“L’infettivologia del 3° millennio: AIDS ed altro”

VI Convegno Nazionale

15-17 maggio 2014

Paestum

“Single Tablet Regimen: la terapia ideale?”

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Università di Catania

6th Infectivology Today®

Sopravvivenza pazienti HIV+ in ART

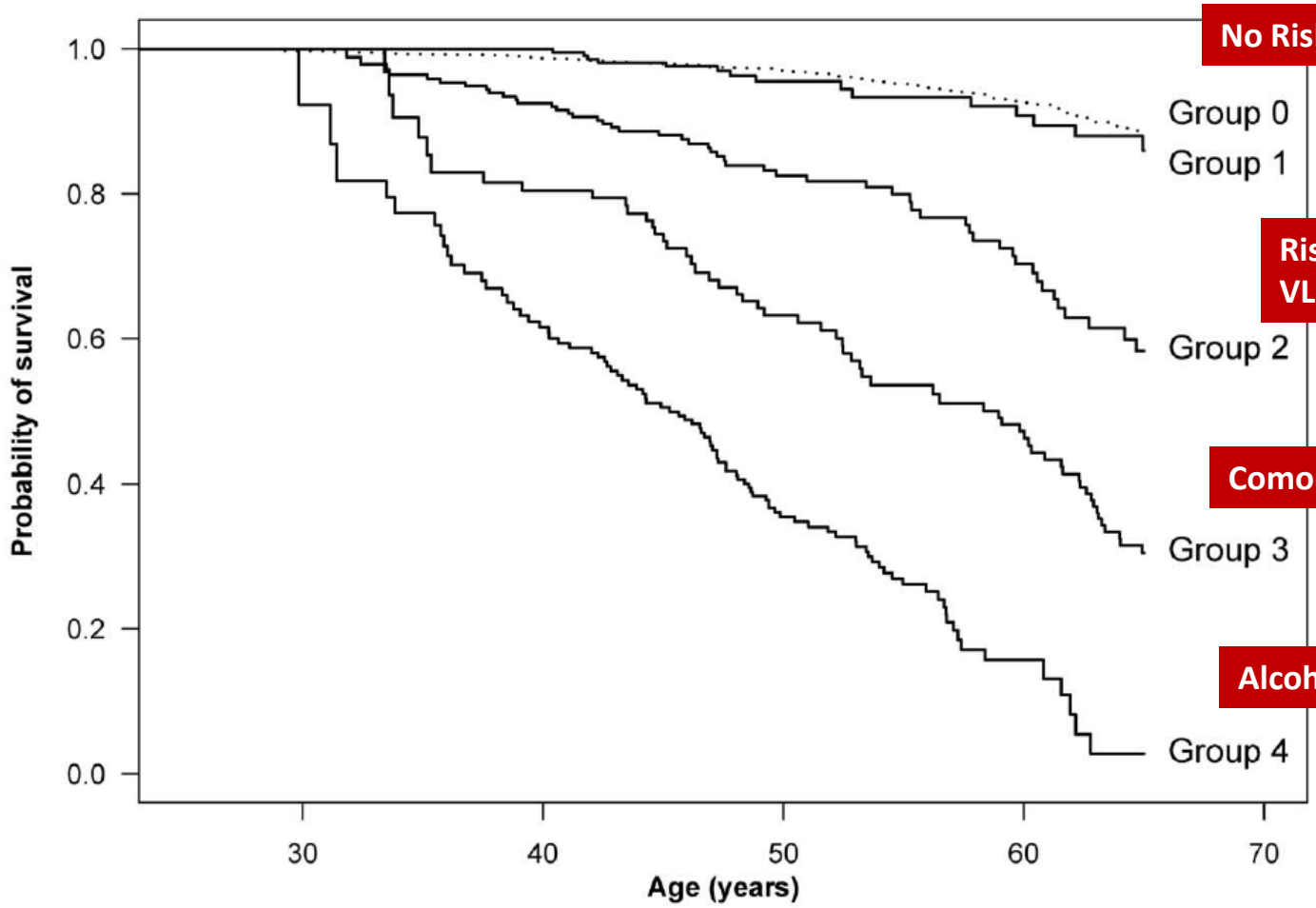
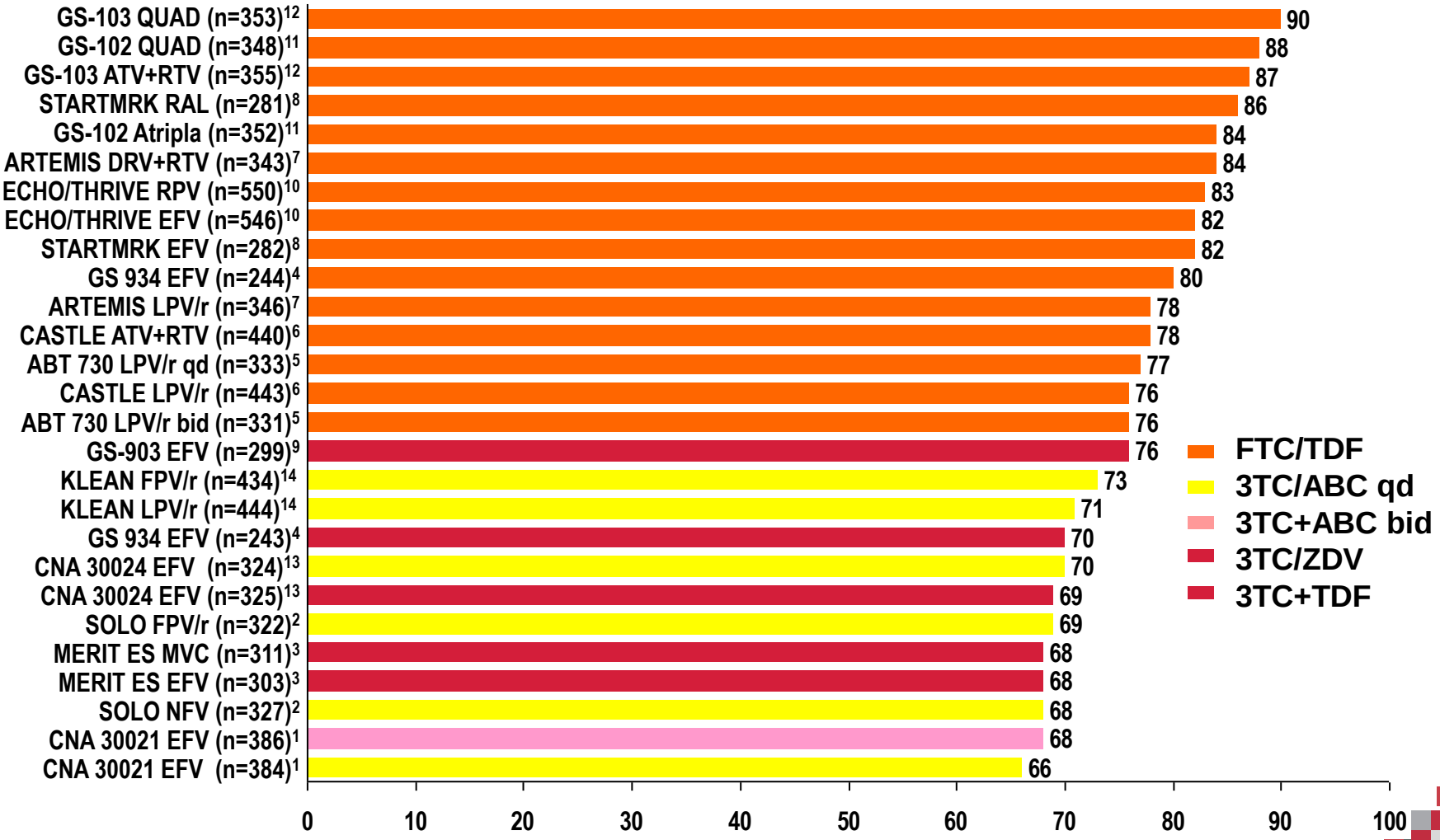


Figure 1. Cumulative survival for HIV-infected patients starting HAART and persons from the general population. Time was calculated from 1 year after start of HAART. The study population was categorized as: Group 0: Population comparison cohort (dotted line, N = 9,068). Group 1: HIV-infected patients without HIV risk factors, comorbidity or alcohol/drug abuse (N = 871). Group 2: HIV-infected patients with HIV risk factors, but no comorbidity or alcohol/drug abuse (N = 704). Group 3: HIV-infected patients with comorbidity, but no alcohol/drug abuse (N = 379). Group 4: HIV-infected patients with alcohol/drug abuse (N = 313). *HIV risk factors:* detectable viral load (>49 copies/ml) and/or CD4 below 200 cells/ul at the last measurement prior to the index date and/or AIDS- defining disease as of the index date. *Comorbidity:* diagnosed with comorbidity as defined in the Charlson Comorbidity Index before index date. *Abuse:* diagnosed with drug or alcohol abuse before index date or reporting drug abuse as route of HIV transmission.

doi:10.1371/journal.pone.0022698.g001

Registrational Treatment-Naive Clinical Trials: Cross-Study Comparison*

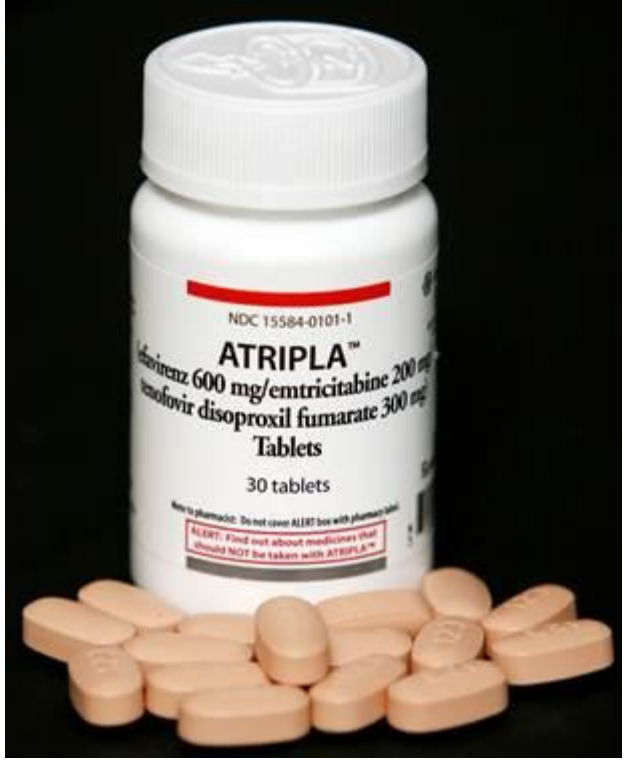
HIV RNA <50 c/mL at Week 48



Current ART

What can be improved?

- Virological efficacy
- Resistance
- Tolerability
- Long term toxicity
- Convenience
- Cost

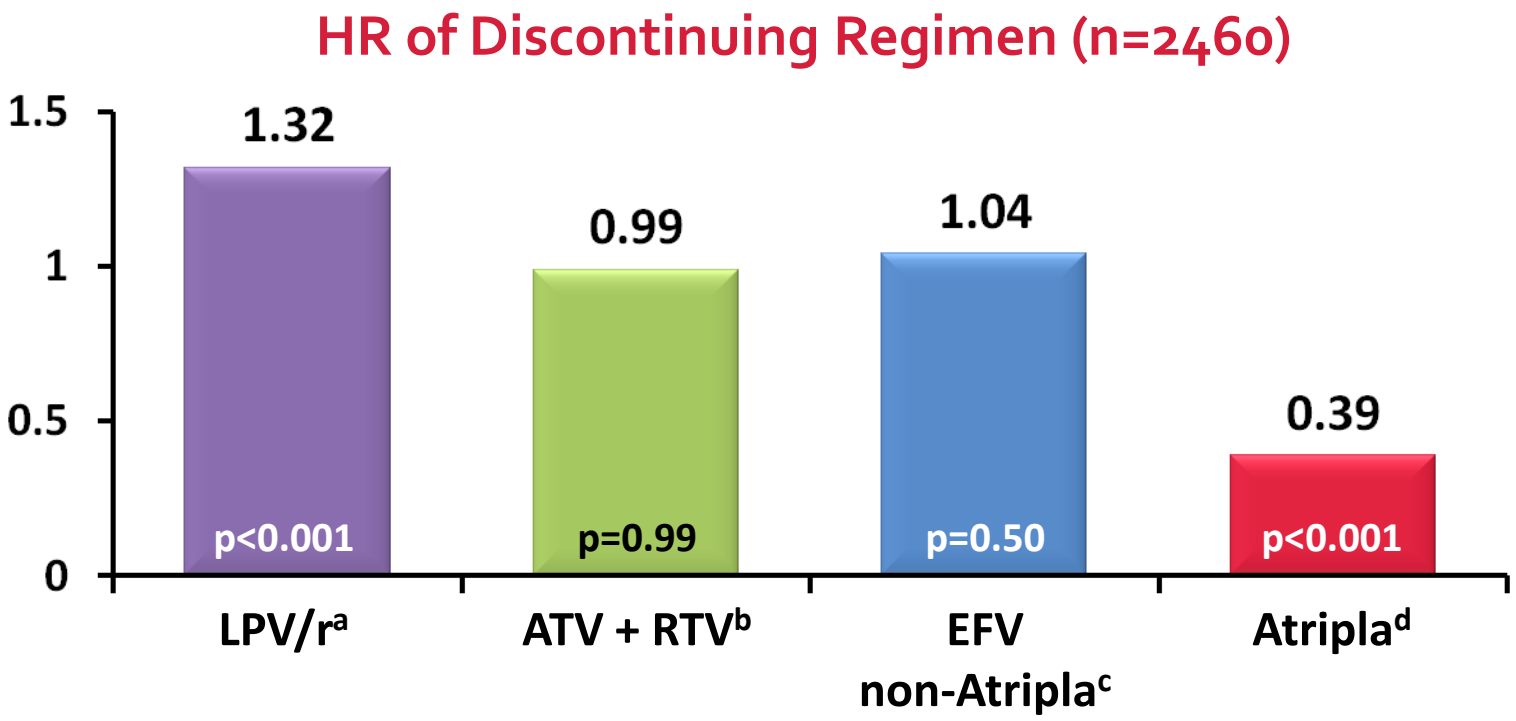

NDC 15584-0101-1
ATRIPLA™
Tablets
30 tablets


Eviplera®
200 mg/25 mg/245 mg
film-coated tablets
emtricitabine/rilpivirine/
tenofovir disoproxil
30 film-coated tablets.
Oral use.
Gilead Sciences Intl Ltd
Cambridge
CB21 6GT
United Kingdom
GILEAD
Eviplera®
200 mg/25 mg/245 mg
film-coated tablets
emtricitabine/rilpivirine/
tenofovir disoproxil
30 film-coated tablets.
Oral use.
EU/1/11/737/001
GILEAD


Stribild®
150 mg/150 mg/
200 mg/245 mg
film-coated tablets
Elvitegravir/cobicistat/
emtricitabine/
tenofovir disoproxil
30 film-coated tablets
Oral use
GILEAD
Stribild®
150 mg/150 mg/
200 mg/245 mg
GILEAD

Differences in Discontinuation Risk of Specific Regimens vs EFV/FTC/TDF Single Tablet Regimen

Retrospective cohort using US claims data from the PharMetrics Integrated Outcomes Database; N=37,244 HIV patients (1/03–12/08)



- **Atripla had 61% lower discontinuation rate vs. all other regimens**

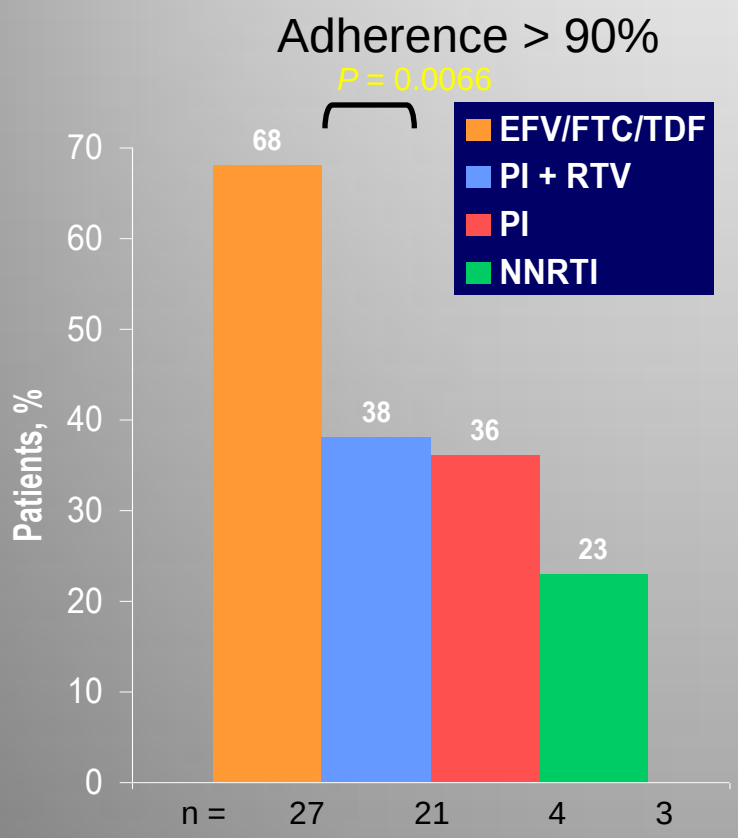
Reference regimen for HR is: a) regimens without LPV/r; b) regimens without ATV ± RTV; c) regimens without EFV; d) all regimens other than Atripla

