

**Desayuno con el experto, ViiV Healthcare GSK
VII Sesiones Clínicas GEVIHSS-IAPAC**

**FOSAMPRENAVIR
EN EL TARV 2010**

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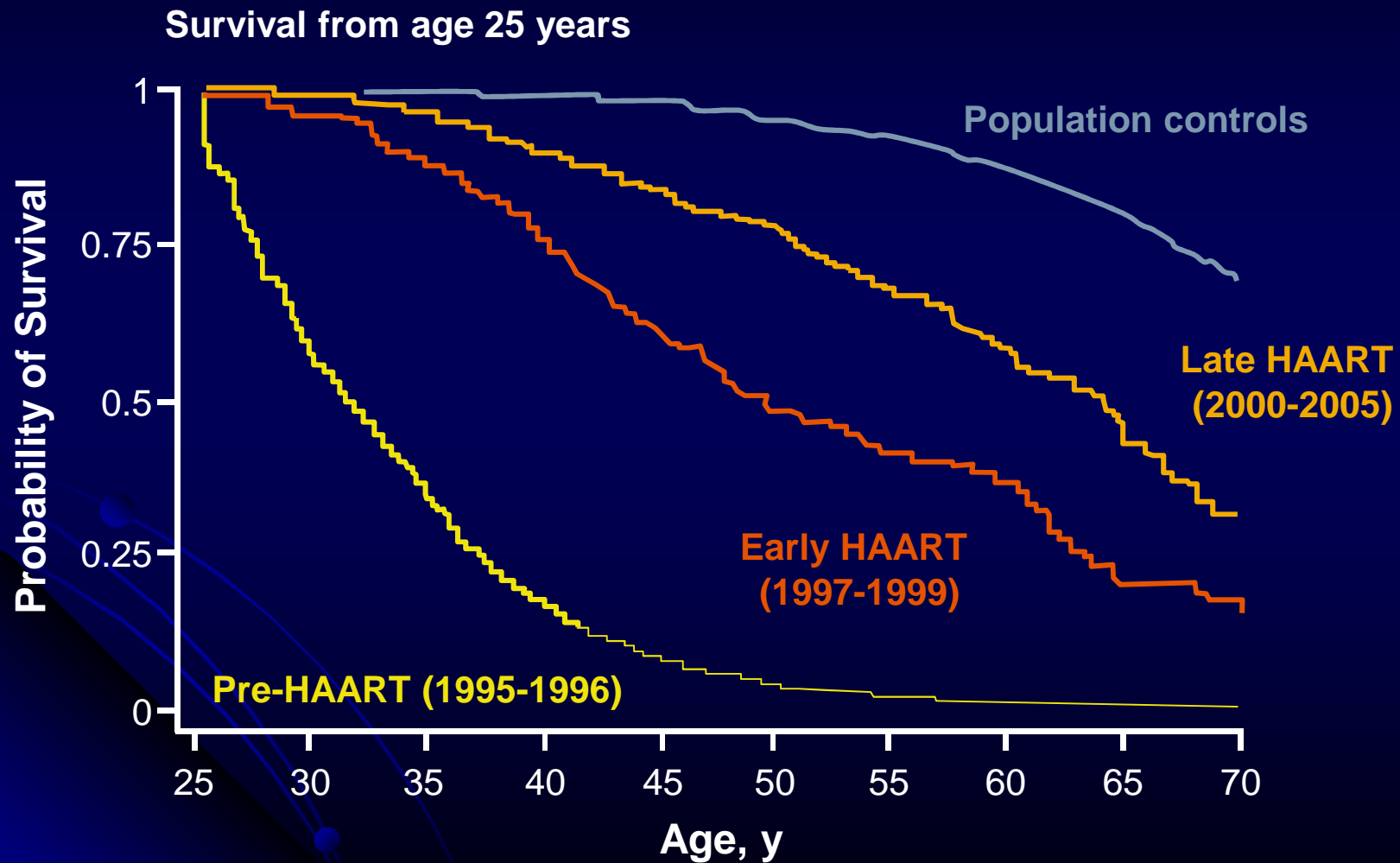
Coordinador, Comité de Atención Integral CONASIDA



Objetivos de la terapia antiviral

- **PROLONGAR** la vida y mejorar la calidad de vida
 - SUPRIMIR la carga viral bajo el límite de detección (<50 copias) por tanto tiempo como sea posible
 - MEJORAR la función inmune (elevar cuentas CD4s)
- **MINIMIZAR** la toxicidad medicamentosa, y manejar los efectos secundarios e interacciones medicamentosas
- **OPTIMIZAR** y extender el uso de la terapia actual

Expectativa de vida de pacientes en la era TARAA



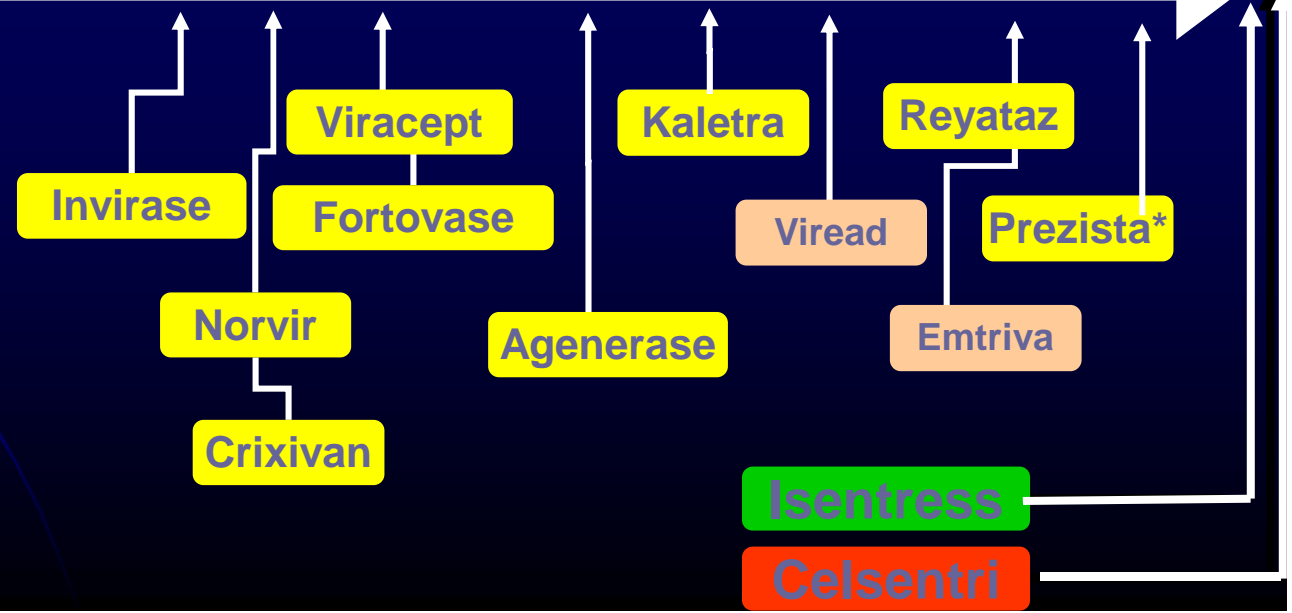
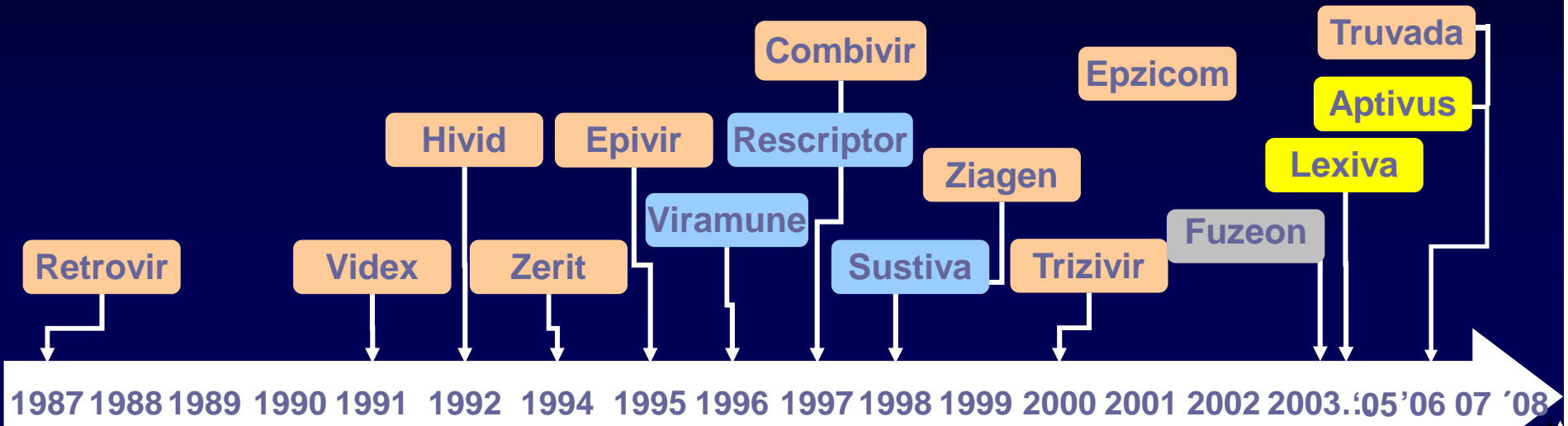
Expectativa de vida en individuos con tratamiento antirretroviral combinado

Expectativa de vida (ajustada a edad)	1996-1999	2000-2002	2003-2005
A la edad de 35 años	25.0 (SE 0.42)	30.1 (SE 0.31)	37.3 (SE 0.37)

* Individuals in high-income countries: a collaborative analyses

Adapted from The Antiretroviral Therapy Cohort Collaboration, *Lancet* 2008;372:293-299

Antirretrovirales aprobados 2010



NRTI	PI
NNRTI	Fusion inhibitors
Integrase inhibitors	CCR5 inhibitors

Algunas preguntas del TARV 2010

- Cuantos medicamentos nuevos tendremos en los siguientes 5 años
 - Serán suficientes para las demandas de pacientes multirresistentes?
- Podemos reciclar medicamentos?
- Cual es la terapia inicial ideal
- Cual es la secuencia ideal de tratamientos

Es importante realizar una terapia individualizada usando nuestros recursos de la mejor manera posible

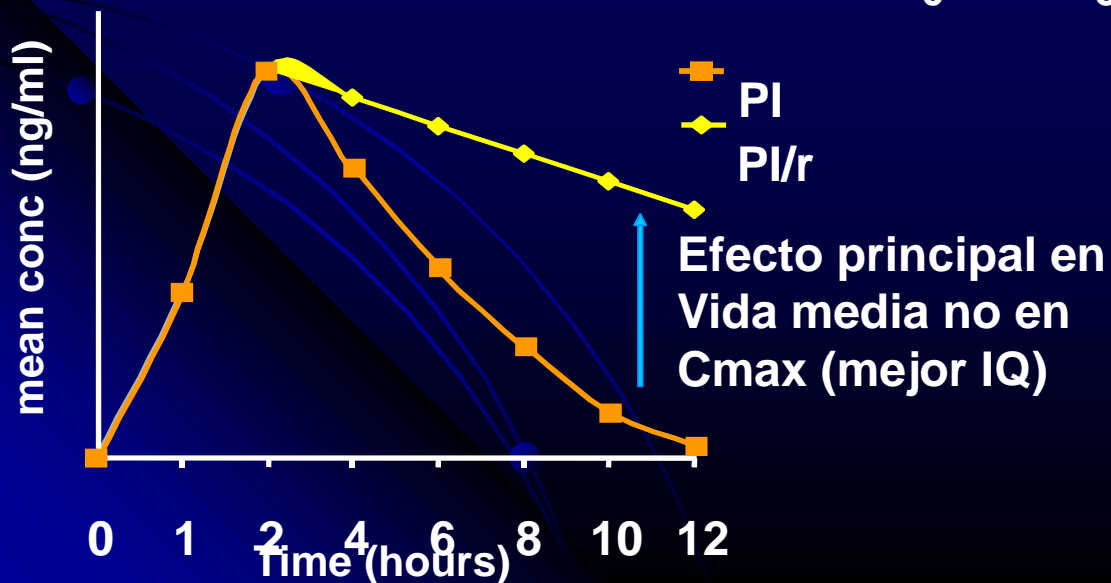
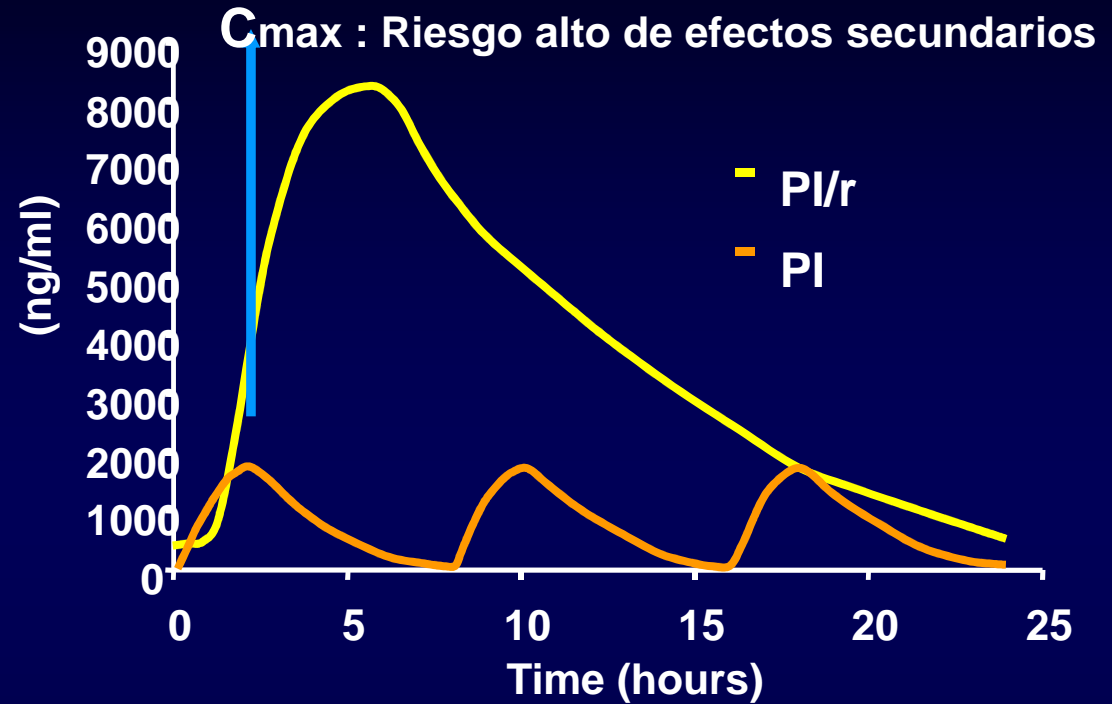
Fosamprenavir (Telzer®)



