Curso EVES. 13 de diciembre de 2012

¿QUÉ HAY DE NUEVO EN EL TRATAMIENTO ANTIRRETROVIRAL?

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¿POR QUÉ HABLAR DE ESTE TEMA?

Eficacia del TAR de rescate avanzado: Proporción de pacientes con CV <50 c/mL

TAR DE INICIO	
Estudio	%
GEMINI	65
KLEAN	66
MERIT	69
CASTLE	78
ARTEMIS	84
MK-004	87
5142	89

TAR DE RESCATE		
Estudio	Global	≥ 2 ARV activos
POWER	46	73
MOTIVATE	56	61
VICTOR E1	56	72
DUET	61	80
BENCHMRK	65	75
TITAN	70	80
TRIO	---	86

REGÍMENES DE TAR DE INICIO ACTUALES SEGÚN LOS EC

Estudio	Duración	Régimen farmacológico	Interrupciones por EA,*%
AI424-089[1]	96 semanas	ATV + d4T + 3TC ATV/RTV + d4T + 3TC	3 8
GS934[2]	48 semanas	EFV + TDF + FTC EFV + ZDV/3TC	5 11
KLEAN[3]	48 semanas	FPV/RTV + ABC/3TC LPV/RTV + ABC/3TC	12 10
ARTEMIS[4]	48 semanas	DRV/RTV + TDF/FTC LPV/RTV + TDF/FTC	3 7
CASTLE[5]	48 semanas	ATV/RTV + TDF/FTC LPV/RTV + TDF/FTC	2 3
HEAT[6]	48 semanas	ABC/3TC + LPV/RTV TDF/FTC + LPV/RTV	4 6
GEMINI[7]	48 semanas	SQV/RTV + TDF/FTC LPV/RTV + TDF/FTC	4 7

1. Malan N, et al. IAS 2007. Abstract WEPEB024. 2. Arribas JR, et al. IAS 2007. Abstract WEPEB029. 3. Eron J Jr, et al. Lancet. 2006;368:476-482. 4. DeJesus E, et al. ICAAC 2007. Abstract 718-b. 5. Molina JM, et al. CROI 2008. Abstract 37. 6. Smith K, et al. CROI 2008. Abstract 774. 7. Walmsley SL, et al. EACS 2007. Abstract PS1.4.

Inconveniencia del TARV en la primera época del TARGA: Número de pastillas

Reducción del número de comprimidos y tomas

1996-97

2-3 tomas / 12-28 pastillas

2001-02

1-2 tomas / 5-7 past

2003-04

1 toma / 3-4 past

Ribera E, et al. *Enferm Infecc Microbiol Clin* 2008; 20 (Supl. 2):48-57

2010: MÚLTIPLES REGÍMENES PREFERENTES QD

Atripla®*

KIV/EFV

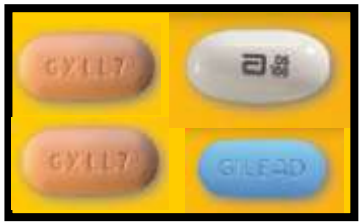
TRU/ATV/r (300/100) QD

TRU/DRV/r* (800/100) QD**

TRU/LPV/r (800/200) QD**

TRU/SQV/r*? (1500/100) QD

TRU/FPV/r*? (1400/100) QD



* Atripla® no está indicado en España en el tratamiento de pacientes naive.
* SQV/r y FPV/r no aprobados en Europa para su uso QD.
** Consideraciones uso de LPV/r QD puede estar asociado con una reducción de la supresión virologica y un mayor riesgo de diarrea comparado con la dosis recomendada BID. Ficha Técnica Kaletra® (Septiembre 2009).
*** Dosificación pendiente de aprobación en España. Ficha técnica Darunavir® (Julio 2009)
Ficha técnica Sustiva® (Junio 2009), Ficha técnica Atripla® (Octubre 2009), Ficha técnica Kivexa® (Julio 2009); Ficha técnica Truvada® (Junio 2009); Ficha técnica Telzir® (Mayo 2009); Ficha técnica Invirase® (Abril 2009). Ficha técnica Reyataz ® (Septiembre 2009).

STR

Insights into Reasons for Discontinuation According to Year of Starting First Regimen of Highly Active Antiretroviral Therapy in a Cohort of Antiretroviral-Naïve Patients

P Cicconi; A Cozzi-Lepri; A Castagna; EM Trecarichi; A Antinori; F Gatti; G Cassola; L Sighinolfi; P Castelli; A d'Arminio Monforte

Posted: 02/25/2010; HIV Medicine. 2009;11(2):114-120.

Objectives The aim of the study was to determine whether the incidence of first-line treatment discontinuations and their causes changed according to the time of starting highly active antiretroviral therapy (HAART) in an Italian cohort.

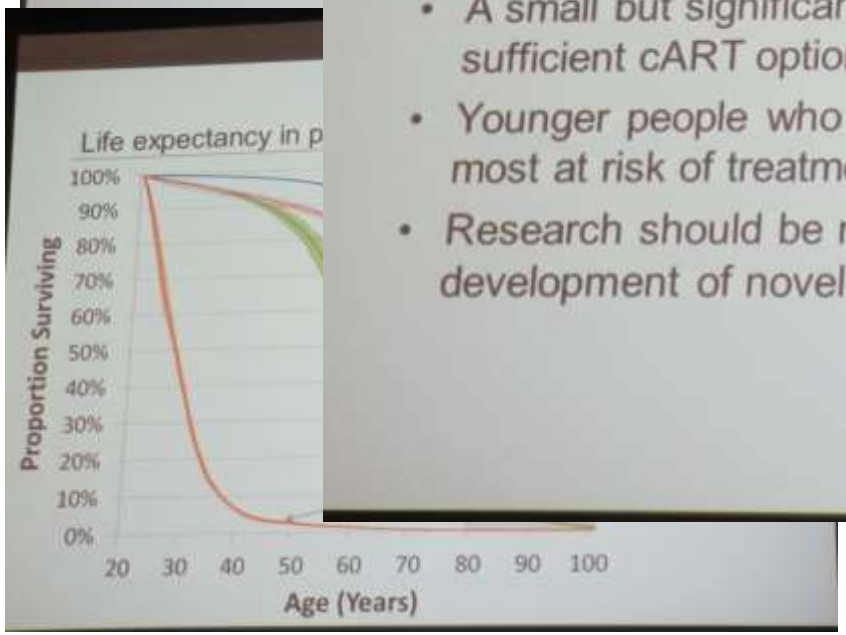
Methods We included in the study patients from the Italian COhort Naïve Antiretrovirals (ICoNA) who initiated HAART when naïve to antiretroviral therapy (ART). The endpoints were discontinuation within the first year of ≥1 drug in the first HAART regimen for any reason, intolerance/toxicity, poor adherence, immunovirological/clinical failure and simplification. We investigated whether the time of starting HAART (stratified as 'early', 1997–1999; 'intermediate', 2000–2002; 'recent', 2003–2007) was associated with the probability of reaching the endpoints by a survival analysis.

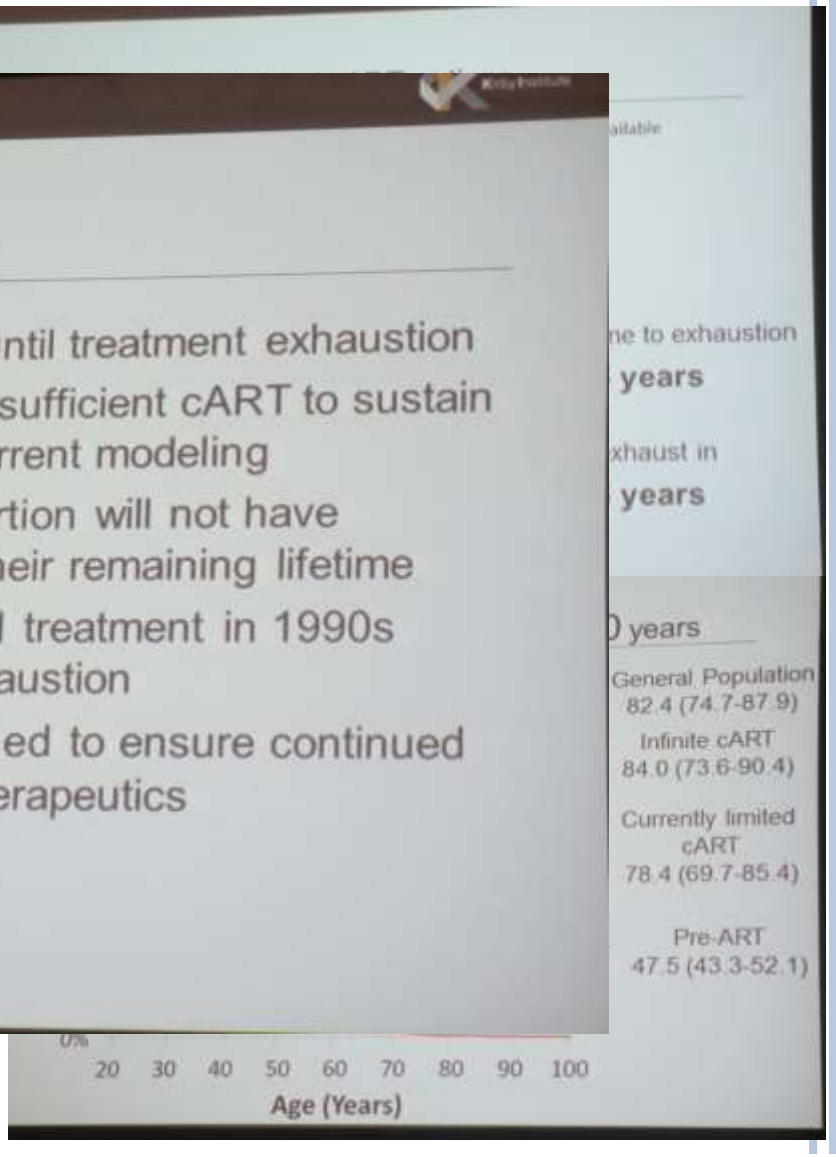
Results Overall, the 1-year probability of discontinuation of ≥1 drug in the first regimen was 36.1%. The main causes of discontinuation were intolerance/toxicity (696 of 1189 patients; 58.5%) and poor adherence (285 of 1189 patients; 24%). The hazards for all-reason change were comparable according to calendar period [2000–2002, adjusted relative hazard (ARH) 0.82, 95% confidence interval (CI) 0.69–0.98; 2003–2007, ARH 0.94, 95% CI 0.76–1.16, *vs.* 1997–1999; global *P*-value=0.08]. Patients who started HAART during the 'recent' period were less likely to change their initial regimen because of intolerance/toxicity (ARH 0.67, 95% CI 0.51–0.89 *vs.* 'early' period). Patients who started in the 'intermediate' and 'recent' periods had a higher risk of discontinuation because of simplification (ARH 15.26, 95% CI 3.21–72.45, and ARH 37.97, 95% CI 7.56–190.64, *vs.* 'early' period, respectively).

Conclusions It seems important to evaluate reason-specific trends in the incidence of discontinuation in order to better understand the determinants of changes over time. The incidence of discontinuation because of intolerance/toxicity has declined over time while simplification strategies have become more frequent in recent years. Intolerance/toxicity remains the major cause of drug discontinuation.

Implications

- Limited knowledge of time until treatment exhaustion
- Most people will likely have sufficient cART to sustain life expectancy based on current modeling
- A small but significant proportion will not have sufficient cART options for their remaining lifetime
- Younger people who initiated treatment in 1990s most at risk of treatment exhaustion
- Research should be maintained to ensure continued development of novel HIV therapeutics





O132 13.50–14.05 **Currently available medications may not be sufficient for lifelong treatment of HIV**

James Jansson, University of New South Wales, Sydney, Australia

Características de los ARV que influyen en su elección como parte del régimen inicial de TAR

- Eficacia
- Tolerabilidad y seguridad
- Conveniencia (nº de pastillas y tomas)
- Interacciones
- Gestación
- Coste económico

AGENDA

- Momento de inicio del TAR
- Tratamiento como prevención
- Guías de tratamiento. Pautas de inicio
- Nuevos fármacos
- Nuevas estrategias

AGENDA

- Momento de inicio del TAR

¿Cuándo iniciar el tratamiento?

Categoría Clínica	CD4/mm³	GESIDA 11	DHHS 11	IAS 1	EACS 09
Síntomática	Cualquier valor	Iniciar tratamiento	Iniciar tratamiento	Iniciar tratamiento	Iniciar tratamiento
Embarazo		Iniciar tratamiento	Iniciar tratamiento	Iniciar tratamiento	Iniciar tratamiento
Asintomática	<350	Iniciar tratamiento	Iniciar tratamiento	Iniciar tratamiento	Iniciar tratamiento
	350–500	Tratamiento (Salvo excepciones)	Tratamiento	Tratamiento	Recomendar en algunas situaciones*
	>500	Diferir tratamiento salvo en algunas situaciones *	50% Iniciarlo 50% Opcional	Considerarlo salvo en algunas situaciones #	Diferir tratamiento

*
Caída en la cifra de CD4+ > 100/mm3 en un año
Carga viral de VIH > 100.000 copias/mL,
Edad superior a 60 años
Hepatitis crónica por VHB o VHC
Nefropatía asociada al VIH
Riesgo cardiovascular elevado
Riesgo aumentado de transmisión del VIH (ej parejas serodiscordantes)

#
Controlador de élite (carga viral de VIH < 50 copias/mL)
Cifra muy estable de CD4+ y una carga viral baja.

Recommendations of the DHHS and the IAS-USA Guidelines Panels: When to Start

DHHS Guidelines CD4+ Cell Count or Clinical Condition	IAS-USA Guidelines CD4+ Cell Count or Clinical Condition
▪ CD4 + count < 350 cells/mm³ (AI) ▪ CD4 + count 350-500 cells/mm³ (AII) ▪ CD4 + count > 500 cells/mm³ (BIII)	▪ CD4+ cell count < 500 cells/mm³ ▪ CD4+ cell count > 500 (BIII)
▪ History of AIDS-defining illness (AI) ▪ Pregnancy (AI) ▪ HIV-associated nephropathy (AII) ▪ HBV coinfection (AII) ▪ Patients at risk of transmitting HIV to sexual partners (AI, heterosexuals; AIII, others)	▪ Pregnant women (AIa) ▪ Older than 60 yrs of age (BIIa) ▪ Active hepatitis B virus coinfection (AIIa) ▪ Hepatitis C virus coinfection (CIII)* ▪ HIV-associated nephropathy (AIIa) ▪ Primary infection (BIII)†

*Patients with hepatitis C virus coinfection and CD4+ count > 500/mm³ may delay antiretroviral therapy until after completion of hepatitis C virus treatment.
†Regardless of symptoms.

DHHS Guidelines March 2012. Thompson MA, et al. JAMA. 2012;308:387-402.

Condition	Current CD4+ lymphocyte count [ii,iii]	
	350-500	> 500
Asymptomatic HIV infection	C	D
Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis	R	R
Primary HIV infection	C	C
Pregnancy (before third trimester)	R	R
Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:		
HIV-associated kidney disease	R	R
HIV-associated neurocognitive impairment	R	R
Hodgkin's lymphoma	R	R
HPV-associated cancers	R	R
Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy	C	C
Autoimmune disease – otherwise unexplained	C	C
High risk for CVD (> 20 % estimated 10-yr risk) or history of CVD	C	C
Chronic viral hepatitis		
HBV requiring anti-HBV treatment	R	R
HBV not requiring anti-HBV treatment	C/R [iv]	D
HCV for which anti-HCV treatment is being considered or given	R [v]	D [vi]
HCV for which anti-HCV treatment not feasible	R	C

Changing Criteria for Antiretroviral Therapy Initiation in DHHS Guidelines

CD4+Count, cells/mm^3	1998	2001	2006	2008	2009	2012
> 500	Offer if VL > 20K	Offer if VL > 55K	Consider if VL ≥ 100K	Consider in certain groups*	Consider†	Treat
350-500	Offer if VL > 20K	Consider if VL > 55K	Consider if VL ≥ 100K	Consider in certain groups*	Treat	Treat
200-350	Offer if VL > 20K	Offer, but controversy exists	Offer after discussion with patient	Treat	Treat	Treat
< 200 or symptomatic	Treat	Treat	Treat	Treat	Treat	Treat

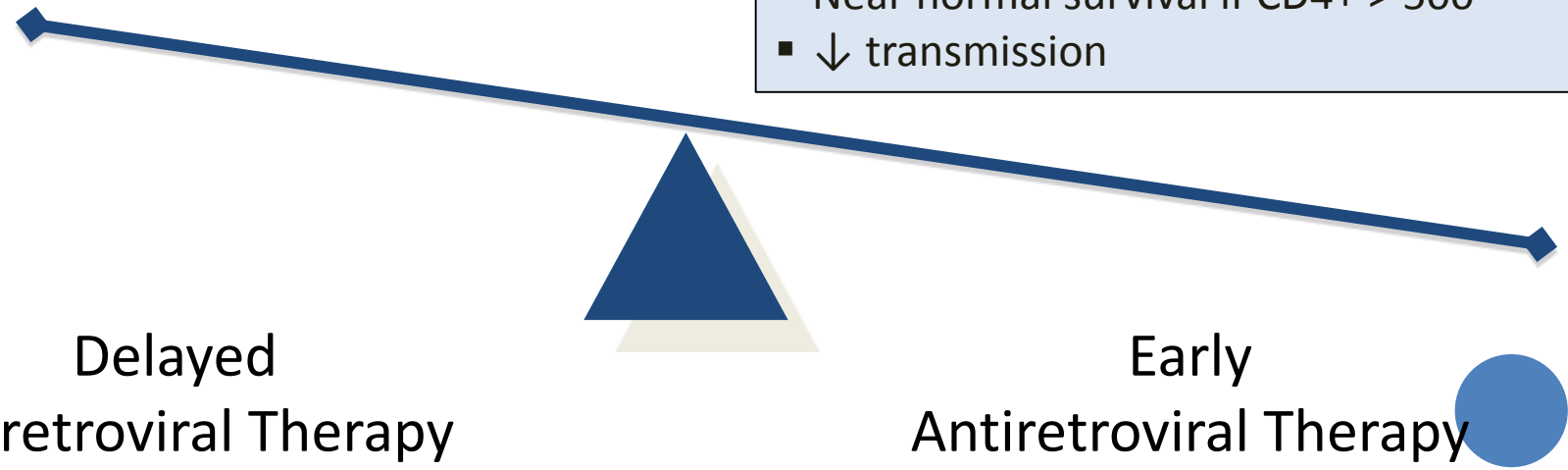
*Pregnant women, patients with HIV-associated nephropathy, and patients with HBV that requires treatment.
†50% of panel members recommended starting antiretroviral therapy; 50% of members viewed treatment as optional.

Wilkin T, et al. Available at: http://inpractice.com.

When to Start Therapy: Balance Now Favors Earlier Antiretroviral Therapy

- Drug toxicity
- Preservation of limited Rx options
- Risk of resistance (and transmission of resistant virus)

- ↑ potency, durability, simplicity, safety of current regimens
- ↓ emergence of resistance
- ↓ toxicity with earlier therapy
- ↑ subsequent treatment options
- Risk of uncontrolled viremia
- Near normal survival if CD4+ > 500
- ↓ transmission

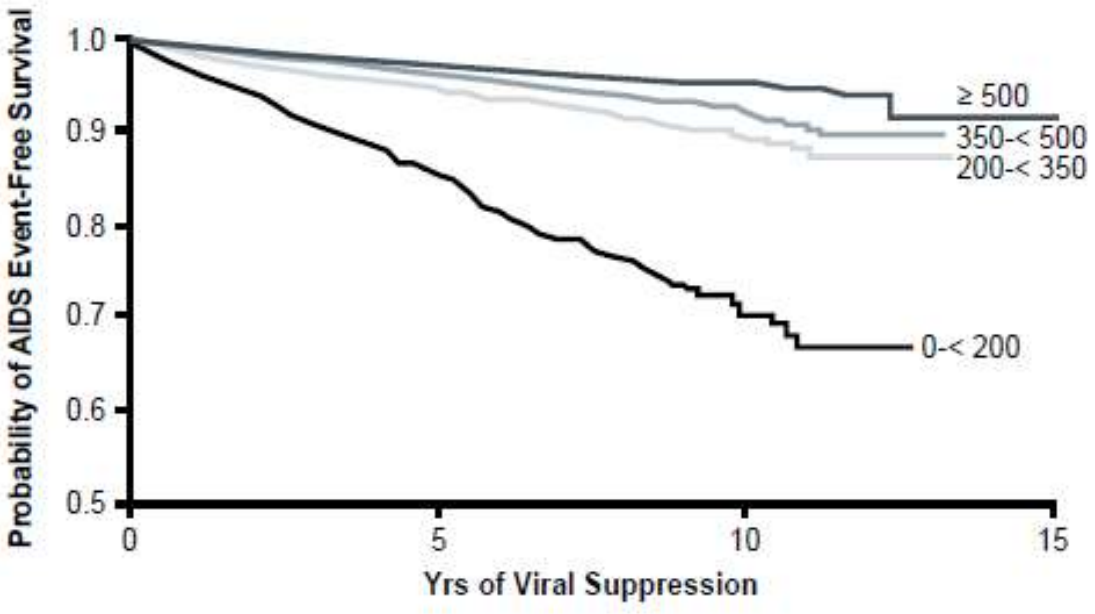


Delayed Antiretroviral Therapy

Early Antiretroviral Therapy

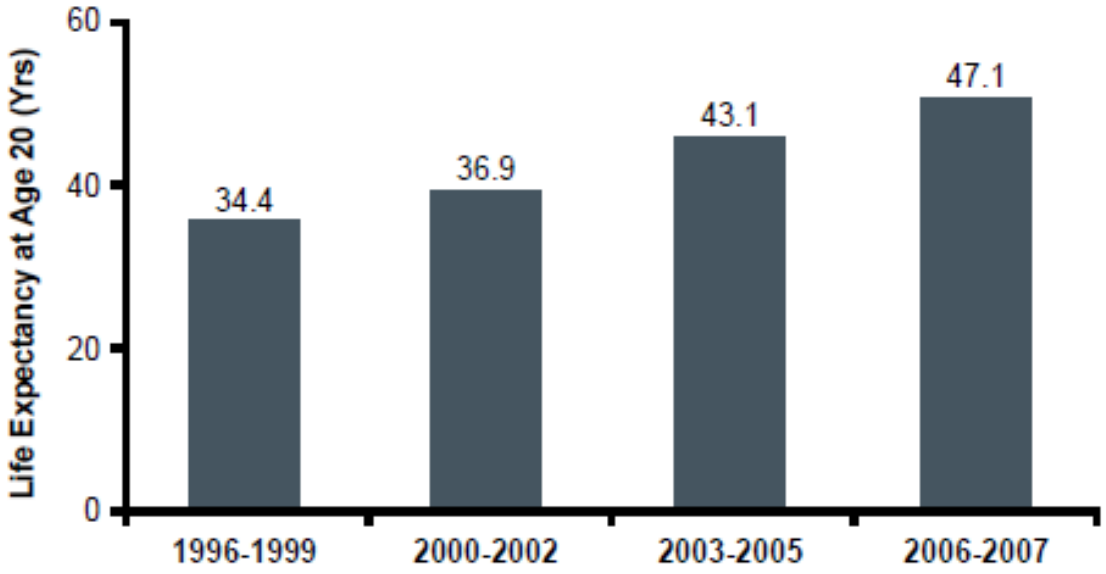
Slide from Joel E. Gallant, MD, MPH.

COHERE: AIDS Event-Free Survival by CD4+ Count in Pts With Suppressed VL



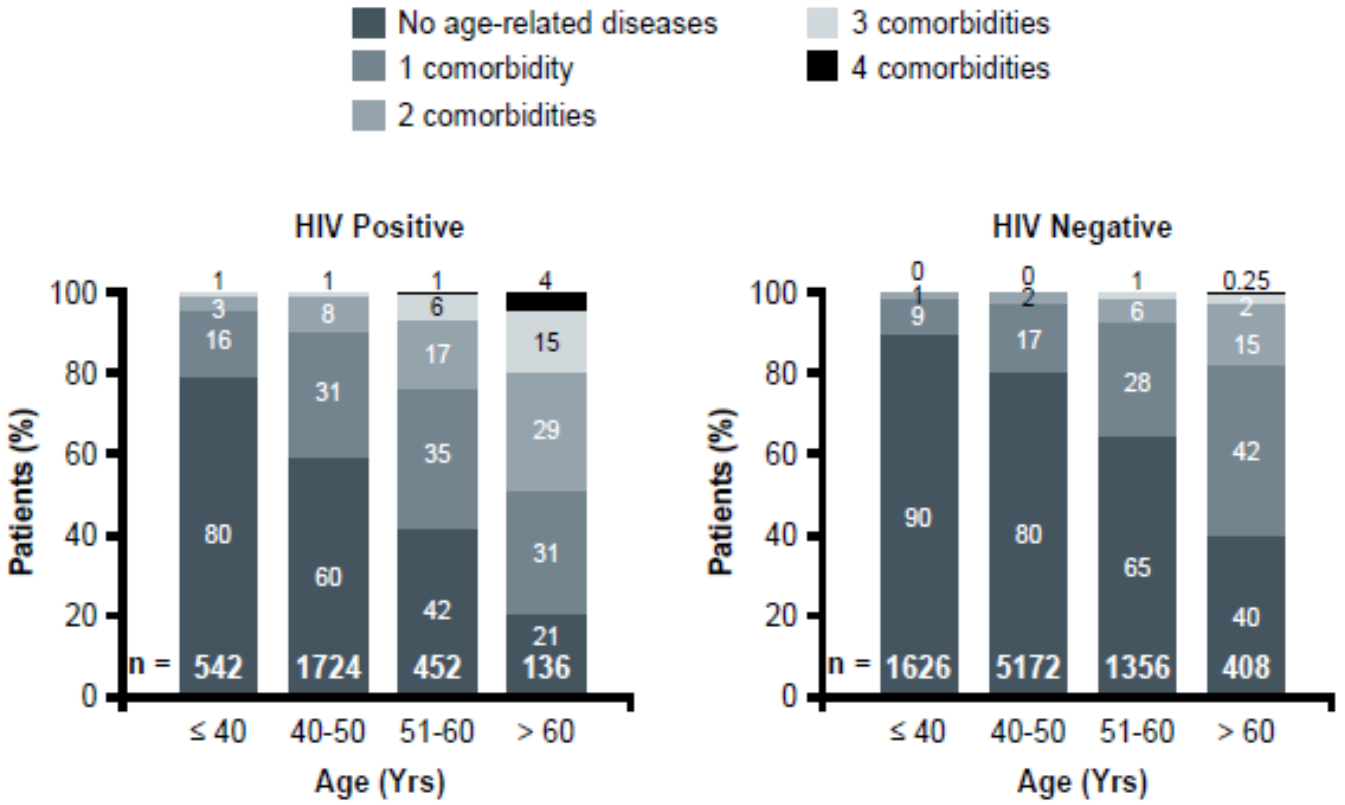
COHERE. PLoS Med. 2012;9:e1001194.

