARV en el tiempo

1987: Zidovudina  
1991: Didanosina  
1992: Zalcitabina  
1994: Stavudina  
1995: Lamivudina, **Saquinavir**  
1996: Nevirapina, **Ritonavir, Indinavir**  
1997: Delavirdina, **Nelfinavir**  
1998: Abacavir, Efavirenz  
1999: **Amprenavir**  
2000: **Lopinavir/ritonavir**  
2001: Tenofovir  
2003: T-20, **Atazanavir**, Emtricitabina,  
2004: **Fosamprenavir**  
2005: **Tipranavir**  
2006: **Darunavir**  
2007: Maraviroc  
2008: Raltegravir, Etravirina



# Impact of Expanded HAART Availability on New HIV Diagnoses

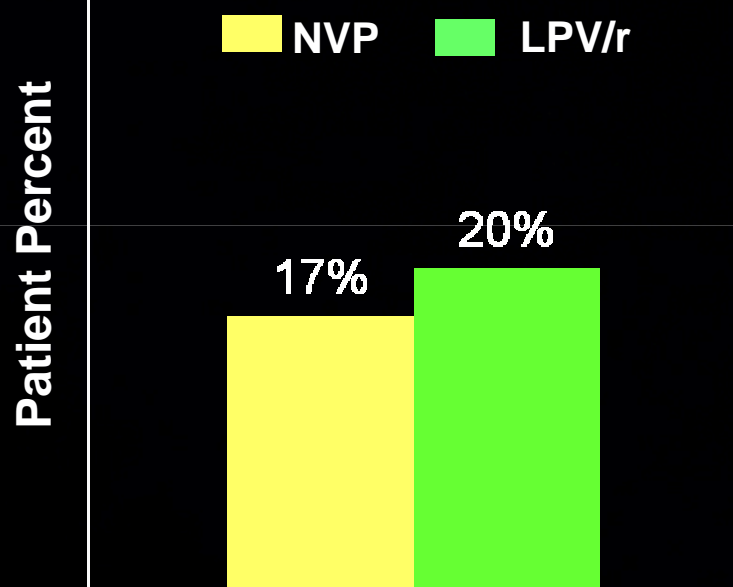
- Evaluation of association between expansion of ART coverage, population level HIV viral load and new HIV diagnoses in British Columbia
- Expansion of ART access in 2004-2009 associated with a significant decline in new HIV diagnoses
- After 2007, ~50% decrease in new HIV diagnoses among IDU occurred and associated with a decline in proportion of HIV+ IDU with plasma HIV-1-RNA level >1500 copies/mL from ~50% (2000-2004) to ~20% (2009) ( $P<0.001$ )



# ACTG 5208/OCTANE 2: Results at 168 Weeks

## Virologic Failure or Death

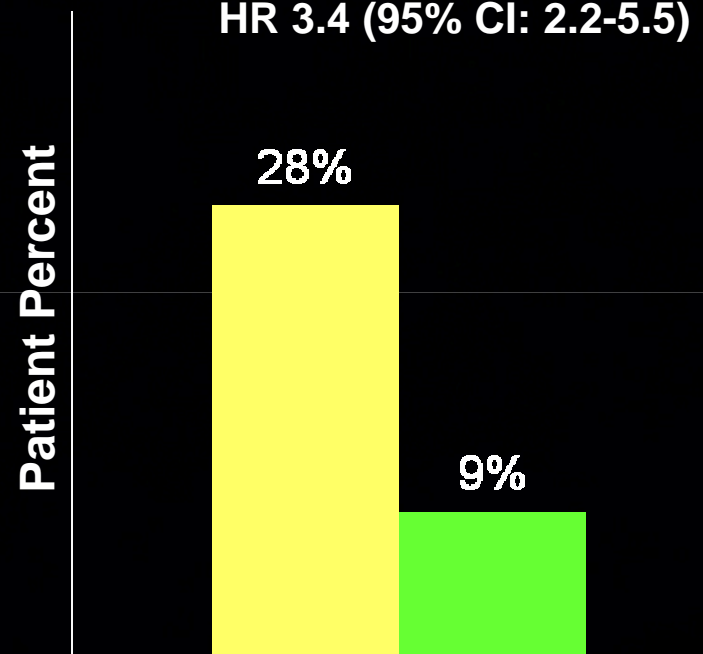
HR 0.85 (95% CI: 0.56-1.29)



- VF: LPV/r 17% vs. NVP 15%
- Death: LPV/r 3% vs. NVP 2%

## Discontinuation

HR 3.4 (95% CI: 2.2-5.5)



- Pts D/C due to AE: NVP 35 vs. LPV/r 0  
Hepatic events 20, rash 12, hepatic/rash 2

*Si tu tienes una manzana y yo tengo una manzana y las cambiamos, cada uno de nosotros seguirá teniendo una manzana. Pero si tú tienes una idea y yo tengo otra idea y las intercambiamos, cada uno de nosotros tendrá dos ideas.*

George Bernard Shaw