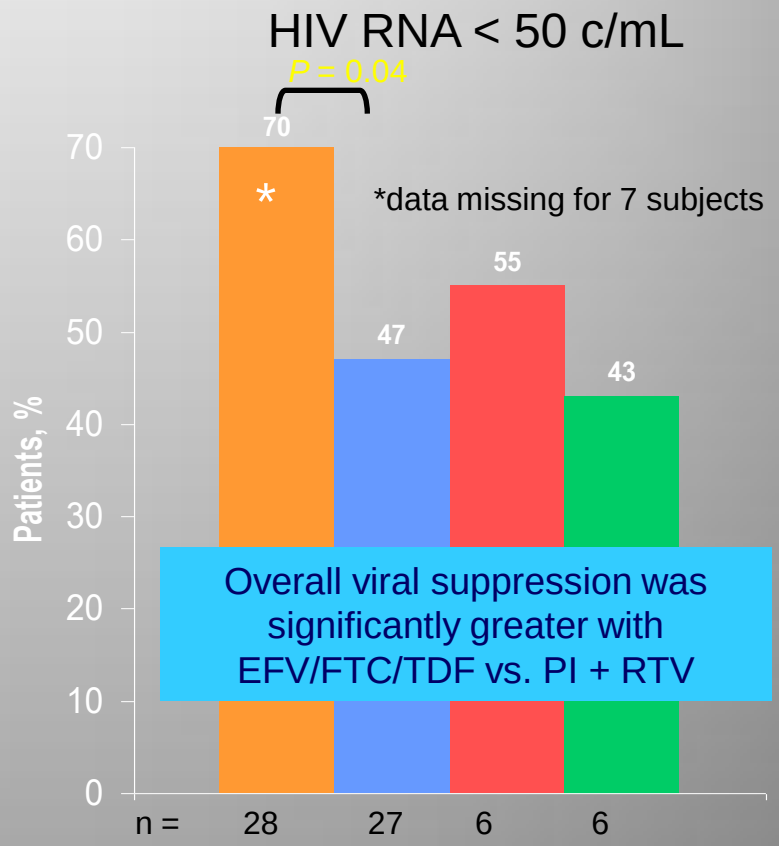
Juday T, *et al. AIDS Care* 2011;23(9):1154–62

REACH Cohort Adherence Study

Adherence and Efficacy Results

Patients recruited from a cohort of HIV+ homeless and marginally housed individuals and from public health clinics in San Francisco





"Simplification of therapy represents an important step forward in supporting adherence and treatment success."

Bangsberg D, et al.

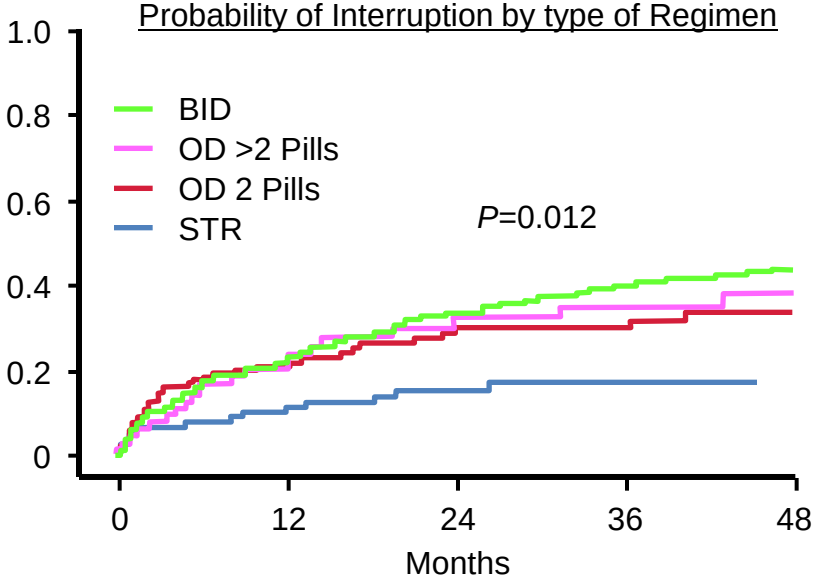
Durability and Persistency of STRs

Reduced Risk of Treatment Interruption

Retrospective evaluation of STR formulations impact on drug interruptions in 2 Italian centres for 533 patients starting EFV (May 1998 to March 2012)

- **Primary endpoint: discontinuation of EFV for different reasons (virological failure [VF], side effects, central nervous system side effects [CNS-SE] or any other cause)**

Probability of Interruption by type of Regimen



% Patients with Treatment Interruption

Cause of Interruption (%)	STR	Non-STR	p-value
VF	0	9	0.05
CNS adverse effects	13	7	NS
Patient decision	2	12	0.01

Adjusted HR for Treatment Interruption (any cause)

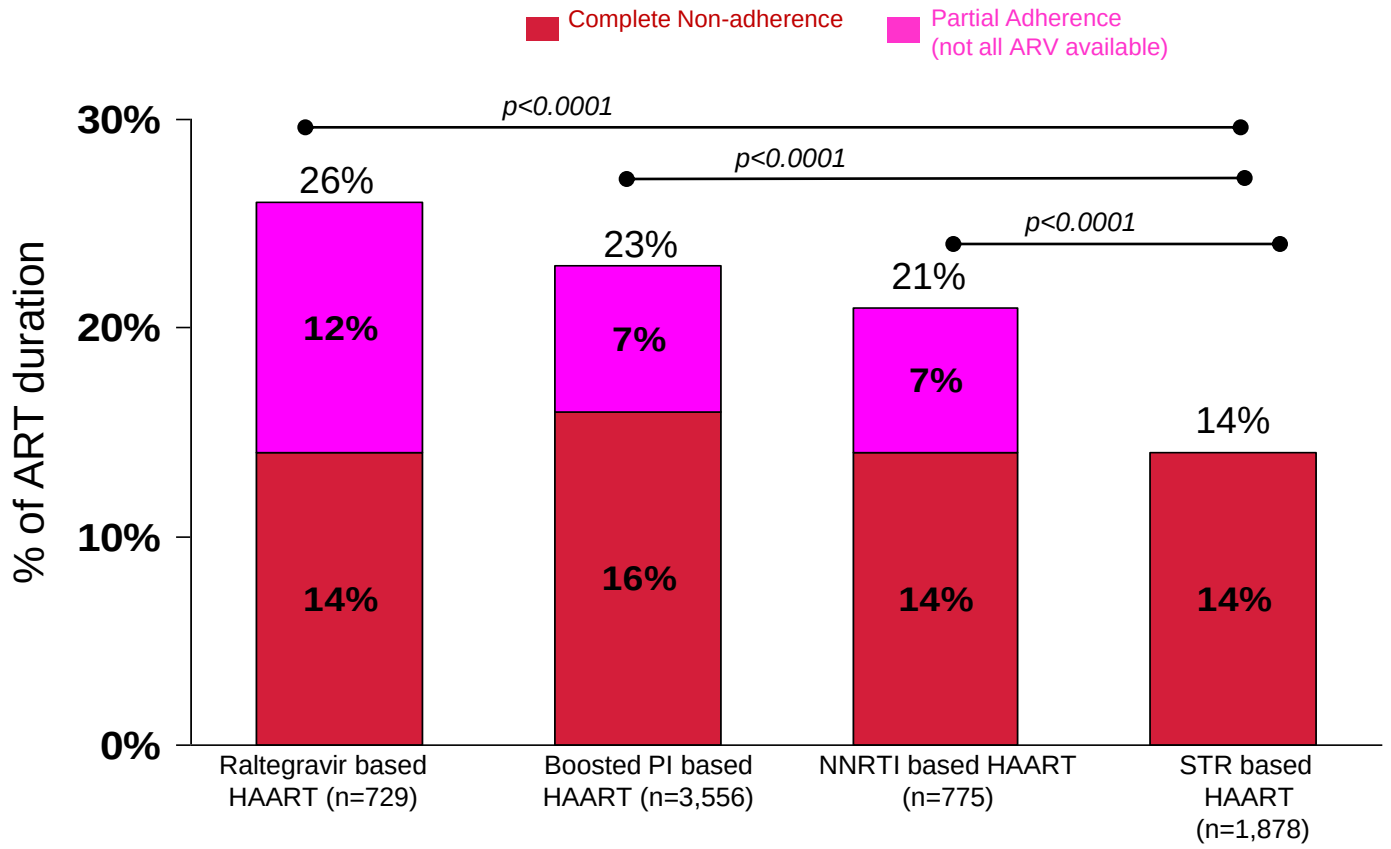
	aHR	95% CI	p-value
STR	0.48	0.25-0.90	0.023
Male Gender	0.67	0.49-0.92	0.028
IDU	1.71	1.14-2.57	0.01
Naïve (vs. Switched)	1.43	1.04-1.96	0.028

Despite keeping CNS toxicity, EFV-based STR was associated with reducing the risk of treatment interruption.

Fabbiani, et al

Medicaid Database
Partial Adherence to ART & hospitalisations

Retrospective analysis of US Medicaid Claims Database (n=6,938) receiving 2 NRTIs plus NNRTI or PI or INSTI based ART (2009 – 2011)



- **Complete non-adherence was similar across regimens, while partial adherence was only seen with non-STR regimens**
- **Patients on a STR had significantly better complete adherence to their HIV regimen**

Cohen C, et al. HIV-11 2012; Glasgow, UK. P1

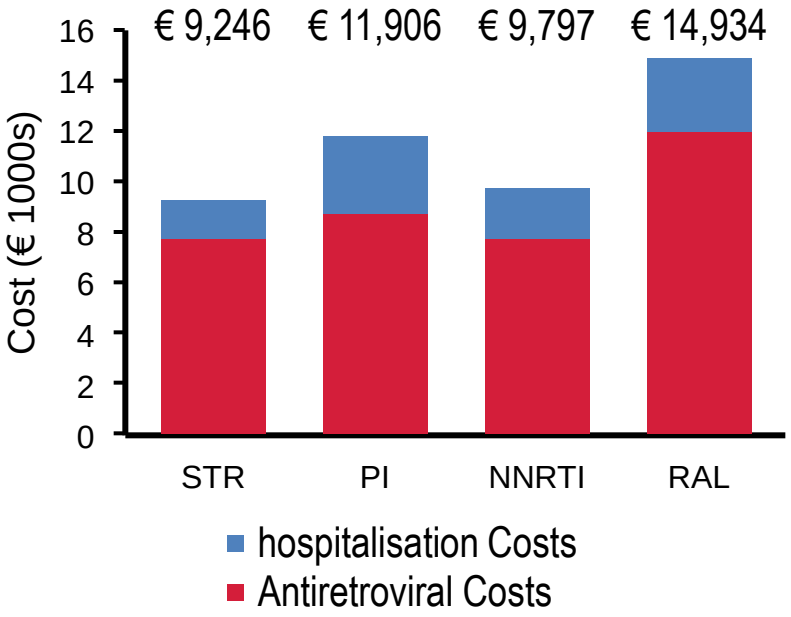
COMPACT: Italy
Adherence, Clinical and Economic Outcomes of STR vs. Multi-Pill Regimens

Evaluation of outcomes in observational, retrospective cohort of 1,604 HIV+ pts (2008-2011)

Risk of hospitalisation

- Using multivariate Poisson regression analysis, selective non-adherence (SNA) of > 3.5% was found to have a 39% increased hospitalisation risk (95% CI 1.09 – 1.77; p = 0.008)

Cost of illness



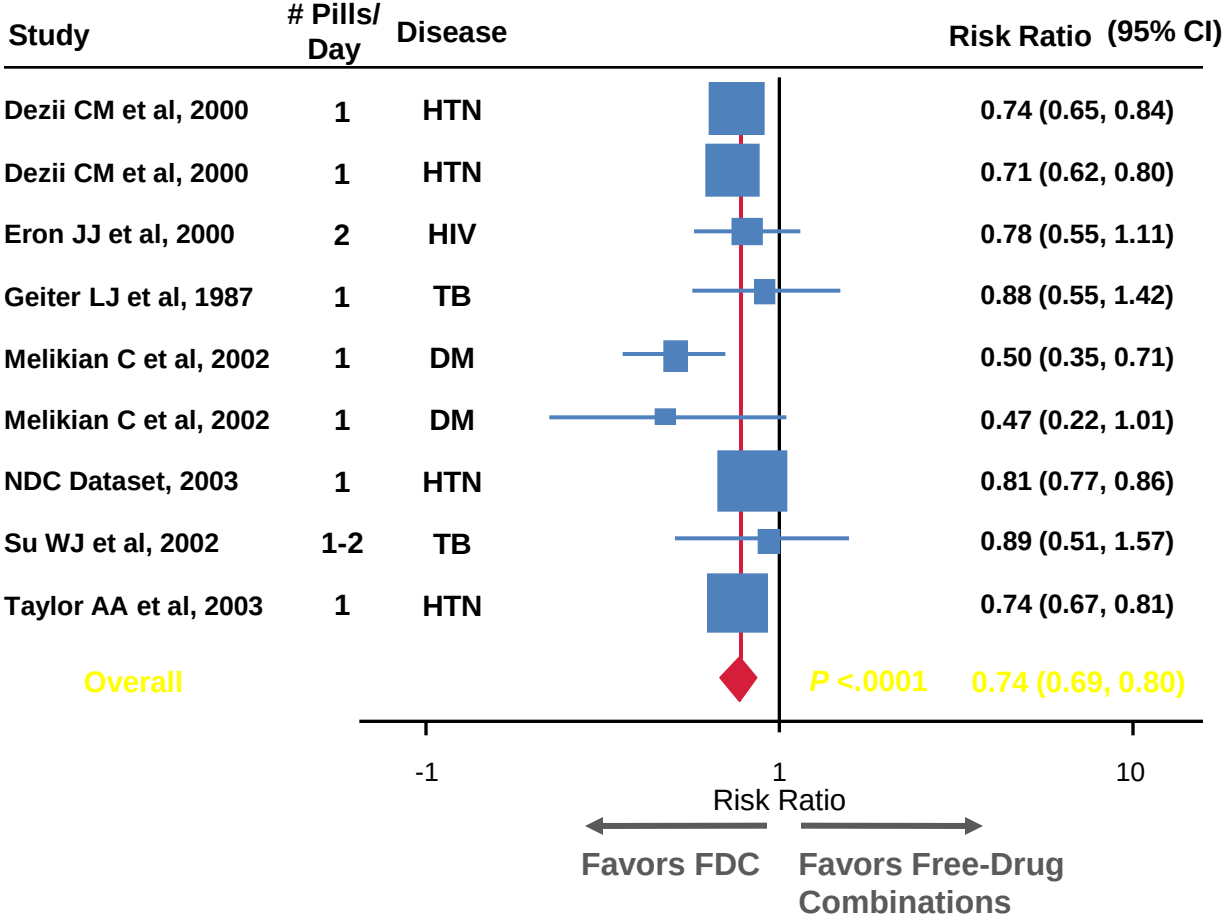
"The use of a STR regimen appears an effective therapeutic option to avoid SNA and, consequently, to prevent virological failure and to reduce hospitalisations."

Antinori A, et al.

Decreased Risk of Nonadherence With FixedDoseCombinations FDC

FDC regimens reduce risk of nonadherence by 26% compared with non-FDC.

Effect of FDCs versus non-FDC on risk of nonadherence



Bangalore S, et al. *Am J Med.* 2007;120:713-719.

Current ART
What can be improved?