NA-ACCORD: Increasing Life Expectancy in HIV+ Adults Receiving ART



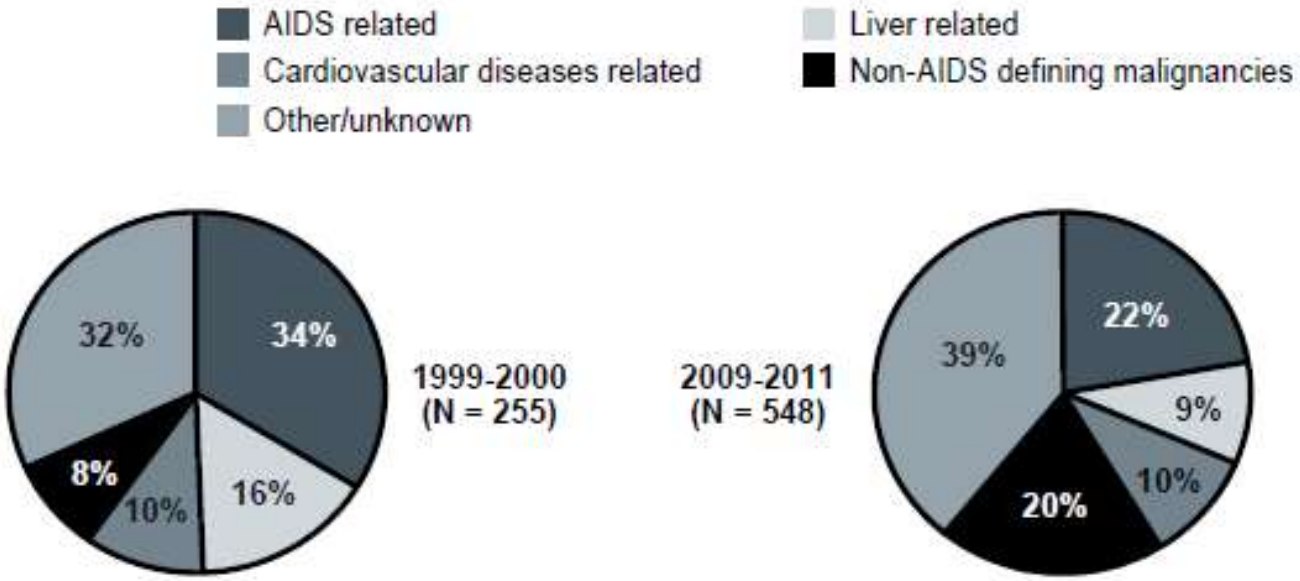
Hogg R, et al. CROI 2012. Abstract 137.

Age-Related Comorbidities in HIV-Infected vs Uninfected Persons



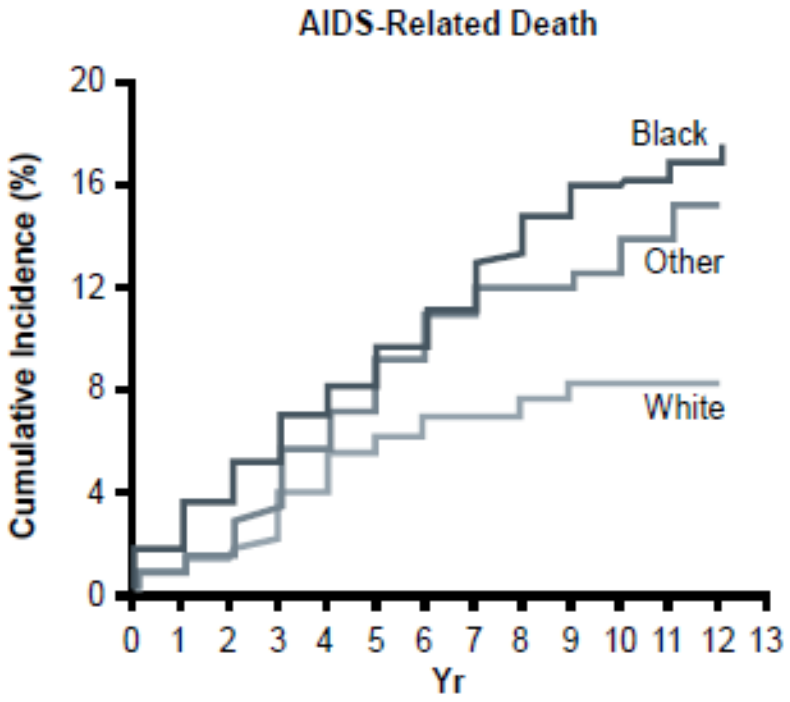
Guaraldi G, et al. Clin Infect Dis. 2011;53:1120-1126.

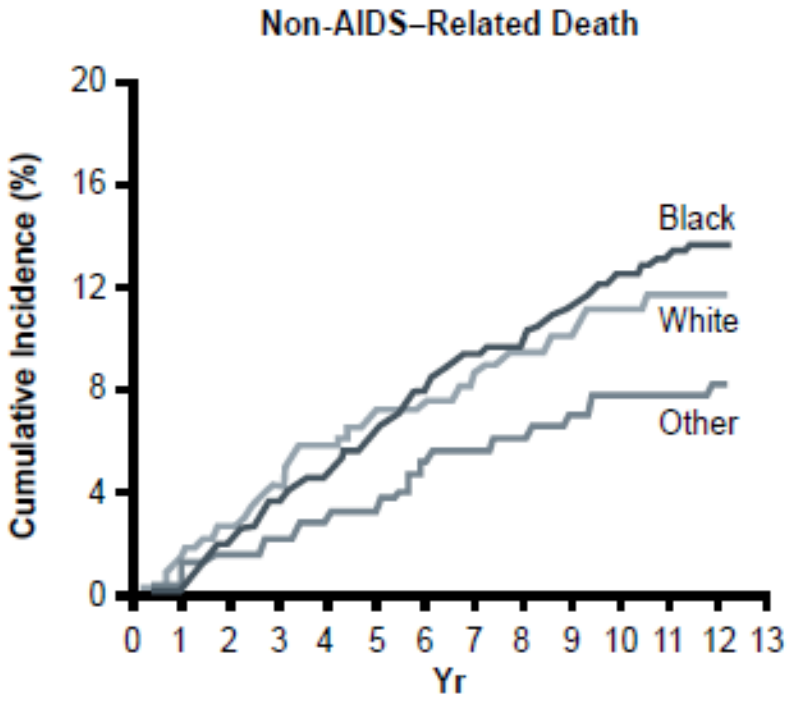
D:A:D: Changes in Causes of Death Over Time, 1999-2011



Weber R, et al. AIDS 2012. Abstract THAB0304.

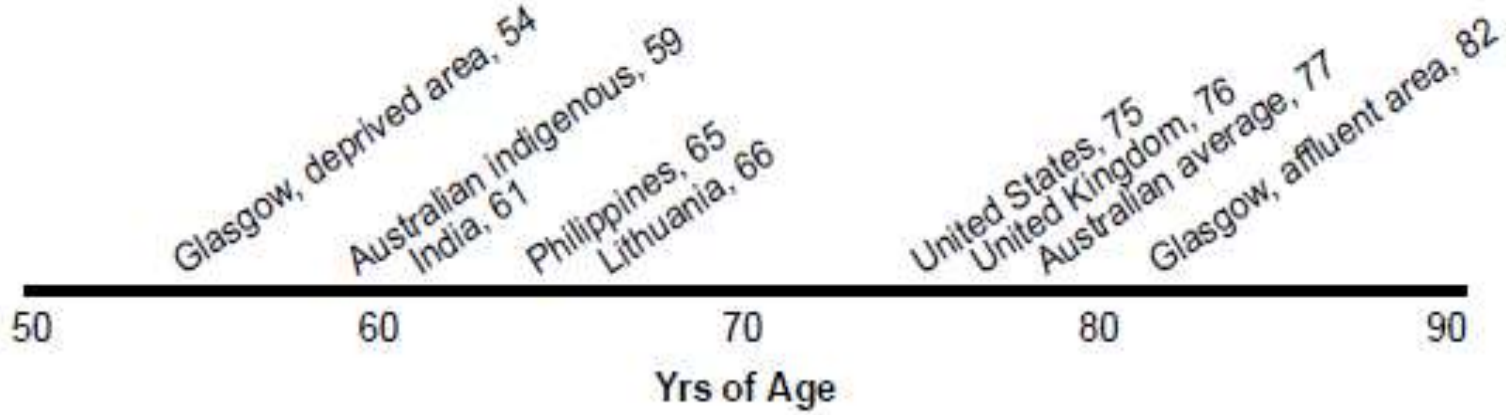
WIHS: Risk of Death in Black vs White HIV+ Women





Murphy K, et al. CROI 2012. Abstract 1045.

Male Life Expectancy at Birth by Geographic Area

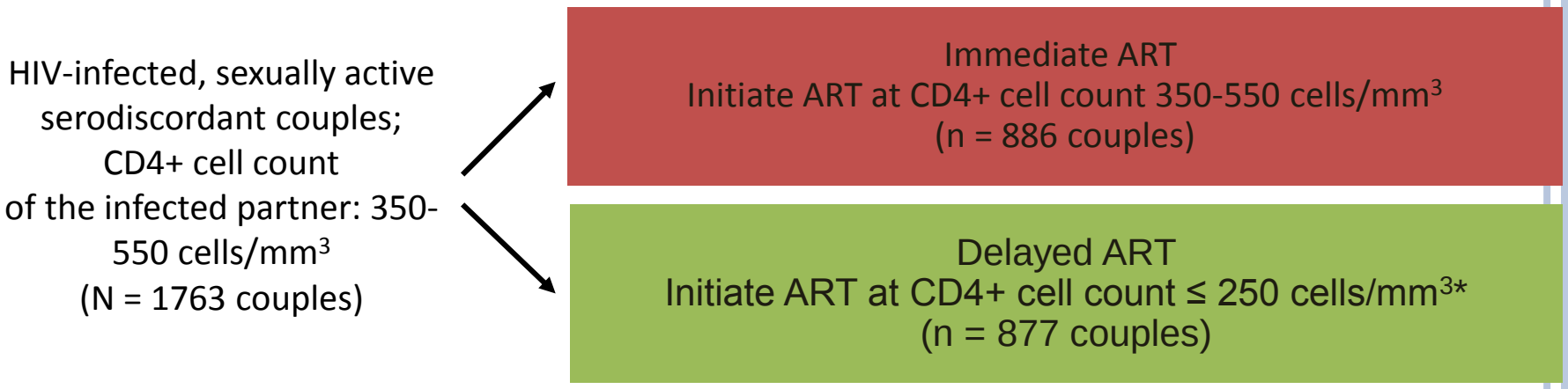


Perry IJ. Social determinants of health and health inequalities. Undated slide presentation

AGENDA

- Tratamiento como prevención

HPTN 052: Immediate vs Delayed ART in Serodiscordant Couples

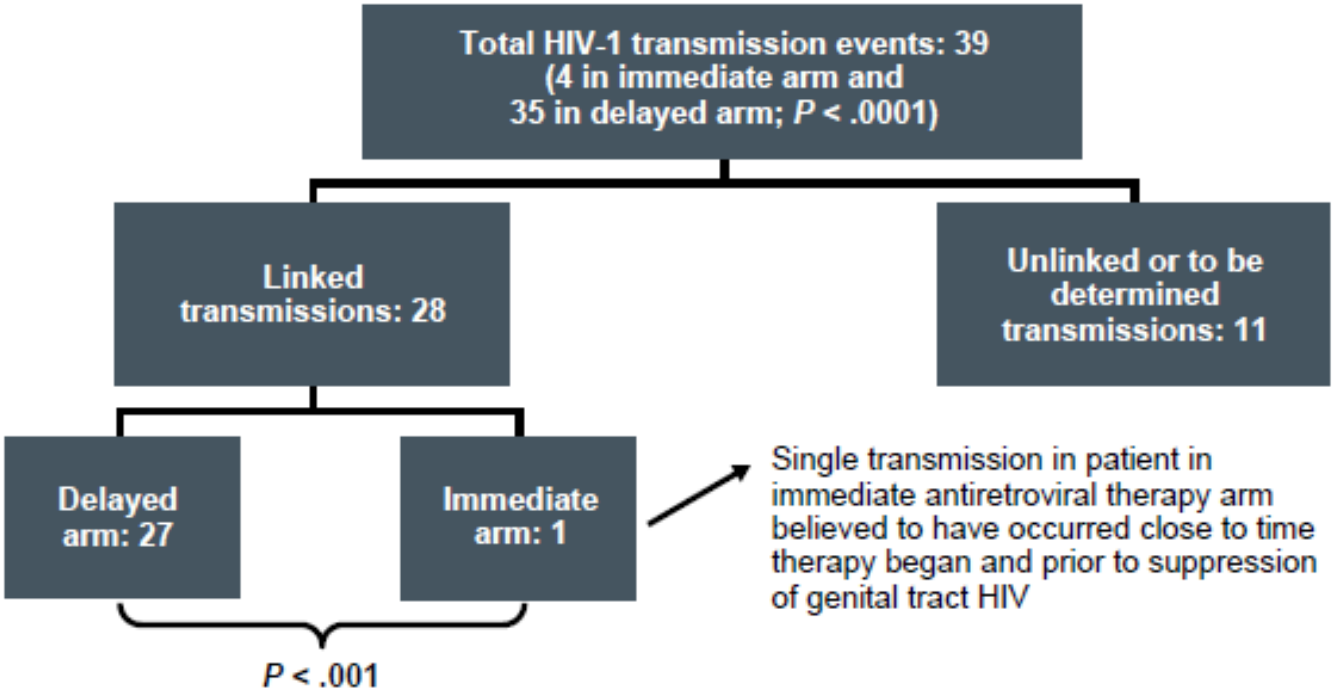


*Based on 2 consecutive values ≤ 250 cells/mm^3.

- Primary efficacy endpoint: virologically linked HIV transmission
- Primary clinical endpoints: WHO stage 4 events, pulmonary TB, severe bacterial infection and/or death
- Couples received intensive counseling on risk reduction and use of condoms

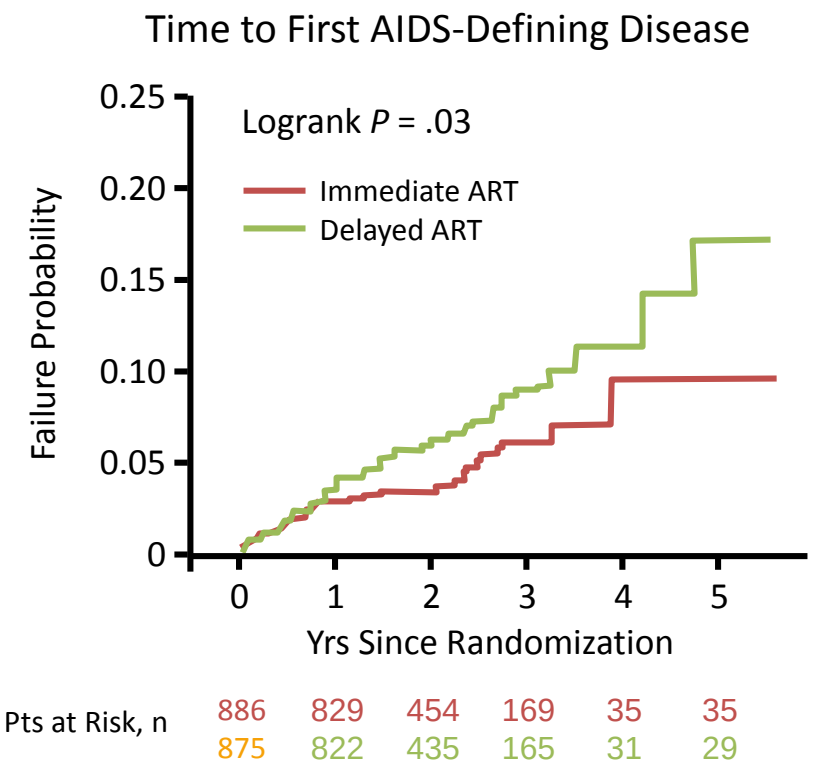
Cohen MS, et al. N Engl J Med. 2011;365:493-505.

HPTN-052: HIV Transmission Events With Early vs Delayed ART



Cohen MS, et al. N Engl J Med. 2011;365:493-505.

HPTN 052: Decrease in AIDS-Related Events in Immediate vs Delayed ART Arms



Subjects Experiencing ≥ 1 AIDS-Related Event	Delayed	Immediate
Tuberculosis, n (%)	**34 (4)**	**17 (2)**
Serious bacterial infection, n (%)	**13 (1)**	**20 (2)**
WHO stage 4 event, n (%)	**19 (2)**	**9 (1)**
Esophageal candidiasis, n	2	2
Cervical carcinoma, n	2	0
Cryptococcosis, n	0	1
HIV-related encephalopathy, n	1	0
Herpes simplex (chronic), n	8	2
Kaposi's sarcoma, n	1	1
CNS lymphoma, n	1	0
Pneumocystis pneumonia, n	1	0
Septicemia, n	0	1
HIV wasting, n	2	0
Bacterial pneumonia, n	1	2

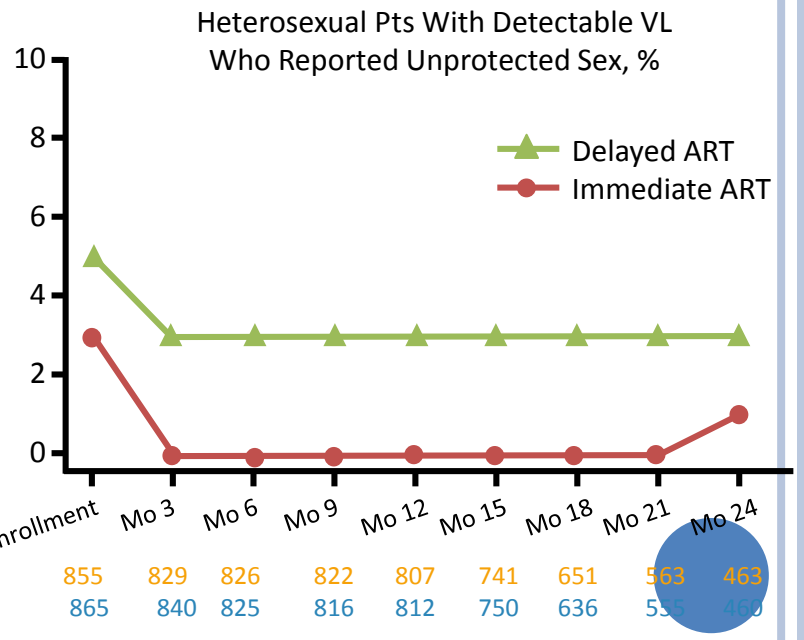
- Non-AIDS events infrequent, with similar numbers of events in each arm

Grinsztejn B, et al. AIDS 2012. Abstract THLBB05. Graphic reproduced with permission

HPTN-052: Decrease in Risk Behavior Over Study Duration

- As part of HPTN-052, all participants received extensive risk counseling, condoms, and STD testing and treatment[1]
  - Recounseled at every 3-mo visit
- Substudy assessed time trends of risk behaviors and compared the change between the 2 treatment arms, adjusting for baseline characteristics including sex, region, substance use, and HIV-1 RNA level[2]

- Heterosexual pts with detectable VL and having unprotected sex at 24 mos
  - Immediate arm: 1%; delayed 3%



1. Cohen MS, et al. N Engl J Med. 2011;365:493-505. 2. Mayer K, et al. AIDS 2012. MOPDC0106. Graphic reproduced with permission.

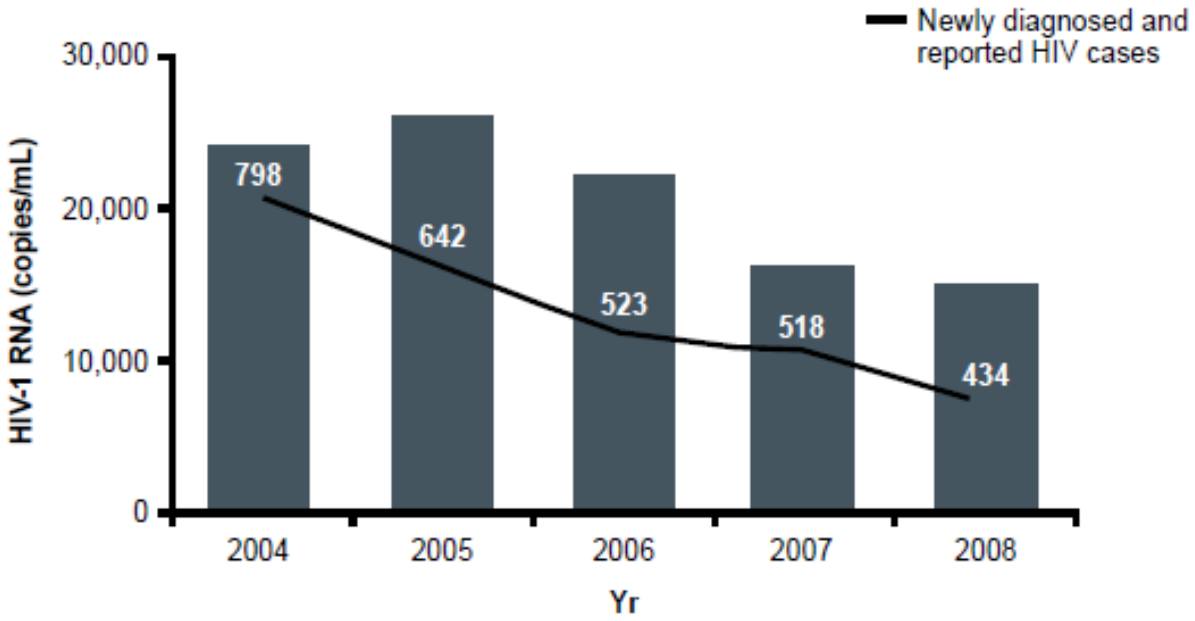
HPTN-052: Cost-effectiveness of Early vs Delayed Therapy in South Africa and India

- Cost-effectiveness* model using HPTN-052 data on transmission and clinical and resource utilization data from South Africa and India†
- In South Africa, early ART projected to increase survival, decrease transmission events, and be cost saving at 5 yrs and very cost-effective on lifetime horizon
- In India, early ART also projected to increase survival, dramatically decrease HIV transmissions, and be cost-effective at 5 yrs and very cost-effective on lifetime horizon

*WHO thresholds: very cost-effective: < 1 x per capita GDP; cost-effective: < 3 x per capita GDP.
†Assumptions: mean CD4+ cell count 449 cells/mm^3; HIV-1 RNA suppression at Wk 48: 92%; lost to follow-up: 3.4 per 100 pt-yrs; average partners: 1.011/mo; transmission rate: 0.103-1.483/100 pt-yrs; GDP South Africa: US$8100; India: US$1400.

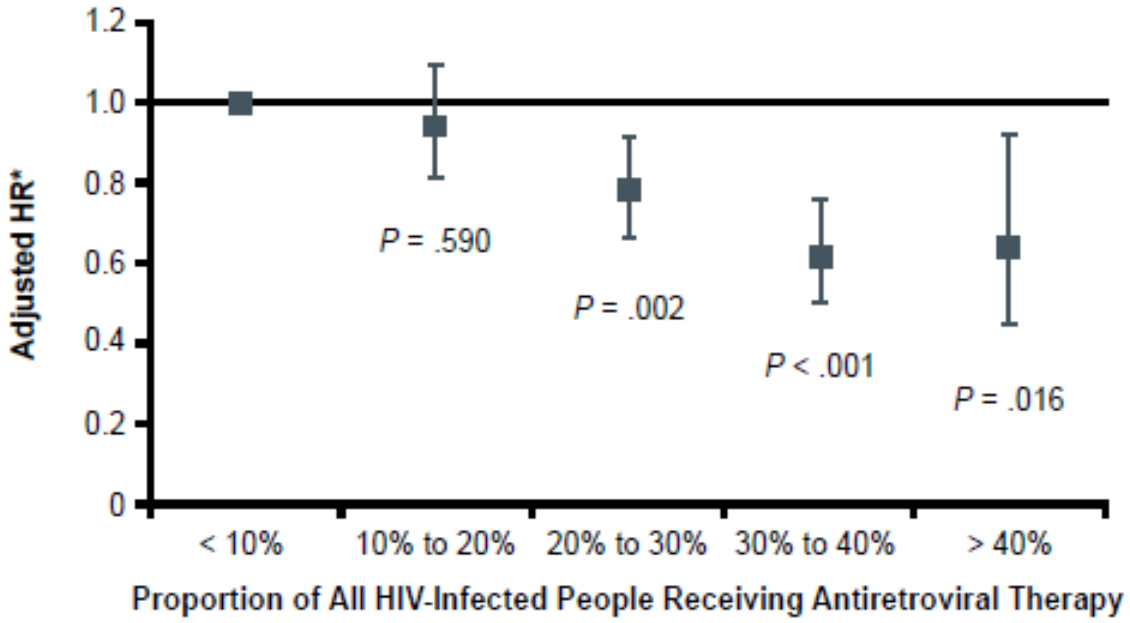
Walensky R, et al. AIDS 2012. Abstract FRLBC01.

Community VL and New Infections in the San Francisco HIV/AIDS Surveillance Area



Das M, et al. PLoS One. 2010;5:e11068..

Increasing ART Coverage Decreases Risk of HIV Acquisition in South Africa

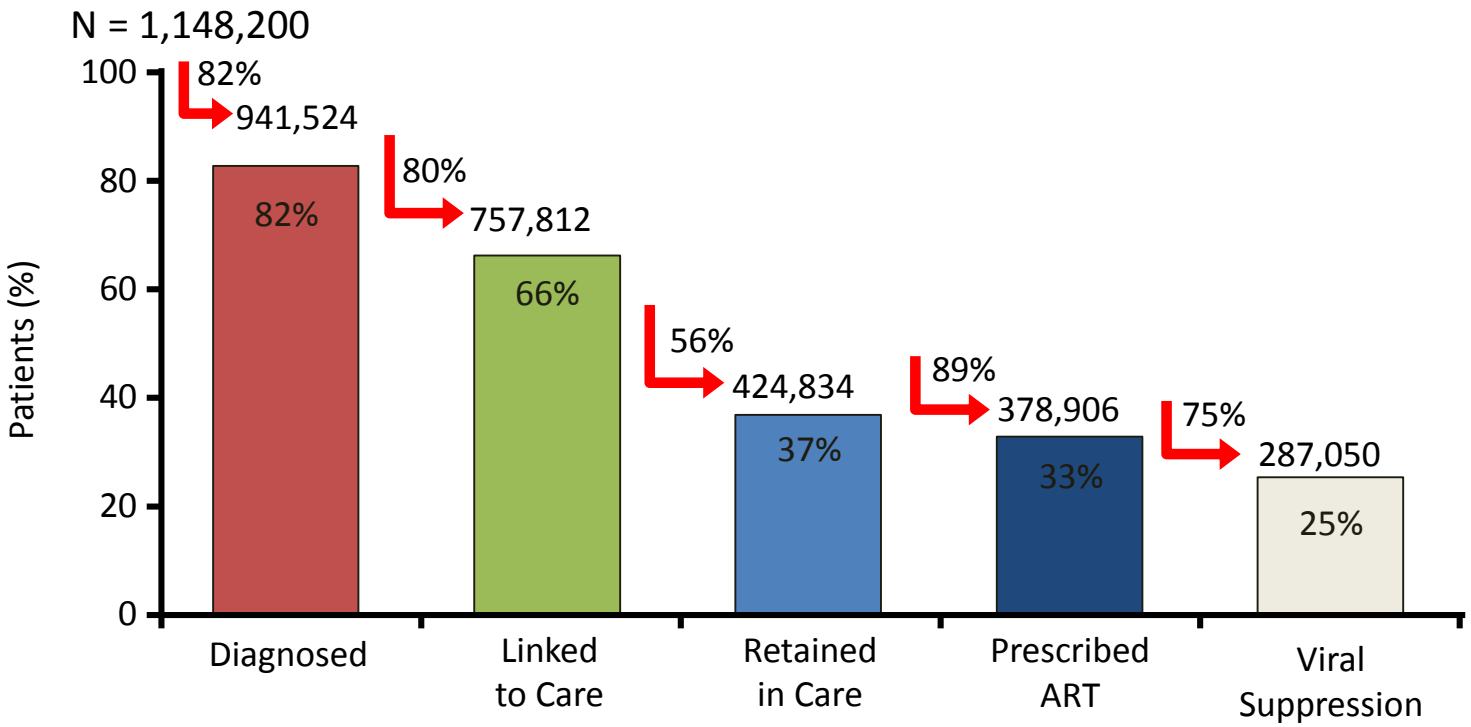


*Adjusted for age, sex, community-level HIV prevalence, urban vs rural locale, marital status, > 1 partner in last 12 mos, and household wealth index.