- Prodroga de Amprenavir
- Potente Efecto Antiviral
- Opciones en Dosificación (BID o QD)
- Barrera Genética Intermedia
- Limitada Resistencia Cruzada

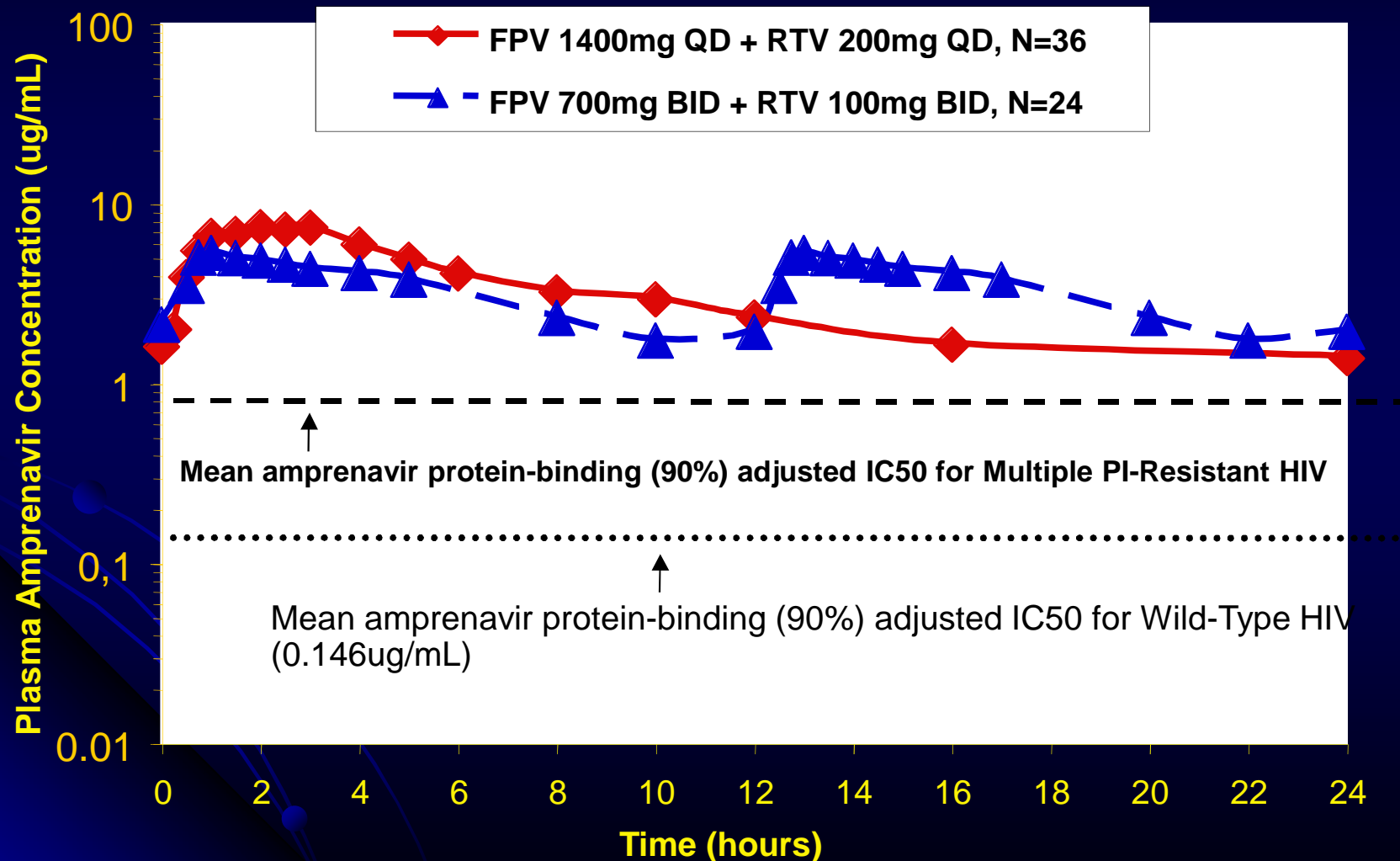
Tipos de reforzamiento con ritonavir

C_{max}
Lopinavir y Saquinavir



Vida Media
Indinavir y FAPV

Concentración media plasmática de APV IC50 in vitro ajustada a unión a proteínas



Fosamprenavir en el TARV 2010

- Datos relevantes de FAPV en 1a línea
- Segunda línea
 - Consecuencias de esquemas con EFV
- Barrera genética y score genotípico de FAPV
- Consecuencias del uso de FPV en resistencia

Opciones para tratamiento ARV inicial en 2010

ITRAN + **ITRAN** + **ITRNN**

ITRAN + **ITRAN** + **IP/r**

PROs y CONs de tendencias de Tx Inicial

NNRTI

- Simple (1 o 2 tabs/día)
- Baja toxicidad a largo plazo
- (Algo) de « forgiveness »
- Resistencia Transmitida
- Baja barrera genética
- Efectos de EFV en SNC
- Uso de EFV en mujeres con potencial reproductivo?

PI/r

- Puede ser simple (2-3 tabs/día)
- Muchas opciones para primera línea o cambio entre misma clase
- No resistencia cruzada en 1ª falla
- Interacciones medicamentosas
- Toxicidad metabólica a

Esquemas Recomendados para Inicio de Tratamiento en México

Tabla 9. Recomendaciones para inicio de ARV en personas sin tratamiento previo

•Opción	•Componentes Nucleós(t)idos		•Opción	•Tercer componente
•Preferido	•Tenofovir-Emtricitabina (AI) coformulación		•Preferido	•Efavirenz** (AI)
•Alternativo	•Abacavir*+Lamivudina (BI) coformulación	+	•Alternativo	•Atazanavir/ritonavir qd (AI) Lopinavir/ritonavir bid (AI) Fosamprenavir/ritonavir bid (BI) Saquinavir/ritonavir bid (BI)

•*Puede tener menor actividad en personas con carga viral igual o mayor a 100,000 copias/mL

**No recomendado en mujeres embarazadas o sin anticoncepción segura o confiable.

Esquemas Recomendados para Inicio de Tratamiento en EUA

<p>Preferred Regimens (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use) The preferred regimens for non-pregnant patients are arranged by order of FDA approval of components other than nucleosides, thus, by duration of clinical experience.</p>	
<p>NNRTI-based Regimen</p> <ul style="list-style-type: none"> • EFV/TDF/FTC¹ (AI) <p>PI-based Regimens (in alphabetical order)</p> <ul style="list-style-type: none"> • ATV/r + TDF/FTC¹ (AI) • DRV/r (once daily) + TDF/FTC¹ (AI) <p>INSTI-based Regimen</p> <ul style="list-style-type: none"> • RAL + TDF/FTC¹ (AI) <p>Preferred Regimen¹ for Pregnant Women</p> <ul style="list-style-type: none"> • LPV/r (twice daily) + ZDV/3TC¹ (AI) 	<p>Comments</p> <p>EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.</p> <p>ATV/r should not be used in patients who require >20mg omeprazole equivalent per day. Refer to Table 14a for dosing recommendations regarding interactions between ATV/r and acid-lowering agents.</p>
<p>Alternative Regimens (Regimens that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)</p>	
<p>NNRTI-based Regimens (in alphabetical order)</p> <ul style="list-style-type: none"> • EFV + (ABC or ZDV)/3TC¹ (BI) • NVP + ZDV/3TC¹ (BI) <p>PI-based Regimens (in alphabetical order)</p> <ul style="list-style-type: none"> • ATV/r + (ABC or ZDV)/3TC¹ (BI) • FPV/r (once or twice daily) + either [(ABC or ZDV)/3TC¹] or TDF/FTC¹ (BI) • LPV/r (once or twice daily) + either [(ABC or ZDV)/3TC¹] or TDF/FTC¹ (BI) • SQV/r + TDF/FTC¹ (BI) 	<p>Comments</p> <p>NVP:</p> <ul style="list-style-type: none"> • Should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C)³ • Should not be used in women with pre-ARV CD4 >250 cells/mm³ or men with pre-ARV CD4 >400 cells/mm³ <p>ABC:</p> <ul style="list-style-type: none"> • Should not be used in patients who test positive for HLA-B*5701 • Use with caution in patients with high risk of cardiovascular disease or with pretreatment HIV-RNA >100,000 copies/mL (see text) <p>Once-daily LPV/r is not recommended in pregnant women.</p>
<p>Acceptable Regimens (Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens.)</p>	
<p>NNRTI-based Regimen</p> <ul style="list-style-type: none"> • EFV + ddI + (3TC or FTC) (CI) <p>PI-based Regimen</p> <ul style="list-style-type: none"> • ATV + (ABC or ZDV)/3TC¹ (CI) 	<p>Comments</p> <p>EFV + ddI + FTC or 3TC has only been studied in small clinical trials.</p> <p>ATV/r is generally preferred over ATV. Unboosted ATV may be used when ritonavir boosting is not possible.</p>

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1-161. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.

Esquemas Recomendados para Inicio de Tratamiento en EUA

Regimens that may be acceptable but more definitive data are needed

CCR5-Antagonist-based Regimen

- MVC + ZDV/3TC¹ (CIII)

INSTI-based Regimen

- RAL + (ABC or ZDV)/3TC¹ (CIII)

PI-based Regimen

- (DRV/r or SQV/r) + (ABC or ZDV)/3TC¹ (CIII)

Comment

With MVC, tropism testing required before treatment. Only patients found to have CCR-5 tropic-only virus (i.e., absence of CXCR4 tropic virus) are candidates for MVC.

Regimens to be Used with Caution (Regimens that have demonstrated virologic efficacy in some studies, but have safety, resistance, or efficacy concerns.)

NNRTI-based Regimens

- NVP + ABC/3TC¹ (CIII)

Comments

Use NVP and ABC together with caution because both can cause hypersensitivity reactions within first few weeks after initiation of therapy.

- NVP + TDF/FTC¹ (CIII)

Early virologic failure with high rates of resistance has been reported in some patients receiving NVP + TDF + (3TC or FTC). Larger clinical trials are currently in progress.