- Virological efficacy
  - Probably not.
- Resistance
  - Potential area of improvement (limited impact)
- Tolerability
  - Overall, not. Some aspects of some drugs
- Long term toxicity
  - Some areas: hyperlipidemia, bone, kidney
- Convenience
  - Alternative STR
- Cost

Available Antiretroviral Agents

Nucleoside RTIs

- Zidovudine (ZDV)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (d_4T)
- Lamivudine ($_3TC$)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Tenofovir DF (TDF)

Boosters

- Ritonavir (RTV)
- Cobicistat (cobi)

Nonnucleos(t)ide RTIs

- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Rilpivirine (RPV)

Integrase Inhibitors

- Raltegravir (RAL)
- Elvitegravir (EVG)
- Dolutegravir (DTG)

Protease Inhibitors

- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Lopinavir/r (LPV/r)
- Atazanavir (ATV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- Darunavir (DRV)

Fusion Inhibitor

- Enfuvirtide (T-20)

CCR5 Antagonist

- Maraviroc (MVC)

Available Antiretroviral Agents

Nucleoside RTIs

- Zidovudine (ZDV)
- Didanosine (ddI)
- Zalcitabine (ddC)
- Stavudine (d_4T)
- Lamivudine ($_3TC$)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Tenofovir DF (TDF)
- TAF

Boosters

- Ritonavir (RTV)
- Cobicistat (cobi)

Nonnucleos(t)ide RTIs

- Nevirapine (NVP)
- Delavirdine (DLV)
- Efavirenz (EFV)
- Etravirine (ETR)
- Rilpivirine (RPV)
- Doravirine

Integrase Inhibitors

- Raltegravir (RAL)
- Elvitegravir (EVG)
- Dolutegravir (DTG)

$CXCR_4$ Inhibitors

Protease Inhibitors

- Saquinavir (SQV)
- Ritonavir (RTV)
- Indinavir (IDV)
- Nelfinavir (NFV)
- Amprenavir (APV)
- Lopinavir/r (LPV/r)
- Atazanavir (ATV)
- Fosamprenavir (Fos-APV)
- Tipranavir (TPV)
- Darunavir (DRV)

Fusion Inhibitor

- Enfuvirtide (T-20)

CCR_5 Antagonist

- Maraviroc (MVC)

STaR[1] & ECHO/THRIVE[2]

Study design

STaR[1]: MultiCentre, international, randomised, open-label, Phase 3b, 96-week study

ARV-naïve
HIV-1 RNA >2500 c/mL
Sensitivity to EFV, FTC, RPV, TDF
(N=786)

Stratified by HIV RNA (≤ or >100,000 c/mL)

n=394 → **RPV/FTC/TDF STR**

n=392 → **EFV/FTC/TDF STR**

48 Weeks **96 Weeks**

Pooled* ECHO[†] and THRIVE[‡2]: Randomised, double-blind, double-dummy, 96-week study

ARV-naïve
HIV-1 RNA >5000 c/mL
No NNRTIs RAM
Sensitivity to the NRTIs
(N=1,096)

n=550 → **RPV+FTC/TDF + EFV Placebo**

n=546 → **EFV+FTC/TDF + RPV Placebo**

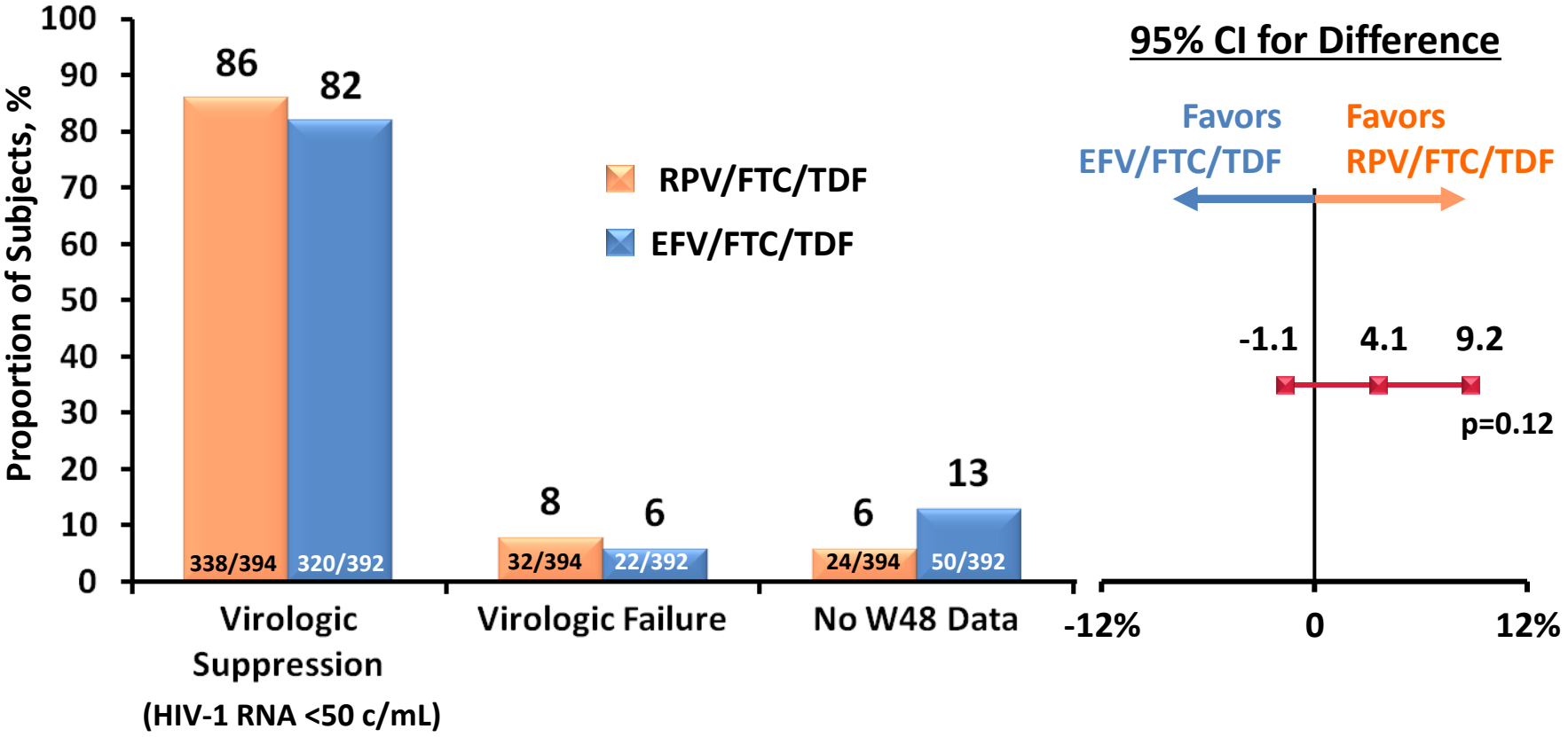
48 Weeks **96 Weeks**

* Pooled ECHO/THRIVE FTC/TDF dataset contains data from 1,096 subjects who received RPV or EFV in combination with FTC/TDF
[†] In the ECHO study, FTC/TDF background regimen (BR) was comprised of 690 subjects
[‡] In the THRIVE study, BR consisted of 2 NRTIs: FTC/TDF (60%, n = 406) or 3TC/ZDV (30%, n = 204) or 3TC/ABC (10%, n = 68)

1. Cohen C, *et al*. HIV-11 2012; Glasgow, UK. Oral 425; 2. Adapted from Nelson M, *et al*. EACS 2011. Belgrade, Serbia. #LBPE7.3/7

Virologic suppression and CD4 change at Week 48
FDA snapshot analysis – ITT population

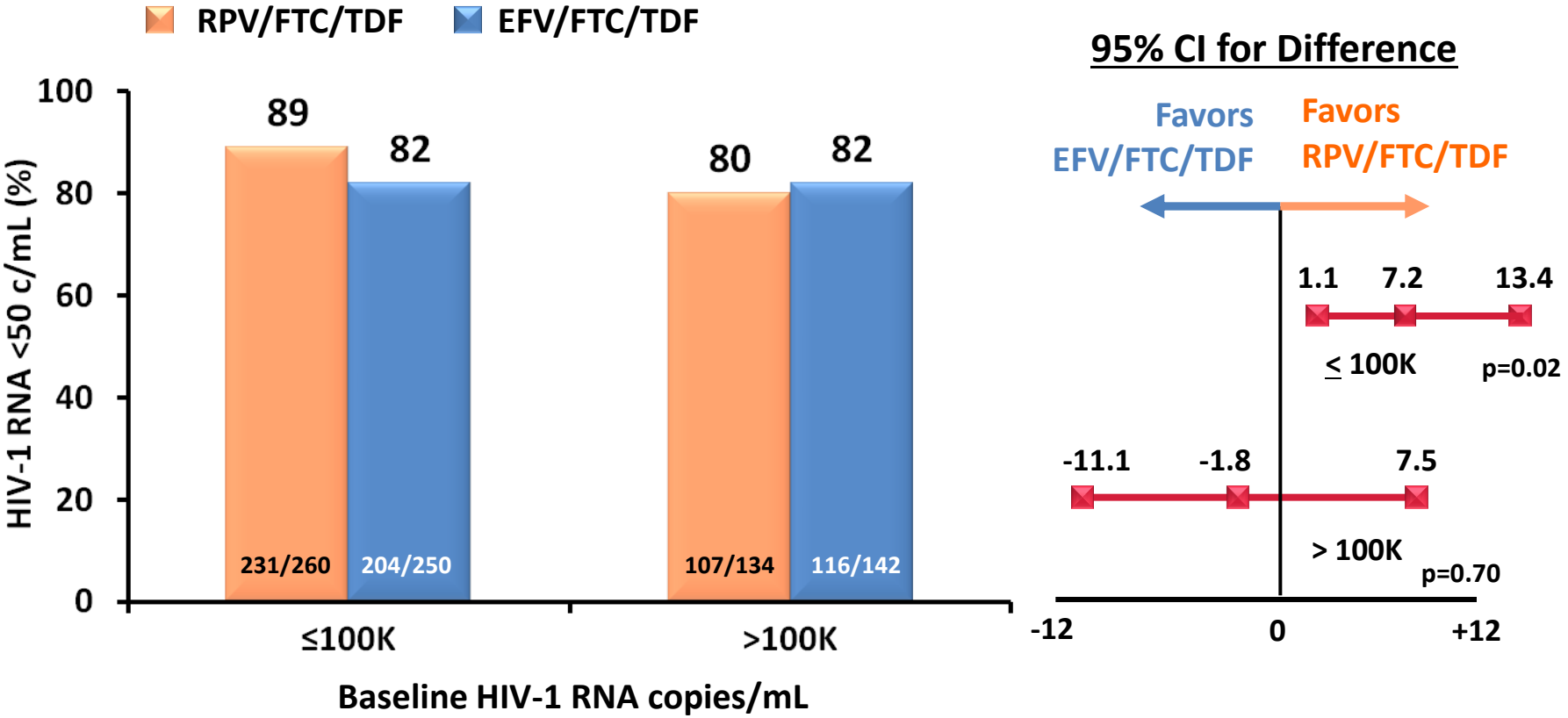
RPV/FTC/TDF is non-inferior to EFV/FTC/TDF



CD4 count change (cells/mm^3): RPV/FTC/TDF +200 vs. EFV/FTC/TDF +191 (p=0.34)

Cohen C, *et al*. HIV-11 2012; Glasgow, UK. Oral 425

Virologic suppression at Week 48 FDA snapshot analysis by baseline HIV-1 RNA stratified by 100,000 copies/mL



RPV/FTC/TDF compared to EFV/FTC/TDF by baseline HIV-1 RNA:

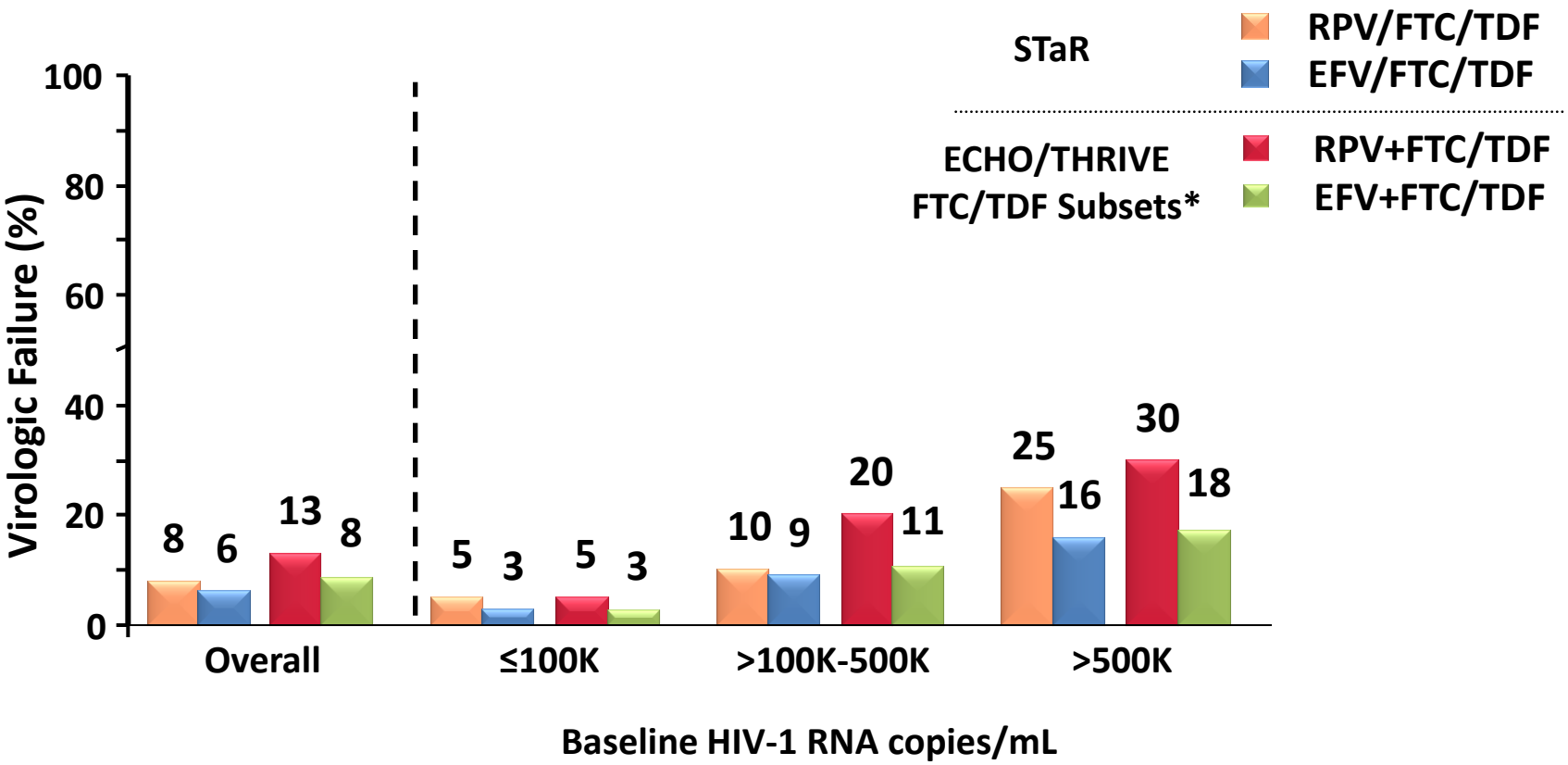
≤100,000 copies/mL - Non-inferior and statistically significant difference

>100,000 copies/mL - Non-inferior efficacy

Modified from Cohen C, *et al*. HIV-11 2012; Glasgow, UK. Oral 425

STaR[1] & ECHO/THRIVE[2]

Virologic Failure at Week 48 per FDA Snapshot Overall and by Baseline HIV-1 RNA



* Please note data from Complera US Prescribing Information. Gilead Sciences Inc. 2012.