Tanser F, et al. CROI 2012. Abstract 136LB..

Improving Control of HIV Begins With Enhanced Detection and Linkage to Care

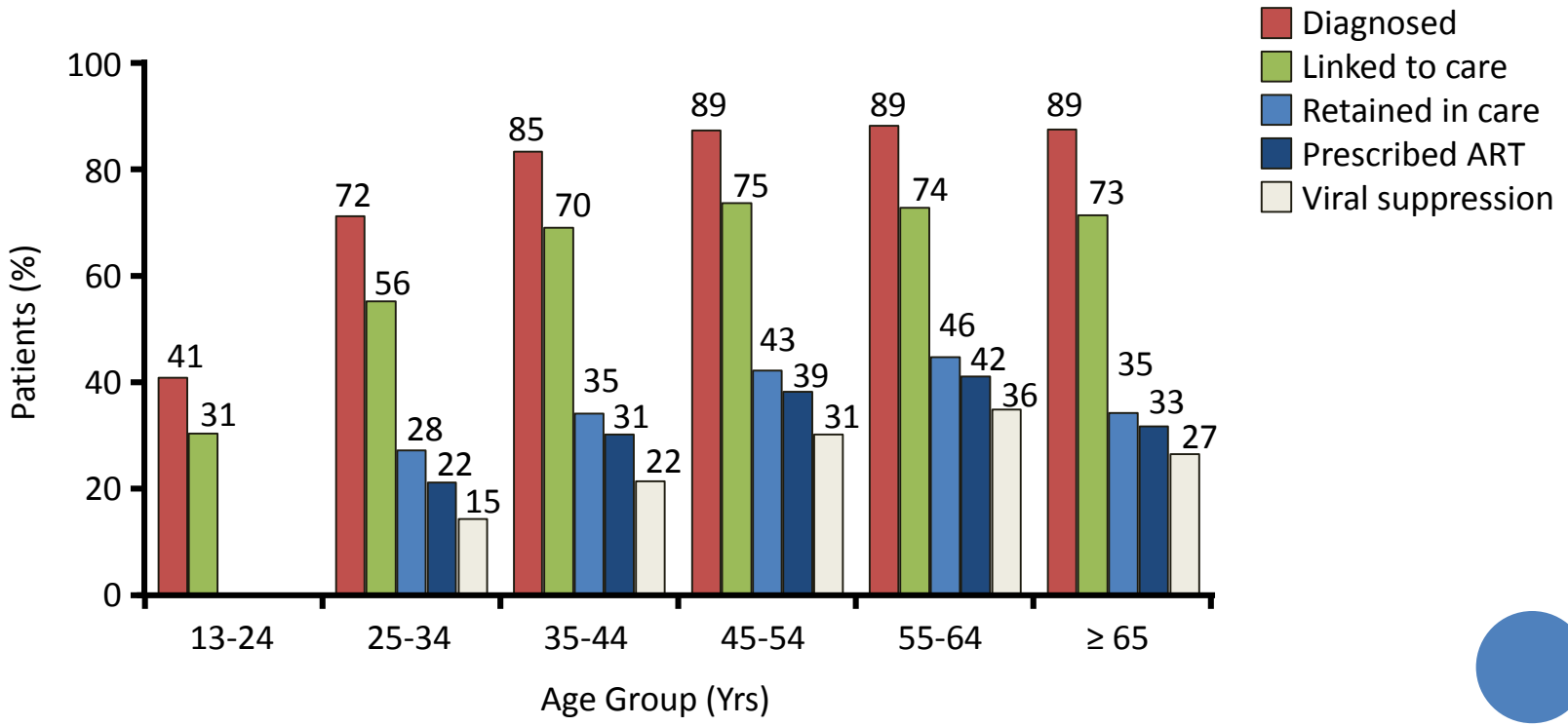
- Data from CDC and Prevention National HIV Surveillance System used to calculate HIV prevalence, undiagnosed HIV prevalence, and linkage to HIV care



Hall HI, et al. AIDS 2012. Abstract FRLBX05.

CDC: Young People Are Less Engaged in Care Than Other Groups

- Individuals 25-34 yrs of age less engaged in each stage of care compared with all older age groups



Hall HI, et al. AIDS 2012. Abstract FRLBX05. Graphic reproduced with permission.

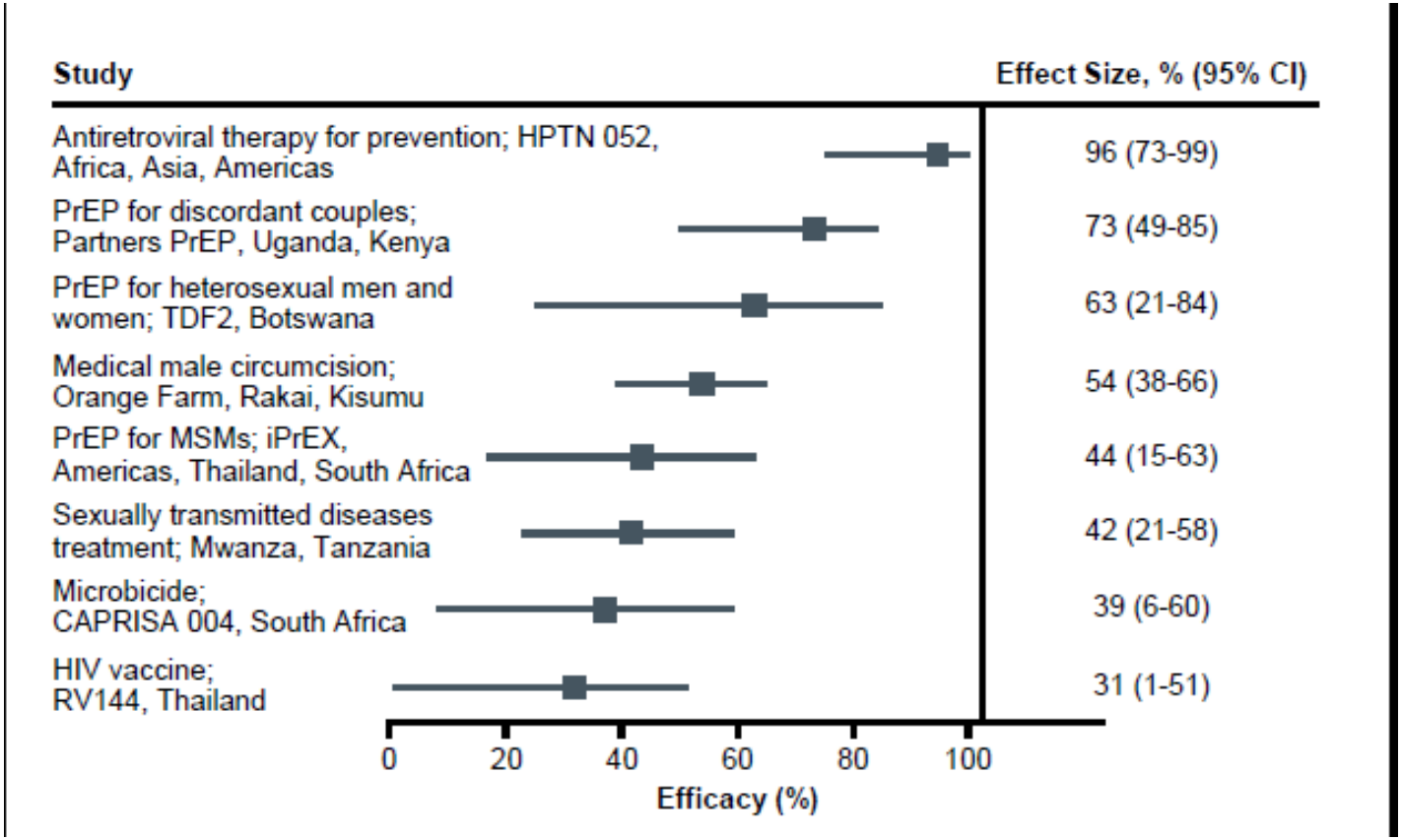
Partners PrEP: Reduction in HIV Acquisition With PrEP

Primary Efficacy Outcome, mITT Analysis	Tenofovir (n = 1584)	Tenofovir/ Emtricitabine (n = 1579)	Placebo (n = 1584)
HIV acquisitions, n	17	13	52
HIV incidence/100 patient-yrs	0.65	0.50	1.99
Efficacy vs placebo, % (95% CI)	67 (44-81)	75 (55-87)	--
▪ *P* value	< .0001	< .0001	--

mITT, modified intent to treat.

Baeten J, et al. N Engl J Med. 2012;367:399-410...

Efficacy of HIV Prevention Strategies From Randomized Clinical Trials



Abdool Karim S, Abdool Karim Q, et al. Lancet. 2011;378:e23-e25.

AGENDA

- Guías de tratamiento. Pautas de inicio

DHHS and IAS-USA 2012: Preferred/ Recommended First-line ART Regimens

	DHHS	ISA-USA
NNRTI based	▪ Efavirenz + tenofovir/emtricitabine	▪ Efavirenz/tenofovir/emtricitabine or • Efavirenz + abacavir/lamivudine*†‡
Boosted PI based	▪ Atazanavir/ritonavir + tenofovir/emtricitabine ▪ Darunavir/ritonavir + tenofovir/emtricitabine	▪ Atazanavir/ritonavir + tenofovir/emtricitabine or • Atazanavir/ritonavir + abacavir/lamivudine*†‡ ▪ Darunavir/ritonavir + tenofovir/emtricitabine
INSTI based	▪ Raltegravir + tenofovir/emtricitabine	▪ Raltegravir + tenofovir/emtricitabi

INSTI, integrase strand transfer inhibitor.
*In HLA-B*5701–negative patients with baseline plasma HIV-1 RNA < 100,000 copies/mL. HLA-B*5701 screening is recommended before abacavir administration to reduce the risk of hypersensitivity reaction.
†Avoiding the use of abacavir might be considered for patients with or at high risk of cardiovascular disease.
‡In patients with HIV-1 RNA < 100,000 copies/mL

DHHS Guidelines March 2012. Thompson MA, et al. JAMA. 2012;308:387-402.

DHHS and IAS-USA 2012: Alternative ART Regimens

	DHHS	ISA-USA
NNRTI based	▪ Efavirenz + abacavir/lamivudine ▪ Rilpivirine/tenofovir/emtricitabine ▪ Rilpivirine + abacavir/lamivudine	▪ Nevirapine + tenofovir/emtricitabine or nevirapine + abacavir/lamivudine*† ▪ Rilpivirine/tenofovir/emtricitabine or rilpivirine+ abacavir/lamivudine*†
Boosted PI based	▪ Atazanavir/ritonavir + abacavir/lamivudine ▪ Darunavir/ritonavir + abacavir/lamivudine ▪ Fosamprenavir/ritonavir (once or twice daily) + abacavir/lamivudine or tenofovir/emtricitabine ▪ Lopinavir/ritonavir (once or twice daily) + abacavir/lamivudine or tenofovir/emtricitabine	▪ Darunavir/ritonavir + abacavir/lamivudine*† ▪ Lopinavir/ritonavir† + tenofovir/emtricitabine or lopinavir/ritonavir† + abacavir/lamivudine*†
INSTI based	▪ Raltegravir + abacavir/lamivudine	▪ Raltegravir + abacavir/lamivudine*† ▪ Elvitegravir/cobicistat/tenofovir/ emtricitabine

*In HLA-B*5701–negative patients with baseline plasma HIV-1 RNA < 100,000 copies/mL. HLA-B*5701 screening is recommended before abacavir administration to reduce the risk of hypersensitivity reaction.
†Avoiding the use of abacavir or lopinavir/ritonavir might be considered for patients with or at high risk of cardiovascular disease.

DHHS Guidelines March 2012. Thompson MA, et al. JAMA. 2012;308:387-402.

Initial combination regimen for antiretroviral-naive adult patients

Recommended regimens (*)

A drug from column A should be combined with the drugs listed in column B (**)

A	B	Remarks
NNRTI	**NRTI**	
• EFV (i) • RPV (ii)	ABC/3TC (vii) or TDF/FTC	• TDF/FTC co-formulated • ABC/3TC co-formulated • EFV/TDF/FTC co-formulated • RPV/TDF/FTC co-formulated
• NVP (iii)	TDF/FTC	• TDF/FTC co-formulated
Ritonavir-boosted PI		
• ATV/r (iv) • DRV/r (iv) • LPV/r (v)	ABC/3TC (vii) or TDF/FTC	• ATV/r: 300/100 mg qd • DRV/r: 800/100 mg qd • LPV/r: 400/100 mg bid or 800/200 mg qd
ITI		
• RAL	TDF/FTC	• RAL: 400 mg bid

Alternative regimen components

Ritonavir-boosted PI	Remarks
• SQV/r	1000/100 mg BID
• FPV/r	700/100 mg bid or 1400/200 mg QD
NRTI	
• TDF-3TC • ZDV/3TC • ddI/3TC or ddI/FTC [viii]	ZDV/3TC co-formulated
CCR5 inhibitor	
MVC [vi]	Only if CCR5 tropic HIV [viii]

Documento de consenso de Gesida/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (Actualización enero 2012)

Tabla 4. Combinaciones preferentes de tratamiento antirretroviral de inicio†

3er Fármaco	Pauta‡	Ensayos clínicos que la sustentan
ITINN	TDF/FTC/EFV[1,2,3]	ECHO, THRIVE, STARTMRK, ACTG 5202, GILEAD 934
	*ABC/3TC+EFV[1,2,4,5]	ACTG 5202, CNA30024
	*TDF/FTC+NVP[2,3,6]	ARTEN, VERXVE
IP/r	TDF/FTC+ATV/r [3,7]	CASTLE, ACTG 5202, ARTEN
	TDF/FTC+DRV/r[3]	ARTEMIS
	*TDF/FTC+LPV/r[3,8]	ARTEMIS, ABT-730, CASTLE, GEMINI, HEAT, PROGRESS
	*ABC/3TC+ATV/r[4,5,7]	ACTG 5202
	*ABC/3TC+LPV/r[5,8]	KLEAN, HEAT
InInt	TDF/FTC+RAL[3]	STARTMRK, QDMRK

† Ordenado por tercer fármaco y por preferencia según método de evaluación objetiva y estructurada elaborado por GESIDA. Se recomienda el uso de preparados que combinen fármacos a dosis fijas. No existe en la actualidad suficiente información que permita considerar como equivalentes terapéuticos a FTC y 3TC, por lo que el uso de uno u otro fármaco en los regímenes seleccionados depende fundamentalmente de la experiencia disponible en su uso conjunto con los otros fármacos de la combinación.

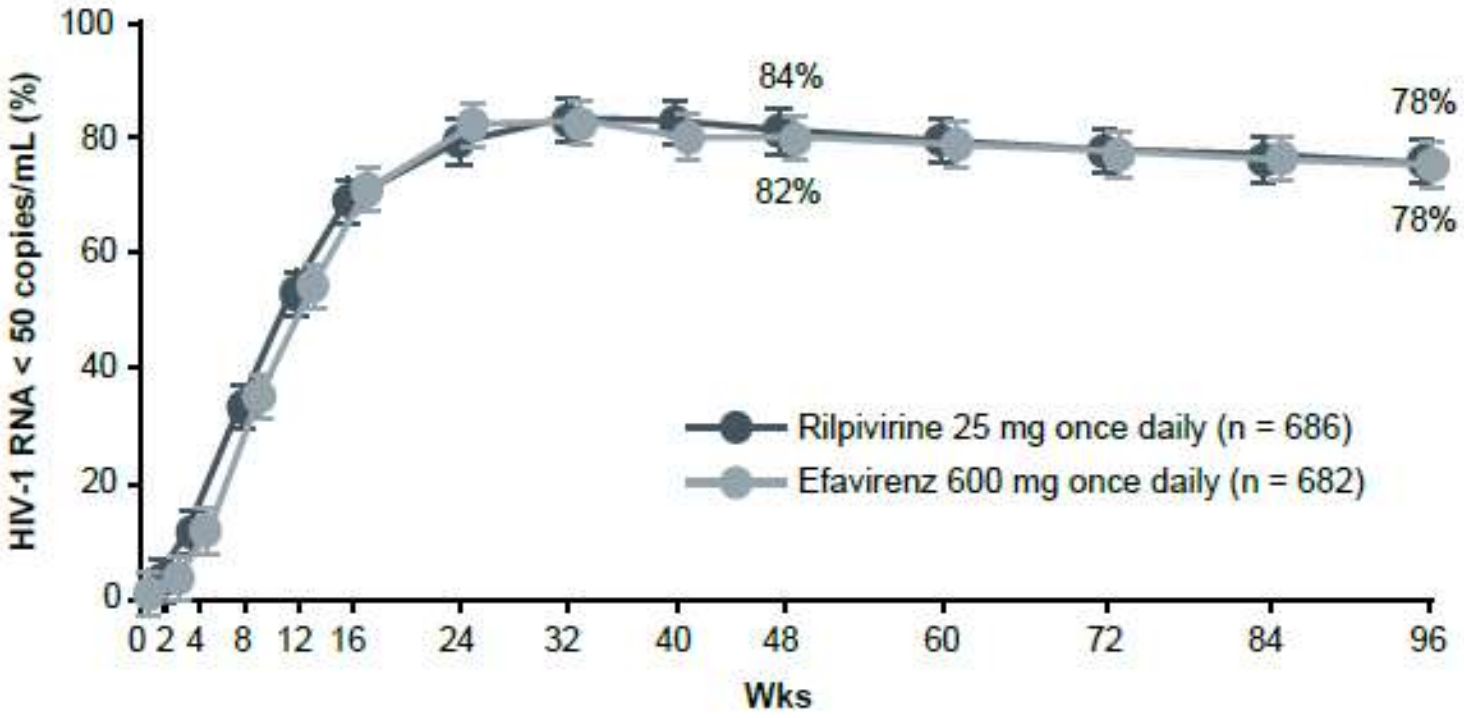
‡ Los comentarios reflejan aspectos que se deben considerar en la elección de régimen, pero no pretenden ser una guía exhaustiva de las precauciones a tomar en el uso de los fármacos. Para mayor información se recomienda revisar el texto del documento así como las fichas técnicas de los fármacos. * Estas pautas no han sido respaldadas como preferentes por la totalidad del panel.

AGENDA

- Nuevos fármacos

Terapia de inicio

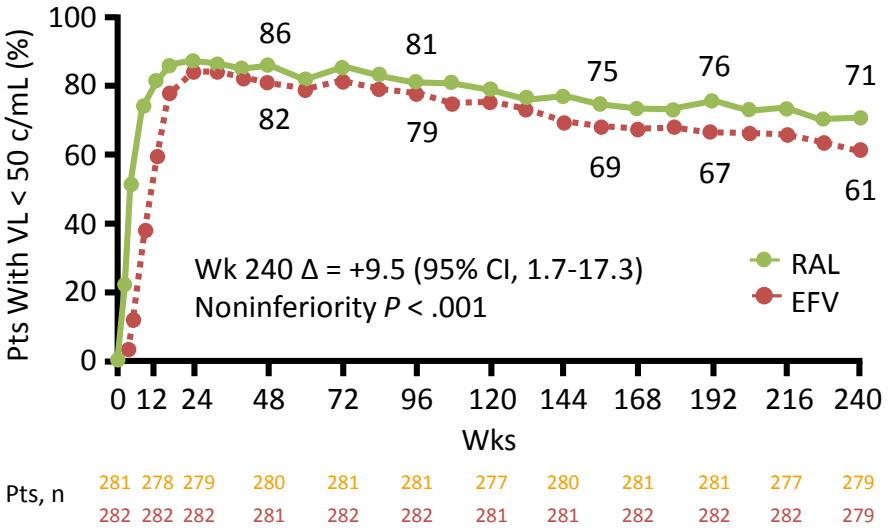
ECHO/THRIVE: Rilpivirine vs Efavirenz at 96-Weeks



Cohen C, et al. IAS 2011. Abstract TULBPE032.

STARTMRK: Final 5-Yr Phase III Results of Efavirenz vs Raltegravir in ART-Naive Pts

- Double-blind phase III trial of EFV vs RAL, each with TDF/FTC, in treatment-naive patients
  - Noninferior at Wk 48 primary endpoint
- At Wk 240 analysis, RAL superior to EFV by VL < 50 c/mL (ITT, NC = F)

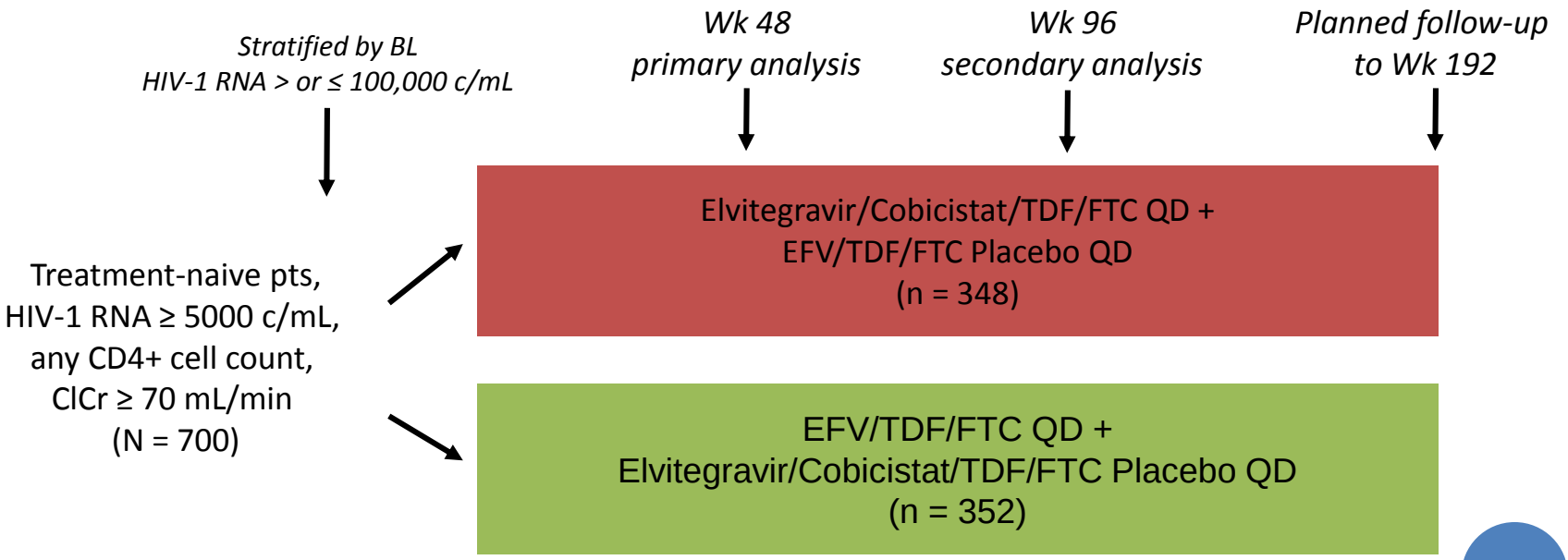


- CD4+ gain: +374 (RAL) vs +312 (EFV)
- Generally consistent virologic and immunologic effects in various demographic and prognostic subgroups (eg, baseline CD4+/VL, age, sex, race, etc)
- Low levels of genotypic resistance among patients with VF and VL > 400 c/mL in both arms
  - RAL, n = 7; EFV, n = 12
- Fewer pts with drug-related adverse events in RAL arm
- Significantly smaller increases in TC, HDL-C, LDL-C, and TG levels with RAL vs EFV

Rockstroh J, et al. AIDS 2012. Abstract LBPE19.

Elvitegravir/Cobicistat/TDF/FTC vs EFV/TDF/FTC in Tx-Naive Pts: Wk-96 Data

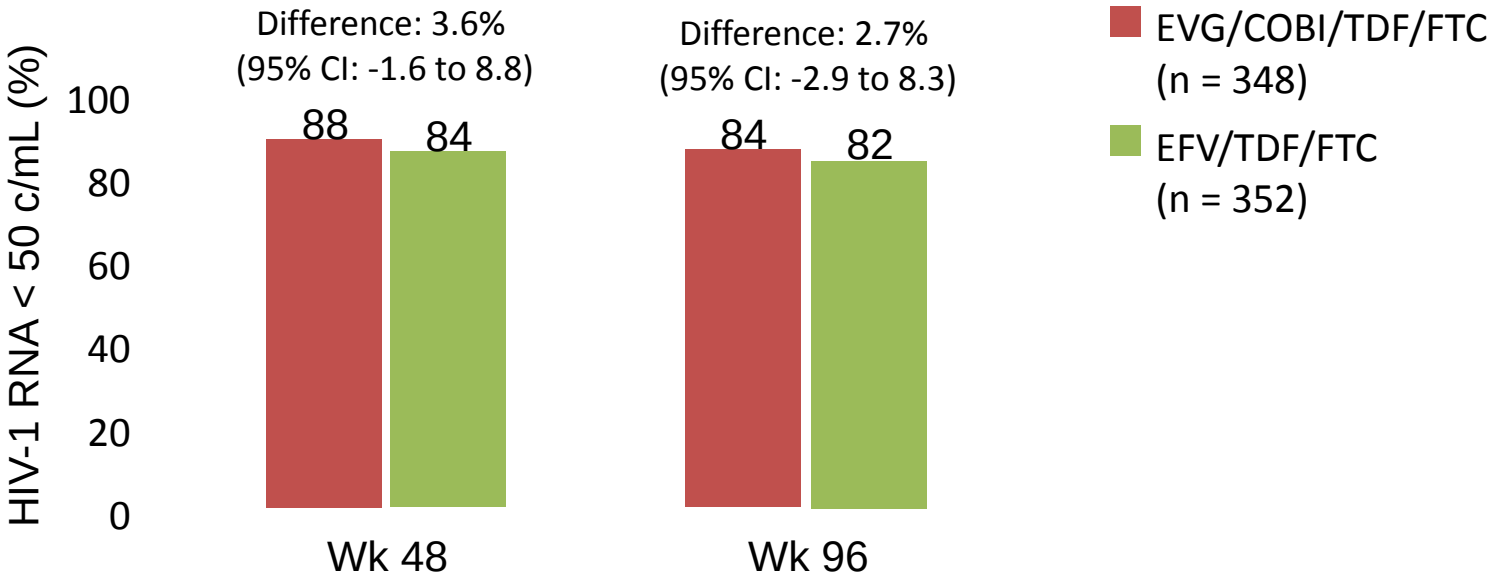
- Multicenter, randomized, double-blinded, active-controlled phase III study[1,2]
  - 1º endpoint: EVG/COBI/TDF/FTC noninferior to EFV/TDF/FTC at Wk 48[2]



1. Zolopa A, et al. Glasgow 2012. Abstract O424A. 2. Sax P, et al. CROI 2012. Abstract 101.

EVG/COBI Regimen Still Noninferior to EFV Regimen at Wk 96

- Efficacy of EVG/COBI maintained within noninferiority margin (-12%) through Wk 96
  - Consistent across subgroups: BL HIV-1 RNA, CD4+ count, age, sex, race
  - CD4+ count increase at Wk 96: +295 (EVG/COBI) vs +273 (EFV)



Zolopa A, et al. Glasgow 2012. Abstract O424A.