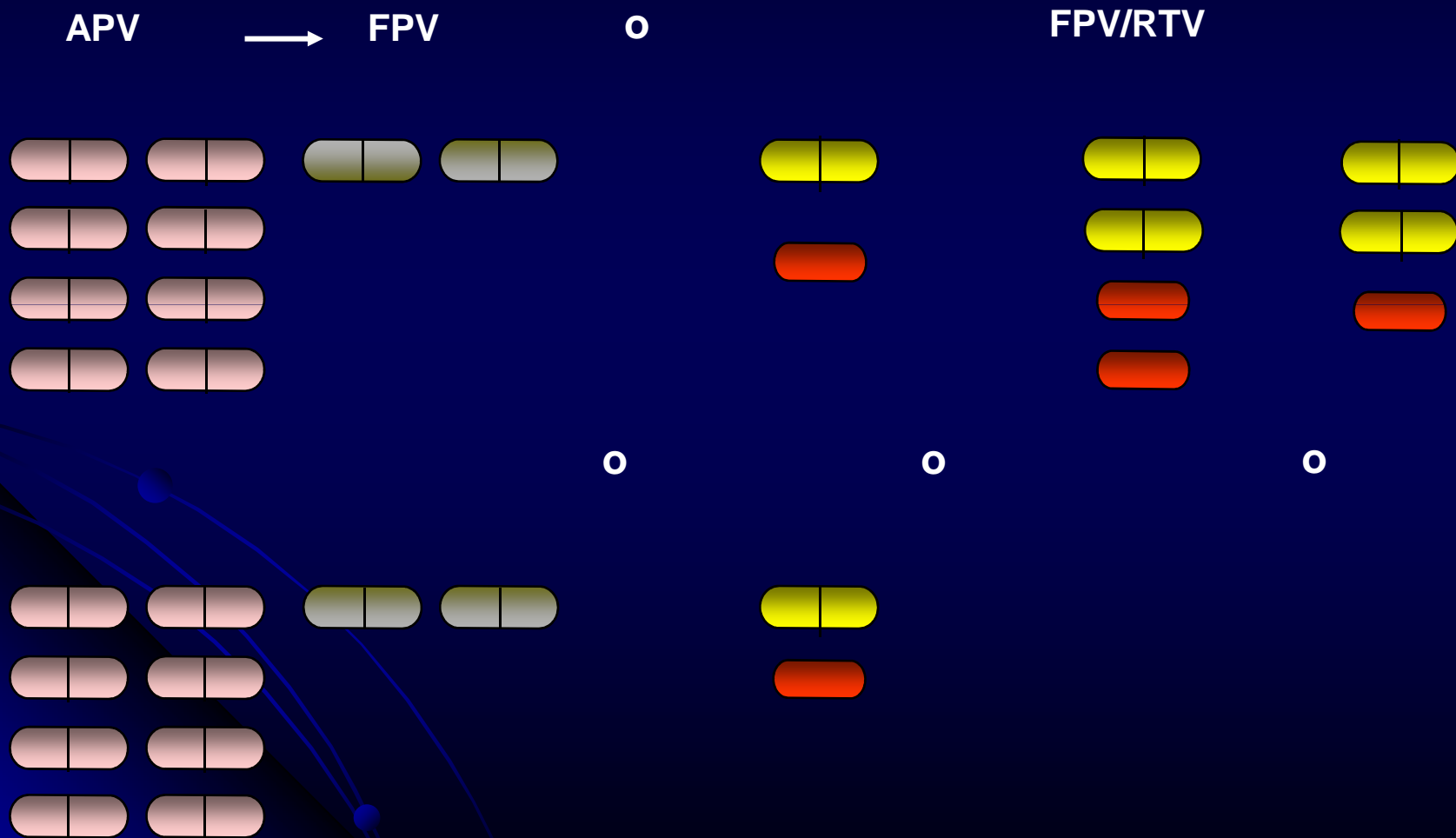
PI-based Regimen

- FPV + [(ABC or ZDV)/3TC¹ or TDF/FTC¹] (CIII)

FPV/r is generally preferred over unboosted FPV. Virologic failure with unboosted FPV-based regimen may select mutations that confer cross resistance to DRV.

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1-161. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.

Evolución de la Dosificación de AMP/FPV



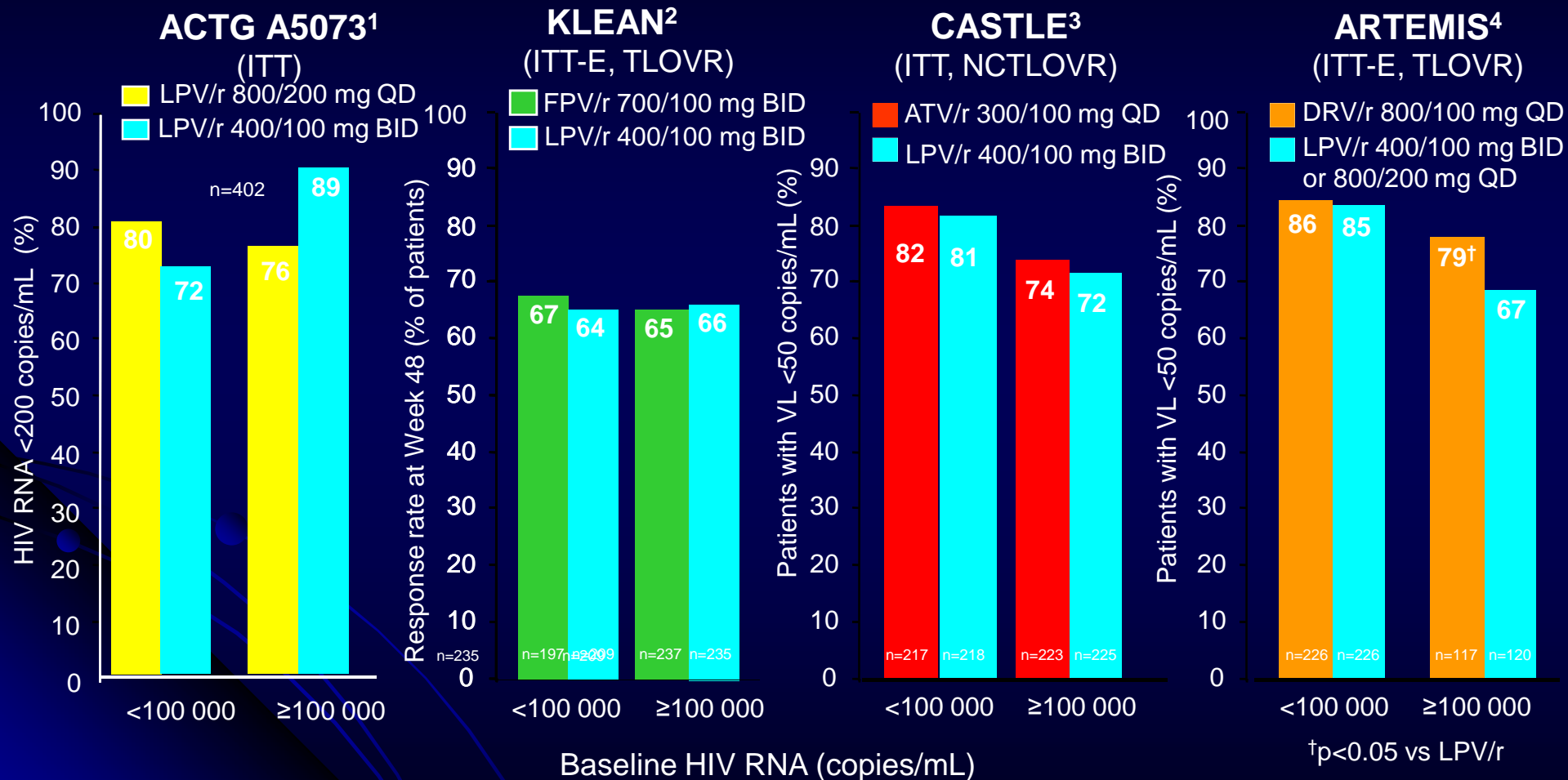
Eficacia Similar de los IPs reforzados en pacientes sin TARV previo

Study Primary Endpoint	Patients With HIV-1 RNA < 50 copies/mL, %	Estimated Difference, %
KLEAN (48 weeks, ITT-E: TLOVR)^[1]		
FPV/RTV 700/100 mg BID + ABC/3TC (n = 434)	66	N/A
LPV/RTV SGC 400/100 mg BID + ABC/3TC (n = 444)	65	
GEMINI (48 weeks, ITT)^[2]		
SQV/RTV 1000/100 mg BID TDF/FTC (n = 167)	65	1.14 (95% CI: -9.60 to 11.90)
LPV/RTV SGC 400/100 mg BID + TDF/FTC (n = 170)	64	
CASTLE (48 weeks, ITT-CVR: NC = F)^[3]		
ATV/RTV 300/100 mg QD + TDF/FTC (n = 440)	78	1.7 (95% CI: -3.8 to 7.1)
LPV/RTV SGC 400/100 mg BID + TDF/FTC (n = 443)	76	
ARTEMIS (48 weeks, ITT: TLOVR)^[4]		
DRV/RTV 800/100 mg QD (n = 343)	84	5.5 (95% CI: -0.3 to 11.2)
LPV/RTV 400/100 mg BID or 800/200 mg QD + TDF/FTC* (n = 346)	78	

*77% of patients received BID dosing throughout study; 83% of patients switched from SGC to tablet formulation.

1. Eron J Jr, et al. Lancet. 2006;368:476-482. 2. Walmsley SL, et al. EACS 2007. Abstract PS1.4. 3. Molina JM, et al. CROI 2008. Abstract 37. 4. Clumeck N, et al. EACS 2007. Abstract LBPS7.5.

IPs potenciados en pacientes sin terapia previa y con carga viral alta



LPV/r QD is not licensed in the EU. The EU licensed dose of DRV/r is 600/100 mg BID.
Data in figures are from different studies and cannot be compared directly.

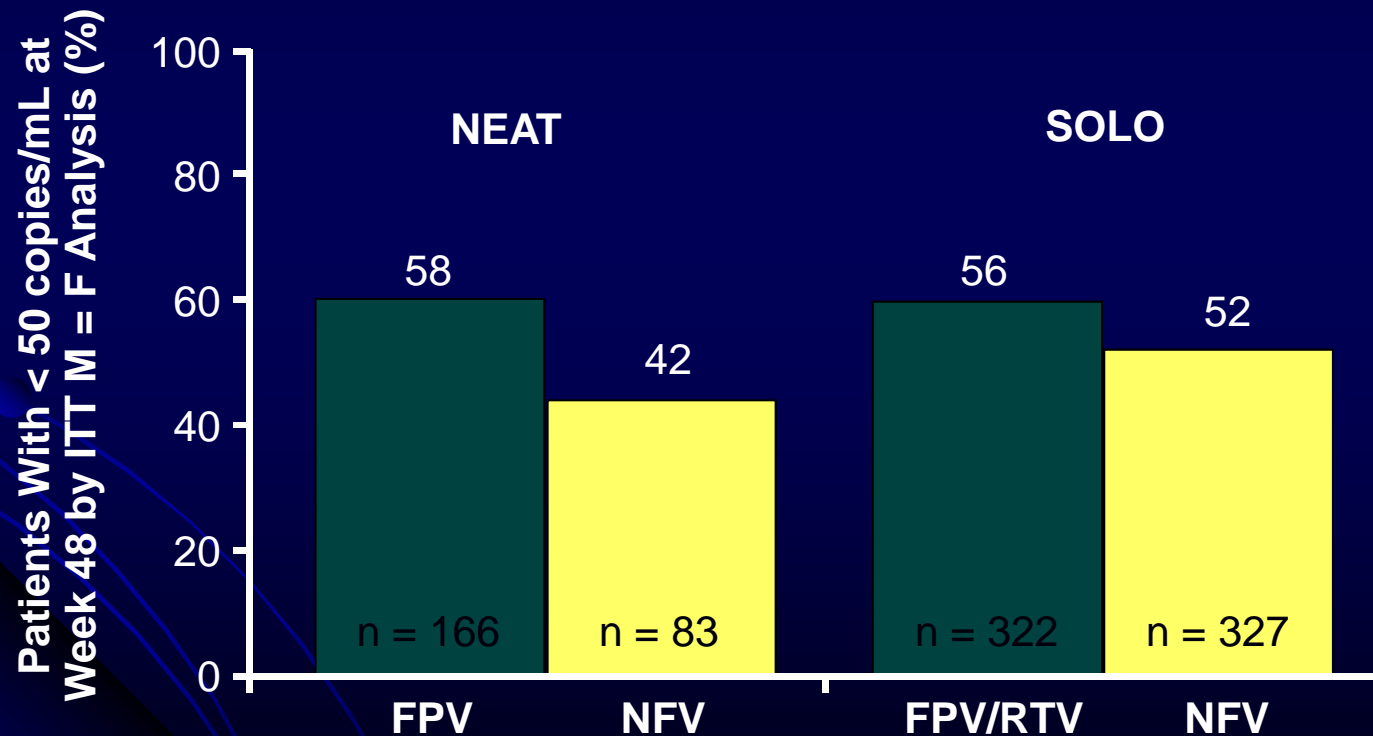
1. Mildvan D, et al. 14th CROI, 2007, Abstract 138;
2. Eron J, et al. Lancet 2006;368:476–482;
3. Molina et al. 15th CROI 2008, Abstract 37
4. De Jesus E, et al. ICAAC 2007, Abstract LBA H-718b

Efectos Adversos Moderados a Graves con IPs (%)

	ATV (ARV Naive)	FPV (ARV Naive)	FPV/RTV (ARV Naive)	IDV	LPV/RTV SGC (ARV Naive)	NFV	SQV
Nausea	6-14	7	7	11.7-31.9	7	3-7	10.8
Diarrhea	1-3	5	10	3-3.3	5-10	14-20	8.1%
Vomiting	3-4	2	6	8.4-17.8	2-6	NA	7.4%
Abdominal Pain	4	1	2	16-16.6	3-10	NA	6.1%
Other	NA	NA	NA	Acid reflux, dyspepsia 1.5-5.4	Flatulence, dyspepsia < 1-5	Flatulence 1-5	Constipation 2

FPV y FPV/RTV como IP inicial: NEAT and SOLO

- International, phase III, open-label, randomized studies



Gathe JC et al. AIDS. 2004;18:1529-1537. Rodriguez-French A, et al. J Acquire Immune Defic Syndr. 2004;35:22-32.