1. Cohen C, *et al*. HIV-11 2012; Glasgow, UK. Oral 425; 2. Nelson M, *et al*. EACS 2011. Belgrade, Serbia. #LBPE7.3/7

STaR[1] & ECHO/THRIVE[2]

Resistance analysis through Week 48

STaR

	EFV/FTC/TDF (n=392)	RPV/FTC/TDF (n=394)
Subjects with Resistance Data	2%	5%
Subjects with Resistance to ARVs	1%	4%
Any Primary NNRTI-R	1%	4%
Key NNRTI-R	K103N (0.3%)	E138K/Q (2%) Y181C/I (2%) K101E (1%)
Any Primary NRTI-R	0.3%	4%
Key NRTI-R	M184I (0.3%)	M184V/I (4%) K65R/N (1%)
Within Baseline (BL) HIV-1 RNA		
≤100,000 copies/mL	1%	2%
100,001–500,000 copies/mL	0	5%
>500,000 copies/mL	4%	19%

The STRs used in STaR, compared to the STR components used in ECHO and THRIVE, demonstrated less emergent resistance

1. Cohen C, *et al.* HIV-11 2012; Glasgow, UK. Oral 425; 2. Nelson M, *et al.* EACS 2011. Belgrade, Serbia. #LBPE7.3/7

Adverse events leading to discontinuation of study drug through Week 48

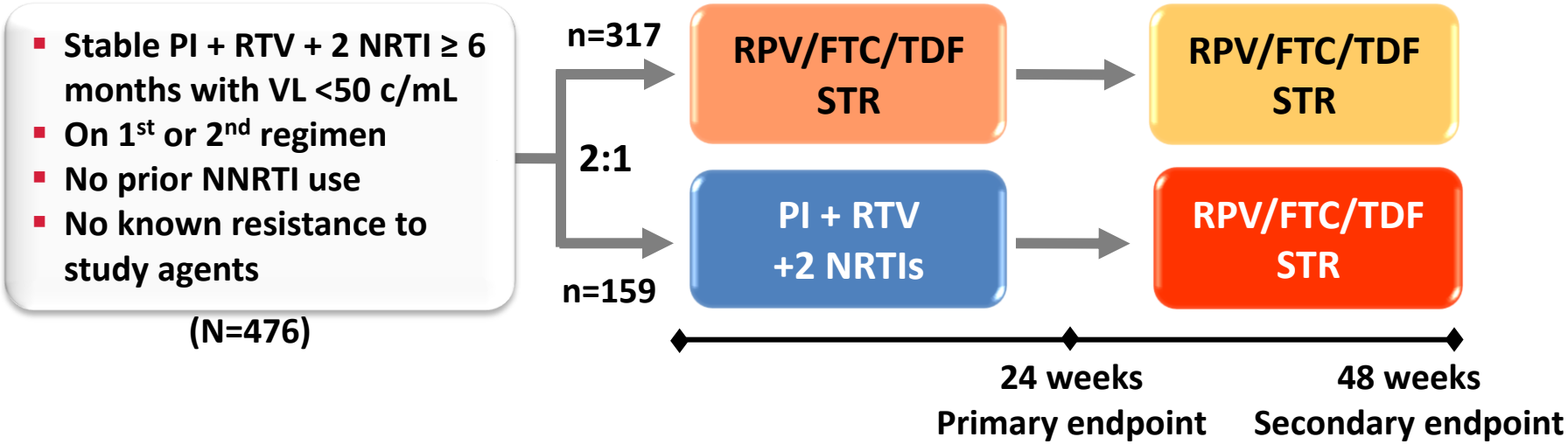
	RPV/FTC/TDF (n=394)	EFV/FTC/TDF (n=392)	
Discontinuations* Due to Adverse Event (AE), n (%)	10 (2.5%)	34 (8.7%)	*p*<0.001
AE leading to discontinuation in >1 subject in either arm			
Nervous System Events			
Dizziness	0	5 (1.3%)	
Abnormal Dreams or Nightmare	0	6 (1.5%)	
Insomnia	1 (0.3%)	3 (0.8%)	
Psychiatric Disorders			
Depression, Anxiety or Depressed Mood	0	9 (2.3%)	
Suicidal Ideation	0	2 (0.5%)	
GI, General, Skin Disorders			
Diarrhoea	0	2 (0.5%)	
Fatigue	0	2 (0.5%)	
Pyrexia	0	2 (0.5%)	
Toxic Skin Eruption	0	2 (0.5%)	

* Per safety population

Cohen C, *et al*. HIV-11 2012; Glasgow, UK. Oral 425

GS-246-106: SPIRIT – Study design

Switching boosted PI to Rilpivirine In-combination with Truvada as a STR
MultiCentre, international, randomised, open-label, Phase 3b, 48-week study



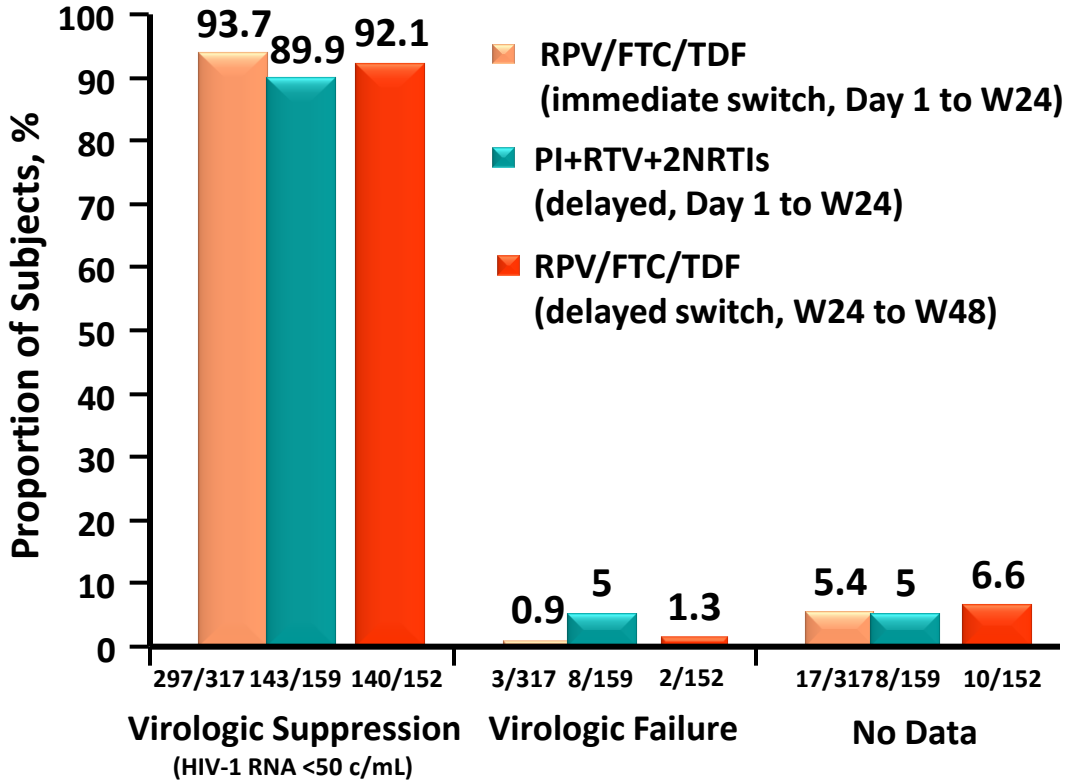
- **Primary Endpoint:** Non-inferiority (12% margin) of RPV/FTC/TDF to PI+RTV+2 NRTIs by FDA snapshot analysis HIV-1 RNA <50 copies/mL at 24 weeks[2]
- **Secondary Endpoints:** Proportion of subjects who have HIV1 RNA <50 copies/mL (missing=excluded) through Week 48, change in fasting lipid parameters and CD4 cell count at 24[2,3] and 48[1] weeks, safety and tolerability to PI+RTV+2NRTIs at 24[2,3] and 48[1] weeks
- **Adherence & Patient reported outcomes:** Visual Analog Scale Adherence, HIV Symptom Index and HIV Treatment Satisfaction Questionnaire[3]
- **Ad Hoc Analysis:** Outcome at 24 weeks for patients with pre-existing resistance mutations[4]

1. Fisher, M, *et al.* HIV-11 2012; Glasgow, UK. P285
2. Palella F, *et al.* IAC 2012; Washington, DC. Oral TUAB0104
3. Tebas P, *et al.* LIPO 2012; Washington, DC. #018
4. White K, *et al.* IHDRW 2012; Stiges, Spain. #P49

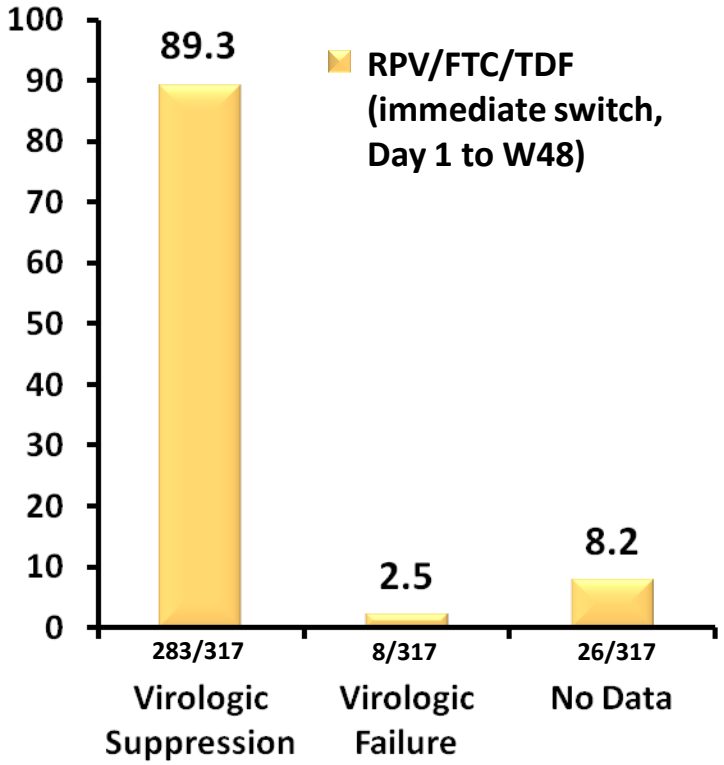
SPIRIT

Virologic suppression at Weeks 24 and 48 FDA snapshot analysis – ITT population

FDA Snapshot at 24 Weeks



FDA Snapshot at 48 Weeks

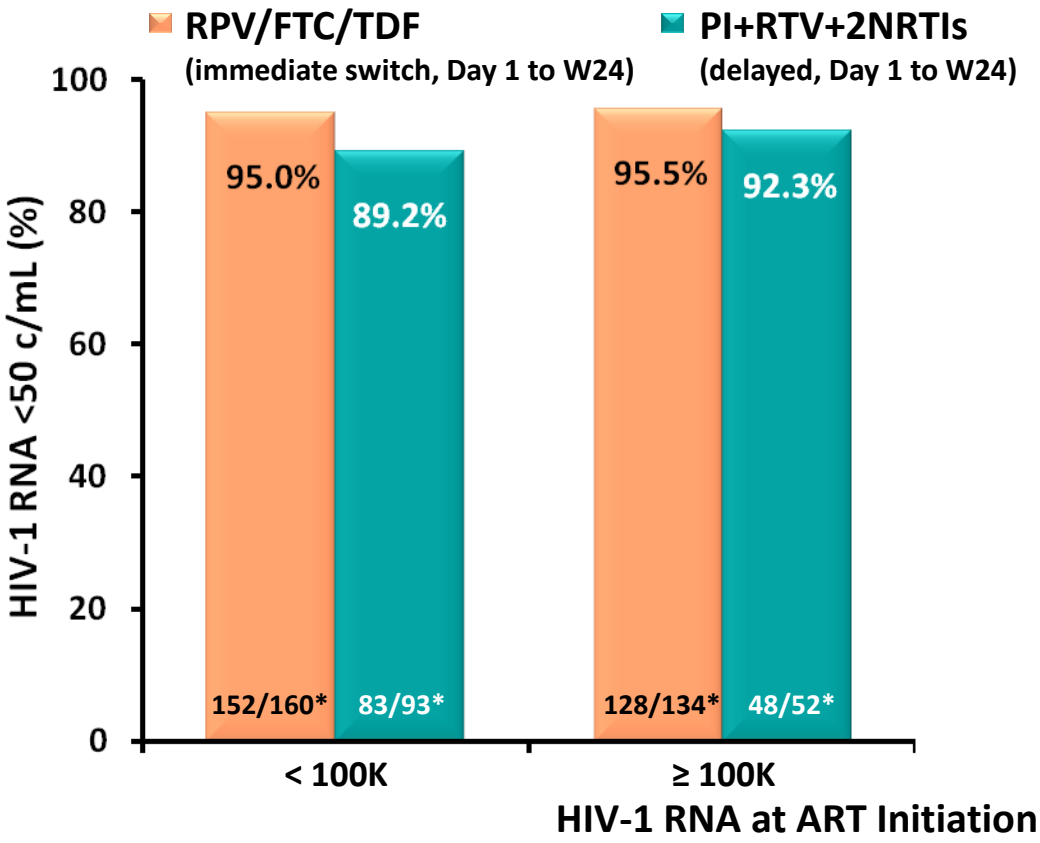


- Switching to RPV/FTC/TDF was non-inferior to remaining on PI+RTV+2NRTIs for 24 weeks
  - Difference 3.8, CI [-1.6, 9.1]
- Similar rates of virologic suppression were seen with 48 weeks of RPV/FTC/TDF

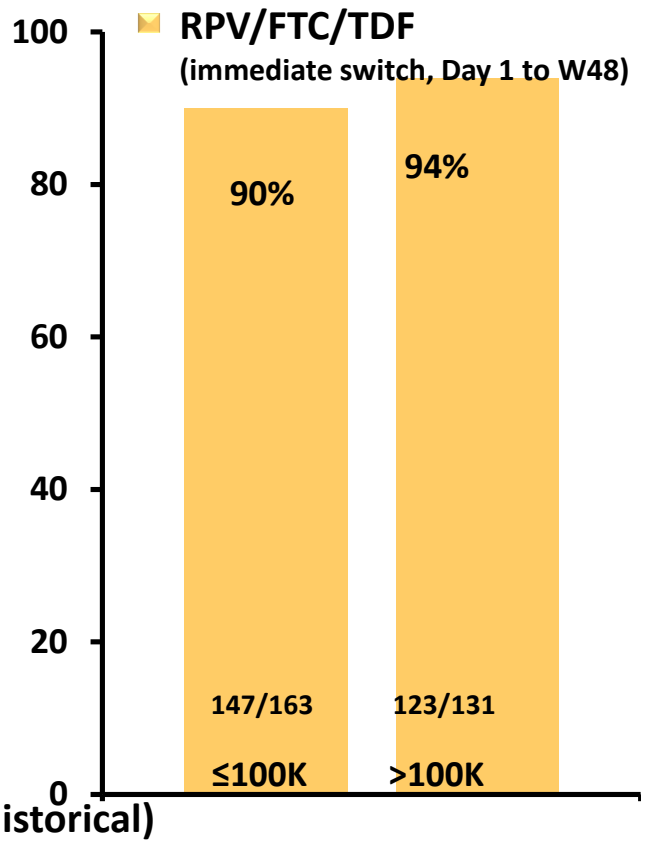
Fisher M, *et al*. HIV-11 2012; Glasgow, UK. P285

Week 24 and 48 virologic suppression (snapshot analysis) stratified by HIV-1 RNA at ART initiation

FDA snapshot at 24 Weeks[1]



FDA snapshot at 48 Weeks[2]



Switching to RPV/FTC/TDF was non-inferior to remaining on PI+RTV+2NRTIs regardless of HIV-1 RNA while ARV naïve (a post-hoc analysis)

*23 (8%) RPV/FTC/TDF and 14 (9%) PI+RTV+2NRTI subjects were excluded from this analysis due to unavailable HIV-1 RNA while ARV naive

1. Palella F, *et al.* IAC 2012; Washington, DC. Oral TUAB0104; 2. Data on file, Gilead Sciences, Inc.

SPIRIT
RPV/FTC/TDF NNRTI and NRTI resistance through Week 48

n (% study arm)	Week 24		Week 48
	RPV/FTC/TDF (Immediate switch, W24) N = 317	PI+RTV+2NRTIs (Delayed switch, W24) N = 159	Total RPV/FTC/TDF (Immediate switch, W48) N = 469*
Subjects with Resistance to ARV Regimen	2 (0.6%)	1 (0.6%)	4 (0.9%)
Emergent NNRTI and NRTI Resistance Mutations	Subject 1†: K103N+L100I+M184I Subject 2: M184I	Subject 1: M184V+K70E/K	Subject 1†: K103N+L100I+M184I Subject 2: M184I Subject 3: E138E/K+M184M/I/V Subject 4: E138K+V108V/I+M184V

- **At Week 24, rates of resistance development were identical at 0.6% for immediate switch vs. PI+RTV+2NRTIs**
  - No subjects develop resistance in delayed switch arm (Wk 24 to 48)
- **Through Week 48, resistance development in <1% of RPV/FTC/TDF subjects**

* Includes Day 1 to Week 48 data on immediate switch arm and Week 24 to Week 48 data on delayed switch arm
† History of efavirenz use

Modified from Fisher M, *et al*. HIV-11 2012; Glasgow, UK. P285

SPIRIT

Treatment response among RPV/FTC/TDF-treated subjects with pre-existing K103N through Week 48

- Twenty-two of 24 (92%) RPV/FTC/TDF-treated subjects with pre-existing K103N achieved virologic suppression (<50 copies/mL)