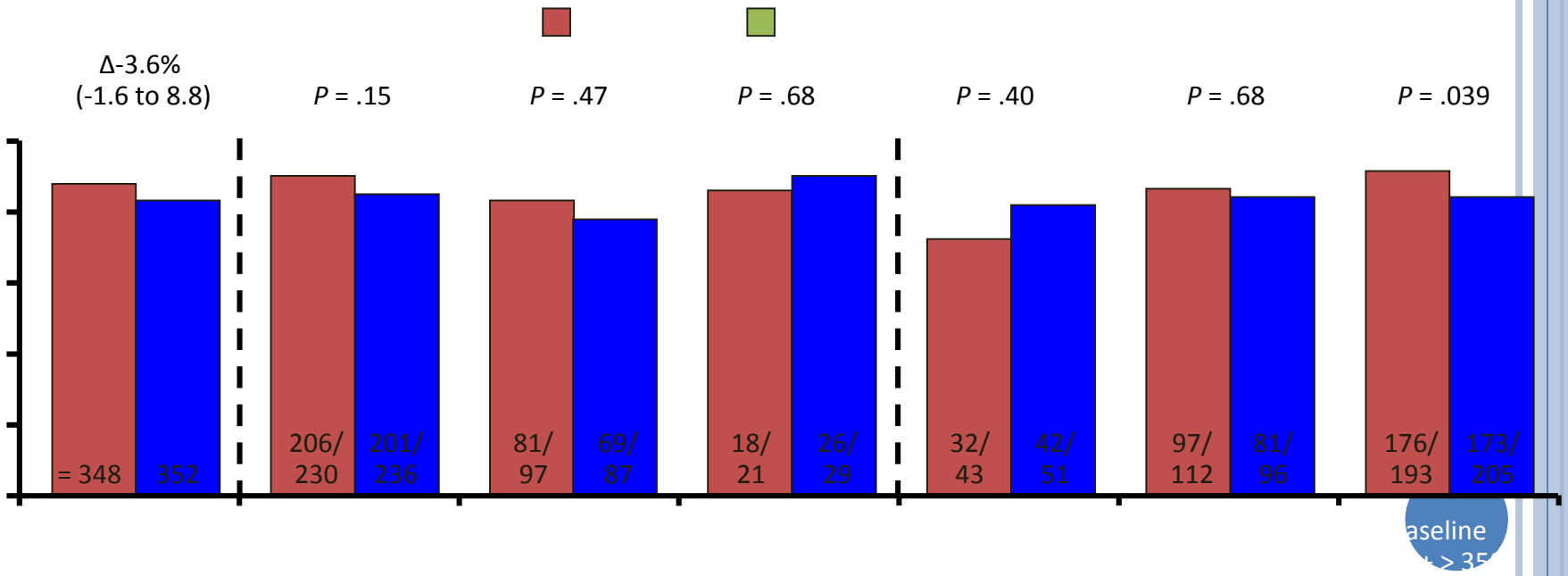
Elvitegravir/Cobicistat Regimen vs EFV Regimen: Resistance/Safety at Wk 96

- Resistance at VF detected in 8 pts per arm through Wk 48, plus 2 additional pts per arm through Wk 96
  - Nearly all pts had primary integrase (9/10) or NNRTI (10/10) resistance mutations
- AE rates between Wks 48-96 low and similar between arms
- 2% of pts discontinued EVG/COBI regimen by Wk 96 due to renal abnormalities vs no patients on EFV regimen
  - Includes 2 pts with creatinine elevation between Wks 48 and 96 (both with baseline eGFR < 70 mL/min, history of HTN and diabetes); creatinine improved after DC
  - No renal tubulopathy between Wks 48 and 96 and no further reduction in median eGFR with EVG/COBI from Wk 48 to 96
- Significantly greater increases in total, LDL, and HDL cholesterol from baseline to Wk 96 in EFV vs EVG/COBI groups (all $P \leq .01$); TC:HDL ratio similar between arms at Wks 48 and 96

Zolopa A, et al. Glasgow 2012. Abstract O424A.

Elvitegravir/Cobicistat/TDF/FTC vs EFV/TDF/FTC: Subgroup Responses

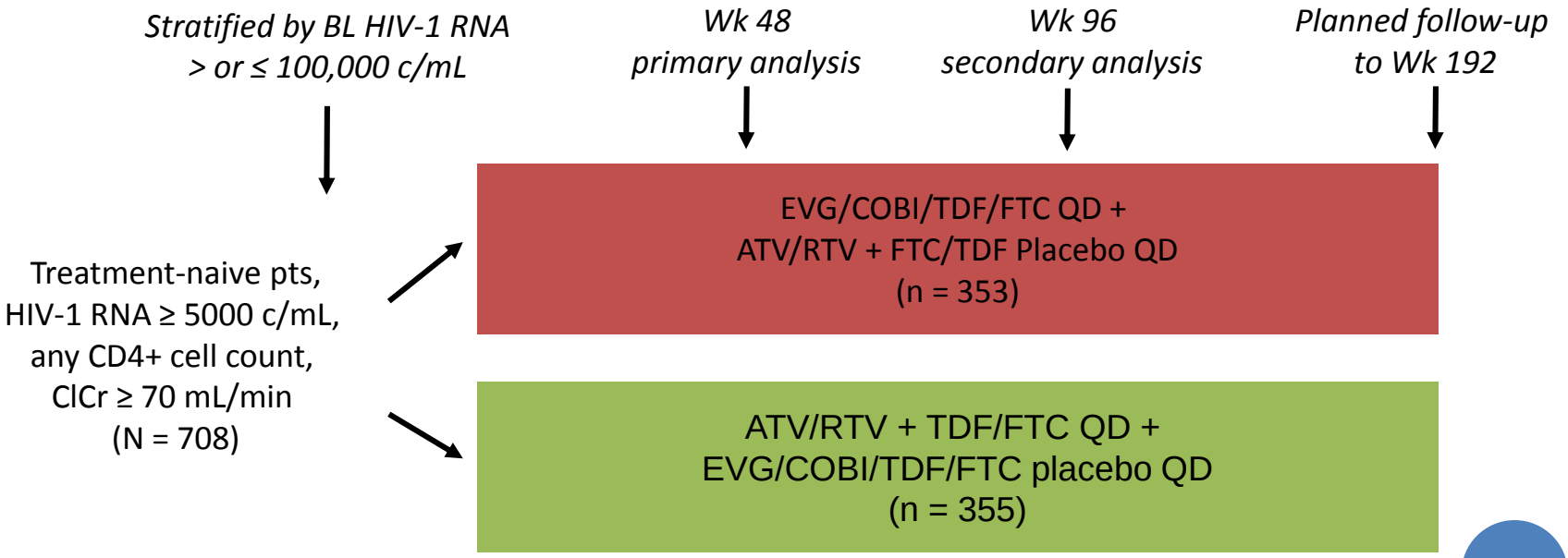
- Randomized, double-blind phase III trial (N = 700)[1,2]
  - Primary endpoint results: EVG/COBI/TDF/FTC noninferior to EFV/TDF/FTC at Wk 48[2]



1. Sax P, et al. AIDS 2012. Abstract TUPE028. 2. Sax P, et al. CROI 2012. Abstract 101. Graphic reproduced with permission.

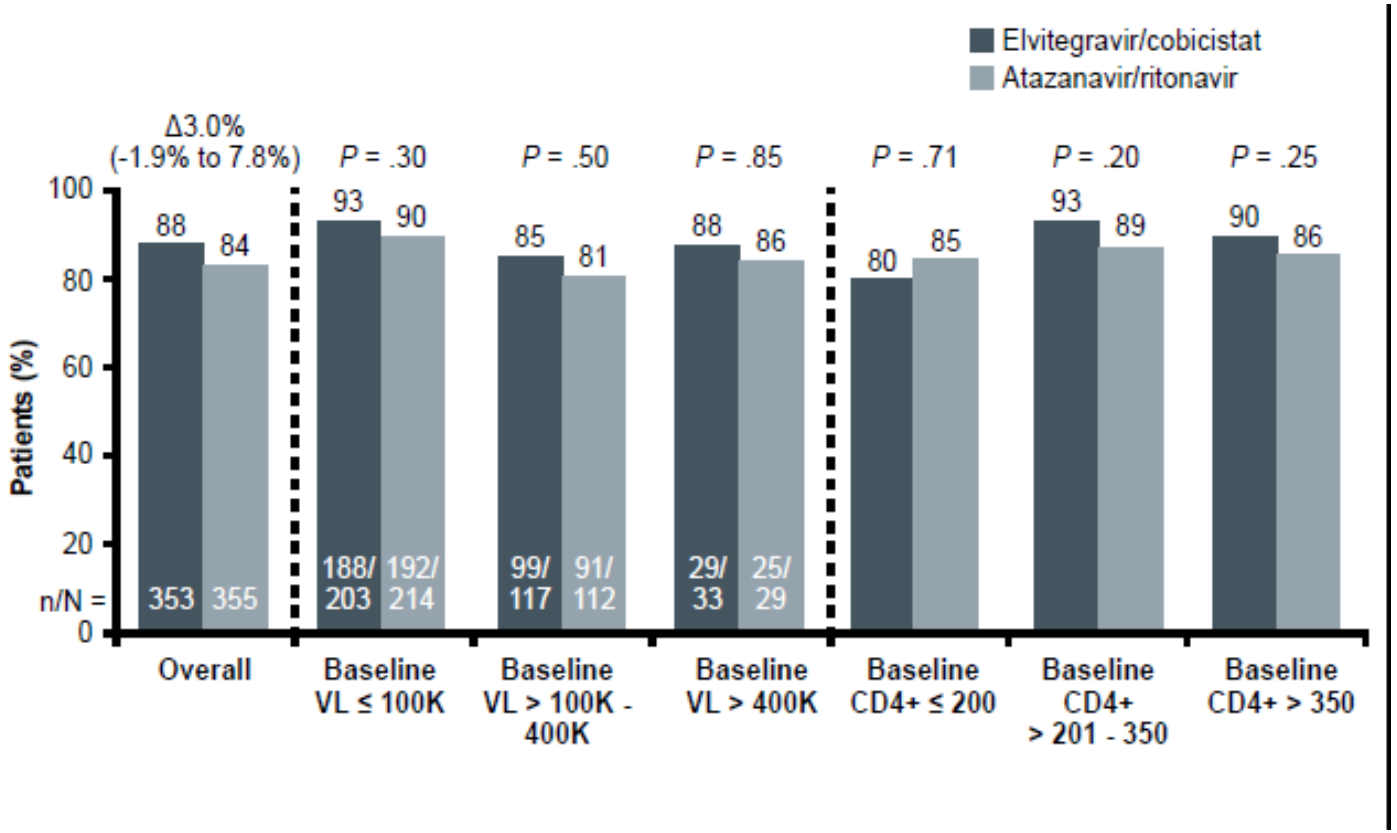
EVG/COBI/TDF/FTC vs ATV/RTV + TDF/FTC in Tx-Naive Pts: Wk-96 Data

- Multicenter, randomized, double-blinded, active-controlled phase III study[1,2]
  - 1º endpoint: EVG/COBI/TDF/FTC noninferior to ATV/RTV + TDF/FTC at Wk 48[2]



1. Rockstroh J, et al. Glasgow 2012. Abstract O424B. 2. DeJesus E, et al. CROI 2012. Abstract 627.

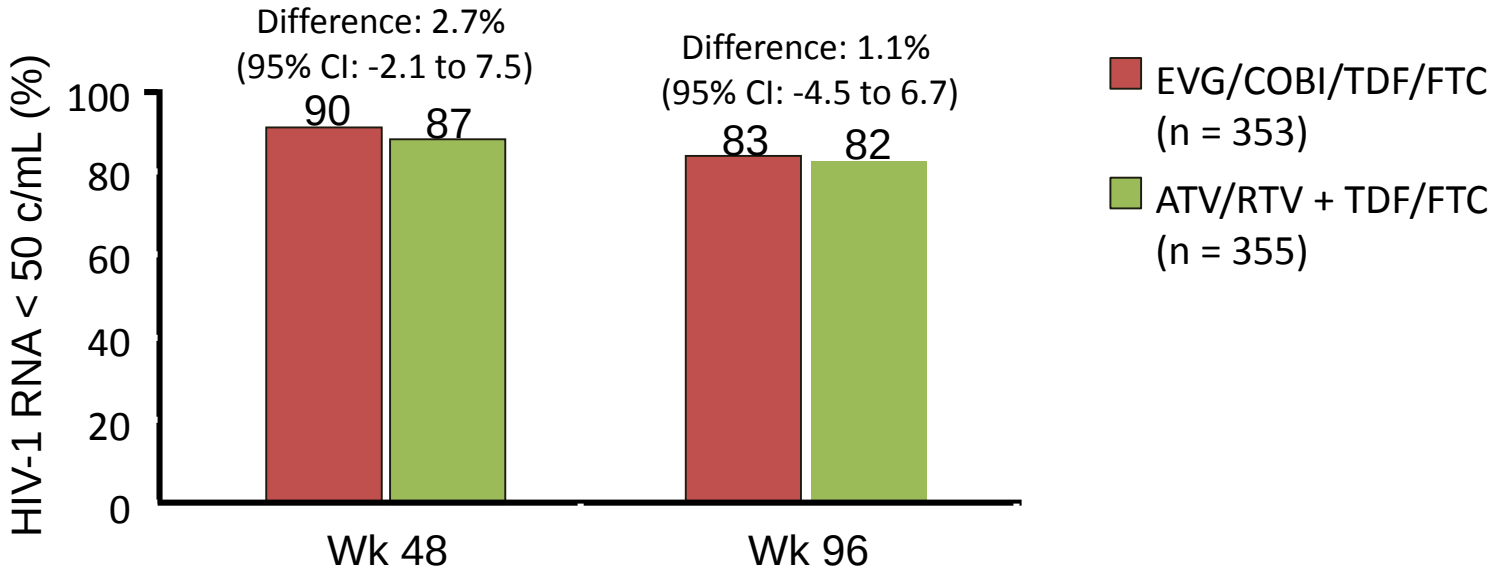
TDF/FTC/EVG/COBI vs TDF/FTC + ATV/RTV at Week 48



DeJesus E, et al. Lancet. 2012;379:2429-2438. DeJesus E, et al. AIDS 2012. Abstract TUPEB043.

EVG/COBI Regimen Still Noninferior to ATV/RTV Regimen at Wk 96

- Efficacy of EVG/COBI maintained within noninferiority margin (-12%) through Wk 96
  - Consistent across subgroups: BL HIV-1 RNA, CD4+ count, adherence, age, sex, race
  - CD4+ count increase at Wk 96: +256 (EVG/COBI) vs +261 (ATV/RTV)



Rockstroh J, et al. Glasgow 2012. Abstract O424B.

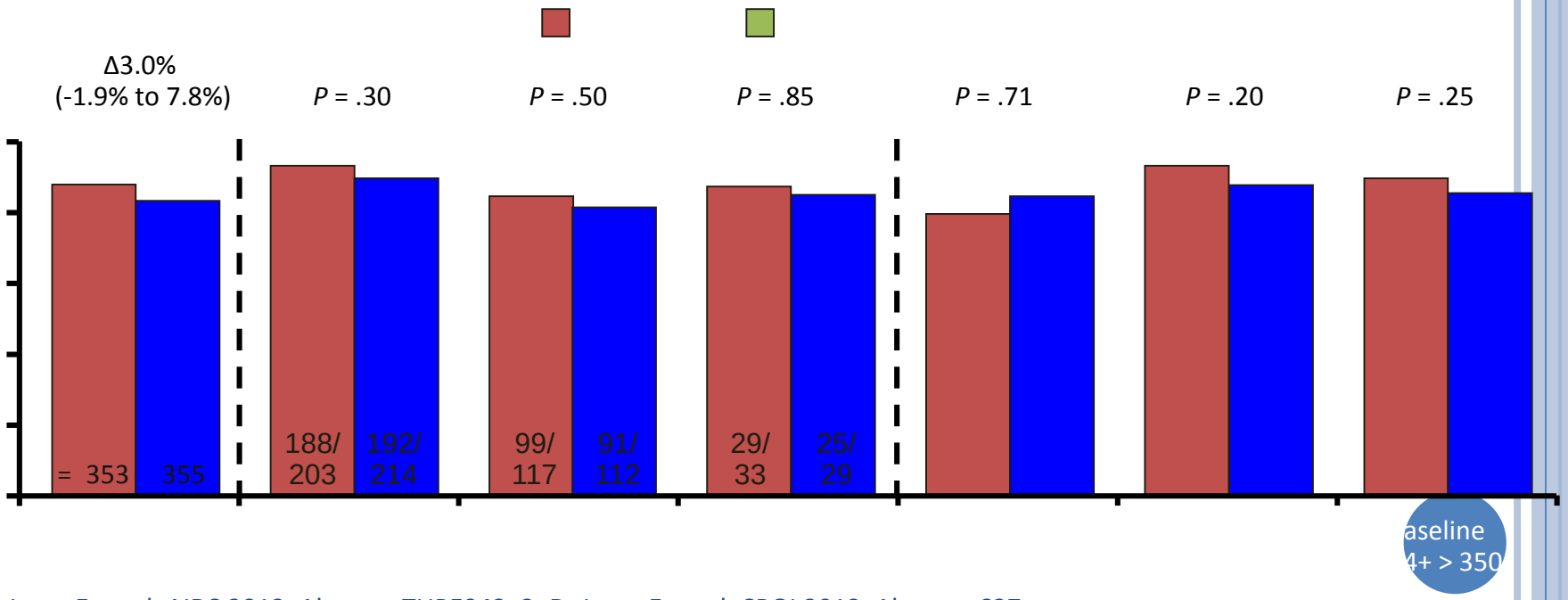
Elvitegravir/Cobicistat Regimen vs ATV/RTV Regimen: Wk 96 Resistance/Safety

- In EVG/COBI arm, resistance at VF detected in 5 pts through Wk 48, plus 1 additional pt through Wk 96 vs 0 pts in ATV/RTV arm
  - Nearly all pts had primary integrase (5/6) and NRTI (5/6) resistance-associated mutations
- AE rates between Wks 48-96 low and similar between arms
- 0.9% of pts discontinued EVG/COBI regimen by Wk 96 due to renal abnormalities vs 0.6% of pts on ATV/RTV regimen
  - Includes 1 pt in each arm with creatinine elevation between Wks 48 and 96; creatinine improved after DC
  - No renal tubulopathy between Wks 48 and 96 and no further reduction in median eGFR with EVG/COBI from Wk 48 to 96
- Grade 3/4 hyperbilirubinemia in 65% of ATV/RTV arm by Wk 96 vs 0.6% with EVG/COBI
- Significantly greater increases in TC with EVG/COBI, in TG with ATV/RTV

Rockstroh J, et al. Glasgow 2012. Abstract O424B.

Elvitegravir/Cobicistat/TDF/FTC vs ATV/RTV + TDF/FTC: Subgroup Responses

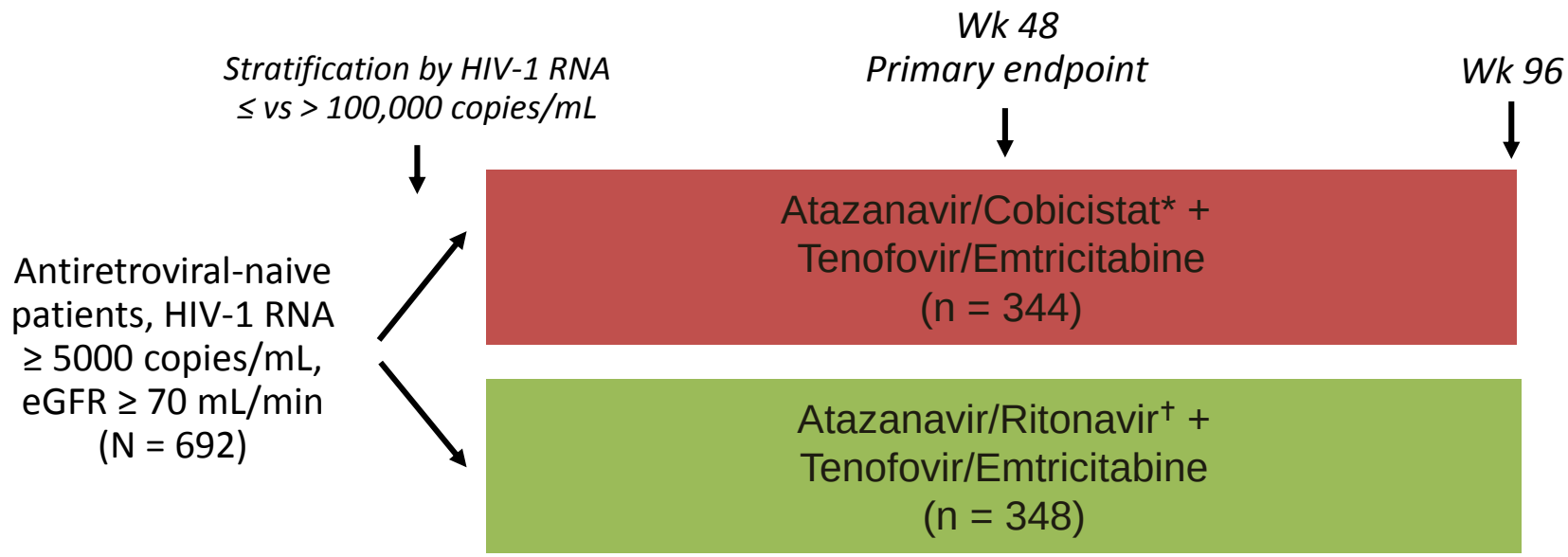
- Randomized, double-blind phase III trial (N = 708)[1,2]
  - Primary endpoint results: EVG/COBI/TDF/FTC noninferior to ATV/RTV + TDF/FTC at Wk 48[2]



1. DeJesus E, et al. AIDS 2012. Abstract TUPE043. 2. DeJesus E, et al. CROI 2012. Abstract 627.
Graphic reproduced with permission.

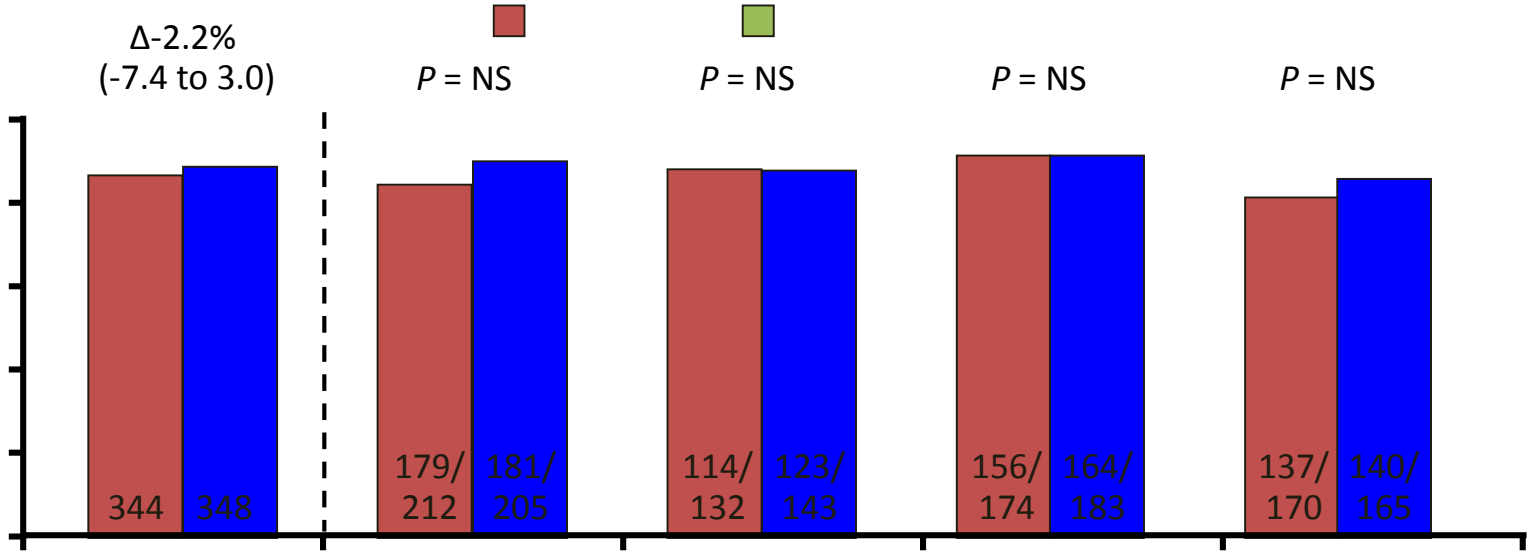
Cobicistat-Boosted vs Ritonavir-Boosted Atazanavir in Treatment-Naive Patients

- Randomized, multicenter, placebo-controlled phase III trial
  - Primary endpoint: VL < 50 c/mL at Wk 48 (FDA snapshot analysis)



Gallant J, et al. AIDS 2012. Abstract TUAB0103.

ATV/COBI vs ATV/RTV: Noninferior Virologic Suppression at Wk 48

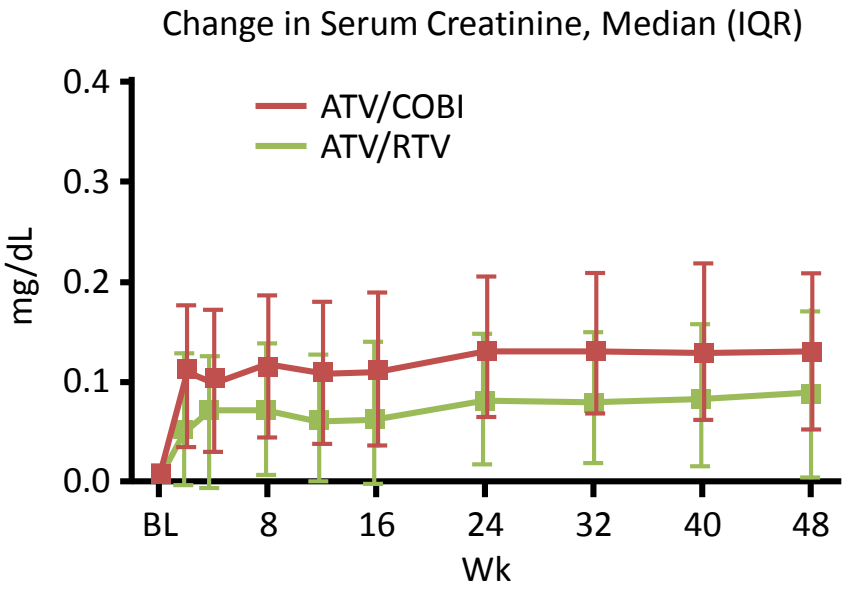


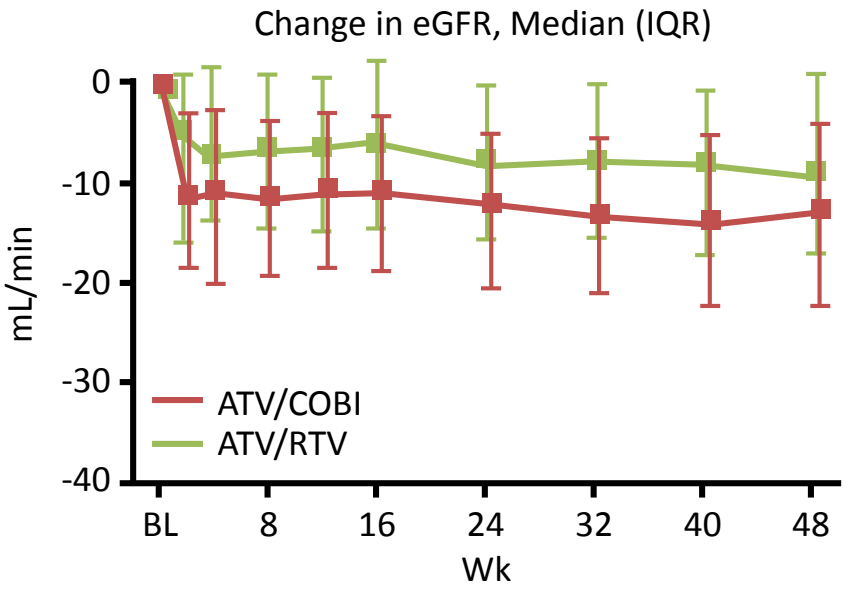
- CD4+ count gain: +213 with ATV/COBI vs +219 with ATV/RTV
- Among 24 pts with suboptimal virologic response and genotype: no primary PI or TDF resistance; M184V/I in 2 pts in COBI arm, 0 in RTV arm

Gallant J, et al. AIDS 2012. Abstract TUAB0103. Graphic reproduced with permission.