KLEAN: FPV/RTV vs LPV/RTV como Tx inicial

- Multicenter, randomized, open-label, phase IIIb noninferiority trial.
- Primary endpoint: HIV-1 RNA < 400 copies/mL at Week 48

Stratified by baseline HIV-1 RNA < vs \geq 100,000 copies/mL

Antiretroviral-naive patients with HIV-1 RNA > 1000 copies/mL; no CD4+ cell count restrictions

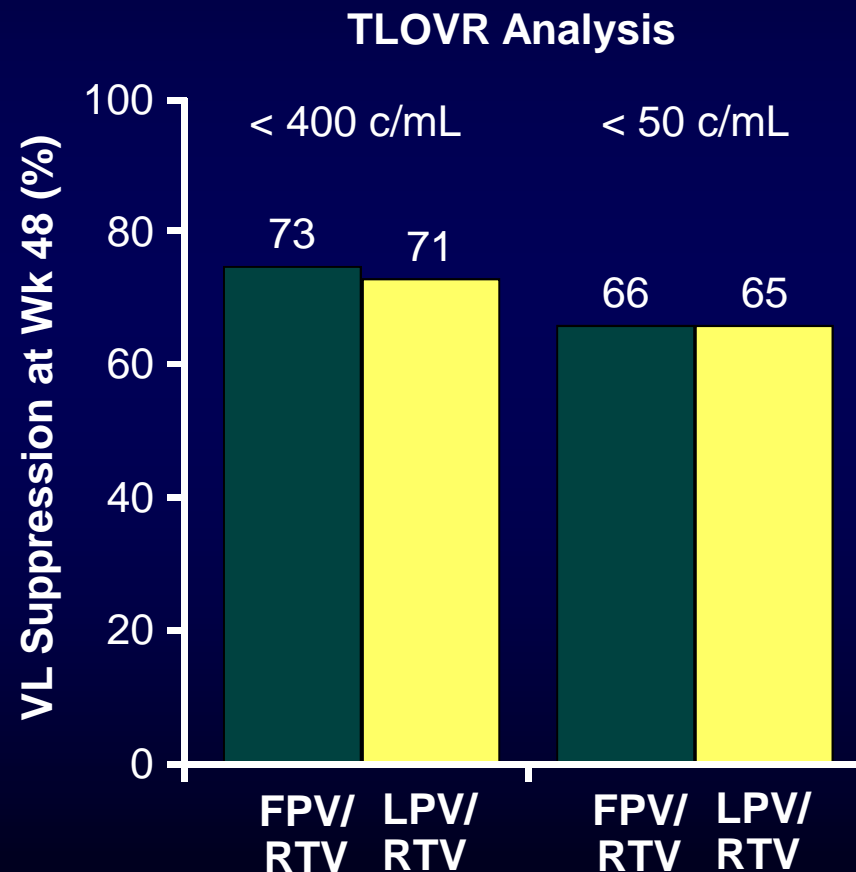
(N = 878)

FPV/RTV 700/100 mg BID + ABC/3TC FDC
(n = 434)

LPV/RTV SGC 400/100 mg BID + ABC/3TC FDC
(n = 444)

KLEAN: FPV/RTV vs LPV/RTV como Tx inicial

- FPV/RTV 700/100 mg BID (n = 434) vs LPV/RTV SGC (400/100 mg BID) (n = 444).
 - Plus ABC/3TC (600/300 mg) QD.
- No difference in virologic outcome overall or stratified by baseline VL or CD4+ count.
- CD4+ gain: +176 (FPV/RTV) vs +191 (LPV/RTV) (ITT-E).



KLEAN: FPV/RTV vs LPV/RTV como Tx inicial

Patient Outcomes at Week 48	FPV/RTV (n = 434)	LPV/RTVSGC (n = 444)
HIV-1 RNA < 400 copies/mL (ITT-E, TLOVR), %	73	71
HIV-1 RNA < 50 copies/mL (ITT-E, TLOVR), %	66	65
Confirmed virologic failure, n (%)	16 (4)	24 (5)
Median increase in CD4+ cell count, cells/mm ³ (IQR)	176 (106-281)	191 (124-287)
Median change in lipid levels, mg/dL (mmol/L)		
• TC	+61.0 (+1.58)	+52.5 (+1.36)
• LDL cholesterol	+28.0 (+0.73)	+22.5 (+0.58)
• HDL cholesterol	+13.0 (+0.34)	+14.0 (+0.36)
• TG	+67.0 (+0.76)	+77.5 (+0.88)

KLEAN: Eventos Adversos

- Similar rates of adverse events and changes in lipid levels in both arms

Events ≥ 1	FPV/RTV, % (n = 436)	LPV/RTV SGC, % (n = 443)
Grade 3/4 events		
● Suspected ABC HSR	2	2
● Diarrhea	2	< 1
Discontinuation of any study drug	12	10
● Due to suspected ABC HSR	7	5
● Due to diarrhea	1	2

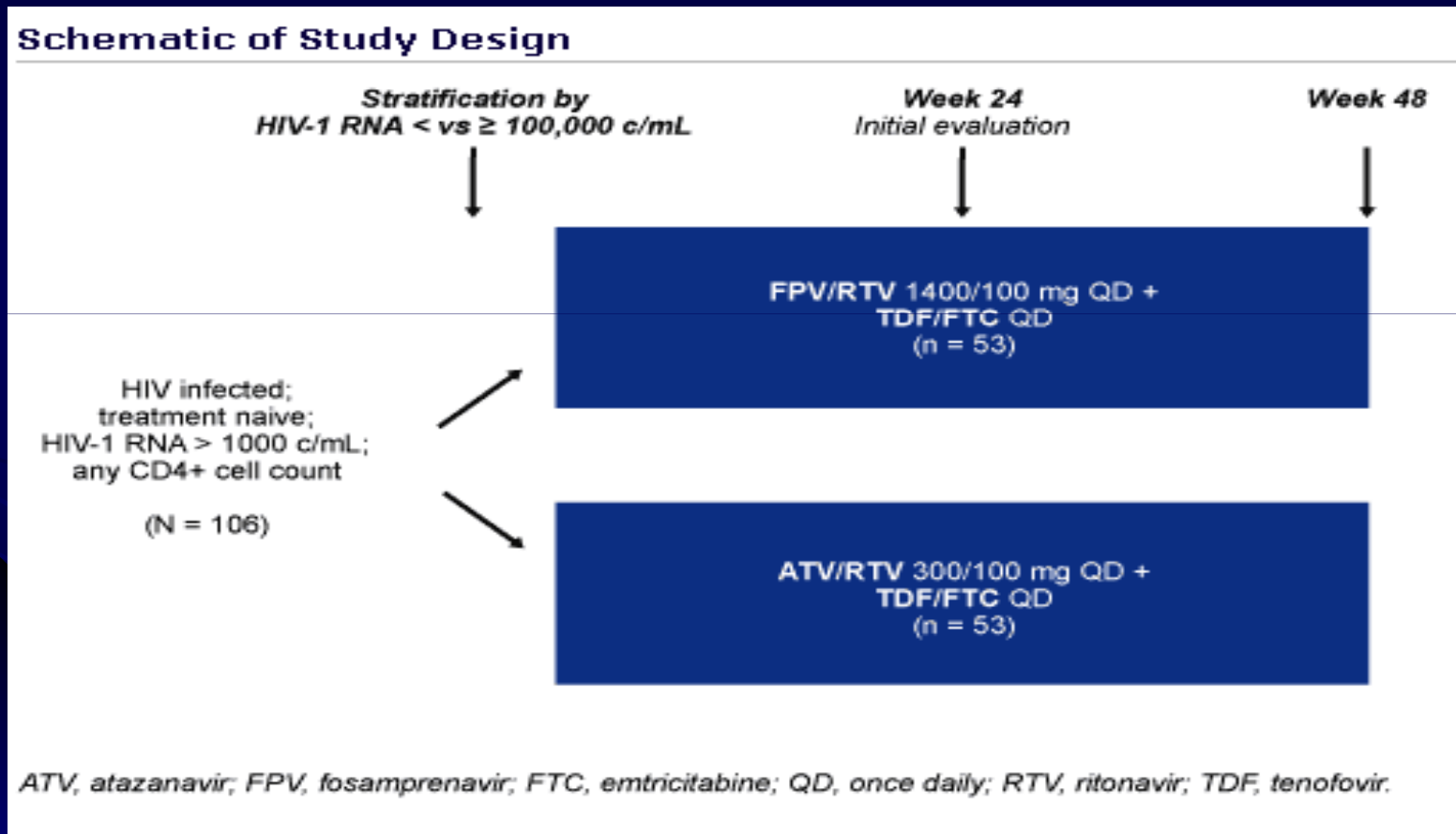


KLEAN: Resistancia en Falla

	FPV/RTV, n (n = 434)	LPV/RTV SGC, n (n = 433)
Confirmed virologic failures	16	24
Unable to sequence	2	3
No treatment-emergent mutations	9	14
Treatment-emergent mutations		
TAMs (M41M/L)	0	1
3TC-associated mutations (M184I, M184V, M184M/V)	3	4
NNRTI-associated mutations (V106V/A)	0	2
PI-associated mutations: all minor (I54I/L, I93I/L, K20K/R, I62I/V)	3	2

ALERT: FPV/RTV vs ATV/RTV en Pacientes sin Tx Previo

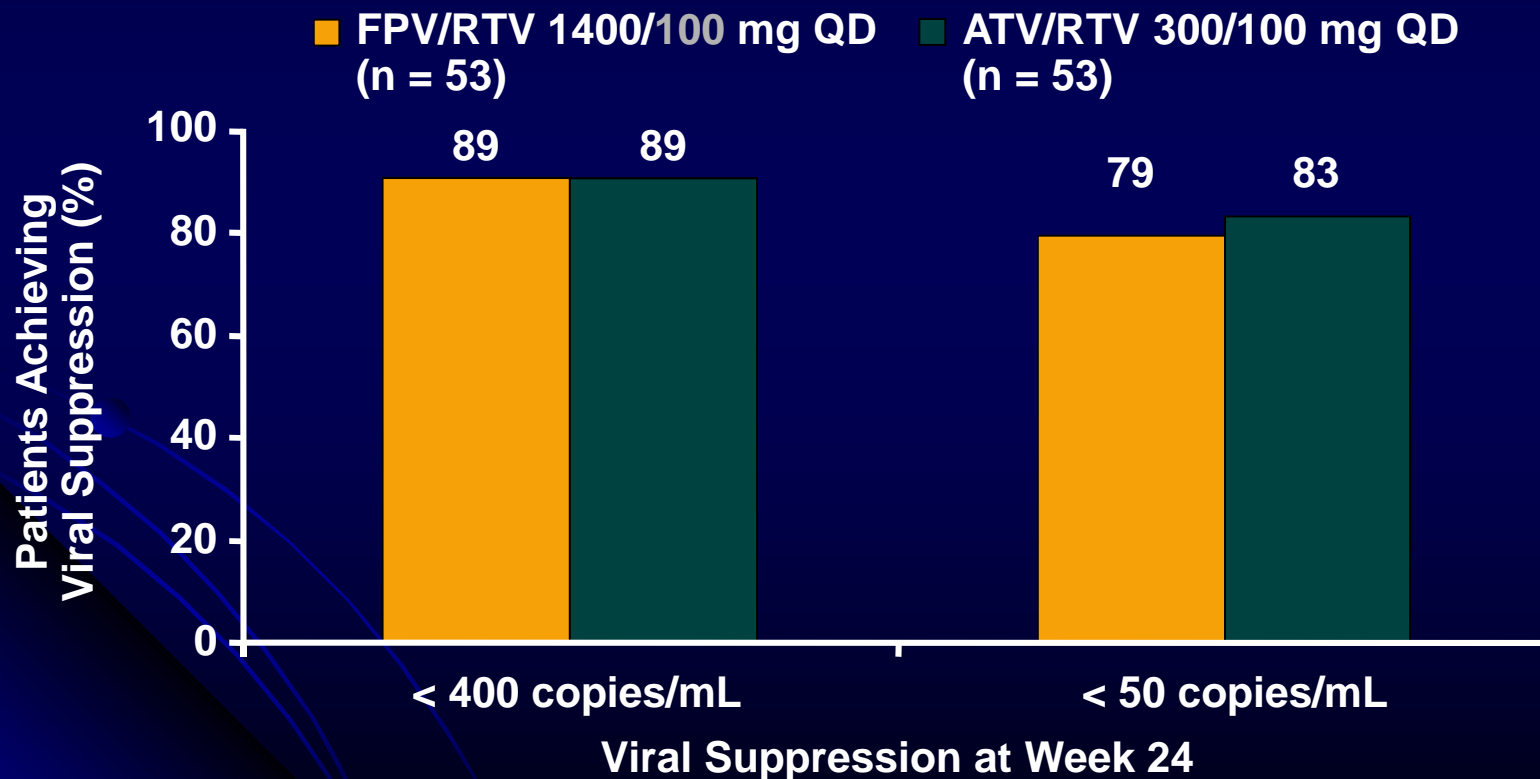
ALERT (COL103952): open-label, prospective, randomized pilot study.