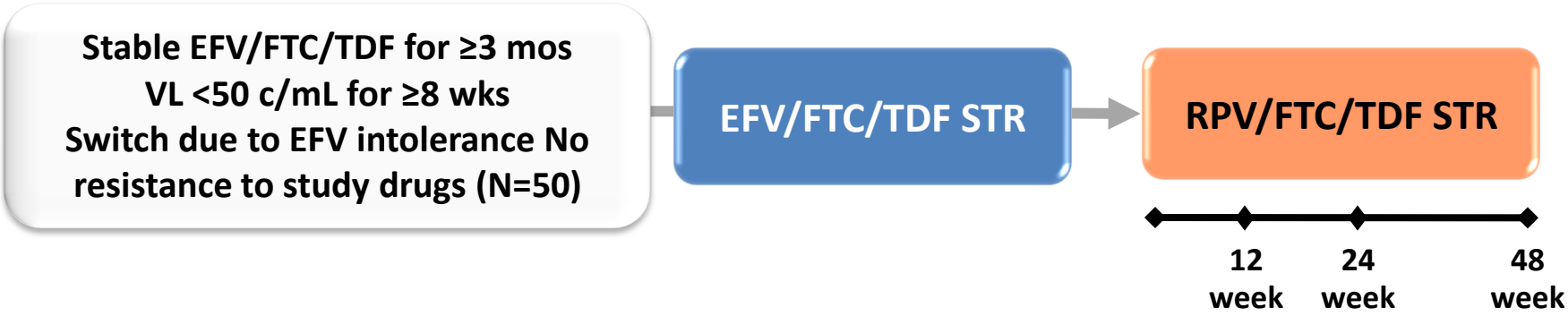
	Immediate, D1 to W48 N = 317	Delayed, W24 to W48 N = 152	Total, D1 to W48 N = 469
Subjects with Pre-existing K103N, n	18	6	24
Snapshot Outcome, n			
Virologic Suppression	17	5	22
Virologic Failure	1[a]	0	1[a]
No Data in Window	0	1[b]	1[b]

[a] Subject with pre-existing K103N and V179I who subsequently acquired M184V, E138K, and V108V/I while on study drug
[b] Missing data during window but on study drug, suppressed at prior visit

Fisher M, *et al*. HIV-11 2012; Glasgow, UK. P285

GS 264-111
Study design

Phase 2b, open-label, multiCentre, 48-week study of immediate switch from EFV/FTC/TDF to RPV/FTC/TDF in stable, virologically controlled subjects



Pre-dose PK samples obtained: Wks 1, 2, 4, 6, 8, and 12

Primary endpoint: HIV-1 RNA <50c/mL at week 12 after switching

Secondary endpoints: Safety and tolerability of RPV/FTC/TDF STR over 24 & 48 wks

HIV-1 RNA <50 c/mL at week 24 and week 48 post-switch

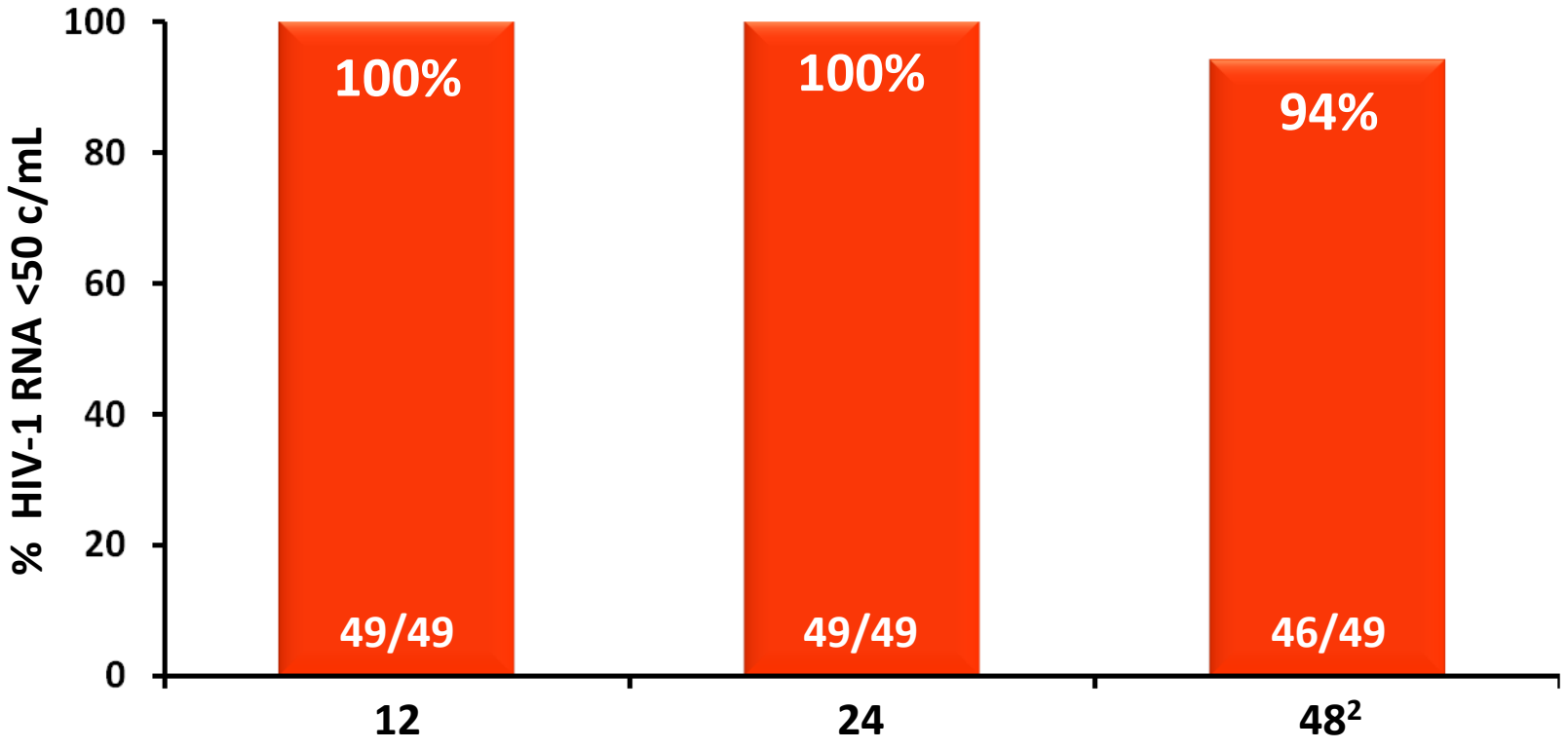
Pharmacokinetics of RPV after switching from EFV

Cohen C, *et al*. EACS 2011. Belgrade, Serbia. Oral LB #PS10/4
Mills A, *et al*. BHIVA 2012. Birmingham, UK. #P186

GS 264-111

Virologic outcomes by ITT-FDA snapshot through week 48

Virologic suppression was maintained in majority of virologically-suppressed subjects who switched from EFV/FTC/TDF to RPV/FTC/TDF through Wk 48



1. Mills A, *et al.* BHIVA 2012; Birmingham, UK. #P186
2. Data on file. Gilead Sciences, Inc.

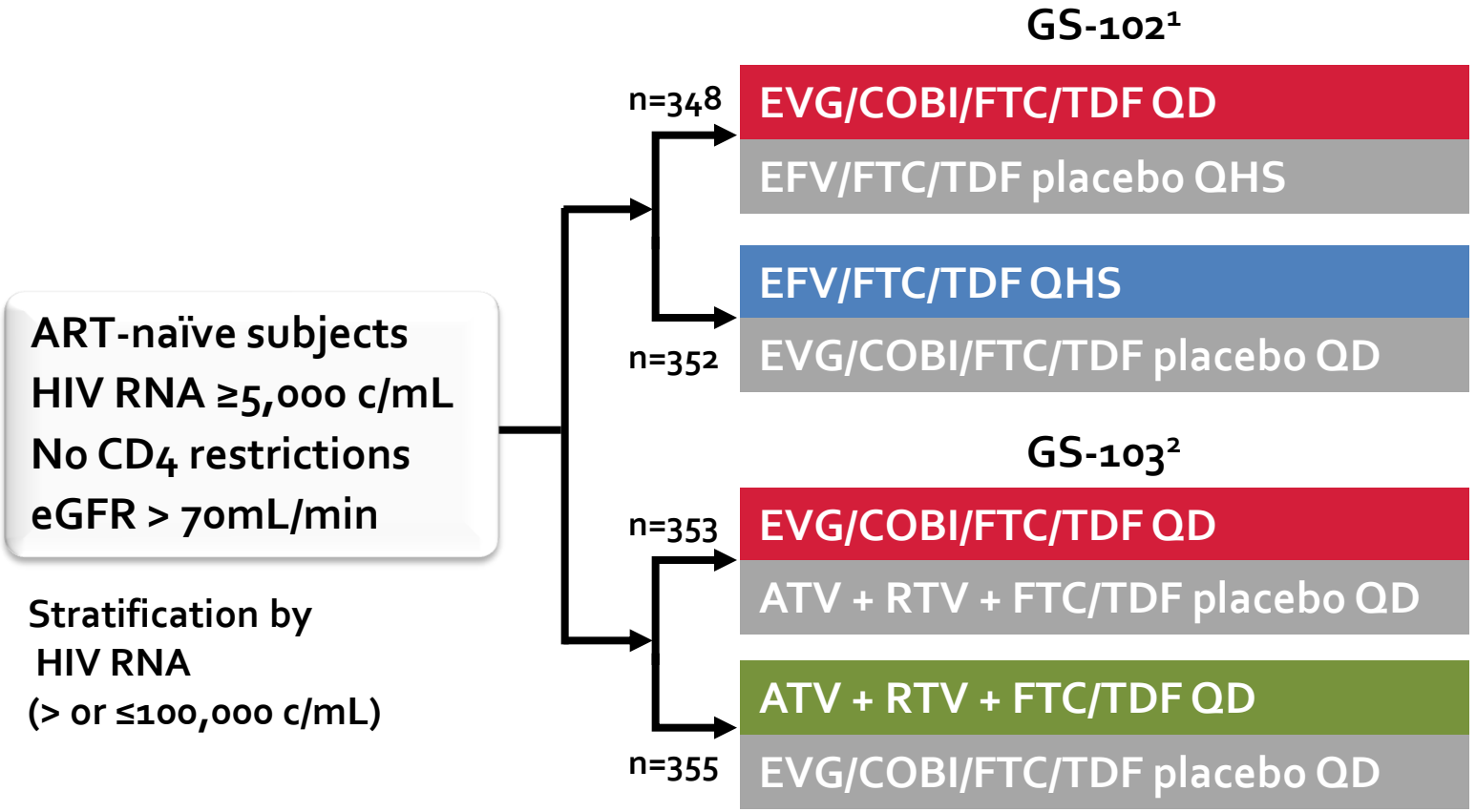
Rilpivirine
Efficacy Studies

- **High rate of success in naïve patients**
  - More virological failures than EFV in patients with high VL
- **Adequate for switching from a PI- or EFV-based regimens**
- **Good tolerability**
- **Low genetic barrier**
- **Convenient (STR)**
  - Interaction with food and PPi

GS-102 & GS-103: EVG/COBI/FTC/TDF

Study Design

Multicenter, randomized, blinded, 192-week studies



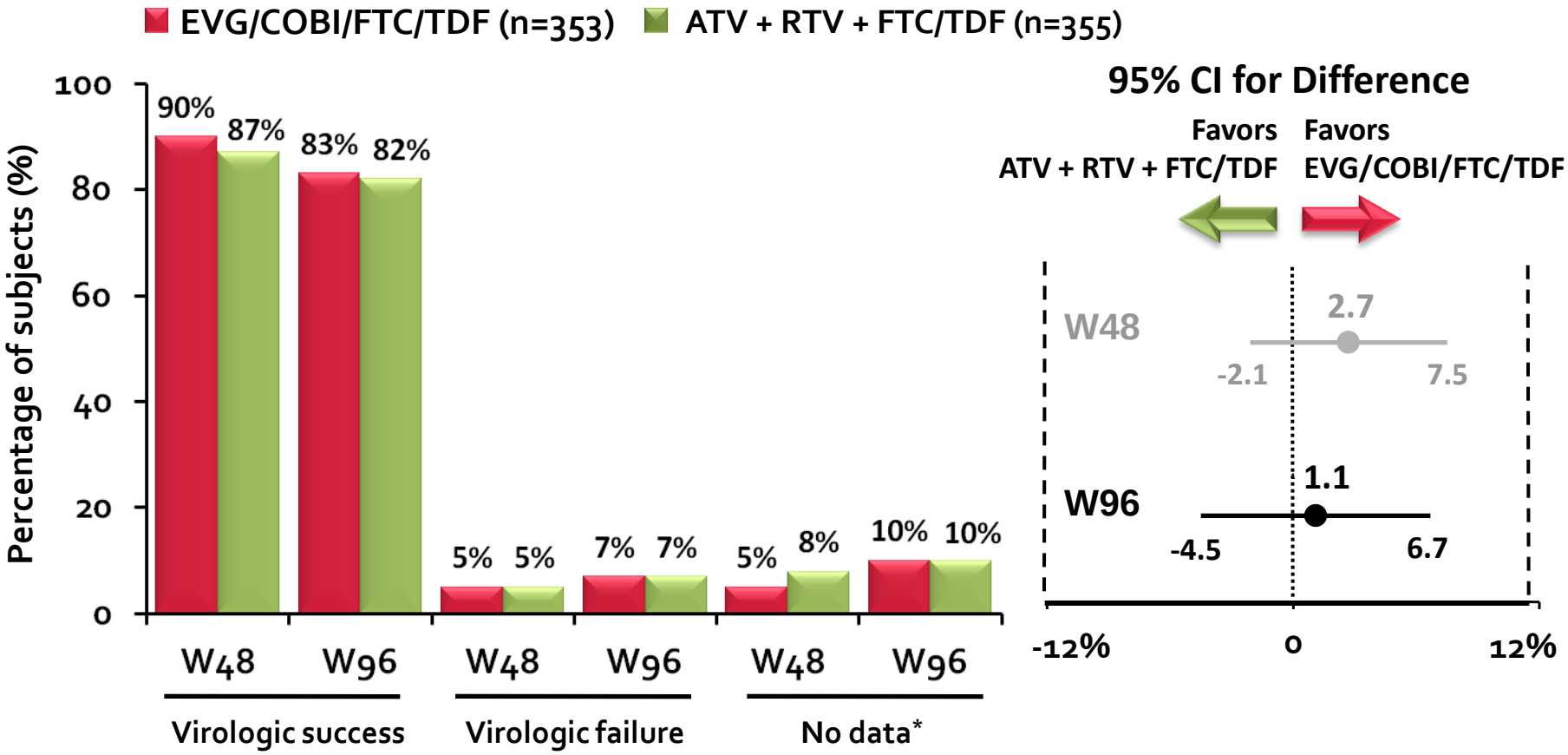
Primary endpoint: Non-inferiority (12% margin) of EVG/COBI/FTC/TDF to comparator arm by FDA snapshot analysis HIV-1 RNA <50 copies/mL at 48 weeks

1. Zolopa A, *et al. JAIDS* 2013. e-published
2. Rockstroh JK, *et al. JAIDS* 2013. e-published

GS-103: EVG/COBI/FTC/TDF vs. ATV + RTV + FTC/TDF

Efficacy Endpoint: HIV-1 RNA <50 c/mL (Snapshot)