ATV/COBI vs ATV/RTV: Changes in Serum Creatinine and eGFR

- COBI ↑ serum creatinine and ↓ eGFR by inhibiting renal creatinine secretion[1]
- COBI does not affect actual glomerular filtration rate[2]



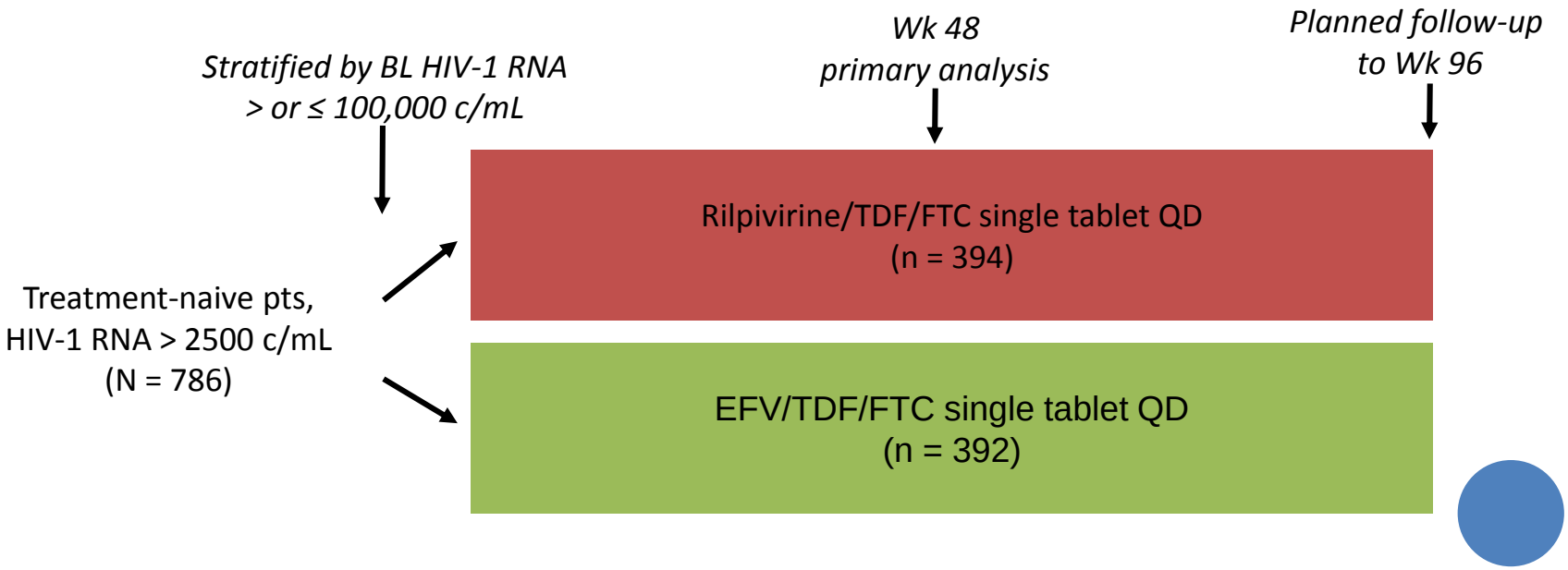


- 6 pts in COBI arm and 5 in RTV arm discontinued therapy due to renal abnormalities[3]
- Higher proportion with hyperbilirubinemia with COBI but discontinuations similar by arm
- 5 of 6 in COBI arm vs 2 of 5 in RTV arm with proximal tubulopathy discontinued therapy

1. Lepist EI, et al. ICAAC 2011. Abstract A1-1724. 2. German P, et al. J Acquir Immune Defic Syndr. 2012;[Epub ahead of print]. 3. Gallant J, et al. AIDS 2012. Abstract TUAB0103. Graphics reproduced with permission.

STaR: Fixed-Dose Rilpivirine/TDF/FTC vs EFV/TDF/FTC in Tx-Naive Pts

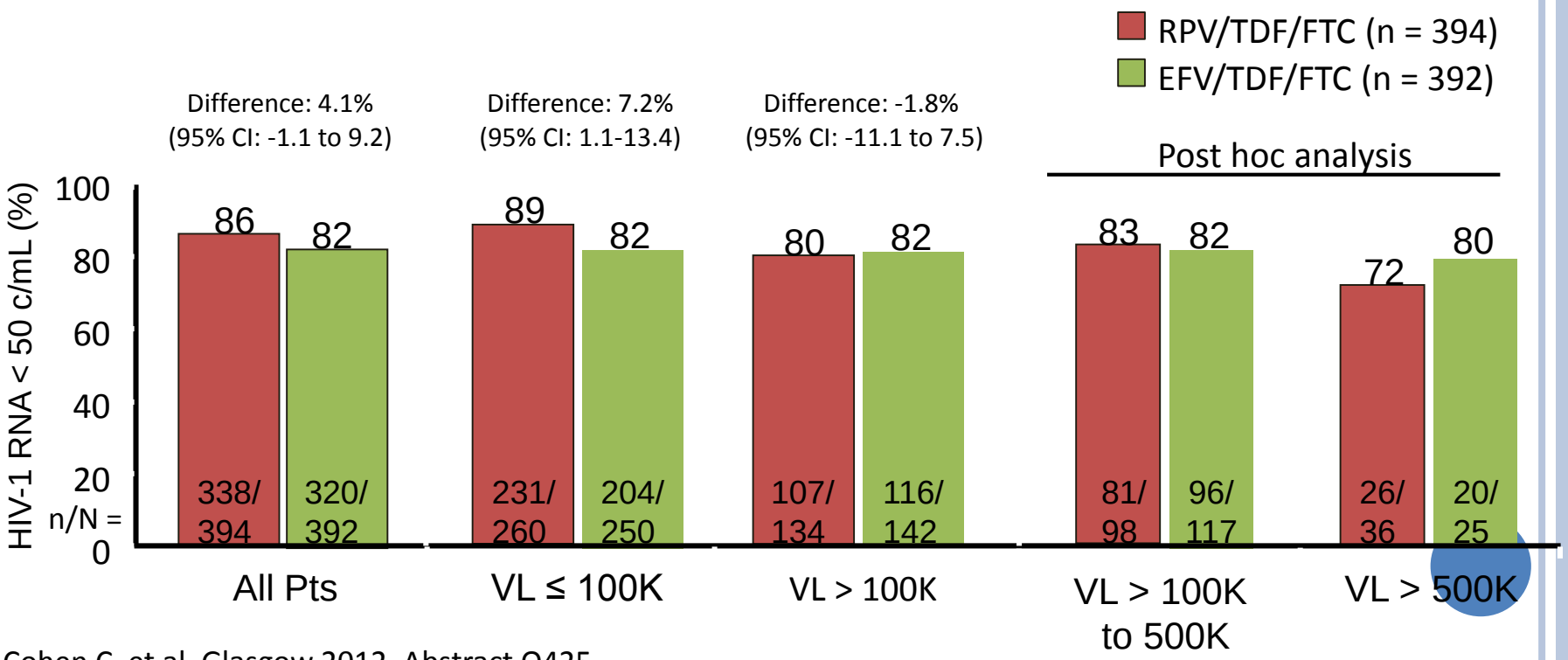
- Multicenter, international, open-label, randomized phase IIIb study
  - First comparison of regimens as single-tablet regimen
  - 1º endpoint



Cohen C, et al. Glasgow 2012. Abstract O425.

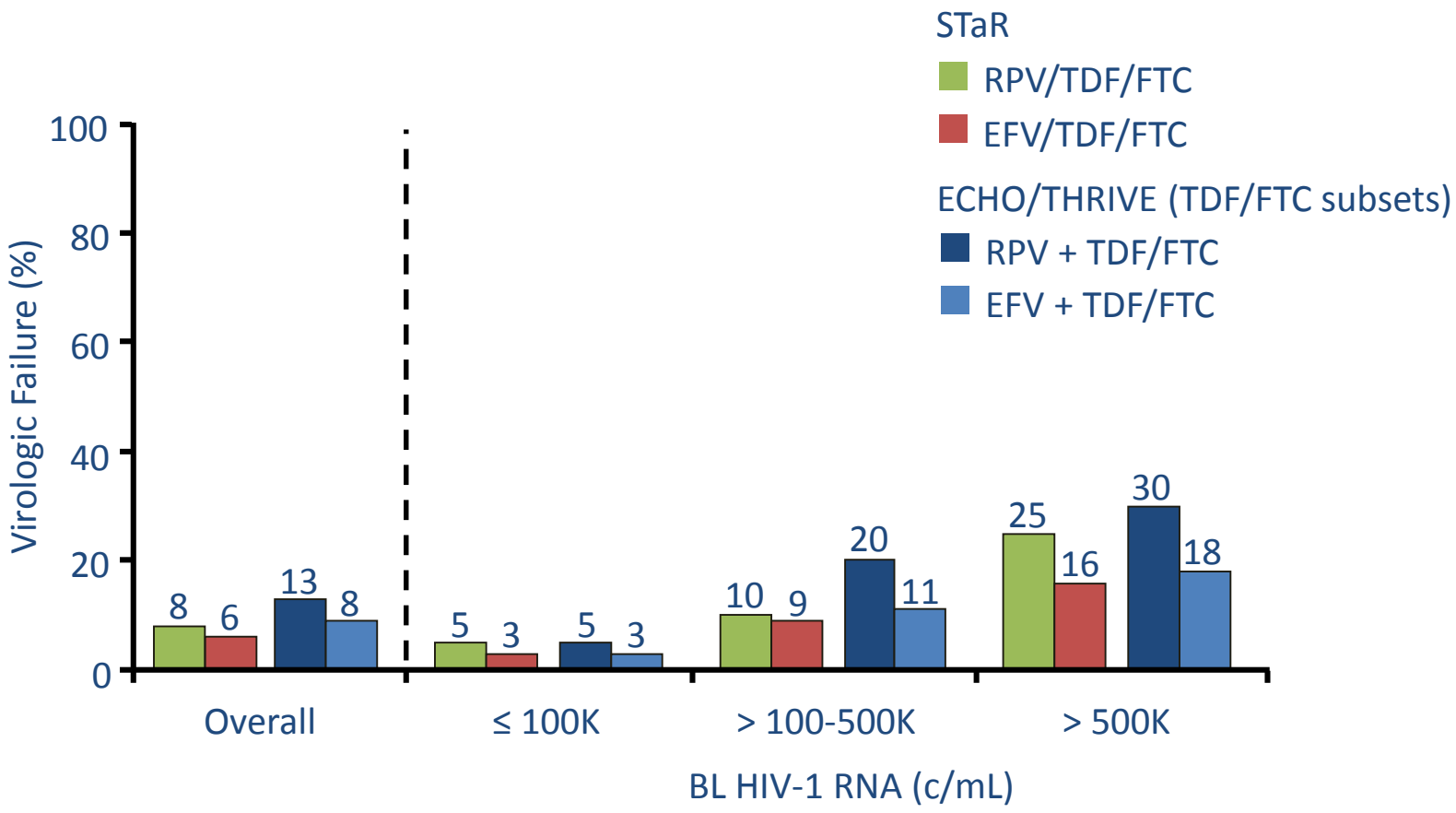
STaR: Efficacy of Rilpivirine/TDF/FTC vs EFV/TDF/FTC at Wk 48

- RPV/TDF/FTC noninferior to EFV/TDF/FTC in overall population and in pts with BL HIV-1 RNA > 100,000 c/mL
  - RPV/TDF/FTC superior to EFV/TDF/FTC in pts with BL HIV-1 RNA ≤ 100,000 c/mL



Cohen C, et al. Glasgow 2012. Abstract O425.

STaR vs ECHO/THRIVE: Virologic Failure by Wk 48



Cohen C, et al. Glasgow 2012. Abstract O425.

STaR: Wk-48 Resistance With Rilpivirine/TDF/FTC vs EFV/TDF/FTC

Pts With Resistance Outcome, %	STaR		ECHO/THRIVE (TDF/FTC Subsets)	
	RPV/TDF/FTC (n = 394)	EFV/TDF/FTC (n = 392)	RPV + TDF/FTC (n = 550)	EFV + TDF/FTC (n = 546)
Resistance analysis data available	5	2	11	3
Detected resistance	**4**	**1**	**7**	**2**
▪ BL VL ≤ 100,000 c/mL	2	1	2	1
▪ BL VL > 100,000-500,000 c/mL	5	0	9	2
▪ BL VL > 500,000 c/mL	19	4	21	7
Primary NNRTI resistance	**4**	**1**	**6**	**2**
▪ K101E	1	--	1	
▪ K103N	--	0.3		1
▪ E138K/Q	2	--	4	--
▪ Y181C/I	2	--	1	--
Primary NRTI resistance	**4**	**0.3**	**7**	**1**
▪ K65R/N	1	--	1	0.4
▪ M184V/I	4	0.3	6	1

Cohen C, et al. Glasgow 2012. Abstract O425.

STaR: Safety of Rilpivirine/TDF/FTC vs EFV/TDF/FTC Through Wk 48

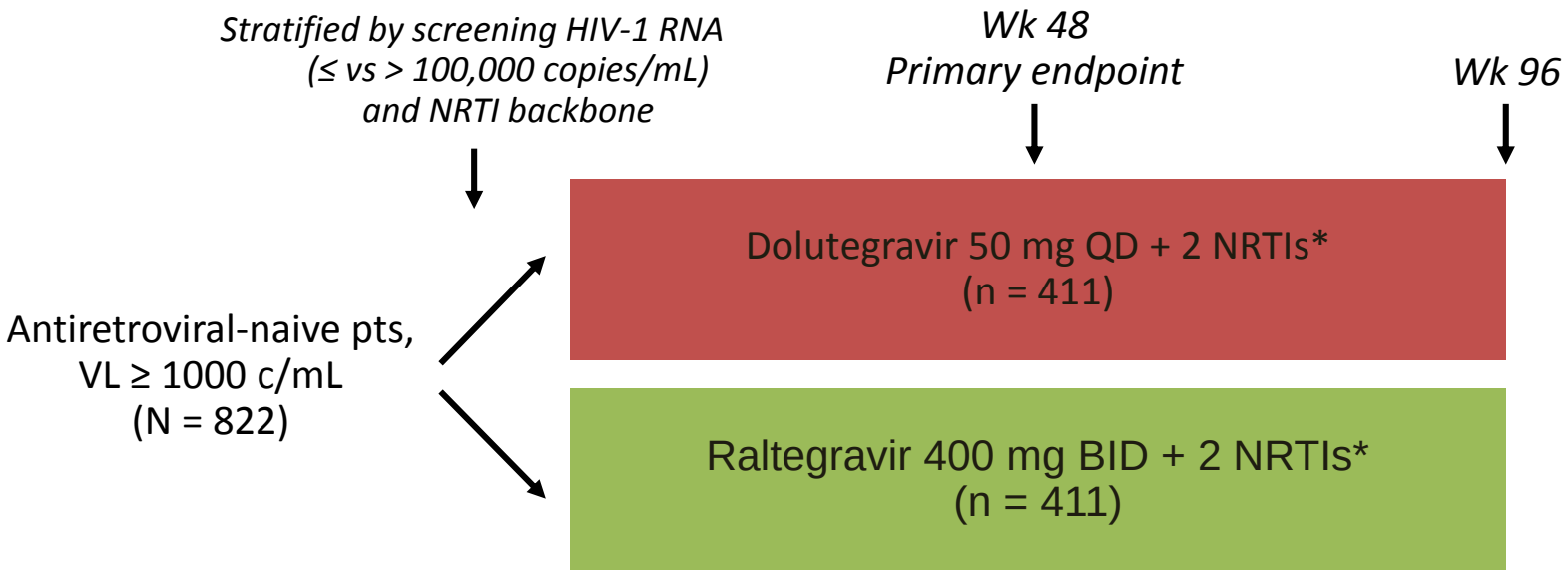
- RPV/TDF/FTC associated with
  - Fewer discontinuations for AEs: 2.5% vs 8.7% ($P < .001$)
  - Lower incidence of CNS AEs: 30% vs 51% ($P < .001$)
  - Lower incidence of psychiatric AEs: 16% vs 38% ($P < .001$)

CNS, Psychiatric AEs Occurring in > 5% of Pts in Either Arm, %	RPV/TDF/FTC (n = 394)	EFV/TDF/FTC (n = 392)
Dizziness, vertigo, balance disorder	8	26
Insomnia	10	14
Somnolence	3	7
Headache	12	14
Abnormal dreams	6	25
Depression	7	9
Anxiety, nervousness	5	9

Cohen C, et al. Glasgow 2012. Abstract O425.

SPRING-2: Dolutegravir QD vs Raltegravir BID in Treatment-Naive Pts at 48 Wks

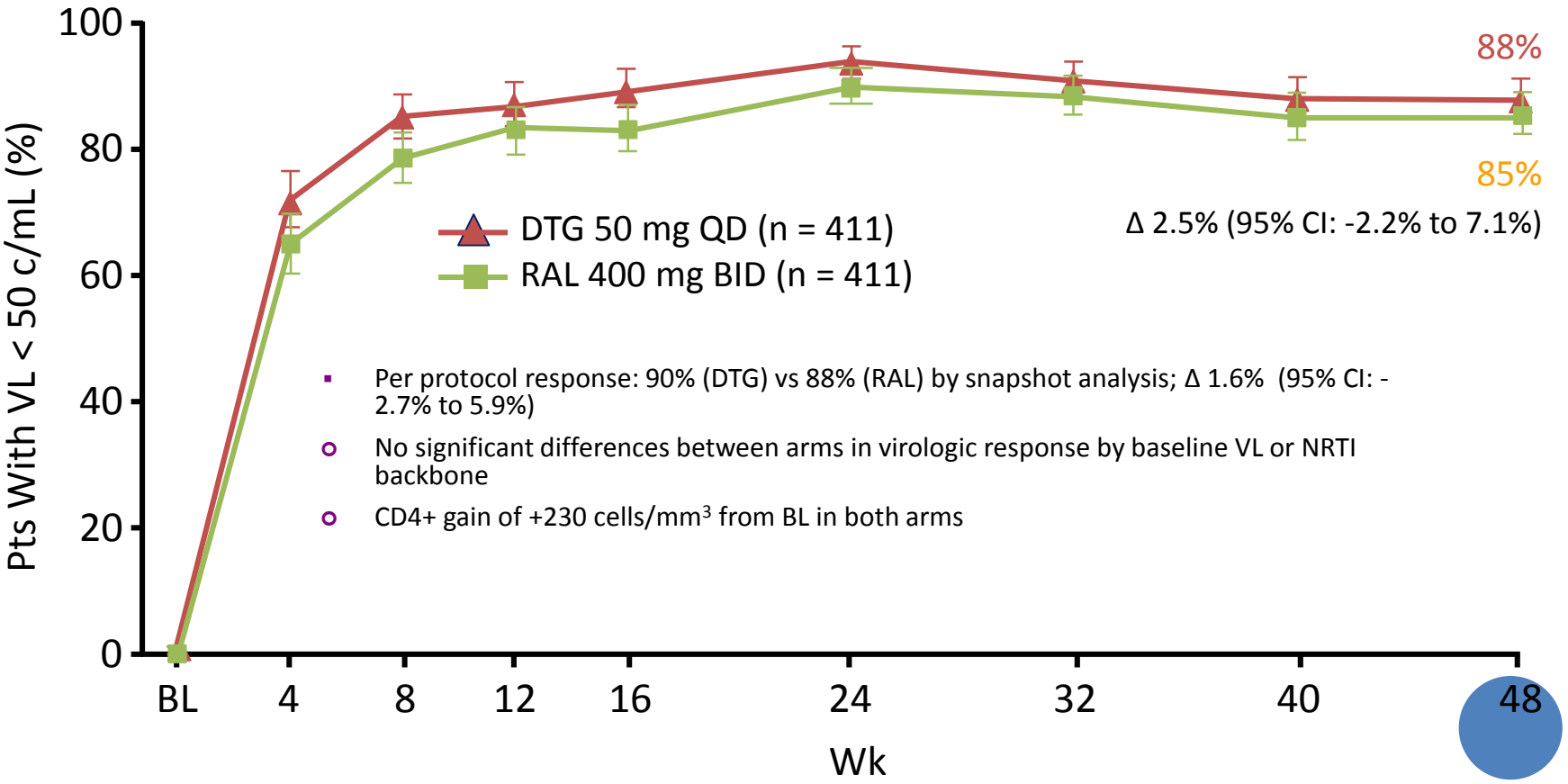
- Randomized, double-blind, placebo-controlled phase III trial
  - Primary endpoint: VL < 50 c/mL at Wk 48 (FDA snapshot analysis)



*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

Raffi F, et al. AIDS 2012. Abstract THLBB04.

SPRING-2: Dolutegravir Noninferior to Raltegravir at 48 Wks



Raffi F, et al. AIDS 2012. Abstract THLBB04. Graphic reproduced with permission.

SPRING-2: Safety and Resistance

- Lower rate of confirmed virologic failure at or after Wk 24 with DTG vs RAL (5% vs 7%)

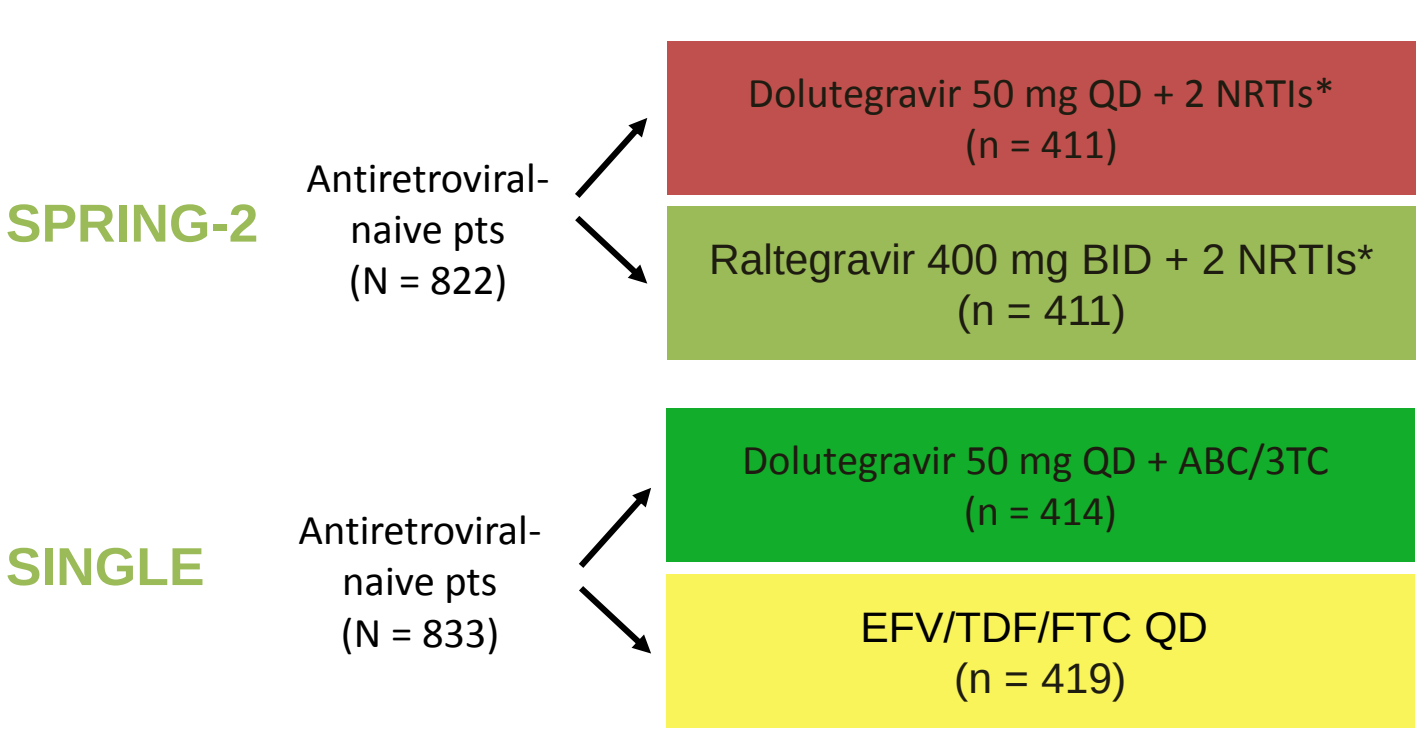
Patients	DTG 50 mg QD (n = 411)	RAL 400 mg BID (n = 411)
Subjects with protocol-defined virologic failure, n	20	28
Resistance, n/N		
▪ INSTI resistance mutations	0/8	1/18
▪ NRTI resistance mutations	0/12	4/19

- DTG had favorable safety profile, comparable to RAL
  - Few AEs necessitating treatment discontinuation (2% in each arm)
  - Greater increase in creatinine with DTG vs RAL (+0.139 vs +0.053 mg/dL)
    - DTG increases serum creatinine by inhibiting renal creatinine secretion but does not affect actual glomerular filtration rate[2]
  - No premature discontinuation for renal events

1. Raffi F, et al. AIDS 2012. Abstract THLBB04. 2. Koteff J, et al. ICAAC 2011. Abstract A1-1728.

Dolutegravir in Tx-Naive Pts: Efficacy by Baseline HIV-1 RNA and NRTI Choice

- Pooled analysis of SPRING-2 and SINGLE phase III trials[1]



Primary analyses:

DTG noninferior to RAL[2]
Δ: 2.5%
(95% CI: -2.2% to +7.1%)

DTG superior to EFV[3]
Δ: 7.4%
(95% CI: +2.5% to +12.3%)

*Investigator-selected NRTI backbone: either TDF/FTC or ABC/3TC.

1. Eron J, et al. Glasgow 2012. Abstract P204. 2. Raffi F, et al. AIDS 2012. Abstract THLBB04.
3. Walmsley S, et al. ICAAC 2012. Abstract H-556b.