- Smith K, Weinberg W, DeJesus E, et al. Efficacy and safety of once-daily boosted fosamprenavir (FPV/r) or atazanavir (ATV/r) with tenofovir (TDF)/emtricitabine (FTC) in antiretroviral-naïve HIV-infected patients: 24-week results from COL103952 (ALERT).
- Program and abstracts of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 27-30, 2006; San Francisco, California. Abstract H-1670a

ALERT: FPV/RTV vs ATV/RTV en Pacientes sin Tx Previo

ITT, MD = F analysis



ALERT: FPV/RTV vs ATV/RTV en Pacientes sin Tx Previo

<i>Outcome at Week 24</i>	<i>Fosamprenavir/Ritonavir (n = 53)</i>	<i>Atazanavir/Ritonavir (n = 53)</i>
HIV-1 RNA < 50 copies/mL, %		
▪ ITT	79	83
▪ OT	84	88
HIV-1 RNA < 400 copies/mL, %		
▪ ITT	89	89
▪ OT	94	94
Mean CD4+ cell count increase, cells/mm³		
	126	166
Mean increase in lipid levels, mg/dL (mmol/L)		
▪ Triglycerides	44 (0.94)	6 (0.06)
▪ Total cholesterol	17 (0.44)	27 (0.69)
▪ LDL cholesterol	4 (0.10)	6 (0.15)
▪ HDL cholesterol	3 (0.07)	7 (0.18)

ITT, intent to treat; OT, on treatment.

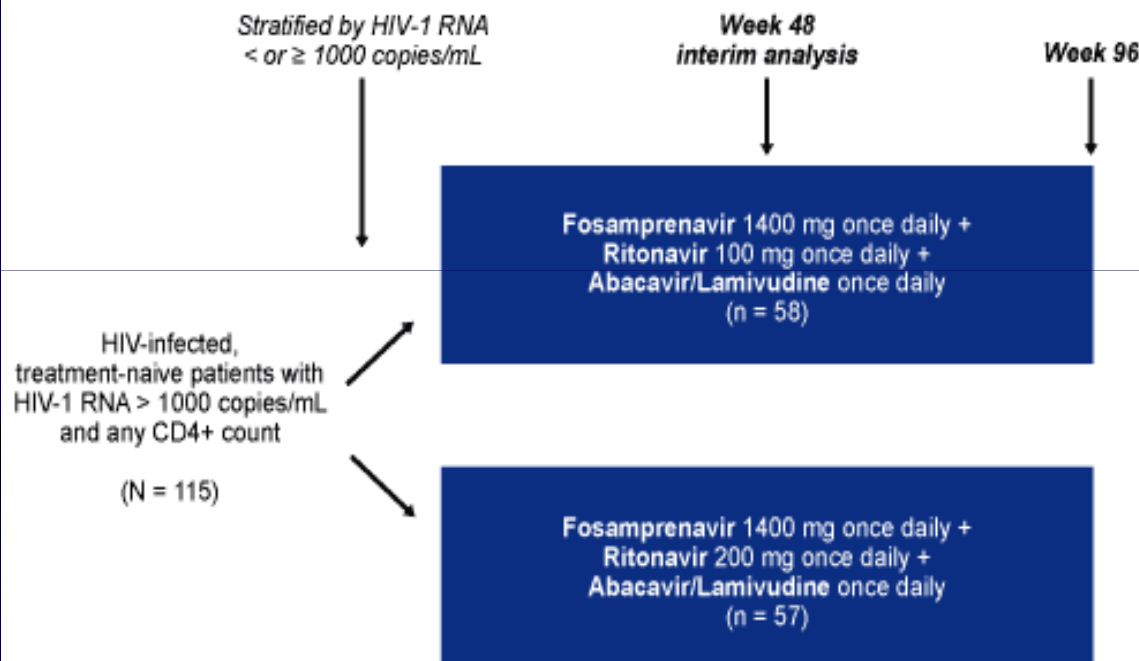
- Both regimens were well tolerated
 - Adverse events observed with atazanavir primarily related to bilirubin elevations

- Smith K, Weinberg W, DeJesus E, et al. Efficacy and safety of once-daily boosted fosamprenavir (FPV/r) or atazanavir (ATV/r) with tenofovir (TDF)/emtricitabine (FTC) in antiretroviral-naïve HIV-infected patients: 24-week results from COL103952 (ALERT).
- Program and abstracts of the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 27-30, 2006; San Francisco, California. Abstract H-1670a

Fos-APV reforzado con 100 mg de ritonavir en pacientes sin tratamiento previo

COL100758: randomized, open-label 96-week trial in treatment-naive patients

Schematic of Study Design



- Body composition and bone mineral density evaluated in 48 participants by DEXA scan at Week 48 interim analysis

Wohl D, Lancaster T, DeJesus E, et al. Determination of body composition changes by total body dual-energy x-ray absorptiometry after 48 weeks of treatment with once-daily fosamprenavir (FPV) boosted with two different doses of ritonavir(r) plus abacavir (ABC)/lamivudine (3TC): COL100758. Program and abstracts of the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia. Abstract TUPEB080.

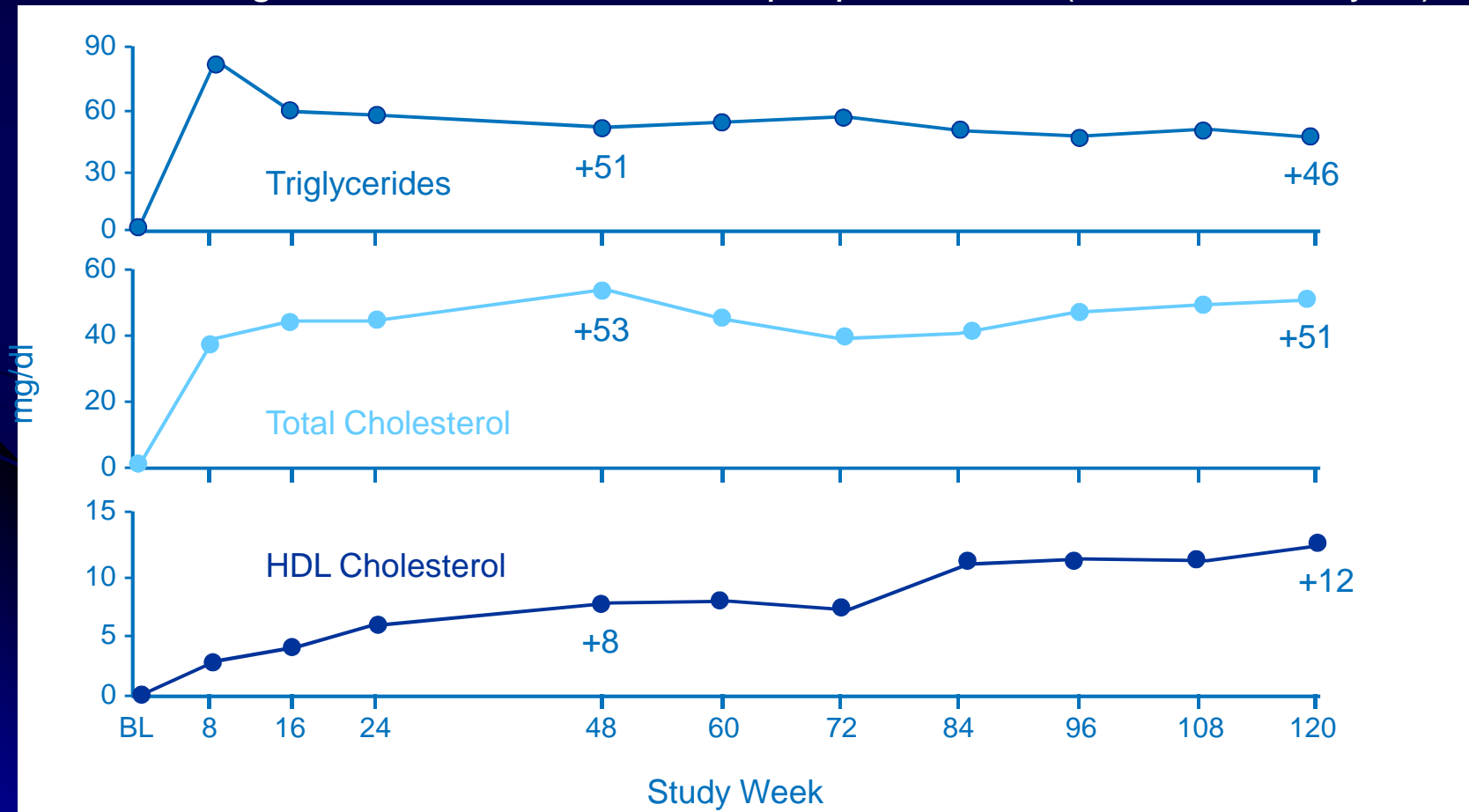
Fos-APV reforzado con 100 mg de ritonavir en pacientes sin tratamiento previo

<i>Parameter</i>	<i>Fosamprenavir/ Ritonavir 1400/100 mg</i>	<i>Fosamprenavir/ Ritonavir 1400/200 mg</i>	<i>P Value</i>
Completed through Wk 48, %	90	75	
HIV RNA < 400 copies/mL (ITT), %	84	67	.026
HIV RNA < 400 copies/mL (on treatment), %	98	84	.018
HIV RNA < 50 copies/mL (ITT), %	79	63	.061
HIV RNA < 50 copies/mL (on treatment), %	92	80	.100
Mean increase in CD4+ cell count, cells/mm ³	198	194	NS

Wohl D, Lancaster T, DeJesus E, et al. Determination of body composition changes by total body dual-energy x-ray absorptiometry after 48 weeks of treatment with once-daily fosamprenavir (FPV) boosted with two different doses of ritonavir(r) plus abacavir (ABC)/lamivudine (3TC): COL100758. Program and abstracts of the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; July 22-25, 2007; Sydney, Australia. Abstract TUPEB080.

APV30005 fosamprenavir/r OD: no incremento mayor de TG y Colesterol entre semanas 48 y 120

Mean change from SOLO baseline in lipid parameters (Observed analysis)



“Secuenciación”

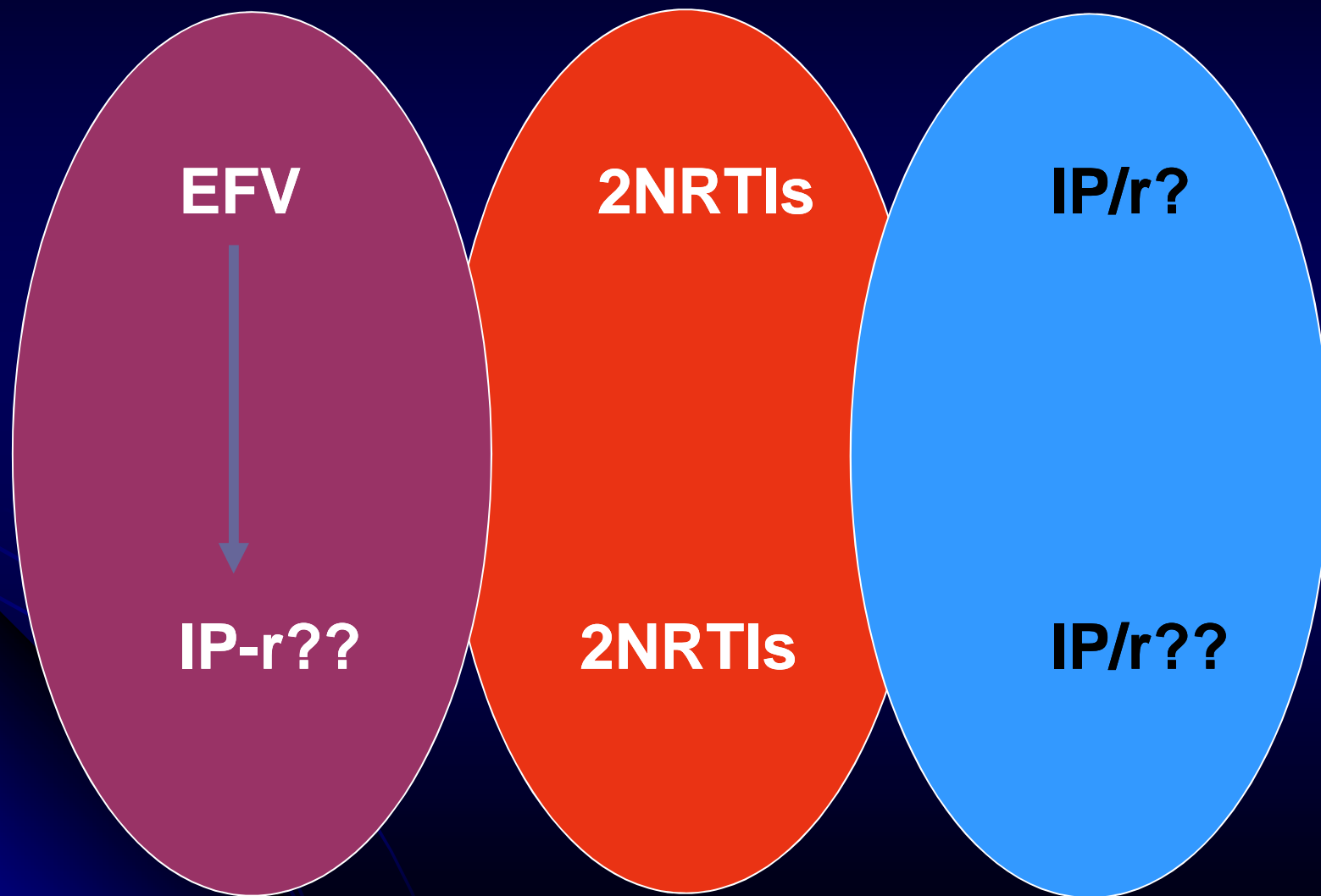


Tabla 13. Secuenciación del tercer componente ante falla al primer esquema de tratamiento antirretroviral