Weeks 48 and 96

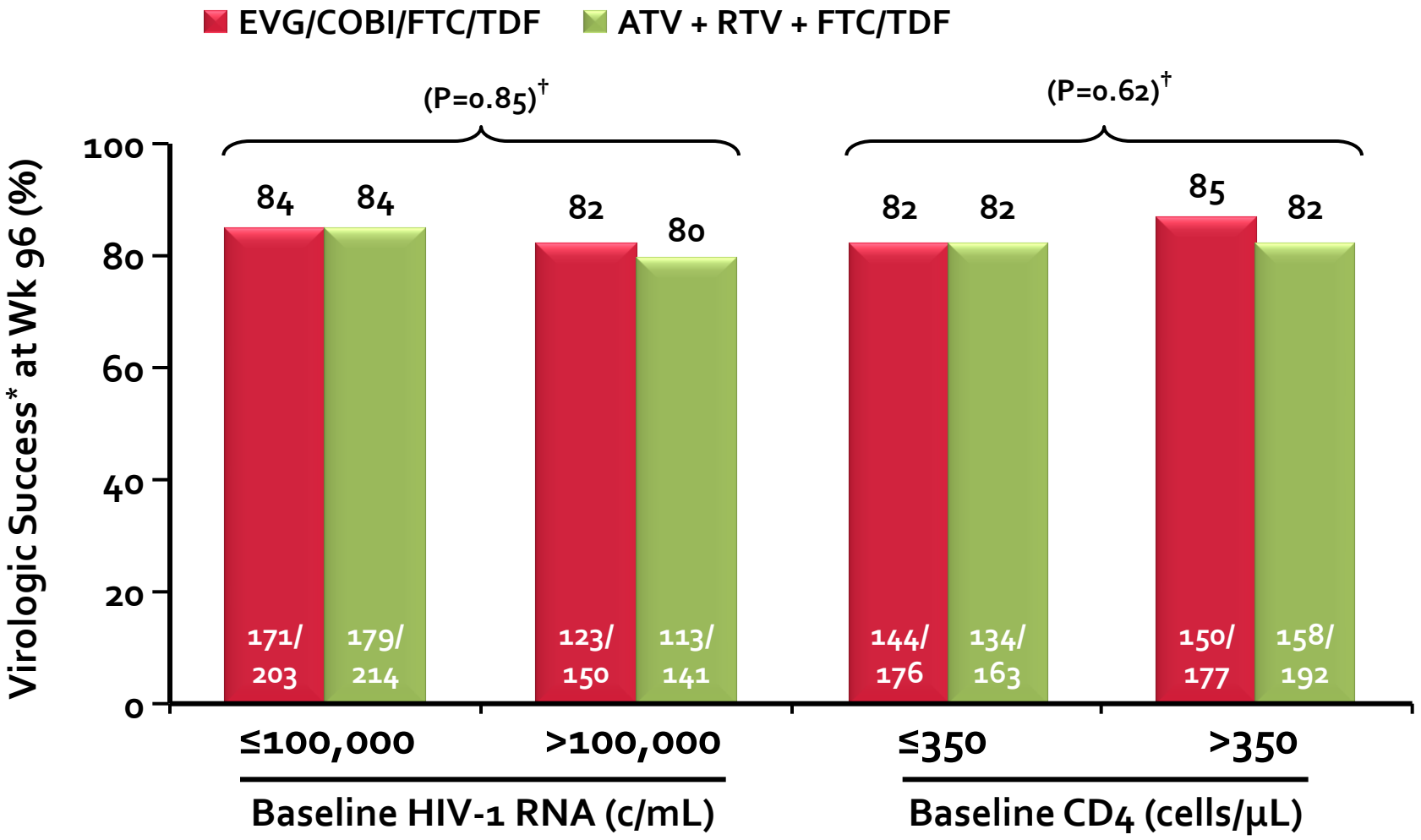


* No virologic data in window defined as: missing HIV RNA data but on study, discontinued drug due to AE or death, or discontinued drug for reasons other than AE, death, and lack/loss of efficacy with last HIV RNA <50 copies/mL. For the Week 48 virologic success, the analysis window is defined as from Study Day 309-378 inclusive and Study Day 631-714 inclusive for Week 96.

Rockstroh JK, *et al. JAIDS* 2013. e-published

GS-103: EVG/COBI/FTC/TDF vs. ATV + RTV + FTC/TDF

Week 96 Efficacy by Baseline VL & CD4



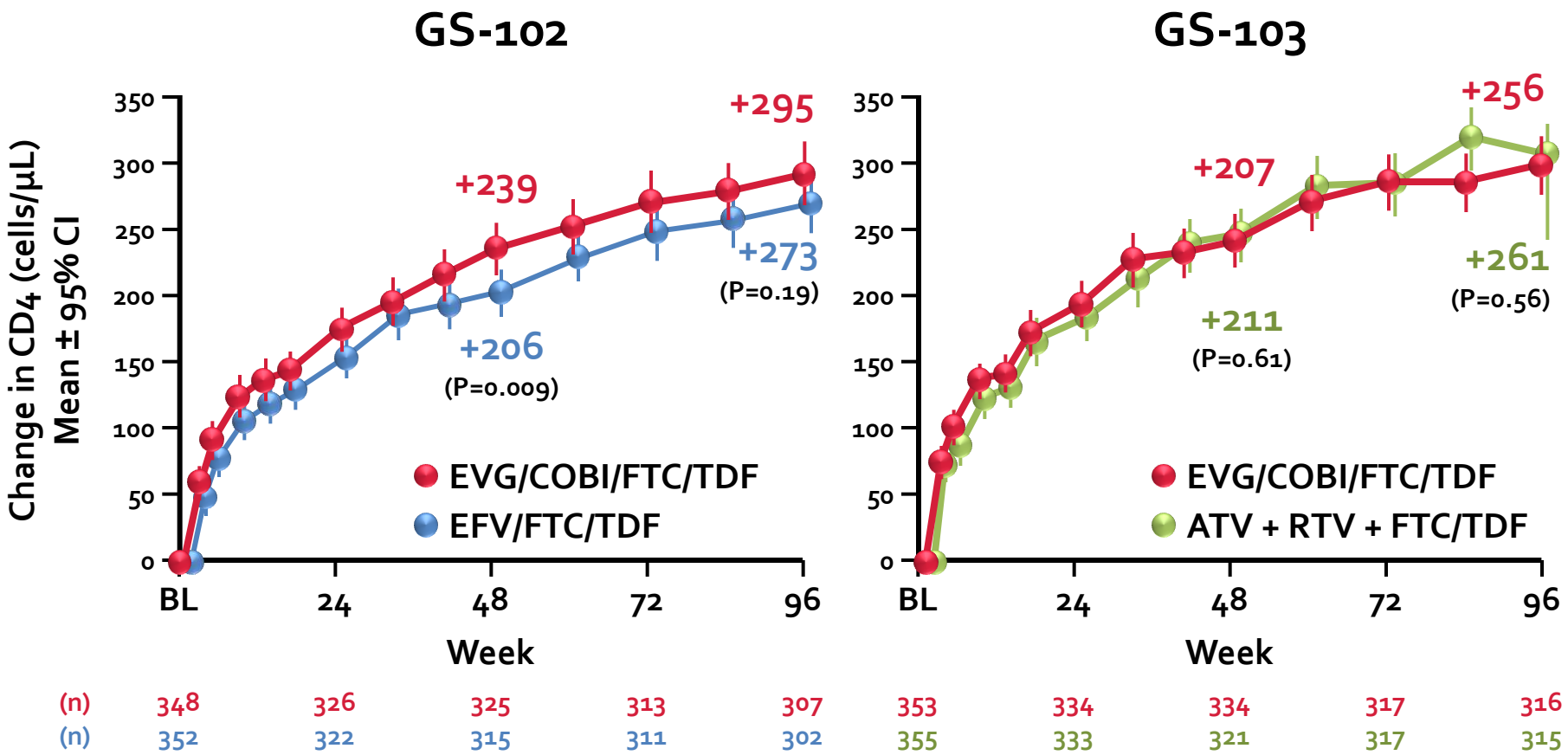
*Virologic success (HIV-1 RNA <50 copies/mL) as defined by FDA Snapshot algorithm

† P-value for the homogeneity test was based on the Wald test of the interaction between treatment and subgroup

Rockstroh JK, *et al.* HIV-11 2012; Glasgow. O424

GS-102 & GS-103: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF and ATV+RTV + FTC/TDF

Mean Change from Baseline in CD4 Cell Counts



1. Zolopa A, *et al. JAIDS* 2013. e-published

2. Rockstroh JK, *et al.* HIV-11 2012; Glasgow. O424
3. Rockstroh JK, *et al. JAIDS* 2013. e-published

GS-103: EVG/COBI/FTC/TDF vs. ATV + RTV + FTC/TDF

Integrase, PI, NRTI Resistance Through Week 48 and 96

n (%)	EVG/COBI/FTC/TDF (n=353)			ATV+RTV+FTC/TDF (n=355)		
		W48	W96*		W48	W96*
Emergent Resistance		5 (1.4%)	6 (1.6%)		0	0
Primary INSTI-R or PI-R		4 (1.1%)	5		0	0
	E92Q	1				
	N155H	2				
	Q148R	2				
	T66I	1				
Primary NRTI-R		4 (1.1%)	5 (1.4%)		0	0
	M184V/I	4	5			
	K65R	1	1			

* Additional specific mutations will be available in later publications

1. DeJesus E, *et al. Lancet* 2012; 379: 2429–38
2. Rockstroh JK, *et al. JAIDS* 2013. e-published

GS-103: EVG/COBI/FTC/TDF vs. ATV + RTV + FTC/TDF

Adverse Events Leading to Study Drug DC

	EVG/COBI/FTC/TDF (n=353)		ATV+RTV+FTC/TDF (n=355)	
AE Leading to Study Drug DC*	W48	W96	W48	W96
Blood creatinine increase	0.3%	0.6%	0	0
Pyrexia	0.6%	0.6%	0	0
Diarrhoea	0.6%	0.6%	0.3%	0.3%
Nausea	0.3%	0.3%	1.1%	1.1%
Vomiting	0.3%	0.3%	0.6%	0.6%
Fatigue	0.3%	0.3%	0.6%	0.6%
Ocular icterus	0	0	1.1%	1.1%
Jaundice	0	0	0.6%	0.6%
Drug eruption	0	0	0.6%	0.6%
Dizziness	0	0	0.6%	0.6%

* >1 subject in either treatment group cumulatively at Week 96

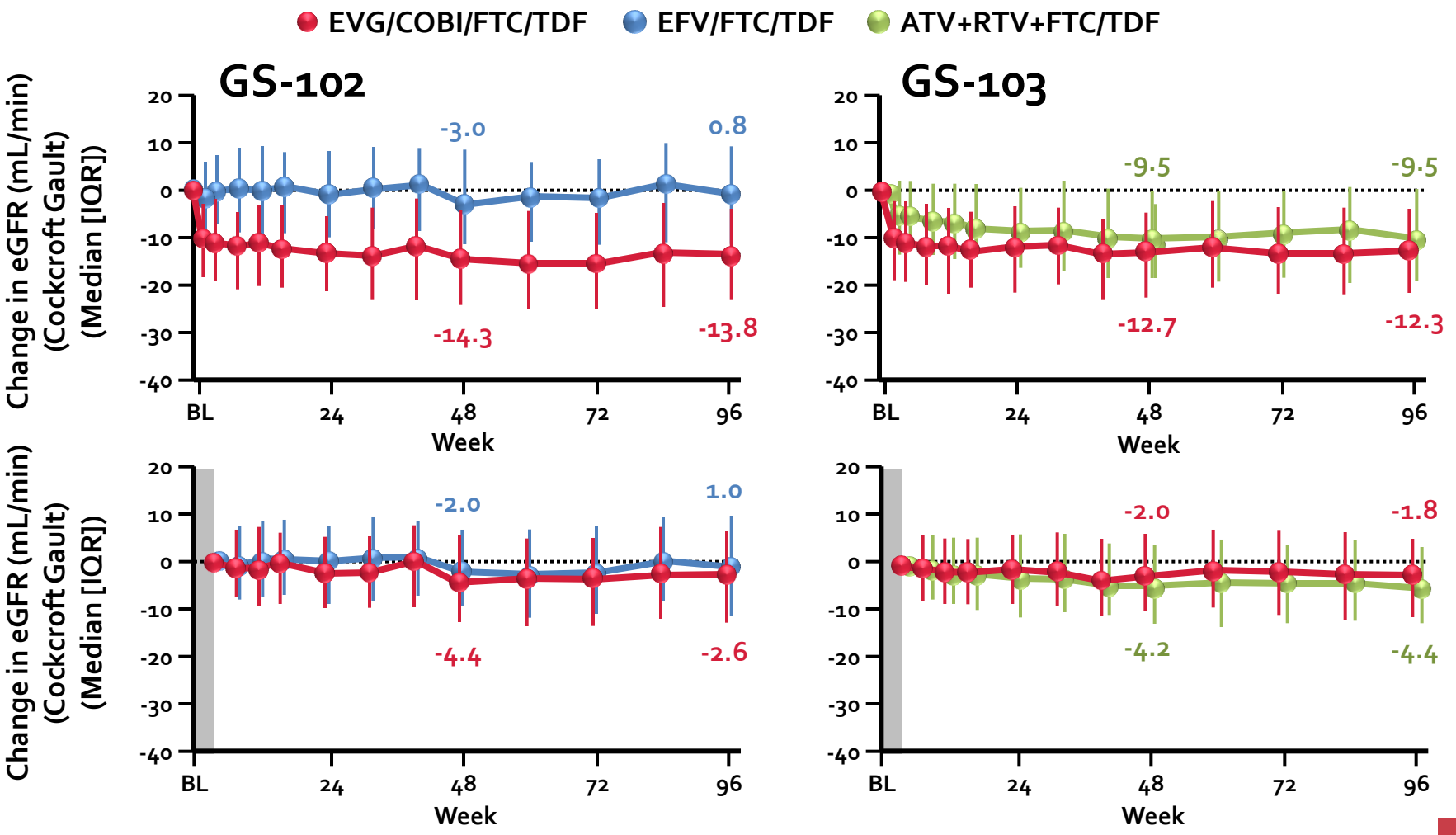
Like in Study 102, no cases of renal tubulopathy between Week 48 and Week 96

- ^ One EVG/COBI/FTC/TDF and one ATV + RTV + FTC/TDF patient DC due to elevation in SCr after Week 48
  - SCr improved after study drug DC in both patients

Rockstroh JK, *et al. JAIDS* 2013. e-published

GS-102 & GS-103: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF and ATV + RTV + FTC/TDF

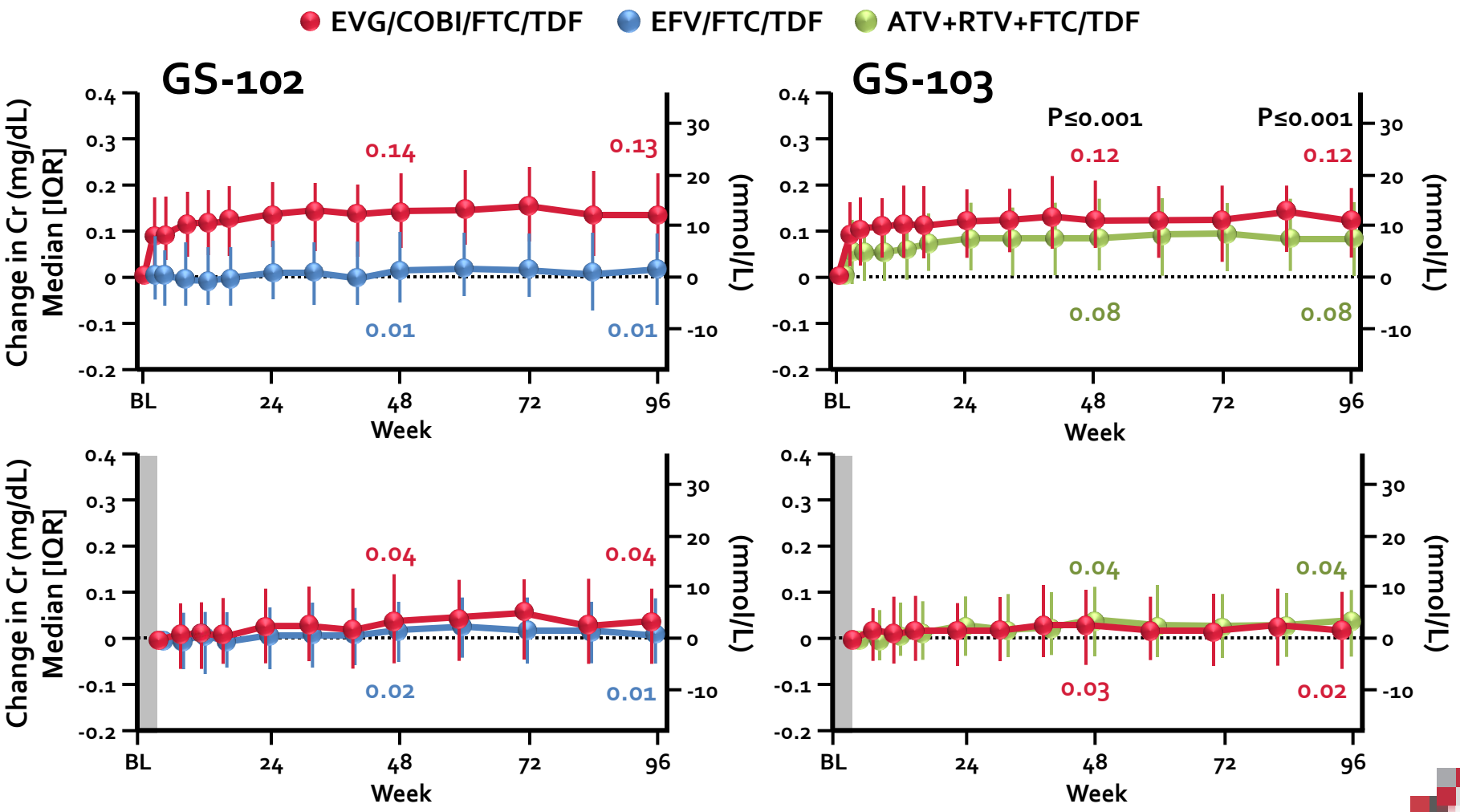
Median eGFR Changes from Baseline or from Week 4