Dolutegravir Effective With ABC/3TC or TDF/FTC, Regardless of BL HIV-1 RNA

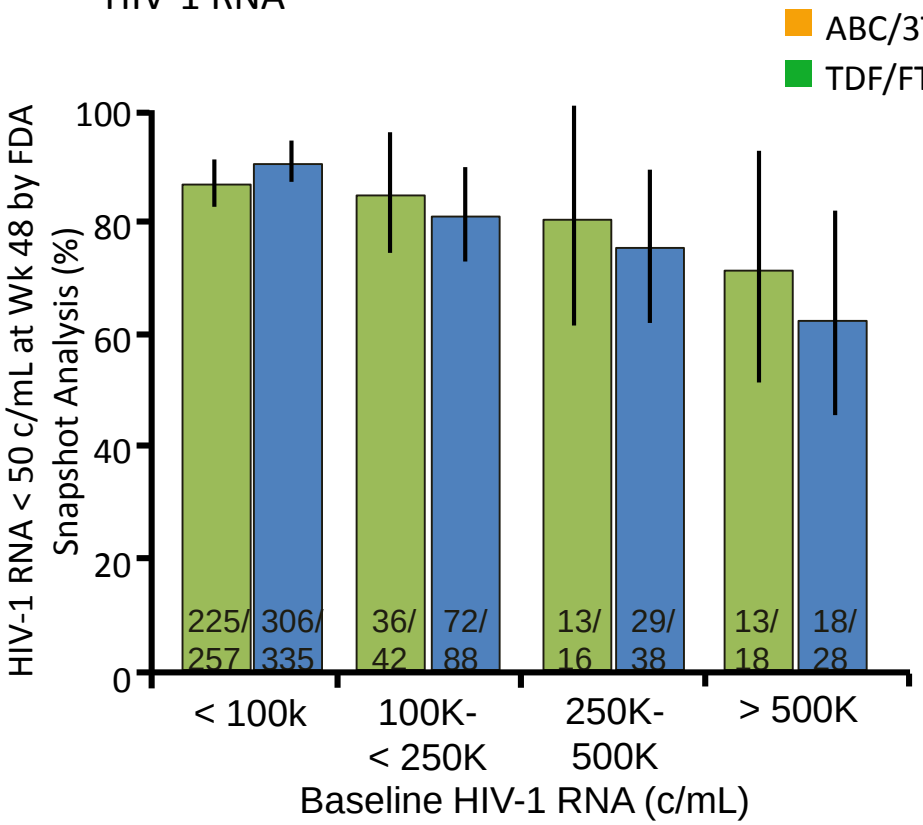
HIV-1 RNA < 50 c/mL at Wk 48 by Subgroup (FDA Snapshot Analysis), %	SPRING-2		SINGLE	
	DTG + NRTIs	RAL + NRTIs	DTG + ABC/3TC	EFV/TDF/ FTC
BL HIV-1 RNA ≤ 100,000 c/mL				
▪ ABC/3TC	87	88	90	--
▪ TDF/FTC	92	91	--	83
BL HIV-1 RNA > 100,000 c/mL				
▪ ABC/3TC	81	82	83	--
▪ TDF/FTC	83	71	--	76

- DTG well tolerated with similar renal safety with either ABC/3TC or TDF/FTC

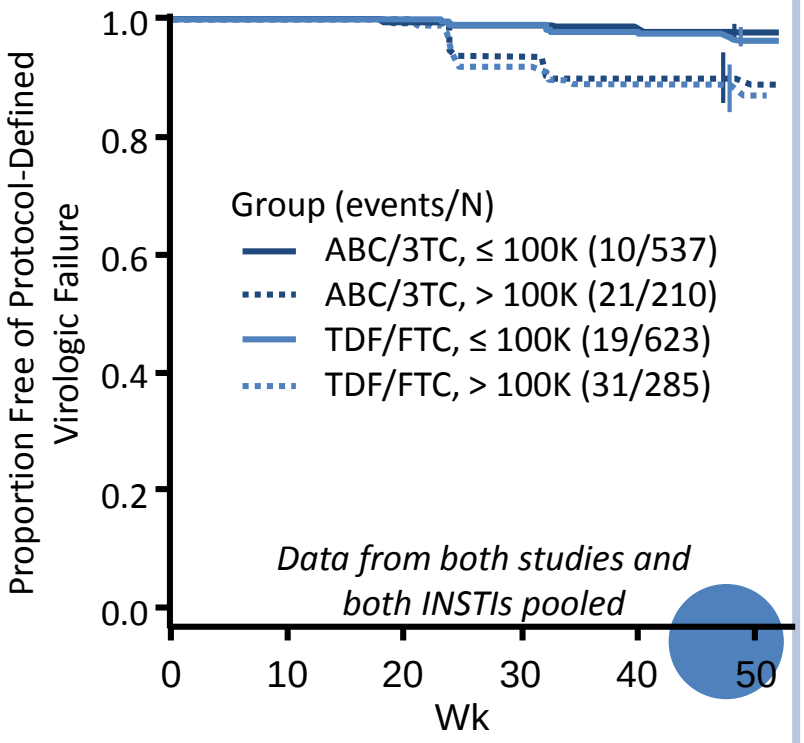
Eron J, et al. Glasgow 2012. Abstract P204.

Similar Efficacy of INSTIs (RAL or DTG) + ABC/3TC or TDF/FTC, Even For High BL VL

- In SPRING-2, similar efficacy with ABC/3TC or TDF/FTC + RAL or DTG, including with high BL HIV-1 RNA



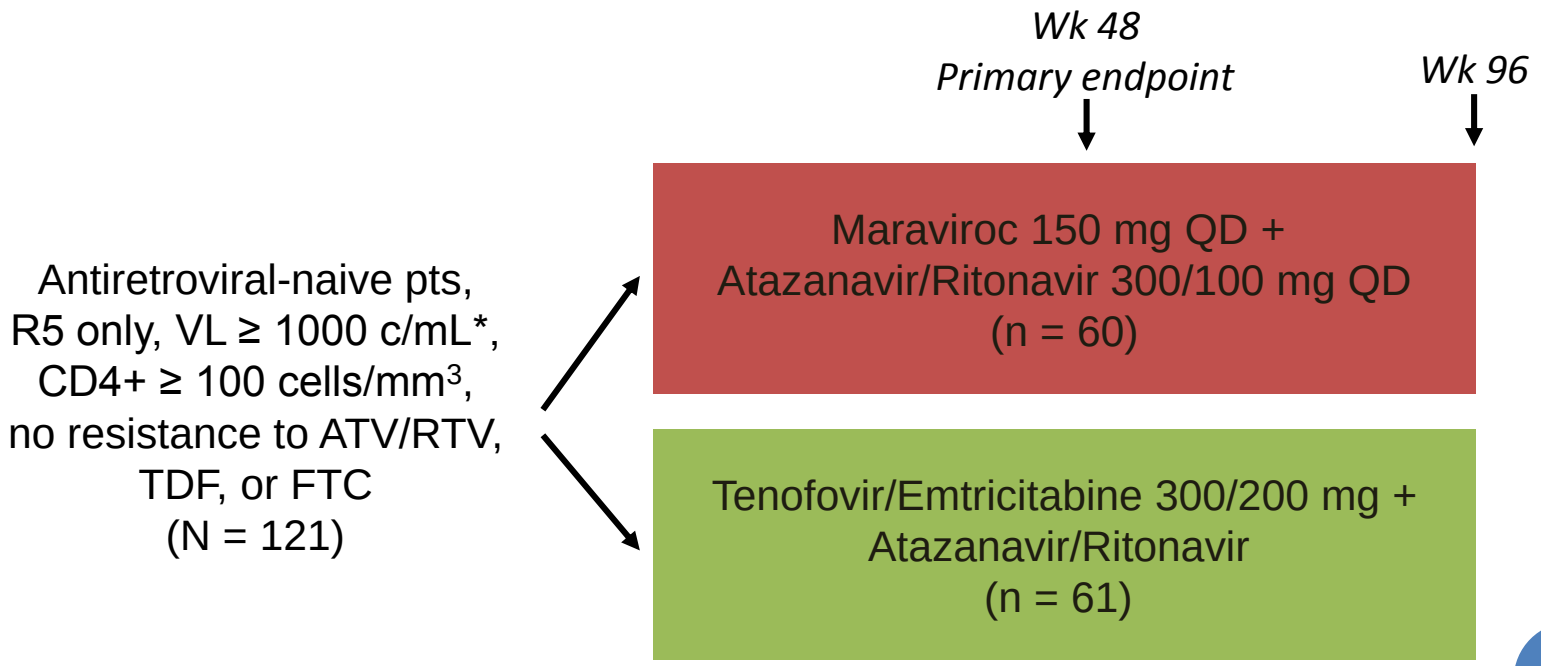
- In pooled analysis, high response rates with ABC/3TC or TDF/FTC at low and high BL HIV-1 RNA levels



Eron J, et al. Glasgow 2012. Abstract P204.

Study A4001078: Wk 96 Data With ATV/RTV Plus MVC or TDF/FTC

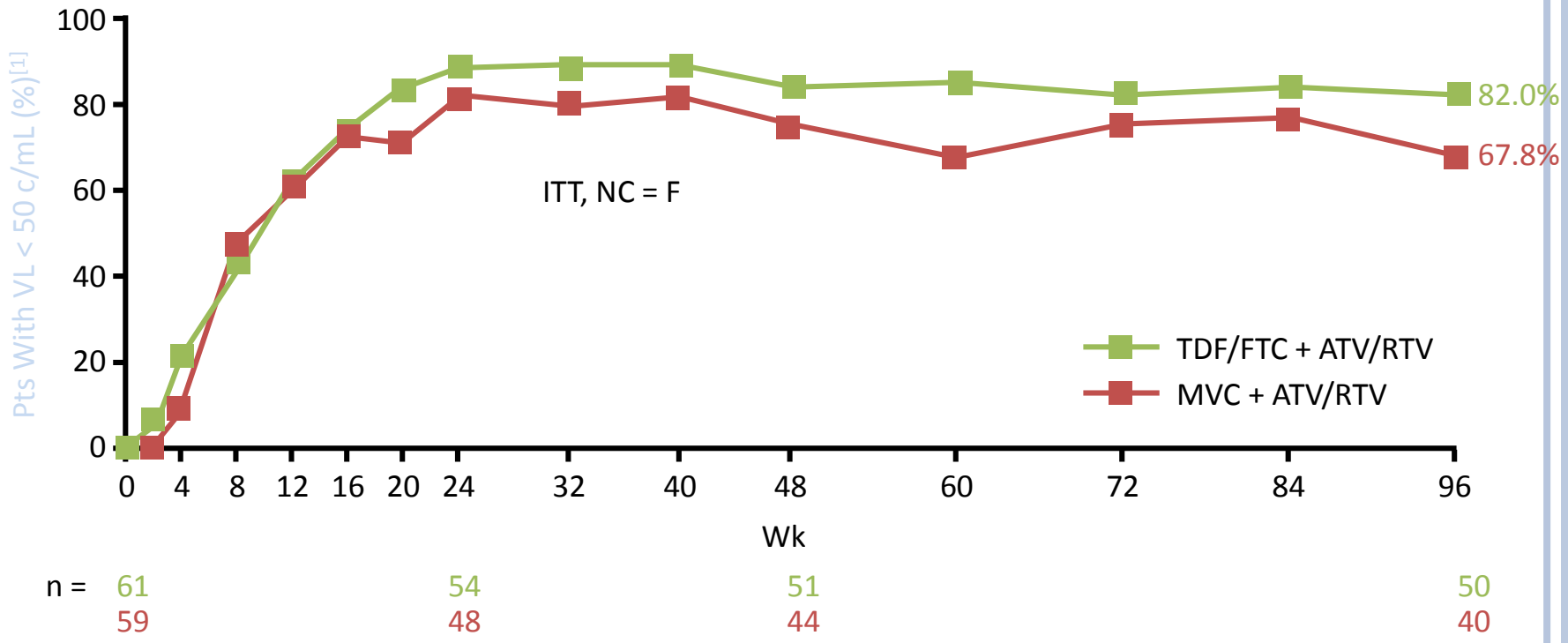
- Open-label phase IIb pilot study
  - Not powered to show treatment difference



*16 pts (27%) in NRTI-sparing arm and 22 pts (36%) in TDF/FTC arm had VL > 100,000 c/mL

Mills A, et al. AIDS 2012. Abstract TUAB0102.

A4001078: Virologic Suppression at Wk 96



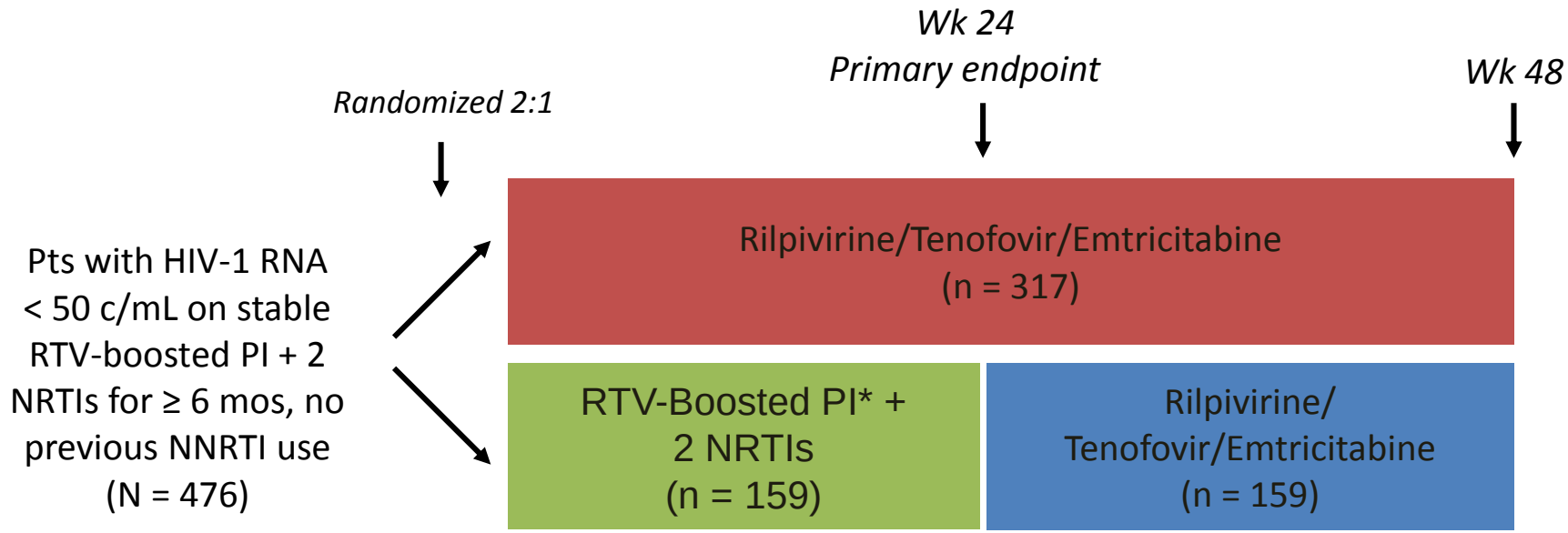
- All pts with detectable viremia at Wk 96 had intermittent periods of virologic suppression
- Grade 3 or 4 hyperbilirubinemia: 70% in MVC arm vs 56% in TDF/FTC arm

Mills A, et al. AIDS 2012. Abstract TUAB0102.

Cambios de tto

SPIRIT: Switch to RPV/TDF/FTC From Boosted PI Regimens in Suppressed Pts

- Multicenter, randomized, open-label switch study
  - 1º endpoint: maintenance of HIV-1 RNA < 50 c/mL at Wk 24 (snapshot analysis)

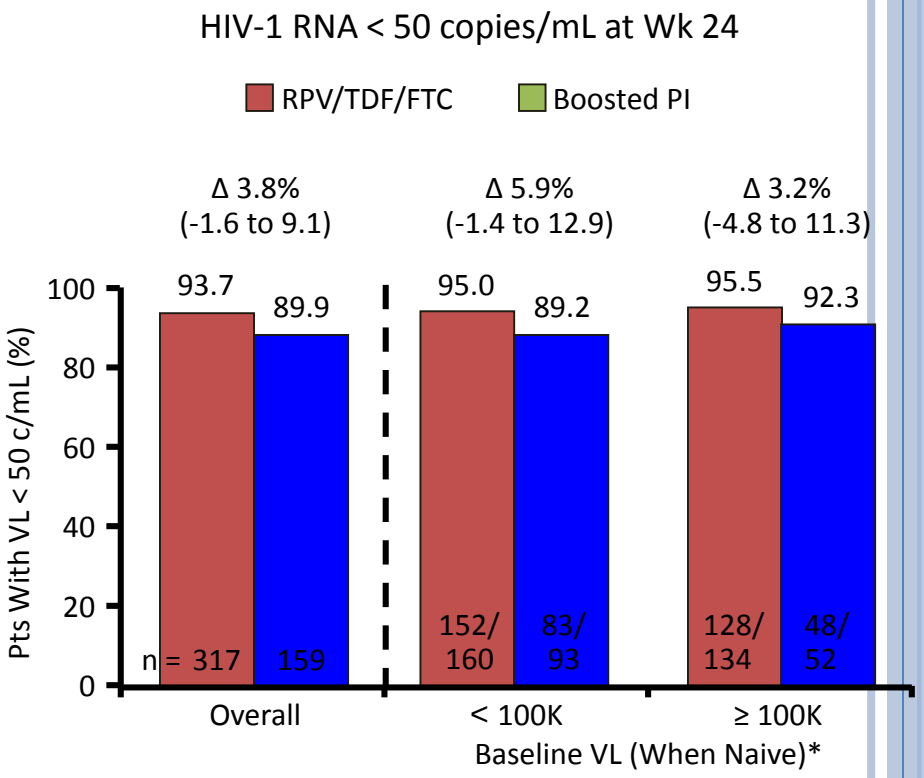


*PIs: ATV/RTV, 37%; LPV/RTV, 33%; DRV/RTV, 20%; FPV/RTV, 8%; SQV/RTV, 2%.

Fisher M, et al. Glasgow 2012. Abstract P285.

SPIRIT: Switch to RPV/TDF/FTC Noninferior to Continued Boosted PI

- Switch to RPV/TDF/FTC noninferior to maintaining boosted-PI regimen at Wk 24
  - 93.7% vs 89.9% with VL < 50 c/mL
  - Noninferiority observed regardless of pretreatment (naive) VL stratum
- All 17 pts with baseline K103N who switched to RPV/TDF/FTC maintained virologic suppression
- Significant reductions in TC, LDL, TG, HDL, TC:HDL ratio ($P < .001$) and in 10-yr Framingham score ($P = .001$) at Wk 24 among RPV/TDF/FTC switch pts

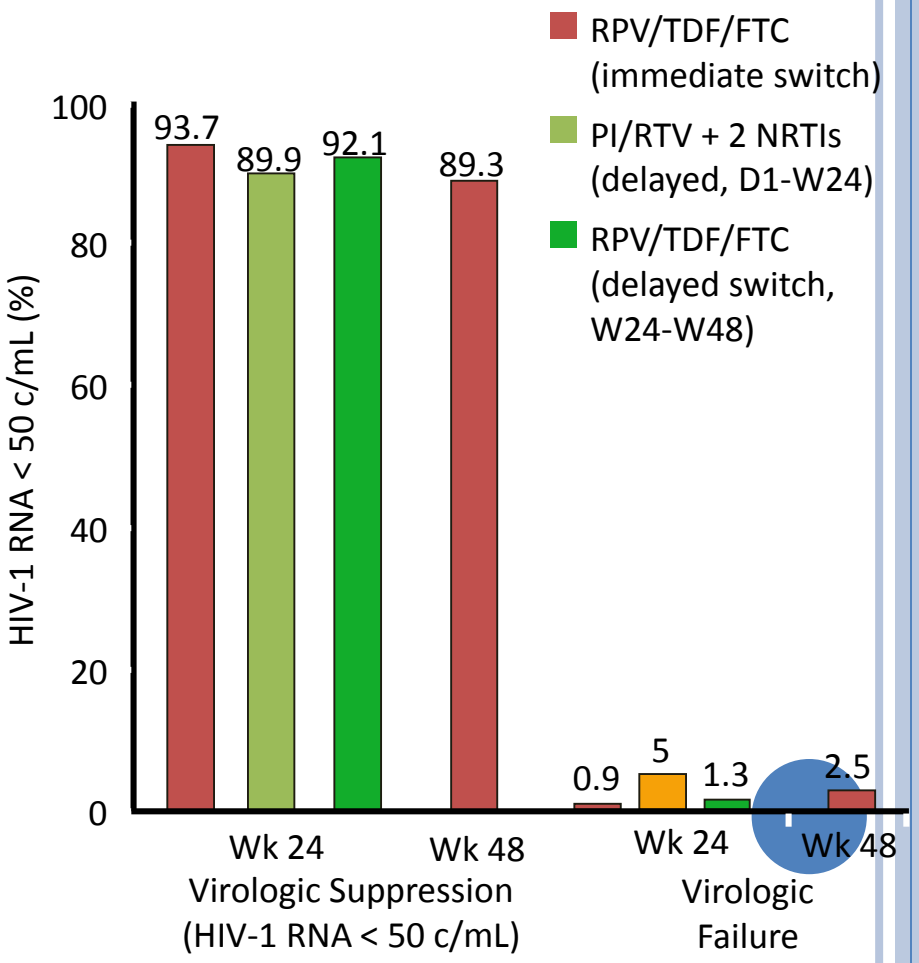


*Excludes 23 RPV and 14 boosted PI pts lacking baseline VL while ARV naive.

Palella F, et al. AIDS 2012. Abstract TUAB0104. Graphic reproduced with permission.

SPIRIT: Switch to RPV/TDF/FTC Noninferior to Continued Boosted PI

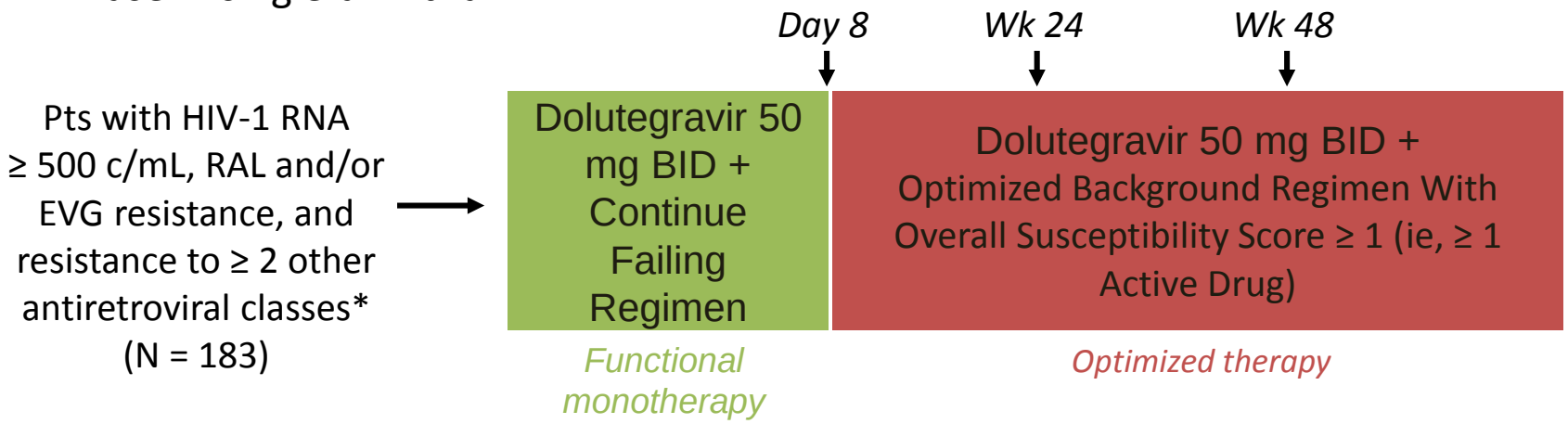
- Switch to RPV/TDF/FTC noninferior to continuing boosted PI regimen at Wk 24
  - 93.7% vs 89.9% with HIV-1 RNA < 50 c/mL
  - Maintained at Wk 48, but 5 additional cases of virologic failure between Wk 24 and 48
  - 17/18 pts with baseline K103N who switched to RPV/TDF/FTC maintained virologic suppression through Wk 48
- Switching associated with reductions in TC, LDL, TG, TC:HDL ratio



Fisher M, et al. Glasgow 2012. Abstract P285.

VIKING-3: Dolutegravir After Failure of Integrase Inhibitor–Based Regimen

- Phase III single-arm trial



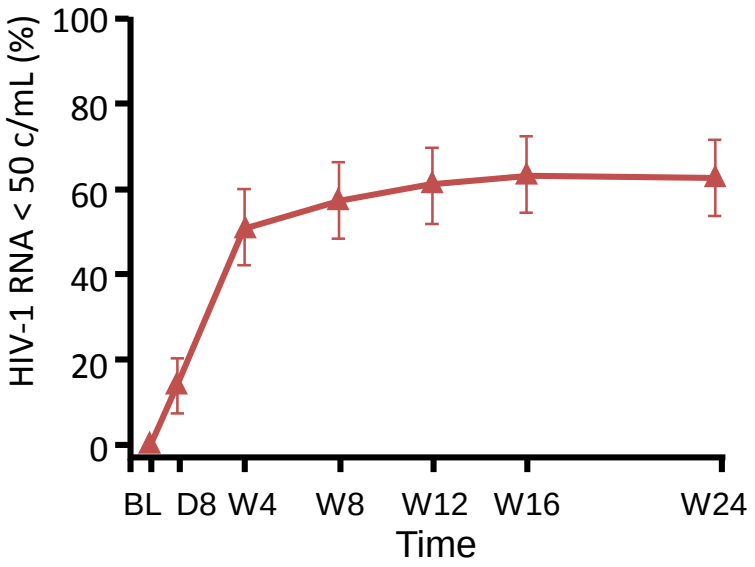
- Mean HIV-1 RNA change from baseline to Day 8
  - Overall: -1.4 $\log_{10}$ copies/mL ($P < .001$)
  - No primary integrase resistance mutations: -1.6 $\log_{10}$ copies/mL
  - Q148 + ≤ 1 secondary integrase resistance mutation: -1.1 $\log_{10}$ copies/mL
  - Q148 + ≥ 2 secondary integrase resistance mutations: -1.0 $\log_{10}$ copies/mL

*Detected at screening or based on historical evidence.

Nichols G, et al. Glasgow 2012. Abstract O232.

VIKING-3: Efficacy of Dolutegravir in INSTI-Experienced Pts at Wk 24

- 63% (72/114) of pts had HIV-1 RNA < 50 c/mL at Wk 24 (snapshot analysis)
  - Virologic nonresponse: 32%
  - Discontinuation for AEs: 4%
- Response rates affected by baseline INSTI resistance but not overall susceptibility score of background regimen

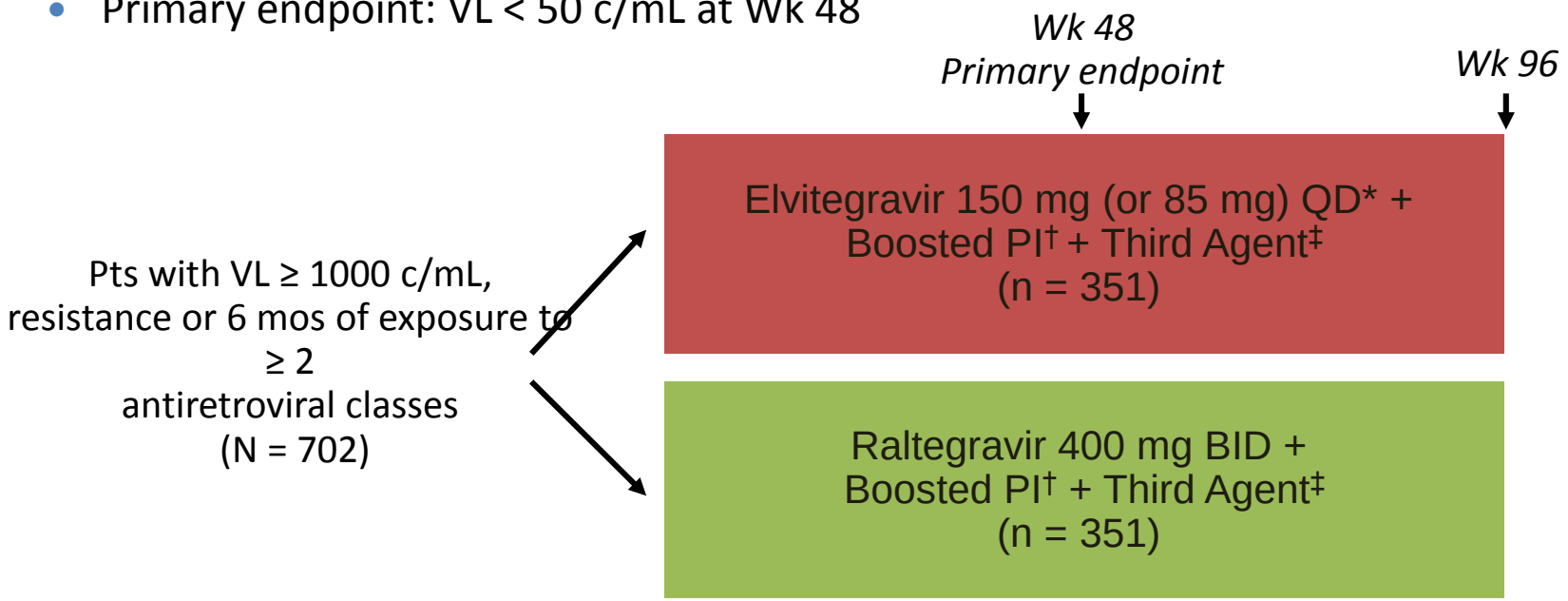


HIV-1 RNA < 50 c/mL at Wk 24 by INSTI Mutation(s), n/N (%)	Overall Susceptibility Score			
	0	1	≥ 2	Total
No Q148	2/2 (100)	24/29 (83)	31/41 (76)	57/72 (79)
Q148 + 1	2/2 (100)	3/7 (43)	4/11 (36)	9/20 (45)
Q148 + ≥ 2	1/2 (50)	0/7 (0)	0	1/9 (11)

Nichols G, et al. Glasgow 2012. Abstract O232.