•ESQUEMA INICIAL	•PRIMER RESCATE
•Esquema inicial con 2 ITRAN Y 1 ITRNN	
•2 ITRAN + EFV o NVP	•2 nuevos ITRAN* + ATZ/r o f-APV/r o LPV/r^ o SQV/r
•Esquema inicial con 2 ITRAN Y 1 IP o IP/r &	
•2 ITRAN + APV/r o f-APV/r	•2 nuevos ITRAN* + LPV/r
•2 ITRAN + ATZ/r	•2 nuevos ITRAN* + LPV/r^
•2 ITRAN + IDV/r ó SQV/r	•2 nuevos ITRAN* + LPV/r^
•2 ITRAN LPV/r	•2 nuevos ITRAN* con DRV/r o TPV/r
•2 ITRAN + NFV	•2 nuevos ITRAN* + LPV/r^o DRV/r o TPV/r de preferencia con genotipo
•Esquema inicial con triple nucleósido	
•ZDV- 3TC- ABC	•TDF/ddI + ATZ/r o f-APV/r o LPV/r o SQV/r +/- EFV&
•Otras combinaciones de 3 ITRAN	•2 nuevos ITRAN* + ATZ/r o f-APV/r o LPV/r o SQV/r +/- EFV&

Estudio CONTEXT

- 315 patients who had failed 1-2 PIs with current treatment failure (HIV RNA ≥ 1000 c/mL at screening) were randomized to receive 2 N(t)RTIs with:
 - F-APV/RTV 1400/200 mg QD
 - F-APV/RTV 700/100 mg BID
 - LPV/RTV 400/100 mg BID
- Subjects did not have to be taking a PI at study entry, ~ 2/3 were receiving a PI at entry.

Exposición previa a ARV en el estudio CONTEXT

	908/r QD (n=105)	908/r BID (n=107)	LPV/r BID (n=103)
Median duration prior PIs (weeks)	149	149	130
≥ 2 Prior PIs taken (% of subjects)	57%	49%	40%
Median duration prior NRTIs (weeks)	234	257	210
≥ 3 Prior NRTIs taken (% of subjects)	70%	79%	64%
Median duration prior NNRTIs (weeks)	87	84	78
≥ 2 Prior NNRTIs taken (% of subjects)	11%	14%	8%

Resistencia Basal del Estudio

CONTEXT

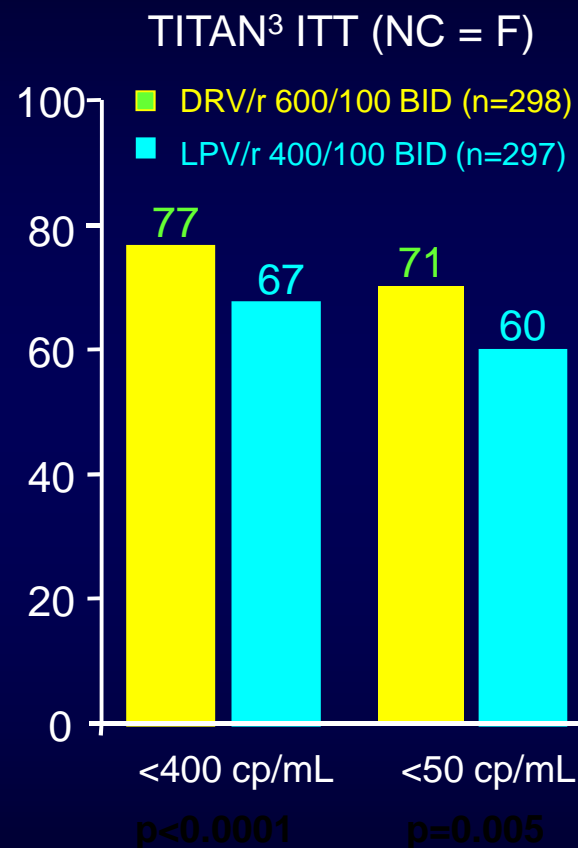
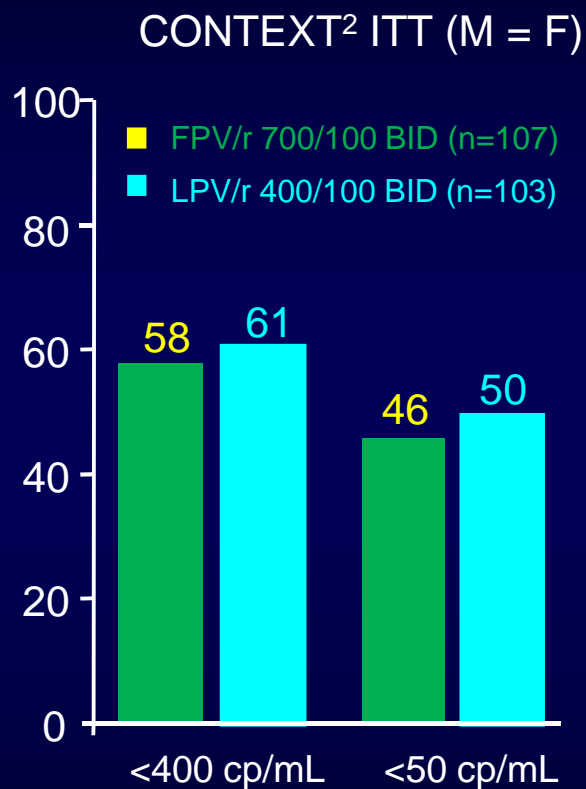
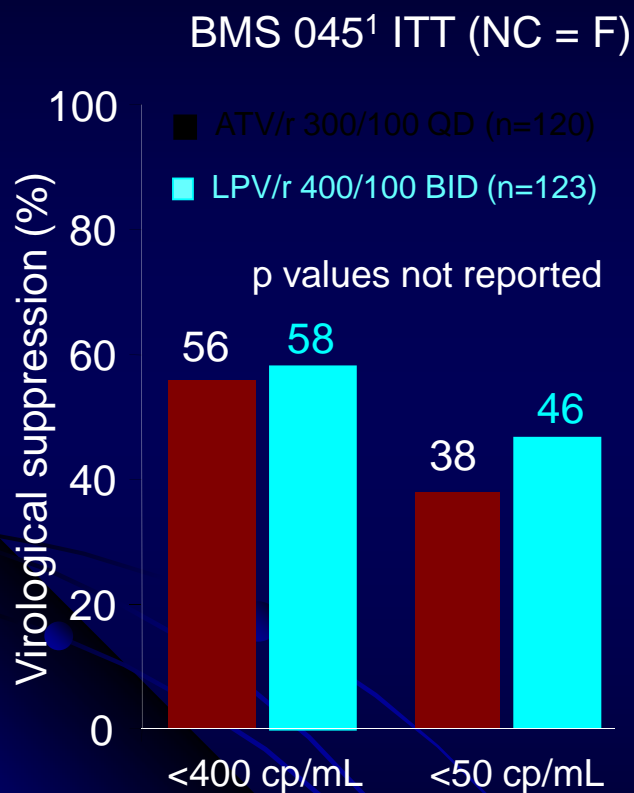
Mean (Median)	908/r QD n=105	908/r BID n=107	LPV/r BID n=103
Primary PI Mutations	1.0 (1.0)	0.9 (1.0)	1.0 (1.0)
≥ 3 Primary PI Mutations	7%	8%	11%
Secondary PI Mutations	2.8 (3.0)	2.8 (3.0)	3.0 (3.0)
Phenotypic resistance to all PIs (>2.5)	8%	16%	9%
NRTI Mutations	2.3 (2.0)	2.6 (3.0)	2.4 (2.0)
TAMs	1.3 (0.0)	1.7 (2.0)	1.4 (1.0)
≥ 3 TAMs	28%	38%	24%
M184I/V	60%	49%	56%

Estudio CONTEXT, Eficacia a 48 semanas

	908/r BID n=107	LPV/r BID n=103
Mean AAUCMBs (Observed)		
log ₁₀ c/mL	-1.53±0.94	-1.76±0.93
Responder (ITT RD=F)		
HIV RNA <400 c/mL	58%	61%
HIV RNA <50 c/mL	46%	50%
Virologic Failures		
HIV RNA >400 c/mL	27%	27%

908/r QD is not recommended for PI-experienced patients (HIV RNA <400 c/mL 50% and HIV RNA <50c/mL 37%)

BMS 045/CONTEXT/TITAN: Supresión virológica a 48 semanas



CD4 gain **110 vs 121**

62 vs 63

88 vs 81

NC=non-completer; M=missing; F=failure. Data in figures are from different studies and can not be compared directly

Adapted from: 1. Johnson M, et al. AIDS 2005;19:685-694; 2. Elston RC, et al. XV IAC 2004 (MoOrB1055) 3. Madruga JV, et al. Lancet 2007; 370:49-58

Barrera Genética relativa de los IPs

- **NFV**
- **SQV, IDV**
- **ATV**
- **LPV, FPV**
- **TPV, DRV**

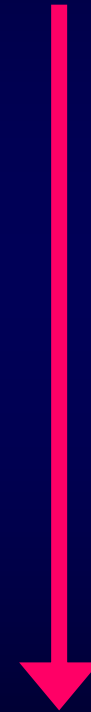


Table 2. Amino acid substitutions in HIV-1 protease associated with VR to fosamprenavir/ritonavir-containing regimens (univariate analysis)

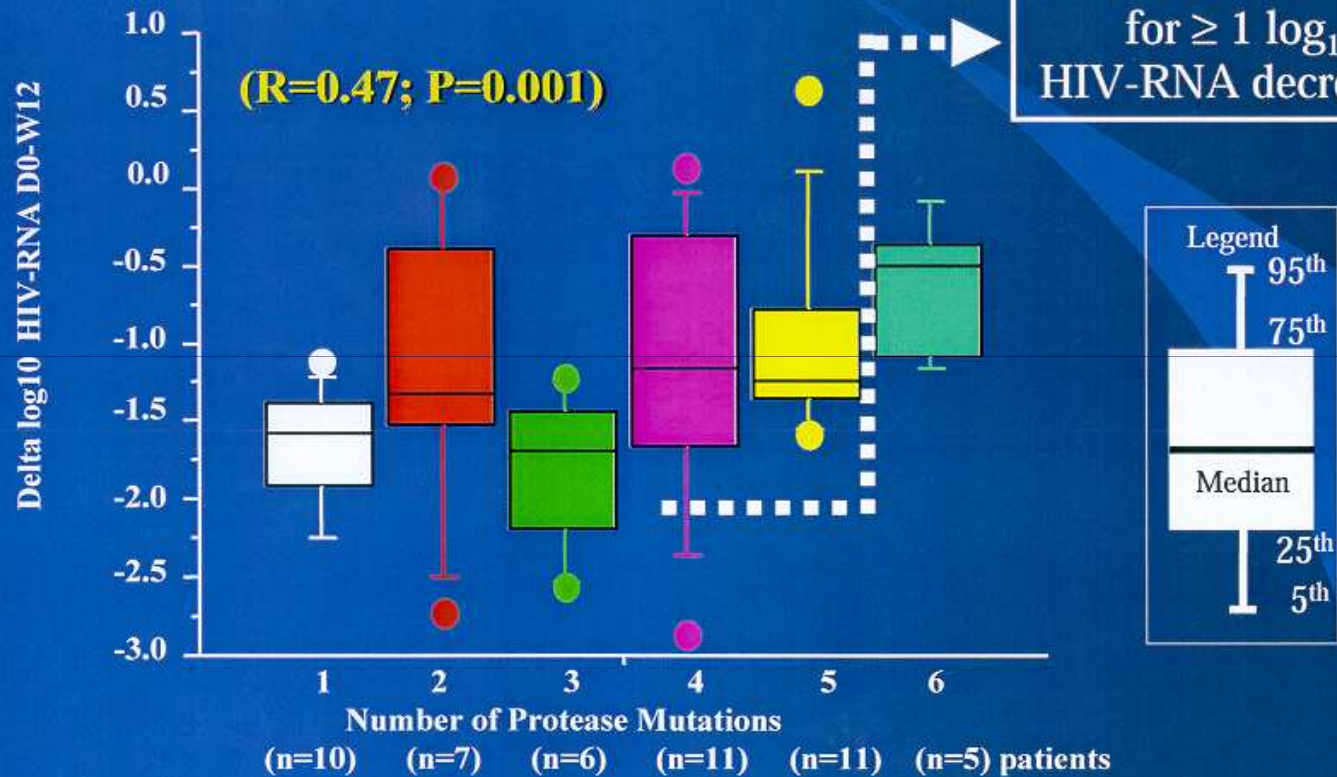
Mutation	Prevalence (%)	Mean VR \pm SD		<i>P</i> value of the Mann-Whitney test
		wild-type	mutated	
L10F/I/V	69.9	-1.75 \pm 1.44	-0.77 \pm 1.29	0.003
L33F	34.2	-1.26 \pm 1.31	-0.70 \pm 1.52	0.033
E34K/G/Q	11.0	-1.16 \pm 1.40	-0.3 \pm 1.22	0.030
M36I	42.5	-1.30 \pm 1.28	-0.75 \pm 1.52	0.042
M46I/L	53.4	-1.38 \pm 1.34	-0.80 \pm 1.42	0.040
I54L/M/V/A/T/S	49.3	-1.58 \pm 1.49	-0.54 \pm 1.11	<0.001
I62V	49.3	-1.32 \pm 1.54	-0.81 \pm 1.22	0.098
A71V	39.7	-1.21 \pm 1.24	-0.85 \pm 1.62	0.064
I72K/L/R/V	24.7	-1.29 \pm 1.29	-0.37 \pm 1.53	0.003
G73S/A/C/T	30.1	-1.22 \pm 1.42	-0.71 \pm 1.31	0.066
V77I	34.2	-0.80 \pm 1.32	-1.57 \pm 1.44	0.041
V82A/F/C/G	32.9	-1.34 \pm 1.37	-0.50 \pm 1.32	0.008
I84V	27.4	-1.19 \pm 1.49	-0.73 \pm 1.10	0.253
N88S	2.7	-0.98 \pm 1.31	-4.07 \pm 1.55	0.039
L90M	54.8	-1.61 \pm 1.57	-0.62 \pm 1.08	0.001