1. Zolopa A, *et al. JAIDS* 2013. e-published
2. Zolopa A, *et al.* HIV-11 2012; Glasgow. O424
3. Rockstroh JK, et al. JAIDS 2013. e-published
4. Rockstroh JK, et al. HIV-11 2012; Glasgow. O424

GS-102 & GS-103: EVG/COBI/FTC/TDF vs. EFV/FTC/TDF and ATV + RTV + FTC/TDF

Median Serum Creatinine Changes from Baseline or from Wk 4

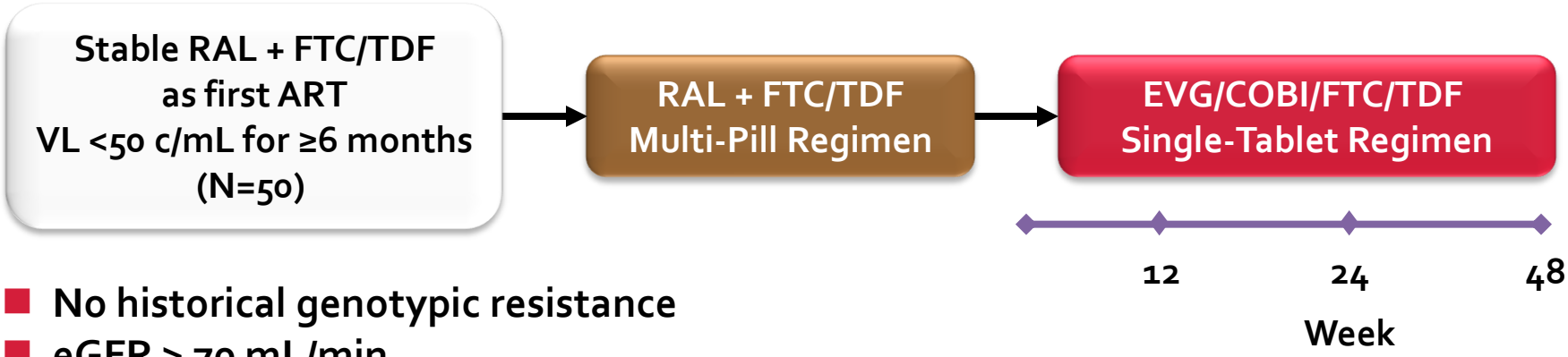


1. Zolopa A, *et al. JAIDS* 2013. e-published
2. Zolopa A, *et al.* HIV-11 2012; Glasgow. O424
3. Rockstroh JK, et al. JAIDS 2013. e-published
4. Rockstroh JK, et al. HIV-11 2012; Glasgow. O424

GS-123: RAL + FTC/TDF Simplification to EVG/COBI/FTC/TDF

Study Design

Phase 3b, open-label, multicenter, 48-week study of immediate simplification from RAL + FTC/TDF to EVG/COBI/FTC/TDF in stable, virologically controlled subjects



- No historical genotypic resistance
- eGFR > 70 mL/min

Primary Endpoint:

HIV-1 RNA <50 c/mL for EVG/COBI/FTC/TDF at Week 12 after simplification

Secondary Endpoints:

Safety and tolerability of EVG/COBI/FTC/TDF over 24 and 48 weeks
HIV-1 RNA <50 c/mL at Week 24 and Week 48

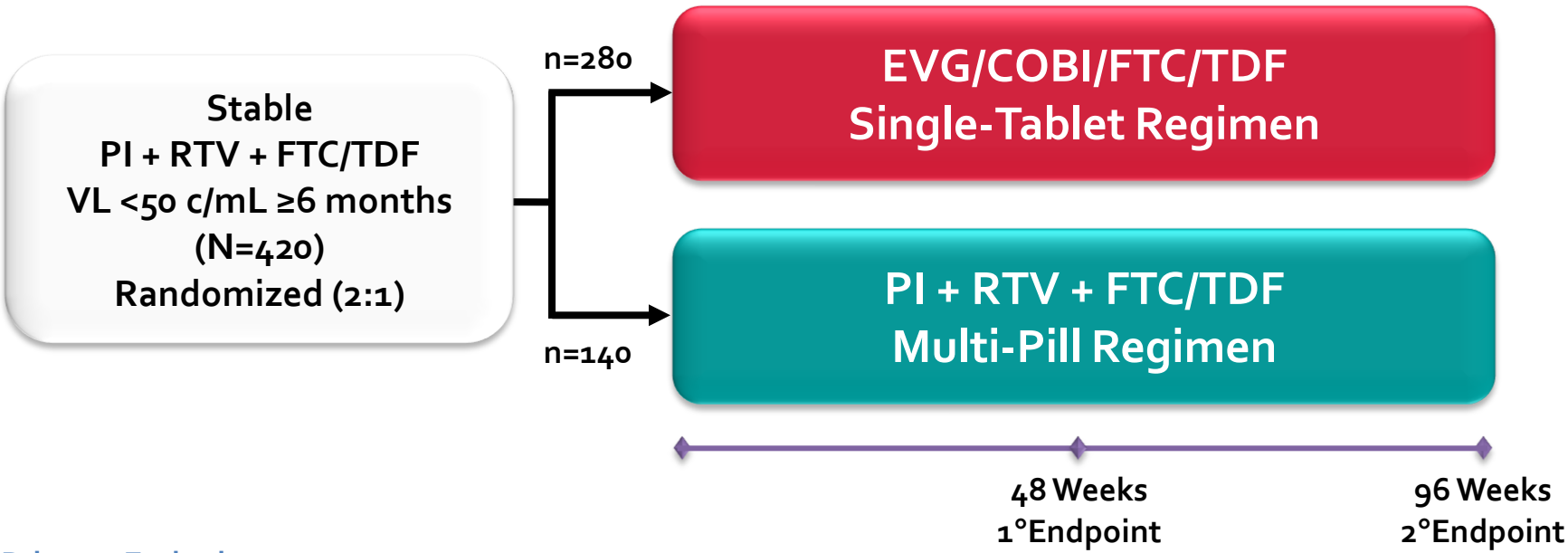
Mills A, *et al. HIV DART* 2012; San Diego

GS-0115: STRATEGY/PI

PI + RTV + FTC/TDF Simplification to EVG/COBI/FTC/TDF

Study Design

Multicenter, international, randomized, open-label, Phase 3b, 96-week study



Primary Endpoint:

Non-inferiority to PI + RTV + FTC/TDF (HIV-1 RNA <50 c/mL at 48 weeks)

Secondary Endpoints:

Change in fasting lipid parameters at 48 weeks

HIV-1 RNA <50 c/mL at 96 weeks

Visual Analog Scale, Adherence Questionnaire, HIV Symptom Index Questionnaire, HIV Treatment Satisfaction Questionnaire Change (HIVTSQc), and Short Form-36 (SF-36)

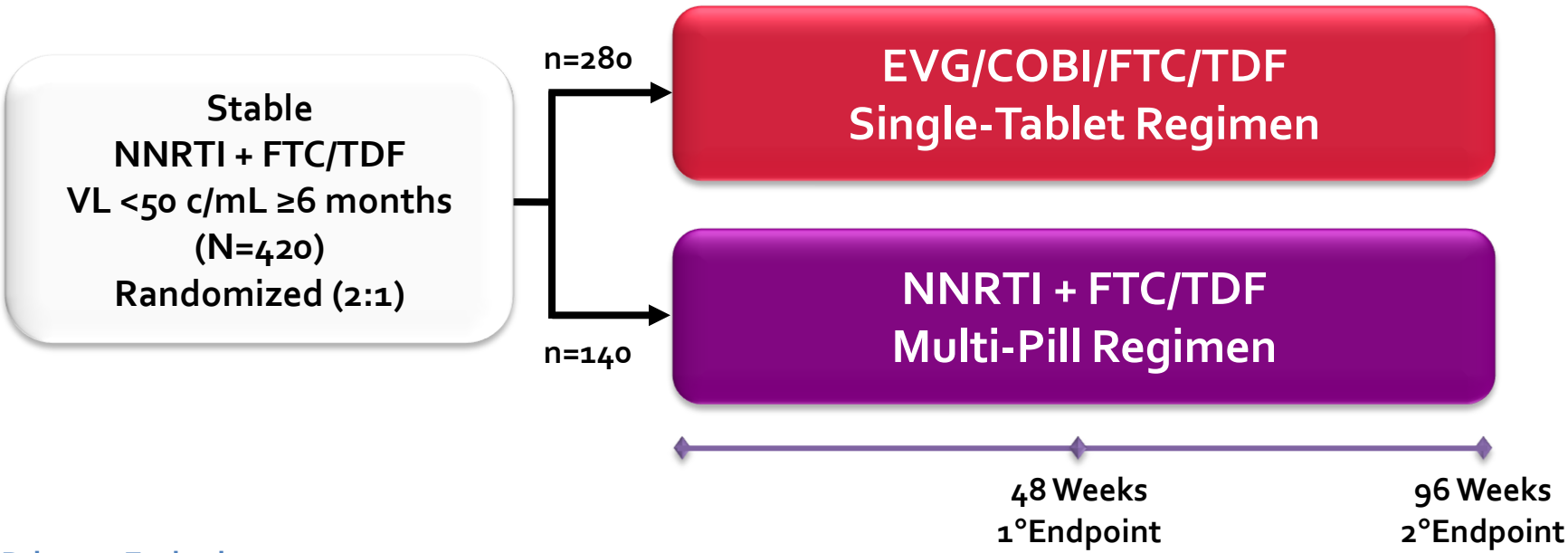
ClinicalTrials.gov identifier: NCT01475838

GS-0121: STRATEGY/NNRTI

NNRTI + FTC/TDF Simplification to EVG/COBI/FTC/TDF

Study Design

Multicenter, international, randomized, open-label, Phase 3b, 96-week study



Primary Endpoint:

Non-inferiority to NNRTI + FTC/TDF (HIV-1 RNA <50 c/mL at 48 weeks)

Secondary Endpoints:

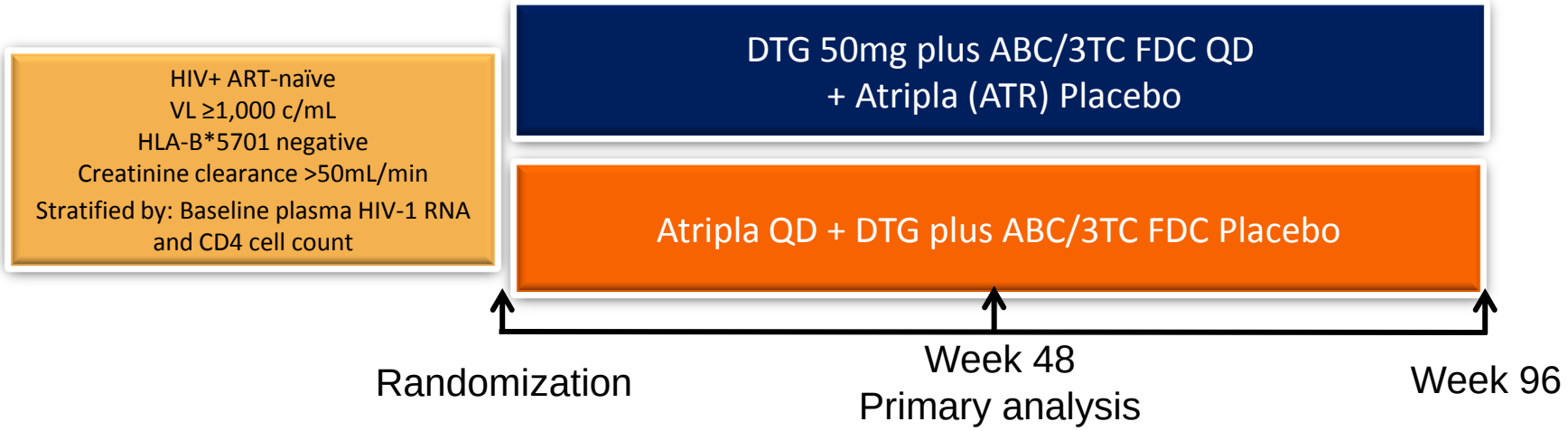
Change in fasting lipid parameters at 48 weeks
Undetectable viral load (<50 c/mL) at 96 weeks
Visual Analog Scale, Adherence Questionnaire, HIV Symptom Index Questionnaire, HIV Treatment Satisfaction Questionnaire Change (HIVTSQc), and Short Form-36 (SF-36)

ClinicalTrials.gov identifier: NCT01495702

Elvitegravir/cobicistat
Efficacy Studies

- **High rate of success in naïve patients**
  - Non inferior to EFV and ATV/r
- **Adequate for switching from a PI-, NNRTI- or RAL-based regimens**
- **Good tolerability**
  - Impact on creatinine clearance/serum creatinine
- **Low genetic barrier**
- **Convenient (STR)**
  - Interactions secondary to cobicistat

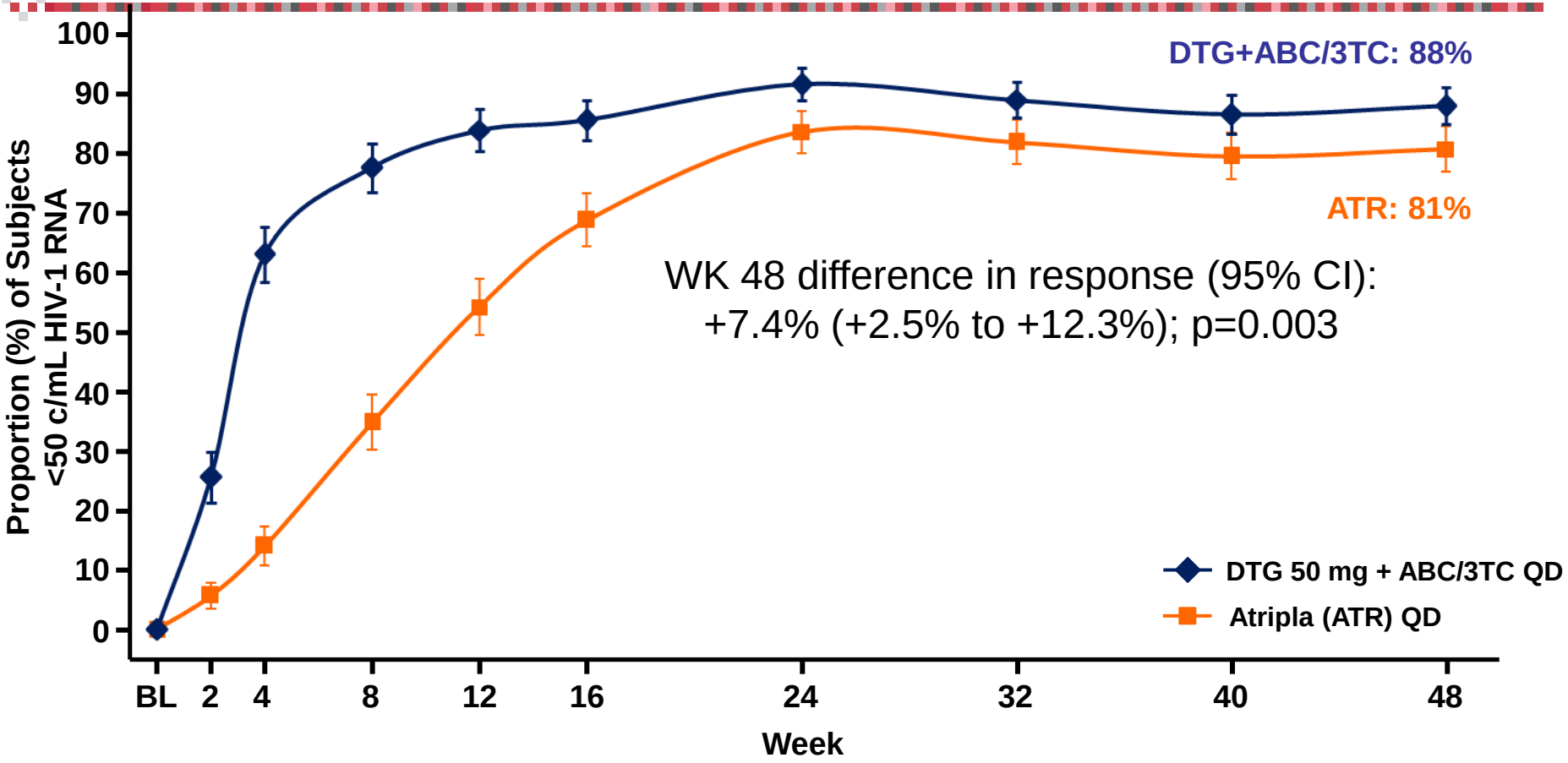
Study Design



Primary endpoint:
Proportion with HIV-1 RNA <50 c/mL at Week 48, FDA snapshot analysis, -10% non-inferiority margin with pre-specified tests for superiority
Secondary endpoints:
Tolerability, long-term safety, immunologic, health outcome and viral resistance