Elvitegravir QD vs Raltegravir BID in ART-Exp Pts: Phase III Results at Wk 96

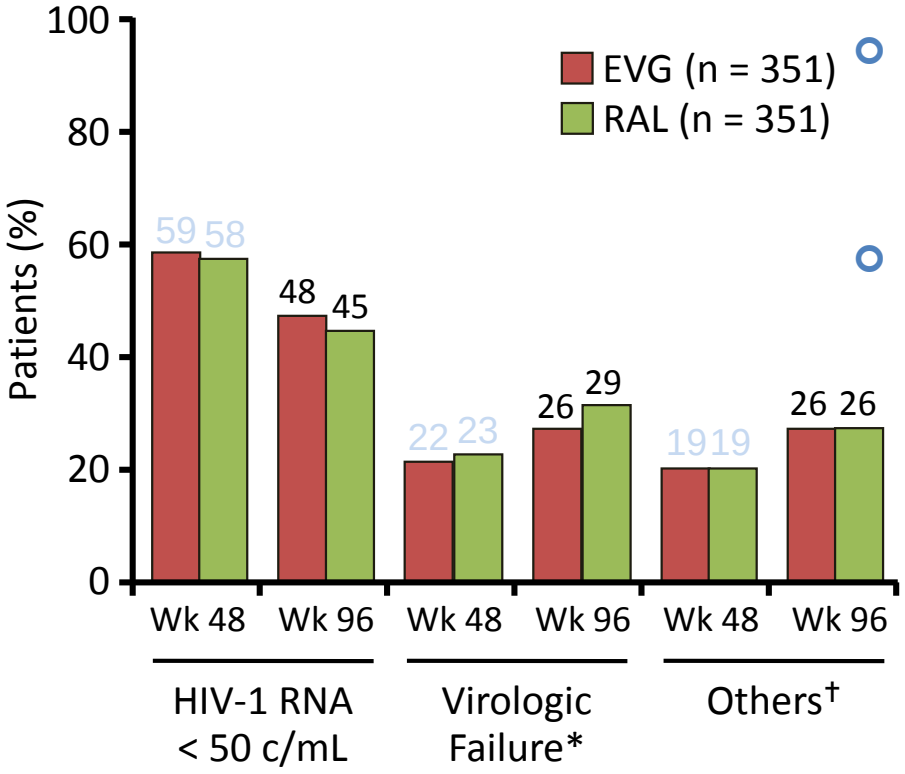
- Randomized, double-blind, placebo-controlled phase III trial
  - Primary endpoint: VL < 50 c/mL at Wk 48



*EVG dose reduced to 85 mg QD for patients taking ATV/RTV or LPV/RTV as part of background regimen.
†Background regimen to include fully active ritonavir-boosted PI, selected using resistance testing.
‡Third active agent selected from ENF, ETR, MVC, or NRTI. Option of also adding FTC or 3TC for patients with M184V/I.

Molina JM, et al. Lancet Infect Dis. 2012;12:27-35.

Elvitegravir Comparable to Raltegravir in Treatment-Experienced Pts at Wk 96



- CD4+ gain: +205 (EVG) vs +198 (RAL) at Wk 96
- Similar rates of treatment-emergent integrase resistance in each arm (7%)
- Similar rates of AEs overall
  - More diarrhea with EVG vs RAL (13% vs 8%)
  - More liver-related AEs leading to study d/c with RAL (1.7% vs 0.8%)

*Includes never suppressed, rebound, switch of background regimen, and discontinuation due to lack of efficacy
†Includes death, discontinuation due to AE, investigator's discretion, lost to follow up, pregnancy, protocol violation, noncompliance, withdrawal of consent.

Elion R, et al. AIDS 2012. Abstract TUAB105.

AGENDA

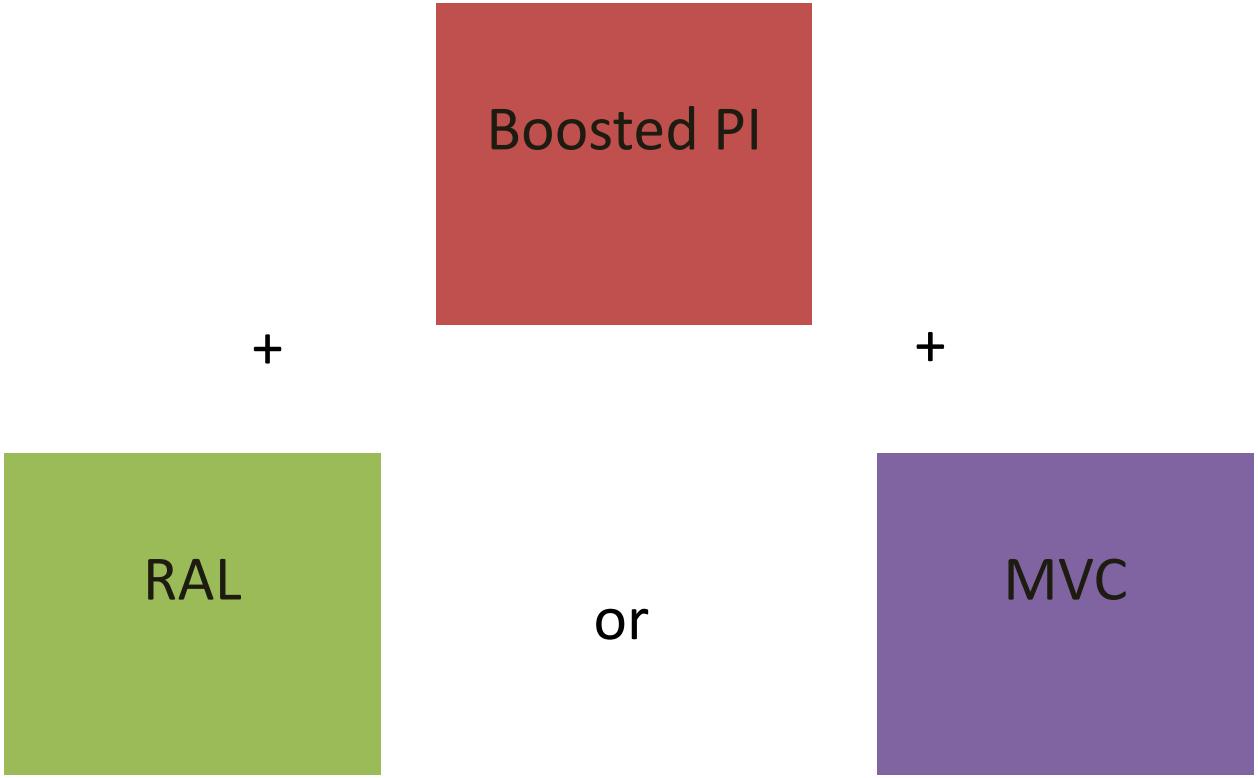
- Nuevas estrategias

NRTI-Sparing Regimens in Clinical Trials

Study	NRTI-Sparing Regimen	Standard of Care Comparator
A5142	Lopinavir/ritonavir + efavirenz	Lopinavir/ritonavir + 2 NRTIs Efavirenz + 2 NRTIs
PROGRESS	Lopinavir/ritonavir + raltegravir	Lopinavir/ritonavir + tenofovir/emtricitabine
CCTG589	Lopinavir/ritonavir + raltegravir	Efavirenz + tenofovir/emtricitabine
SPARTAN	Atazanavir + raltegravir	Atazanavir/ritonavir + tenofovir/emtricitabine
A4001078	Atazanavir/ritonavir + maraviroc	Atazanavir/ritonavir + tenofovir/emtricitabine
ACTG 5262	Darunavir/ritonavir + raltegravir	(single arm)
RADAR	Darunavir/ritonavir + raltegravir	Darunavir/ritonavir + tenofovir/emtricitabine

Riddler SA, et al. N Engl J Med. 2008;358:2095-2106.Reynes J, et al. HIV Clin Trials. 2011;12:255-267. Kozal MJ, et al. HIV Clin Trials. 2012;13:119-130. Portsmouth S, al. IAS 2011 Abstract TUAB0103. Taiwo B, Zheng L, Gallien S, et al. AIDS. 2011;25:2113-2122.Bedimo R, et al. IAS 2011 Abstract MOPE214. ClinicalTrials.gov. NCT01066962.

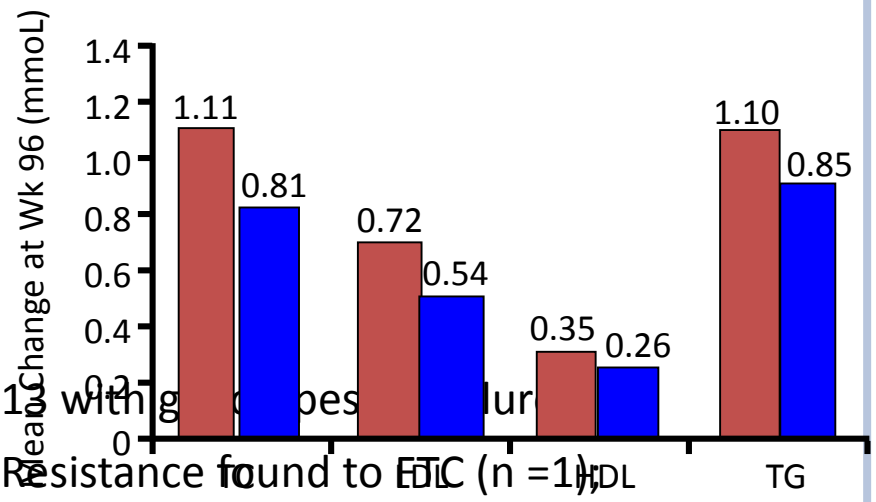
Clinical Trials of NRTI-Sparing Regimens in Treatment-Naive Patients



PROGRESS: LPV/RTV + RAL vs LPV/RTV + NRTIs in Treatment-Naive Patients

- Randomized, open-label, multicenter phase III trial of LPV/RTV BID + RAL BID (n = 101) or TDF/FTC QD (n = 105)
  - Low mean BL VL: 4.25 $\log_{10}$ c/mL
- HIV-1 RNA < 40 c/mL at Wk 96
  - LPV/RTV + RAL: 66%
  - LPV/RTV + NRTIs: 69%
- CD4+ cell count gain at Wk 96
  - LPV/RTV + RAL: + 281 cells/mm^3
  - LPV/RTV + NRTIs: +296 cells/mm^3

- Mean lipid increases numerically higher in NRTI-sparing arm



- 1 with g[illegible]bes[illegible]ur
- Resistance found to FTC (n =1); RAL (n = 2); RAL + LPV (n = 1)

Malave MD, et al. IDSA 2011. Abstract 406

Other NRTI-Sparing Trials With RAL in Treatment-Naive Pts

Study	Arms	Virologic Outcomes HIV-1 RNA < 50 copies/mL	Other Outcomes
SPARTAN[1] (N = 94)	**ATV** 300 mg BID + **RAL** 400 mg BID (n = 63)	Wk 24 (CVR, NC = F): **74.6%**	▪ 4/11 pts with resistance to RAL at VF of NRTI-sparing arm vs 0/8 with ARV resistance in NRTI arm. Trial ended at Wk 24 due to resistance and grade 4 bilirubin abnormalities in RAL arm (21%)
	ATV/RTV 300/100 mg QD + **TDF/FTC** 300/200 mg QD (n = 31)	Wk 24 (CVR, NC = F): **63.3%**	
ACTG 5262[2] (N = 112)	**DRV/RTV** 800/100 mg QD + **RAL** 400 mg BID (single arm)	VF at Wk 48: 26.0%	▪ VF associated with baseline VL > 100,000 c/mL: HR: 3.76 (95% CI: 1.52-9.31; *P* = .004) ▪ 5/25 VFs with genotypes had integrase mutations; all had baseline VL > 100,000 c/mL
RADAR[3] (N = 80)	**DRV/RTV** 800/100 mg QD + **RAL** 400 mg BID (n = 40)	Wk 24 (NC = M): **86.2%**	▪ Lipid changes from BL to Wk 24 numerically greater in the RAL arm than in the TDF/FTC arm ▪ Serum creatinine increased 0.06 mg/dL in both groups
	DRV/RTV 800/100 mg QD + **TDF/FTC** 300/200 mg QD (n = 40)	Wk 24 (NC = M): **87.9%**	

1. Kozal MJ, et al. AIDS 2010. Abstract THLBB204. 2. Taiwo B, et al. CROI 2011. Abstract 551.
3. Bedimo R, et al. IAS 2011. Abstract MOPE214.

NRTI-Sparing Trial With MVC in Treatment-Naive Pts

Study	Arms	Virologic Outcomes HIV-1 RNA < 50 copies/mL	Other Outcomes
A4001078 (N = 120)	**ATV/RTV** 300/100 mg QD + **MVC** 150 mg QD (n = 60)	Wk 48: **74.6%** (ITT)	▪ No emergent resistance mutations detected among 6 pts with virologic failure ▪ No evidence of change in tropism among pts failing MVC ▪ Frequency of all-grade adverse events similar between arms ▪ Grade 3/4 adverse events, including hyperbilirubinemia, numerically higher in MVC arm
	ATV/RTV 300/100 mg QD + **TDF/FTC** 300/200 mg QD (n = 61)	Wk 48: **83.6%** (ITT)	

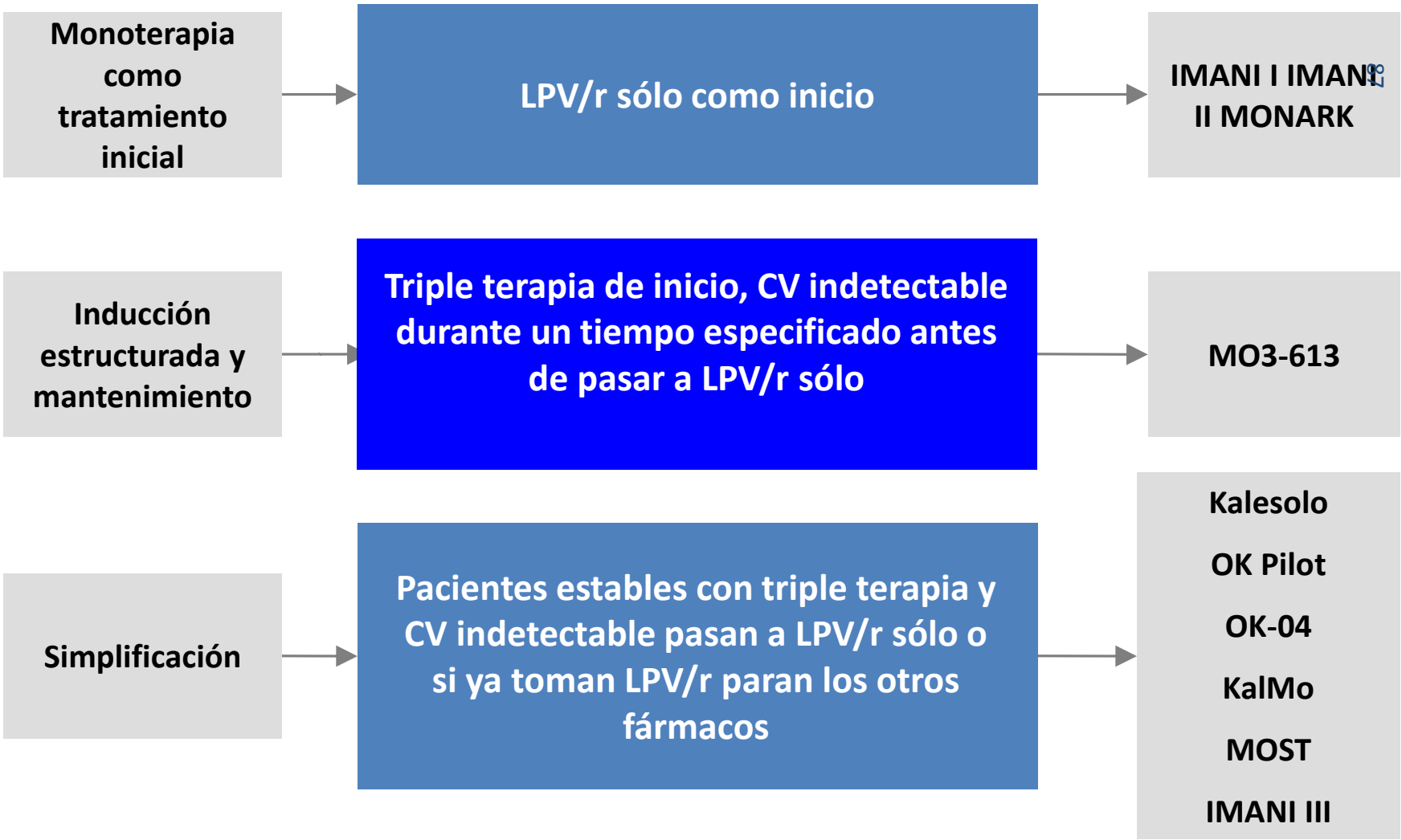
Portsmouth S, et al. IAS 2011. Abstract TUAB0103.

¿Por qué plantear monoterapia con IPs?

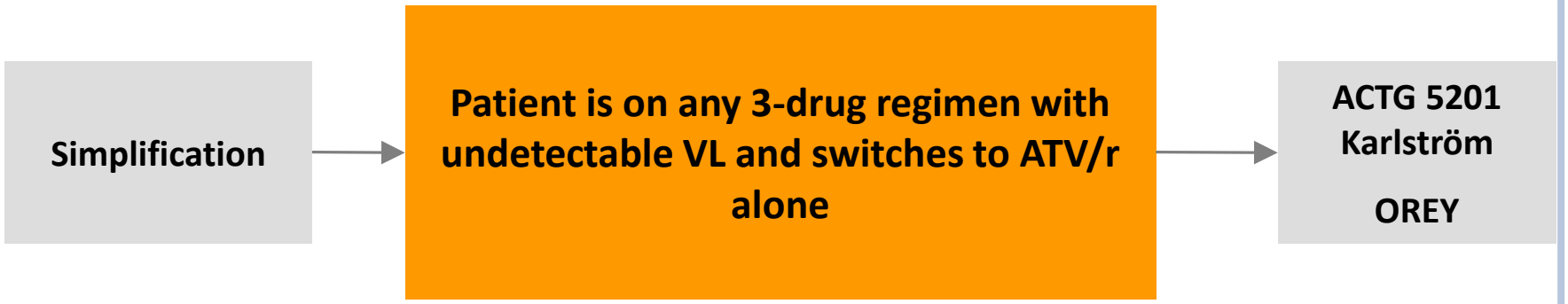
- Preservar futuras opciones de tratamiento
- Mejorar costo-eficacia
- Mejorar y reducir la toxicidad a corto y largo plazo

- La monoterapia necesita demostrar eficacia equivalente al tratamiento habitual antes de ser considerada como una opción de tratamiento

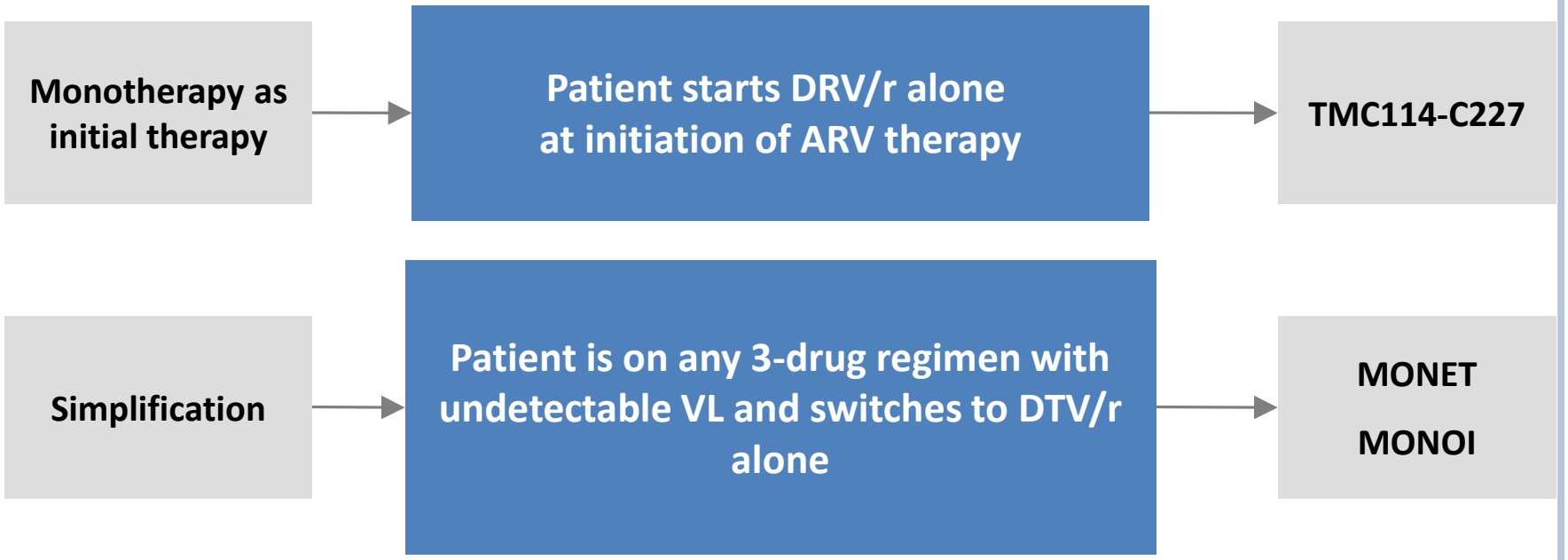
MONOTERAPIA CON LPV/R



Monotherapy with ATV/r



Monotherapy with DRV/r

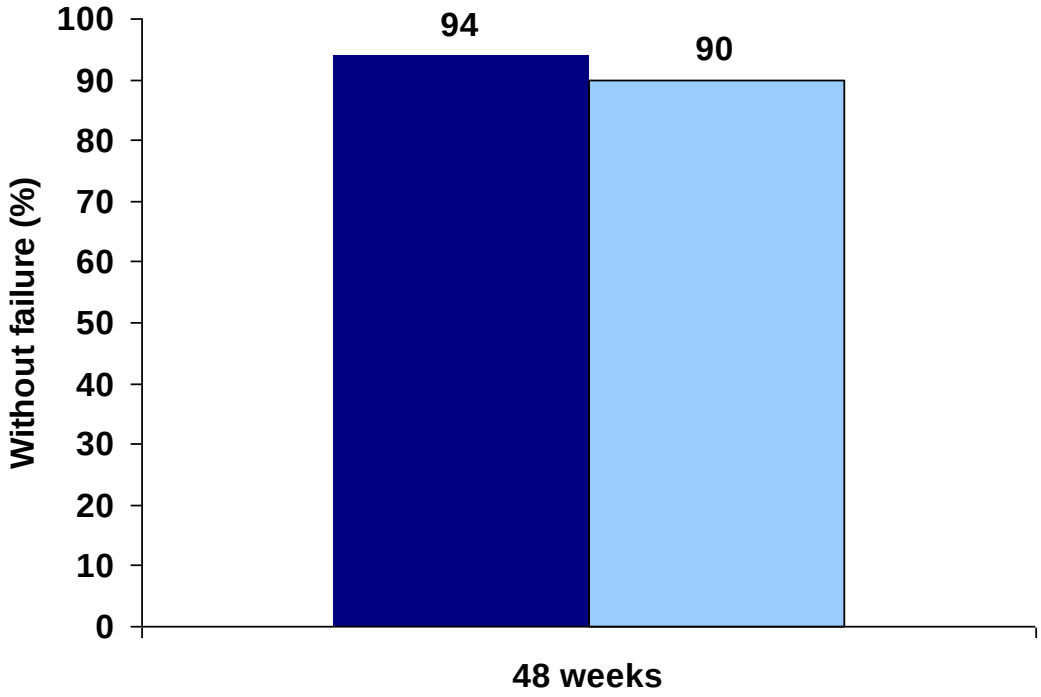


ENSAYOS CLÍNICOS CON IP EN MONOTERAPIA

fármaco	ensayo	Referencia bibliográfica
LPV/r	IMANI 1	Gathe J, et al. *XV IAC,* Bangkok 2004, #MoOrB1057
	IMANI 2	Gathe J, et al. *4th IAS,* Sydney 2007, #WePEB034
	IMANI 3	Gathe J, et al. *12th EACS*, Cologne 2009, #PS4/5
	MONARK	Delfraissey JF, et al. *AIDS* 2008;22:385–393
	M03-613	Cameron W, et al. *J Infect Dis* 2008;198:234–240
	OK Pilot	Arribas J, et al. *J AIDS* 2005;40:280–287
	OK-04	Pulido F, et al. *AIDS* 2008;22:F1–9
	KalMo	Nunes EP, et al. *XVI IAC*, Toronto 2006, #TuAB0102
	MOST	Gutmann LT, et al. *16th CROI*, Montreal 2009, #L-189
	Kalesolo	Meynard J et al, *J Antimicrob Chemother* 2010, Sep 15, epub
DRV/r	MONET	Arribas J, et al. *AIDS* 2010;24:223–230
	MONOI	Katlama C, et al. *5th IAS,* Cape Town 2009, #WeLBB102
	TMC114-C227	Patterson P, et al. *12th EACS*, Cologne 2009, #PS4/4
ATV/r	ACTG 5201	Wilkin T, et al. *J Inf Dis* 2009;199:866–871
	Karlstrom	Karlstrom O, et al. *J AIDS* 2007;44:417–422
	OREY	Pulido F, et al. *12th EACS,* Cologne 2009, #PS4/6
	ATARITMO	Vernazza P, et al. *AIDS* 2007;19:1309–1315

OK-04 Trial: Primary endpoint: Proportion without therapeutic failure at Wk 48* switch included

LPV/r showed non-inferiority to triple therapy in the switch-included analysis



Week 48 difference (Triple-OK)
95% CI: –4.2% (–11.8% to 3.4%)