Mean VR: mean change in plasma HIV-1 RNA (\log_{10} copies/mL) between baseline and month 3 on fosamprenavir/ritonavir in patients without (wild-type) or with (mutated) the corresponding HIV-1 protease substitutions. All mutations are associated with a worse VR, except those indicated in bold which are associated with a better VR.

Mutaciones asociadas a resistencia

- fosAMP/r 700/100 mg bid
 - I50V
 - V32I e I47A/V
 - Al menos 4 mutaciones de las siguientes:
 - L10F/I/V, L33F, M36I, I54A/L/M/S/T/V, I62V, V82A/C/F/G, I84V, L90M

Predictivity of APV Key mutations on the treatment efficacy (Delta of Plasma HIV RNA between baseline and weeks 12)



APV mutations Cut-off
for $\geq 1 \log_{10}$ of
HIV-RNA decrease is 5

APV-associated mutations : L10F/I/V, K20M/R, E35D, R41K, I54V, L63P, V82A/F/T/S, I84V

Barrera Genética relativa de los IPs

● **NFV**

• 1-2 mutaciones

● **SQV, IDV**

● **ATV**

• 3 mutaciones

● **LPV, FPV**

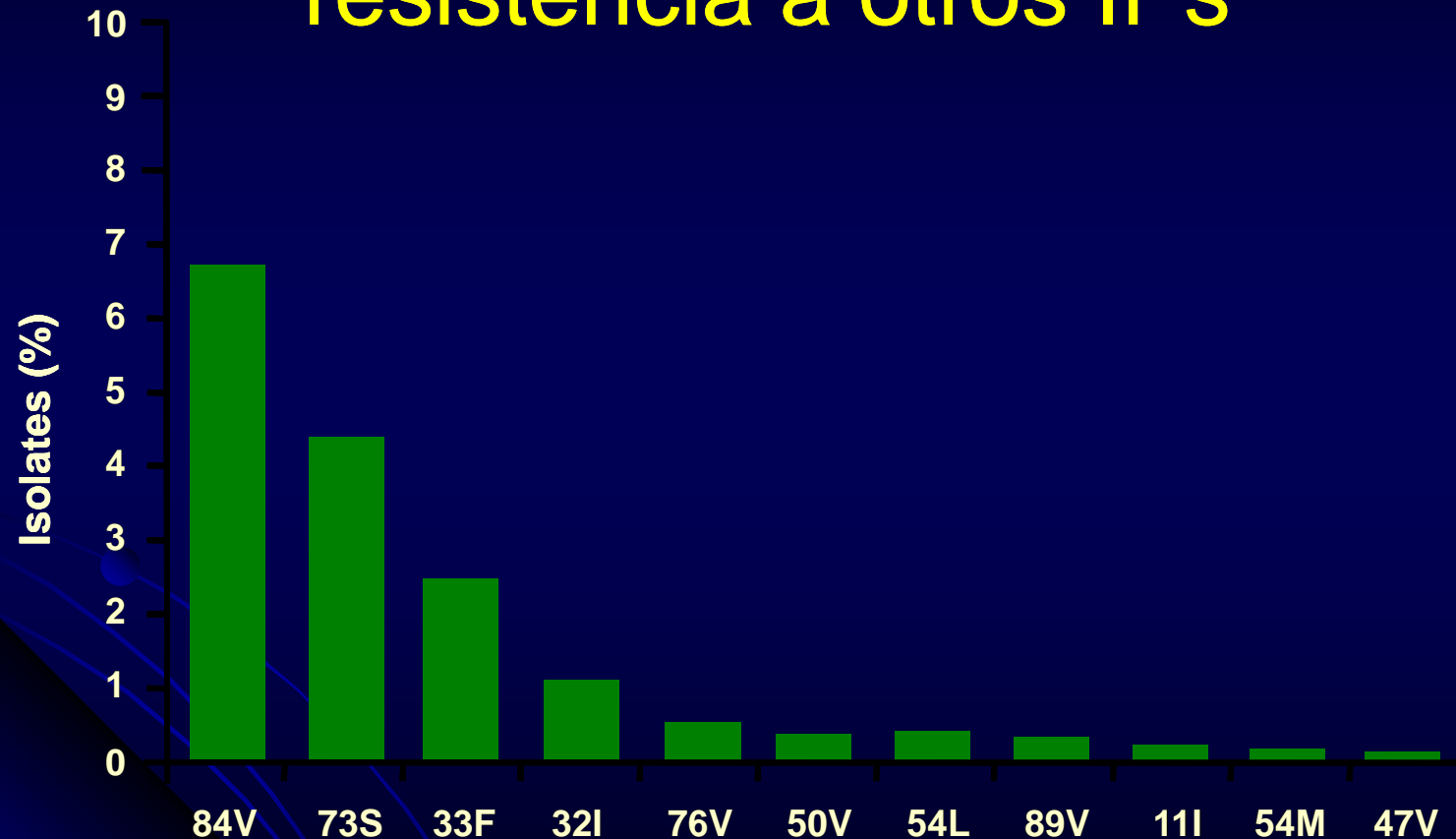
• 4-6 mutaciones

● **TPV, DRV**

• 10-11 mutaciones



Frecuencia de mutaciones de resistencia a DRV en aislados con resistencia a otros IPs*



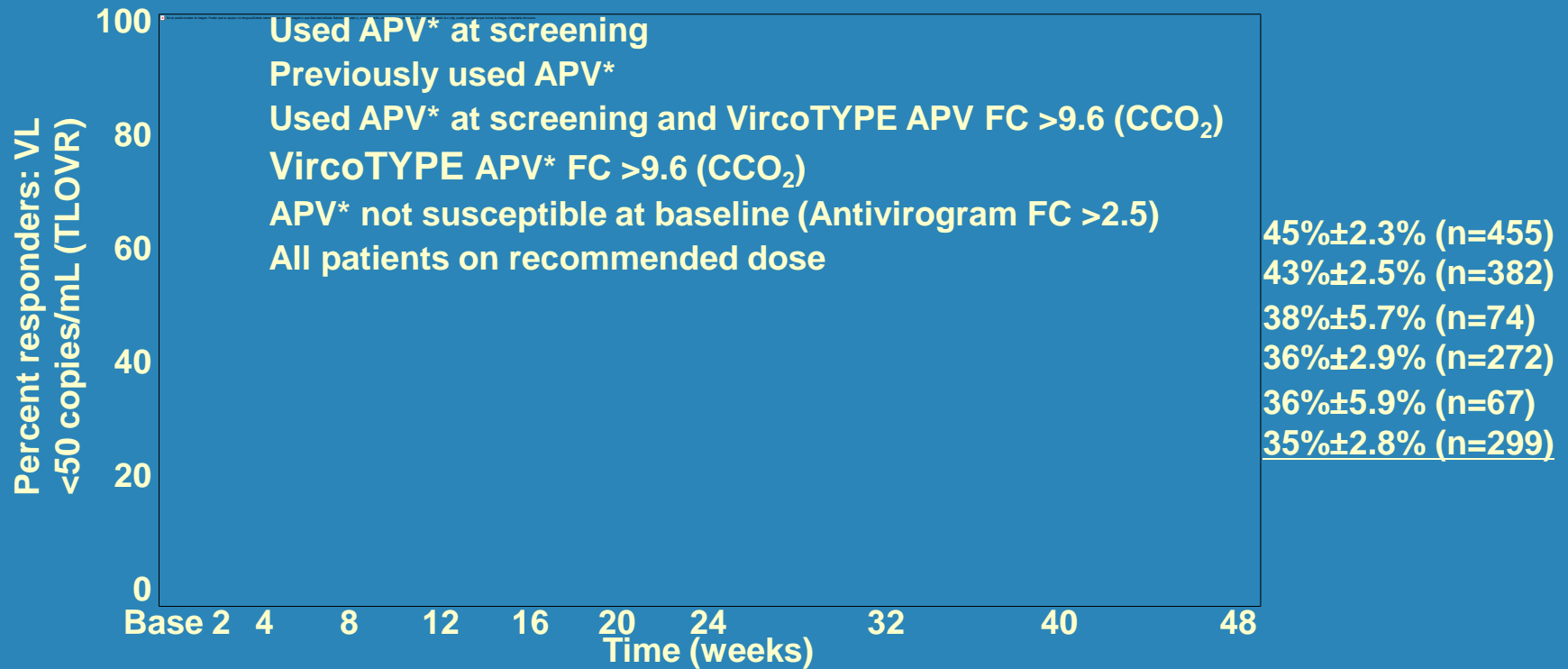
- Seven of the 11 PREZISTA-associated mutations occurred alone in <1% of samples

*As per the FDA mutation list
Prevalence of mutation in the absence of any other PREZISTA-associated mutation
Rhinehart AR, et al. DART 2006. Abstract 16

Combinaciones más comunes de mutaciones asociadas a resistencia a DRV que ocurren en $\geq 0.2\%$ de 108,500 aislados con evidencia de resistencia a IPs

Combination of mutations	Frequency (%)
73S, 84V	2.2
33F, 84V	1.2
32I, 47V	0.6
33F, 73S	0.6
54L, 84V	0.4
33F, 50V	0.3
33F, 54L	0.3
84V, 89V	0.3
76V, 84V	0.2
11I, 84V	0.2
33F, 73S, 84V	0.3
33F, 54L, 84V	0.3
11I, 73S, 84V	0.2
32I, 33F, 47V, 54M	0.2

Proporción de pacientes con CV <50 copies/mL con DRV/r de acuerdo a características basales relacionadas a APV



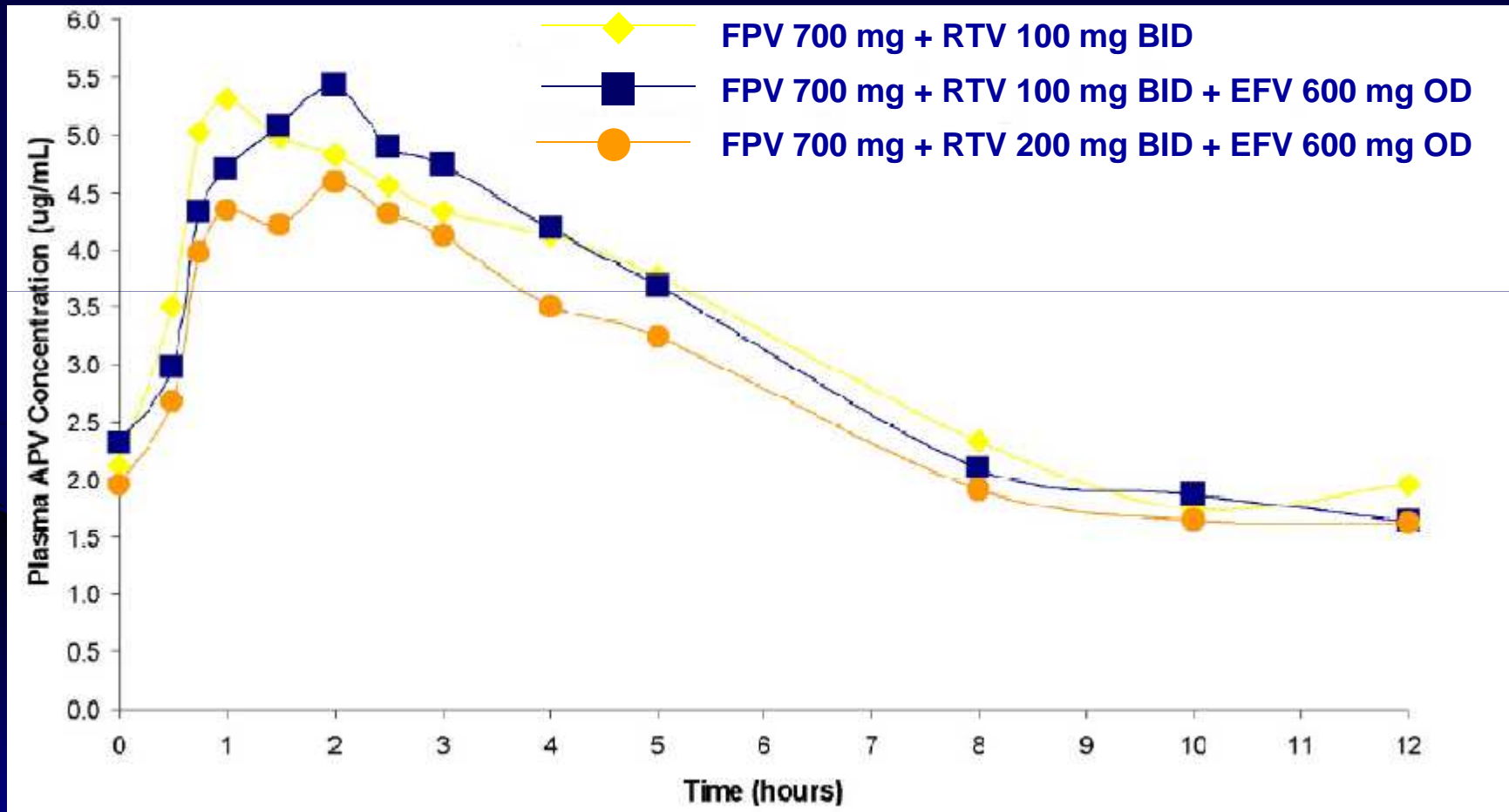
*Including fAPV

Conclusiones en uso de DRV con uso previo de APV

- La falla previa o resistencia a APV o fAPV no impacta en forma diferente a la respuesta de DRV/r que la falla o resistencia a otros IPs

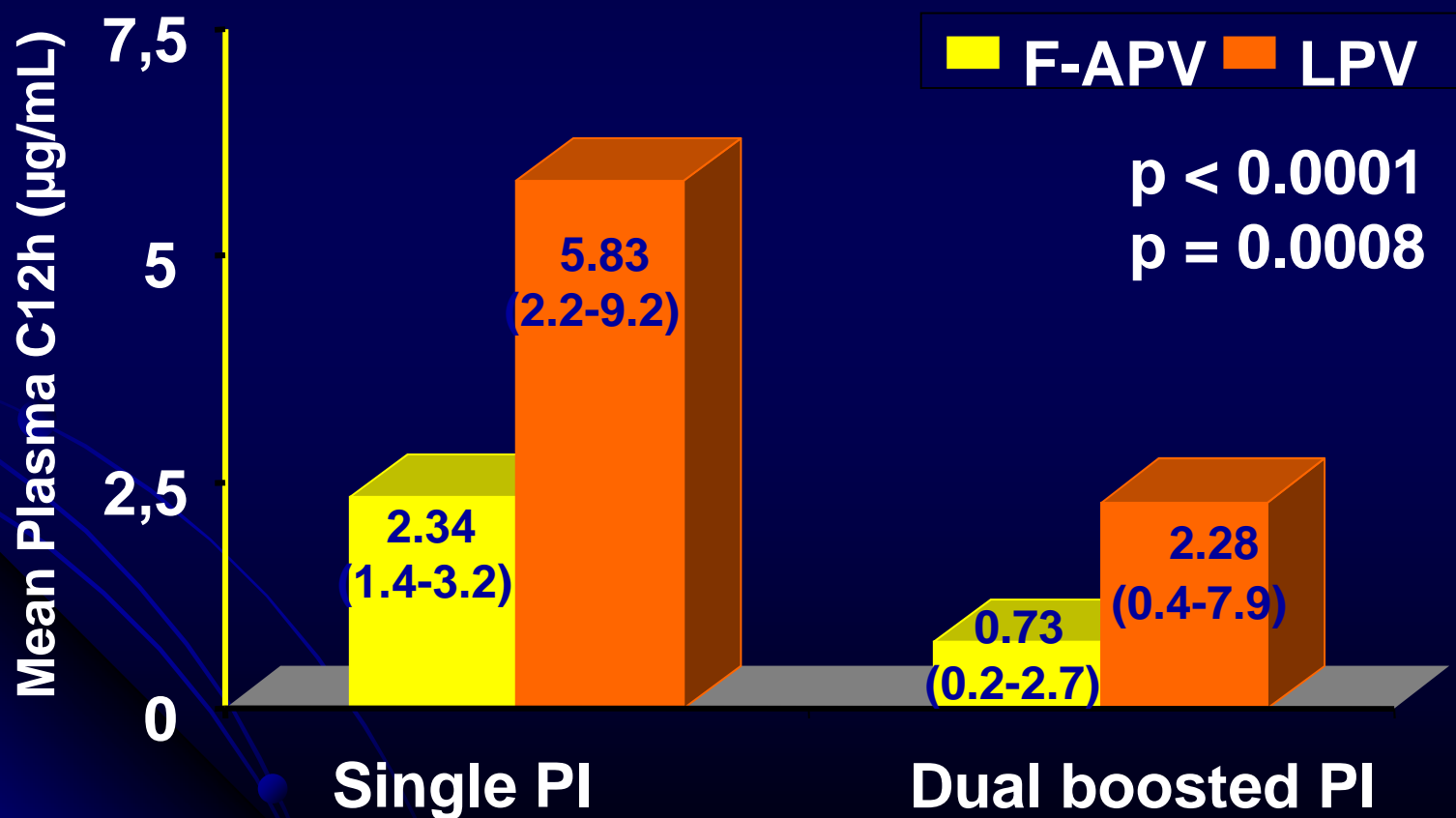
EFV + FPV/RTV

APV median-concentration-time profiles



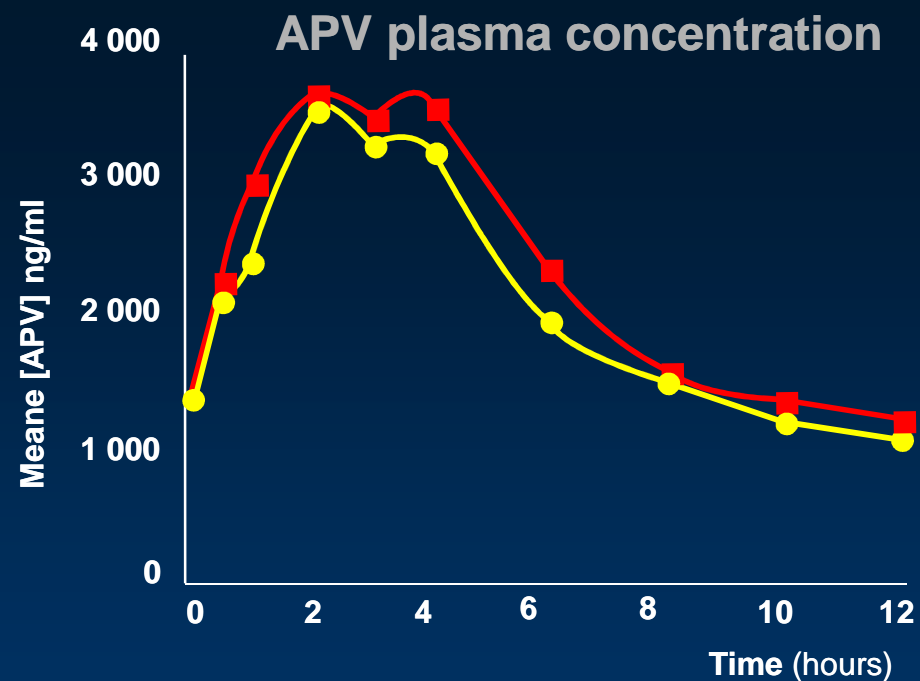
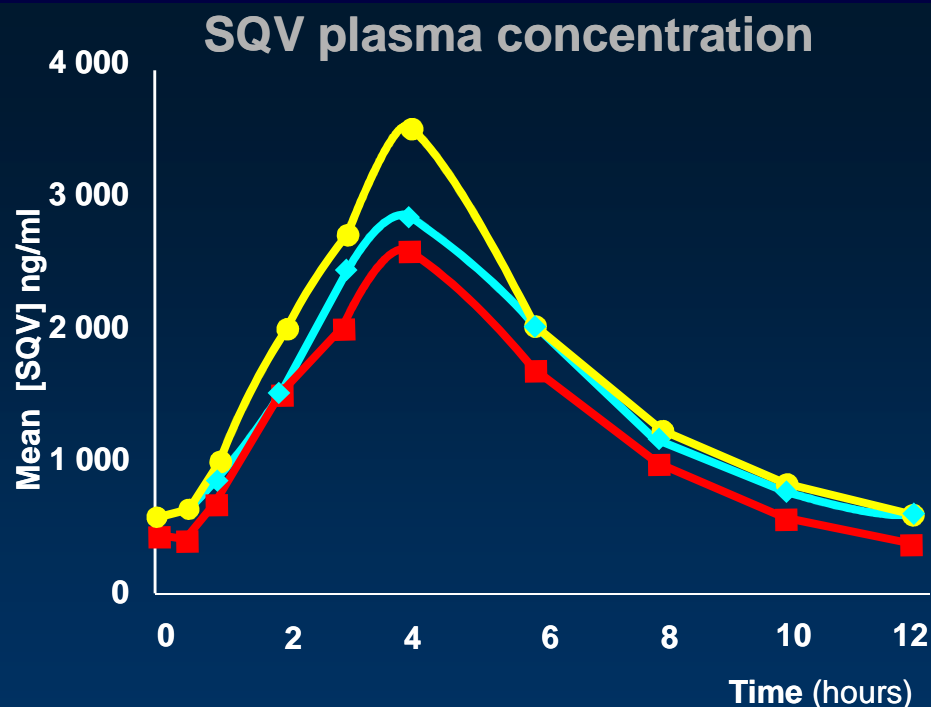
Interacción farmacocinética negativa entre f-APV y LPV/r (ACTG A5143)

1. LPV/r (400/100 mg bid) n = 8 patients,
2. FPV/r (700/100 mg bid) n = 8 patients,
3. LPV/FPV/r (400/700/100 mg bid) n = 15 patients



Saquinavir/fosAmprenavir/r

- Open-label, cross-over PK study in 18 HIV+ patients
- FPV/SQV 700/1000 mg bid + RTV 100 mg or 200 mg bid



- ◆ Day 1 : SQV + RTV 1000/100 mg x 2/j ■ Day 11 : SQV/908 + RTV 1000/700/100 mg x 2/j
- Day 22 : SQV/908 + RTV 1000/700/200 mg x 2/j

Optimal Dosage : SQV/FPV/r : 1000/700/200 BID

Objetivos de la terapia antiviral

- **PROLONGAR** la vida y mejorar la calidad de vida
 - SUPRIMIR la carga viral bajo el límite de detección (<50 copias) por tanto tiempo como sea posible
 - MEJORAR la función inmune (elevar cuentas CD4s)
- **MINIMIZAR** la toxicidad medicamentosa, y manejar los efectos secundarios e interacciones medicamentosas
- **OPTIMIZAR** y extender el uso de la terapia actual

Características diferenciales entre los IPs

	FPV/r	LPV/r	IDV/r	ATV/r	SQV/r
<ul style="list-style-type: none"> • Conveniencia • Tabletas/día 	<p>+ 3 o 4 Sin alimentos, sin hidratación</p>	<p>± 2+2 Con alimentos, sin hidratación</p>	<p>± 2+2 Con alimentos, con hidratación</p>	<p>± 2 Con alimentos, sin hidratación</p>	<p>+ • 2+2 Con alimentos, sin hidratación</p>
<p>Perfil de seguridad</p> <ul style="list-style-type: none"> - GI - Renal - Ictericia - Lípidos 	<p>± + + +</p>	<p>- + + -</p>	<p>± - + ±</p>	<p>± + - ?</p>	<p>± + + ±</p>
Interacciones				<p>TDF PPI</p>	
Indicación	<p>Tx inicial Cambio Falla</p>	<p>Tx inicial Cambio Falla</p>	<p>? Cambio</p>	<p>Tx inicial Cambio</p>	<p>Tx inicial Cambio Falla?</p>

+ Perfil favorable

- Perfil no favorable

Fos-APV: Conclusiones

- ✓ Eficacia demostrada en pacientes con y sin tratamiento previo
- ✓ Bien tolerado
- ✓ Baja cantidad de tabletas
- ✓ Sin restricciones alimentarias
- ✓ Interacciones poco significativas con otros medicamentos
- ✓ Buen perfil lipídico
- ✓ Buen perfil de resistencia



• **GRACIAS**