OK arm: LPV/r monotherapy
Triple arm: LPV/r + 2 NRTIs

OK

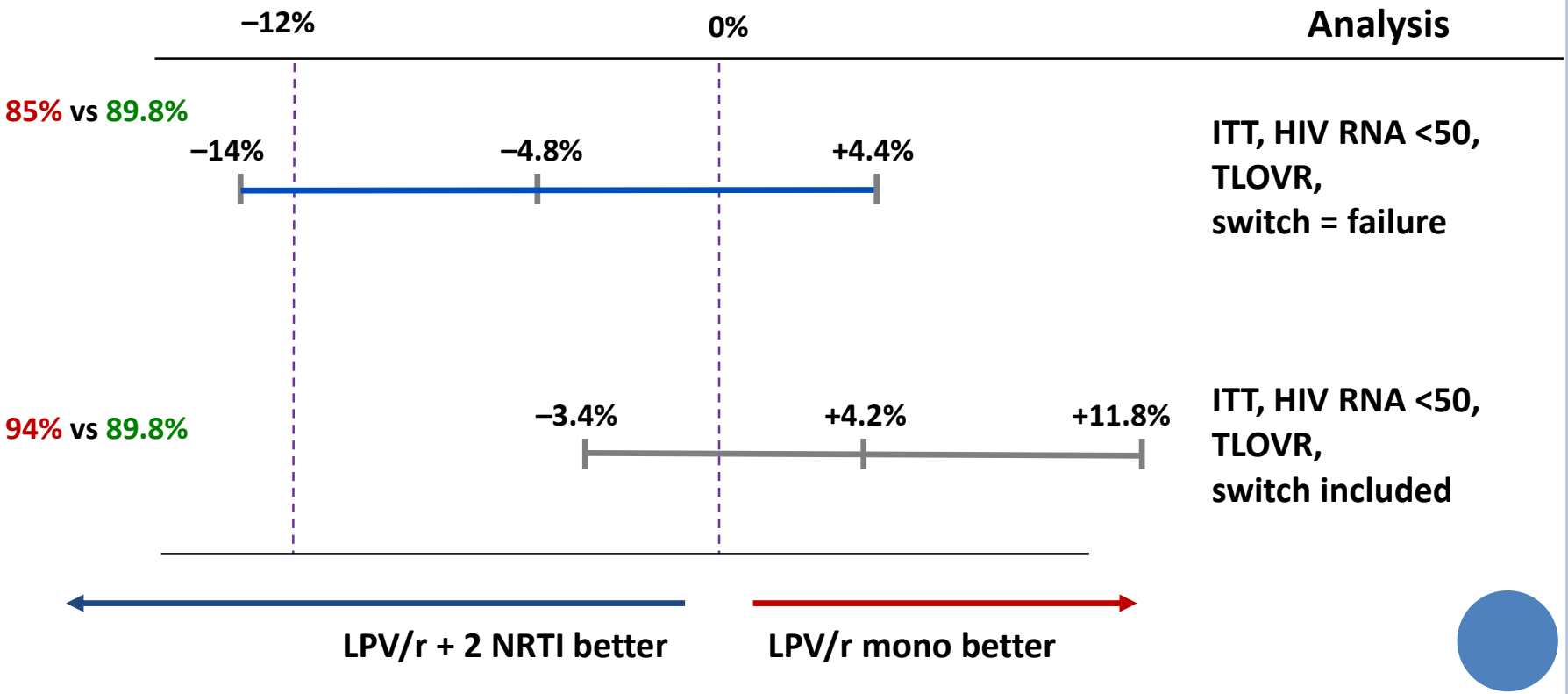
Triple

* Patients in the monotherapy arm who reached and maintained < 50 c/mL after resuming baseline nucleosides are not considered as failures (n = 4)

Pulido F, et al. *AIDS* 2008;22:F1–9

OK-04 Trial: Primary efficacy analysis at Week 48

Difference in Week 48 HIV RNA response rate between LPV/r mono and LPV/r + 2 NRTI arms (difference and 95% CI)



Adapted from Pulido F, et al. *AIDS* 2008;22:F1–9

OK-04 Trial: Genotypic testing through Week 48

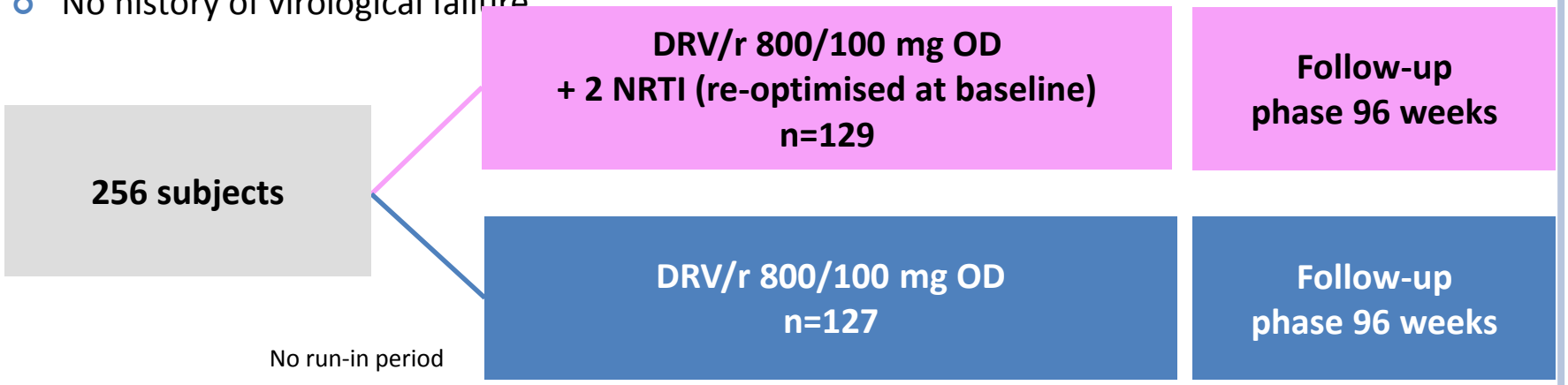
	OK (n=100) LPV/r monotherapy	Triple (n=98) LPV/r + 2 NRTIs
Genotyping population*	11 (11%)	4 (4%)
Isolates with primary PI mutations	2 (2%) [10F, 46I, 82A/V] [54V, 77I, 82A]	1 (1%) [54V, 63P, 71V, 82A]
Isolates without primary PI mutations	9 (9%)	3 (3%)

* All patients with HIV RNA >500 c/mL analysed (blips > 500 c/mL included).

Pulido F, et al. *AIDS* 2008;22:F1–9

MONET: Study design

- Taking 2 NRTIs + either NNRTI or boosted PI at screening (stratified)
- No prior use of darunavir (DRV)
- HIV RNA <50 c/mL for ≥6 months
- No history of virological failure

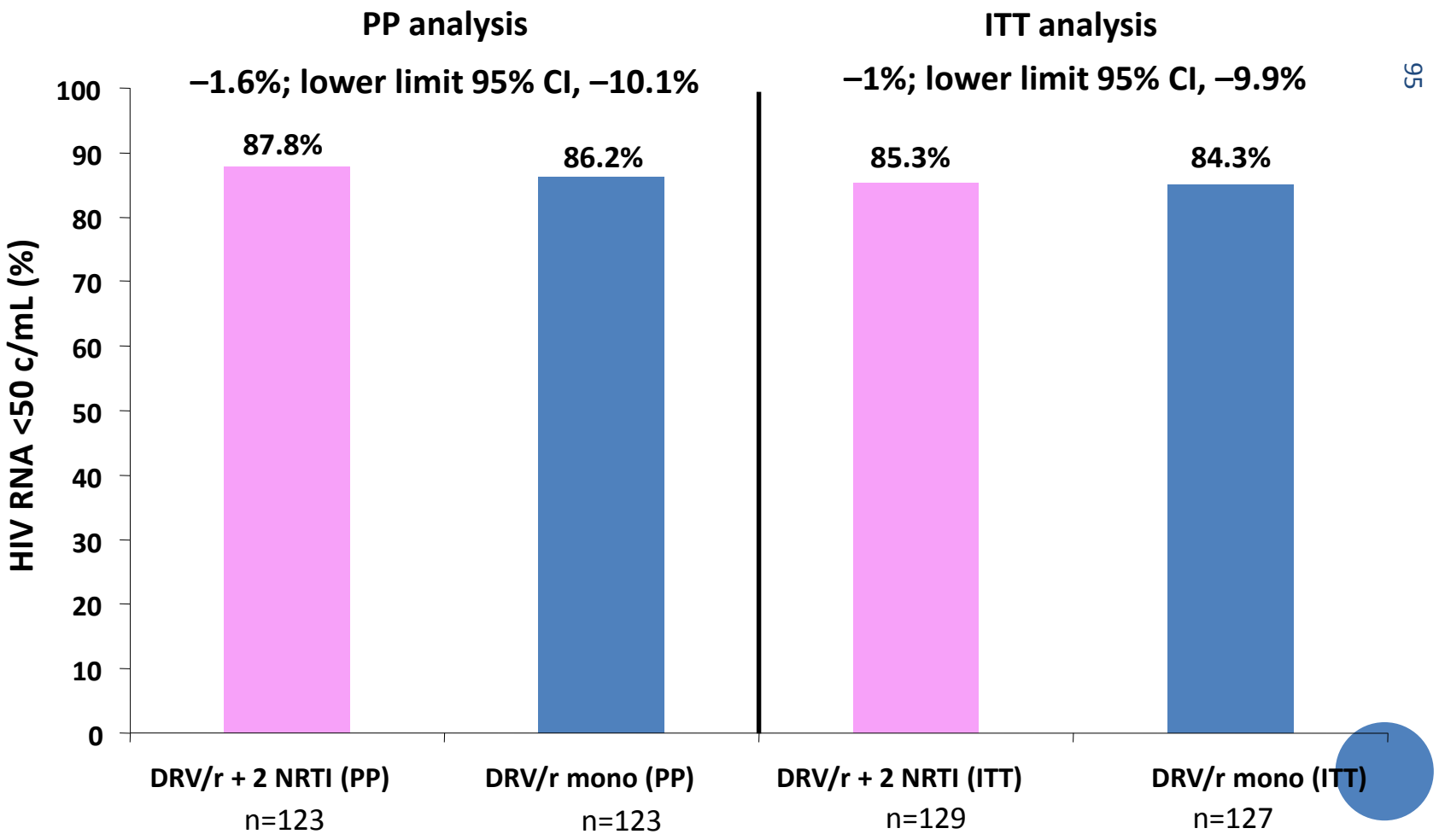


Primary endpoint: HIV RNA <50 at Week 48 (TLOVR); PP; switch = failure

- 2 consecutive HIV RNA >50 c/mL (Roche Amplicor HIV-1 Monitor assay 1.5)
- Stopping DRV/r
- Starting NRTIs in the monotherapy arm
- Stopping NRTIs in the triple-therapy arm (switches in NRTIs were permitted at any time)

Arribas J, et al. *AIDS* 2010;24:223–230

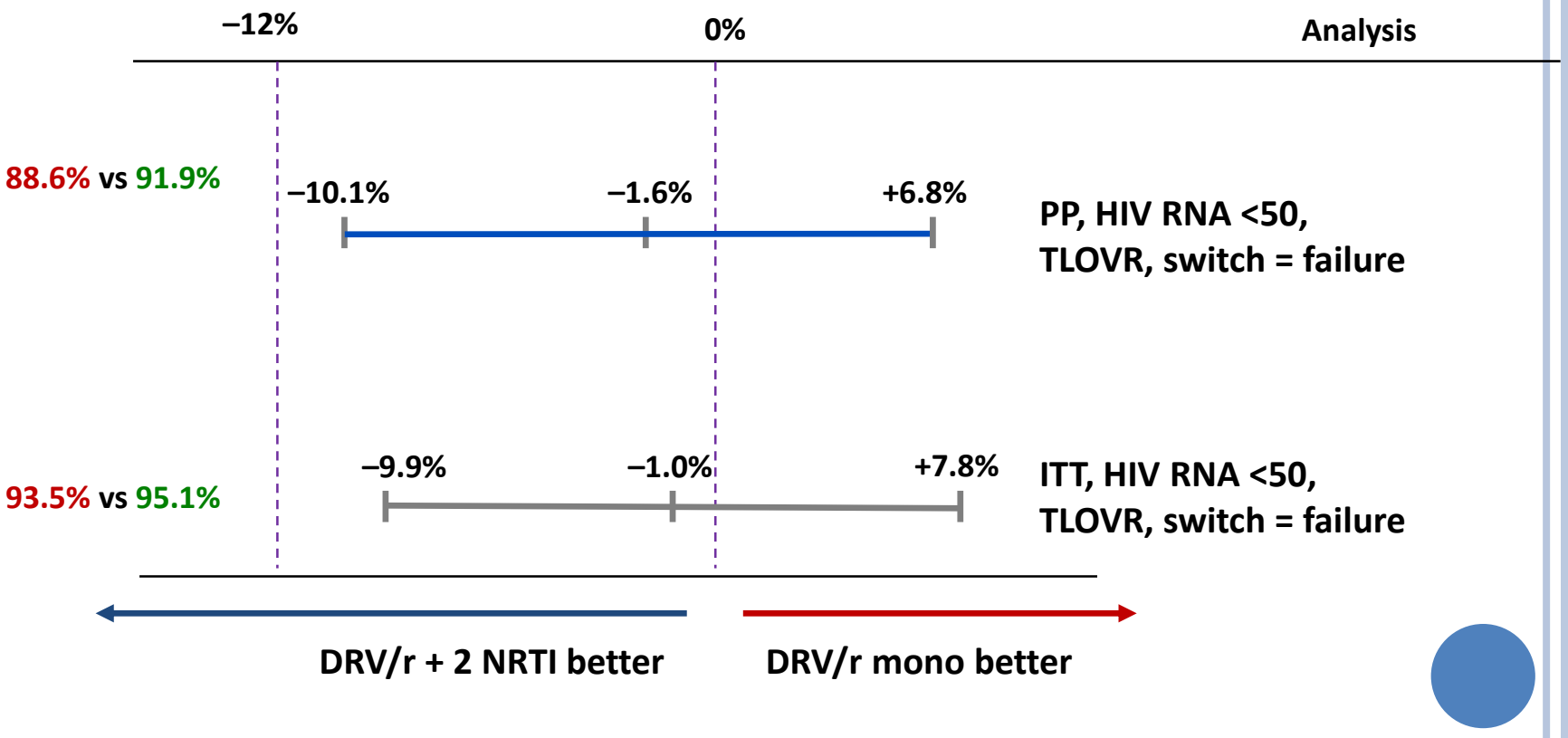
MONET: PRIMARY EFFICACY ANALYSIS



Arribas J, et al. *AIDS* 2010;24:223–230

MONET: Primary efficacy analysis at Week 48

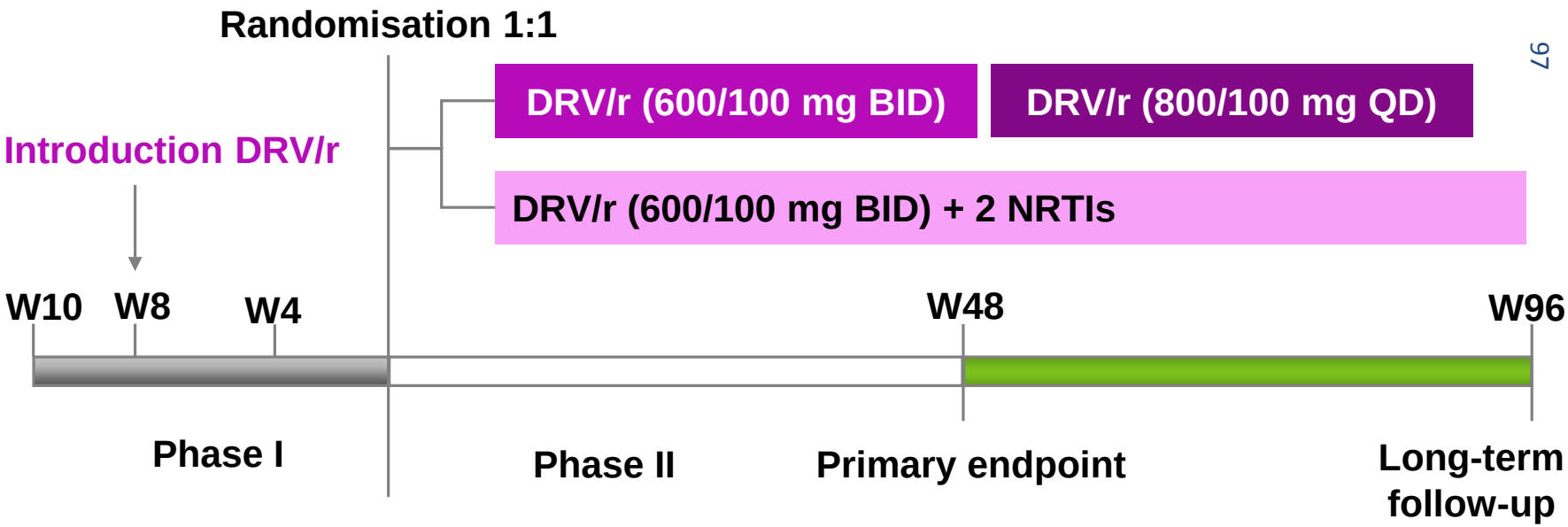
Difference in Week 48 HIV RNA response rate between DRV/r mono and DRV/r + 2NRTI arms (difference and 95% CI; univariate analysis)



Arribas J, et al. *AIDS* 2010;24:223–230

MONOI: STUDY DESIGN

Multicentre, open-label, randomised study



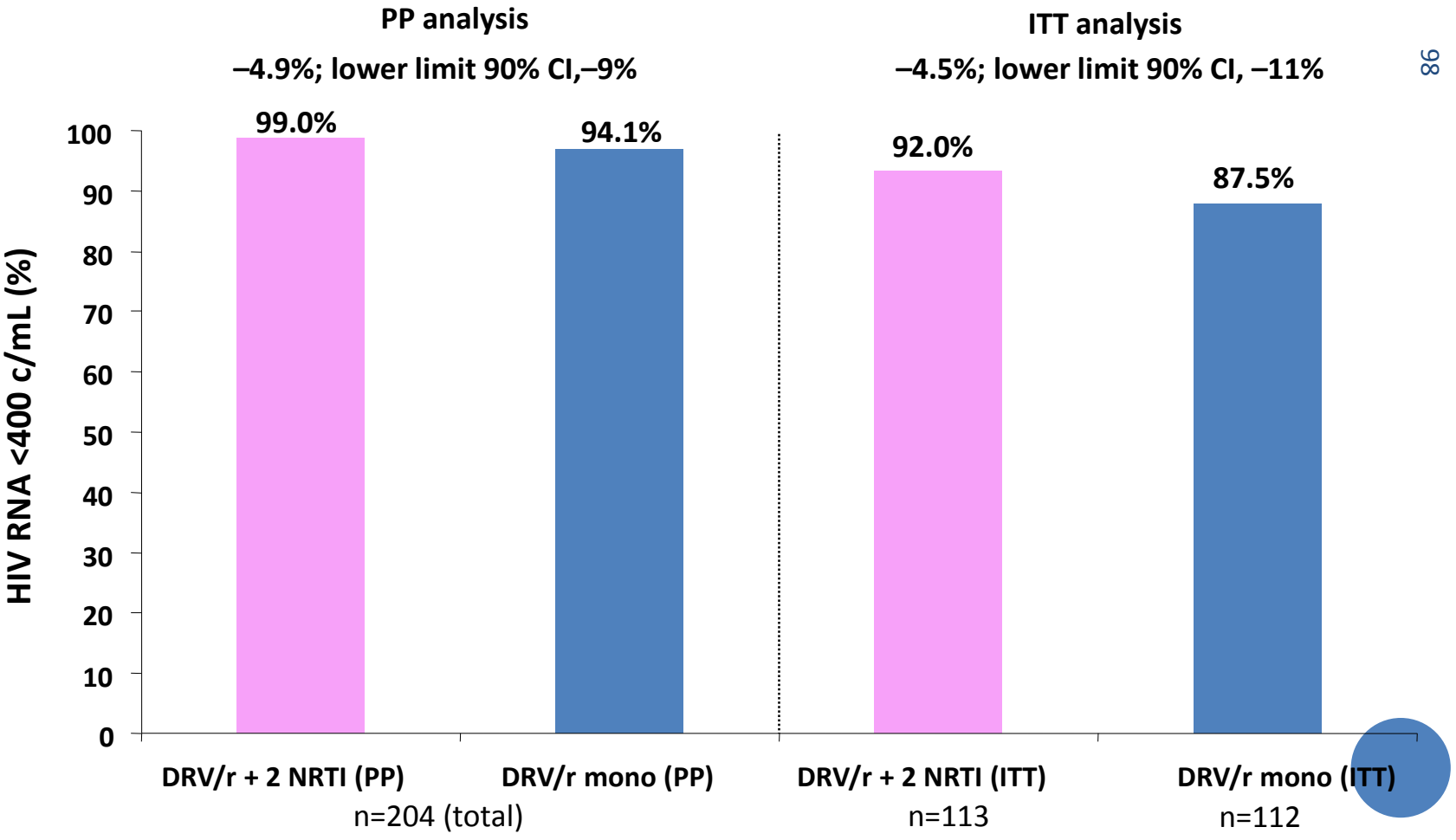
Main inclusion criteria

- HAART ≥18 months
- CD4 count ≥200 cells/mm^3
- HIV RNA <400 c/mL in the last 18 months and <50 c/mL at entry
- No history of PI failure and naïve to DRV

Katlama C, et al. AIDS 2010; 24:2365–2374

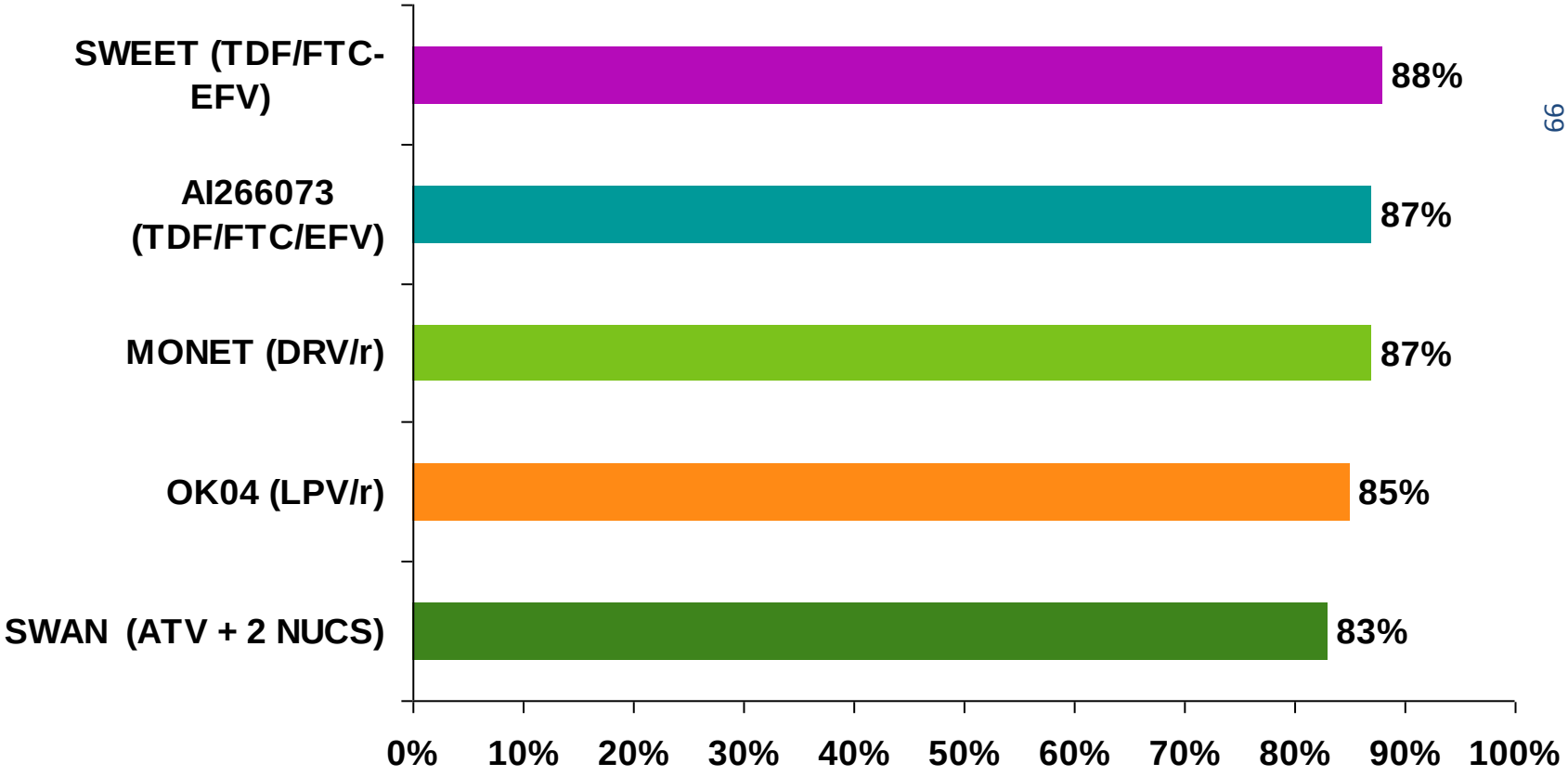
MONOI: PRIMARY EFFICACY ANALYSIS

HIV RNA <400 c/mL at Week 48, switch = failure



Katlama C, et al. *5th IAS*, Cape Town 2009, #WeLBB102

Recent simplification trials: Week 48 HIV RNA <50 c/mL by treatment arm (ITT, M = F)



Gatell J, et al. *Clin Infect Dis* 2007;44:1484–1489; Pulido F, et al. *AIDS* 2008;11:F1–9;
De Jesus E, et al. *48th ICAAC*, Washington DC 2008, #H-1234; Fisher M, et al. *11th EACS*, Madrid 2007, #PS5/7

HIV monotherapy with ritonavir-boosted protease inhibitors: a systematic review

Wo

Conclusion: The overall efficacy of ritonavir-boosted protease inhibitor monotherapy is inferior to HAART. The efficacy improves in patients started on monotherapy after suppressed HIV-RNA for at least 6 months. Ten percent of patients have viral rebound with HIV-RNA levels between 50 and 500 copies/ml. Possible explanations are lack of HIV suppression in particular cells or compartments, alternative resistance mechanisms, and nonadherence. Once proven that reintroduction of NRTIs, in patients with loss of viral suppression, is safe and effective, a broader use of simplification of HAART to protease inhibitor monotherapy might be justified. This review supports that the majority of patients with prolonged viral suppression on HAART can successfully be treated with protease inhibitor monotherapy. Arguments for this strategy are NRTI/NNRTI side effects, NRTI/NNRTI resistance, and costs.

AIDS 2009, **23**:279–291

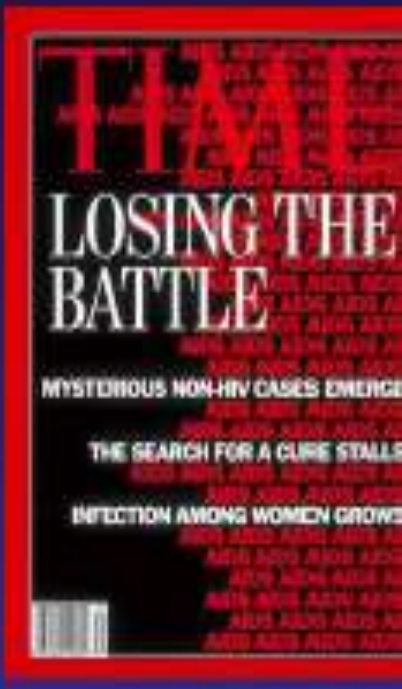
CONCLUSIONES

- Disponemos de tratamientos antirretrovirales muy eficaces y seguros que nos permiten:
  - Distintas combinaciones
  - Distintas estrategias
    - Bi
    - Monoterapia
- Necesitamos continuar con investigación para optimizarlos


TIME
DISEASE DETECTIVES

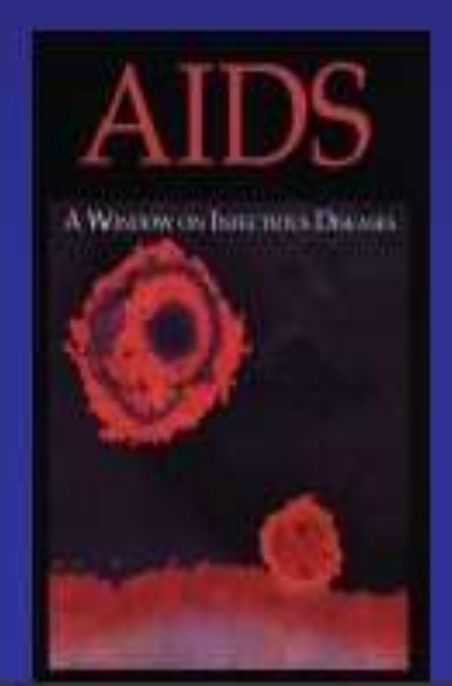

TIME
AIDS
The Growing Threat
What's Being Done


TIME
THE BIG CHILL
How Heterosexuals Are Coping with AIDS


LOSING THE BATTLE


Magic!


TIME
MAN OF THE YEAR


AIDS

The Economist


Gracias por la atención