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Proportion (95% CI) of Subjects <50 c/mL (FDA Snapshot)



- DTG 50mg +ABC/3TC QD was statistically superior to Atripla at Week 48 (primary endpoint)
- Subjects receiving DTG +ABC/3TC achieved virologic suppression faster than Atripla, median time to HIV-1 RNA <50c/mL of 28 days (DTG +ABC/3TC) vs 84 days (Atripla), P<0.0001

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

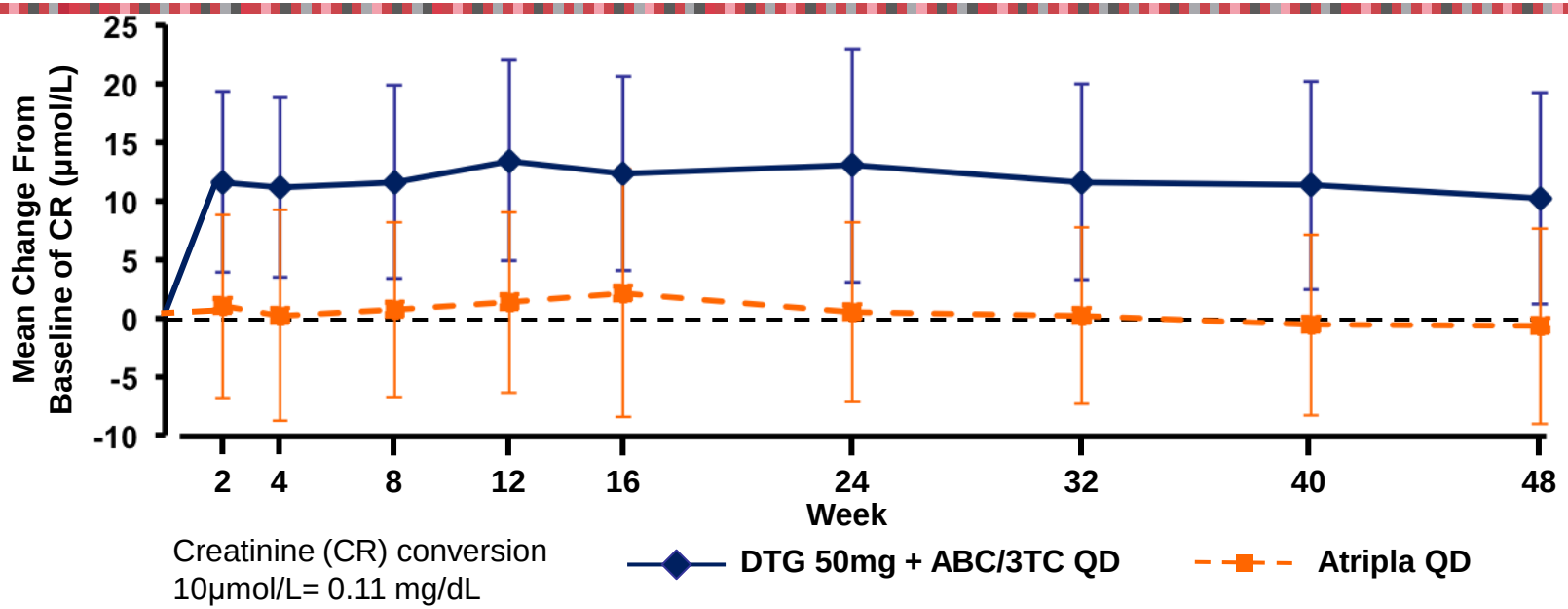
Virology: Resistance

	DTG 50mg +ABC/3TC QD (N=414)	Atripla QD (N=419)
Subjects with PDVF	**18 (4%)**	**17 (4%)**
PDVF genotypic population	**11**	**9**
PDVF Genotypic (RT Results at Baseline and PDVF)	**9**	**9**
NRTI tmt-emergent major mutations	0	1(K65R)
NNRTI tmt-emergent major mutations	0	4 (K101E, K103N, G190A)*
PDVF Genotypic (IN Results at Baseline and PDVF)	**7**	**7**
INI-r tmt-emergent major substitution	0**	0

* n=1 with K101E, n=1 with K103N, n=1 with G190A and n=1 with K103N+G190A
**E157Q/P polymorphism detected with no significant change in IN phenotypic susceptibility

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Renal Safety



	DTG 50 mg+ABC/3TC QD	Atripla QD
Urine albumin/creatinine		
Median change (IQR) from baseline (mg/mmol CR) to Week 48	0.00 (-0.30, 0.30)	+0.05 (-0.20, 0.30)

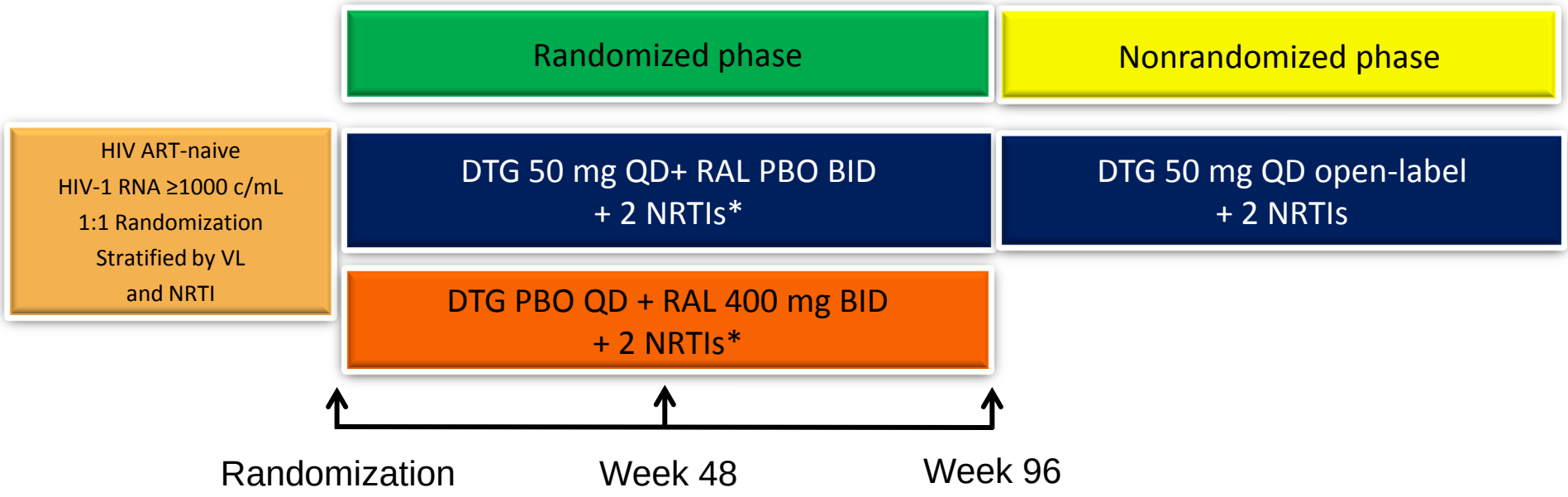
- **Small increase in creatinine due to blockade of Cr secretion[1]**
- **DTG does not affect actual glomerular filtration rate (GFR)[1]**

1. Koteff, J. et al. Br J Clin Pharmacol. In press; 2012 Aug.

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

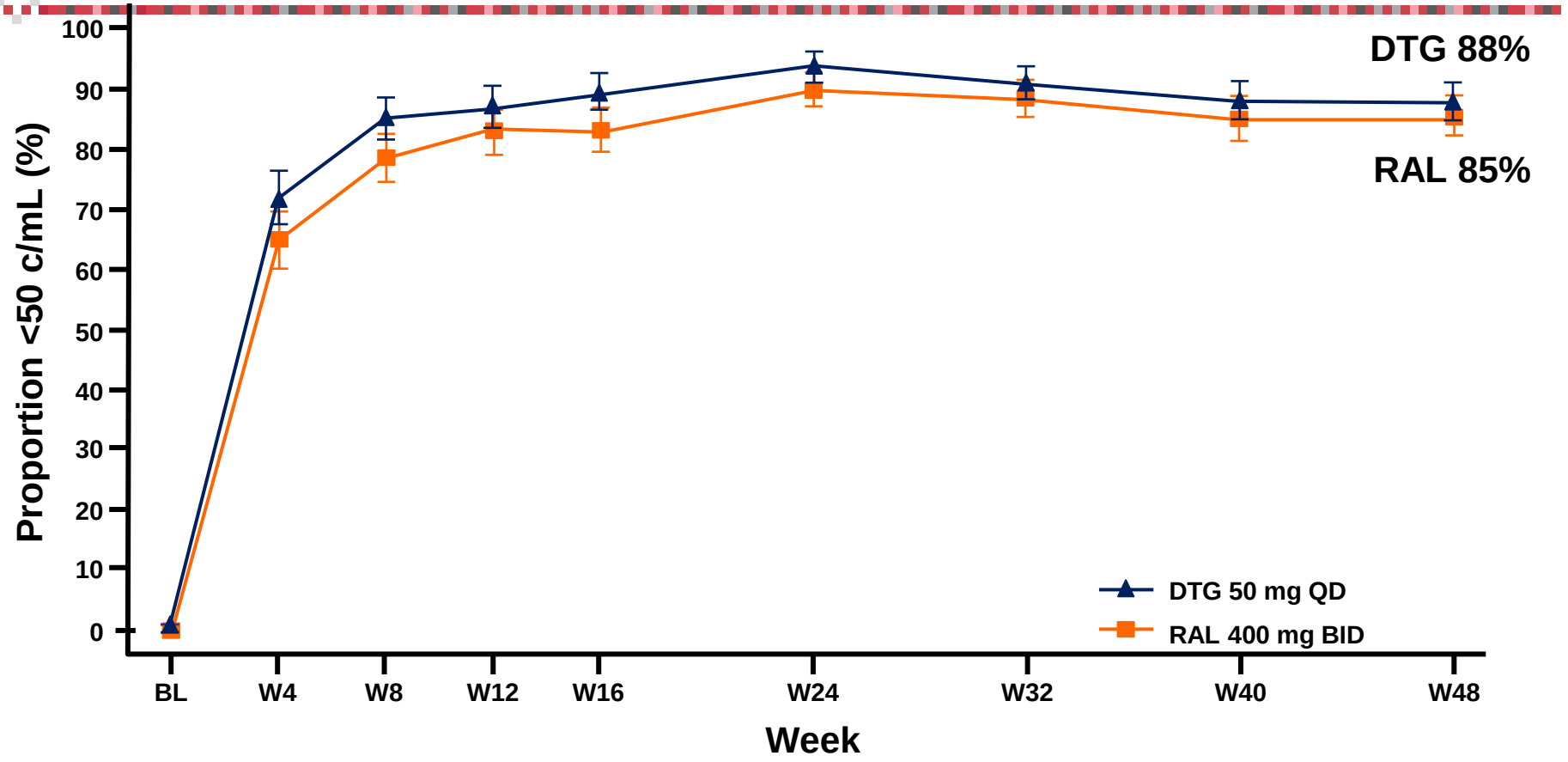
SPRING-2 (ING113086) Study Design

- **Phase III, randomized, double-blind, double-placebo, multicenter, parallel-group, non-inferiority study, ART-naive patients**
- **All arms include 2 NRTI backbone given once daily (ABC/3TC or TDF/FTC)**
- **Primary endpoint: % <50 c/mL at 48 weeks (“snapshot”) , non-inferiority margin 10%**



*Investigator’s selection ABC/3TC or TDF/FTC

Virologic Success Over Time



	Median (IQR) Change From Baseline CD4⁺ Cell Count (cells/mm³)					
	W4		W24		W48	
DTG 50 mg QD	87	(26, 149)	183	(100, 295)	230	(128, 338)
RAL 400 mg BID	88	(32, 163)	182	(94, 296)	230	(139, 354)

Protocol-Defined Virologic Failure (PDVF): Genotype

- **Amongst DTG-treated subjects, no integrase nor NRTI mutations were detected through Week 48**

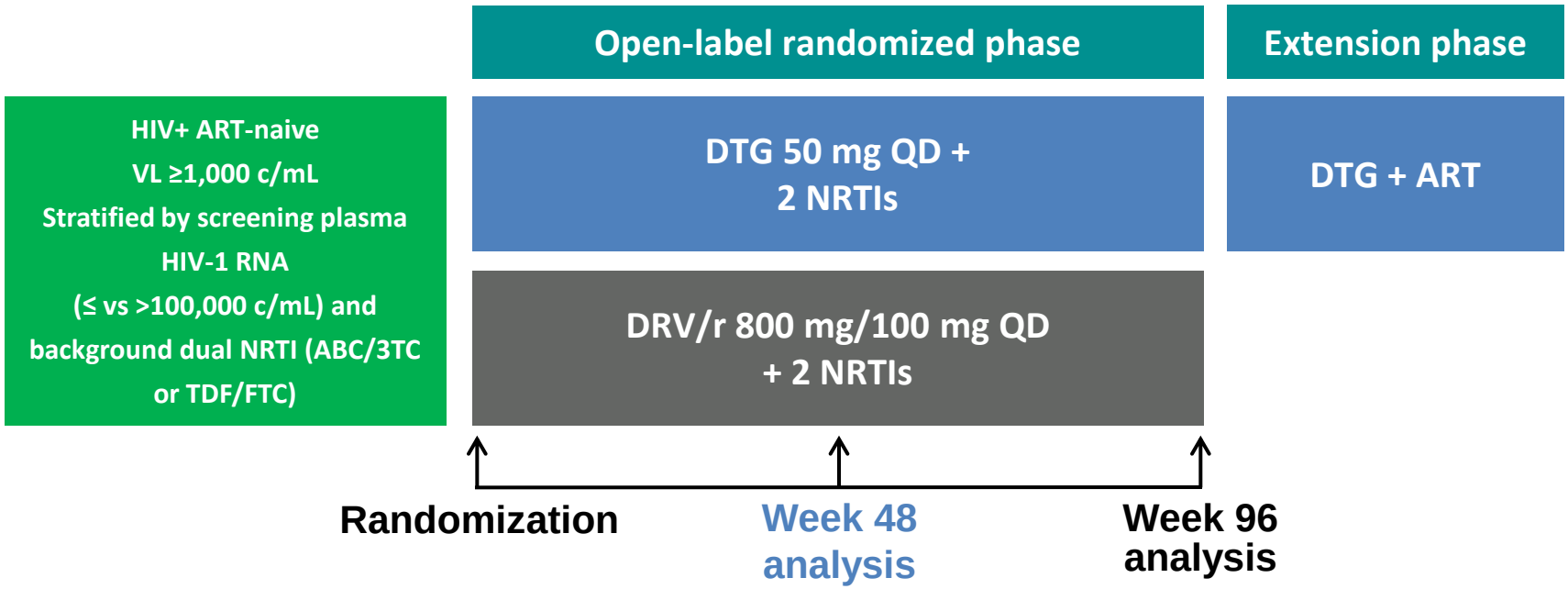
	DTG 50 mg QD n=411	RAL 400 mg BID n=411
Subjects with PDVF	**20 (5%)**	**28 (7%)**
IN genotypic results at BL and time of PDVF	8	18
INI-r mutations	**0**	**1/18 (6%)[a]**
PR/RT genotypic results at BL and time of PDVF	12	19
NRTI-r mutations	**0**	**4/19 (21%)[a,b,c,d]**

Mutations by subject in the RAL 400 mg BID arm:

[a] T97T/A, E138E/D, V151V/I, N155H + A62A/V, K65K/R, K70K/E, M184V

[b, c, d] A62A/V (n=1), M184M/I (n=1), M184M/V (n=1)

FLAMINGO (ING114915) Study Design

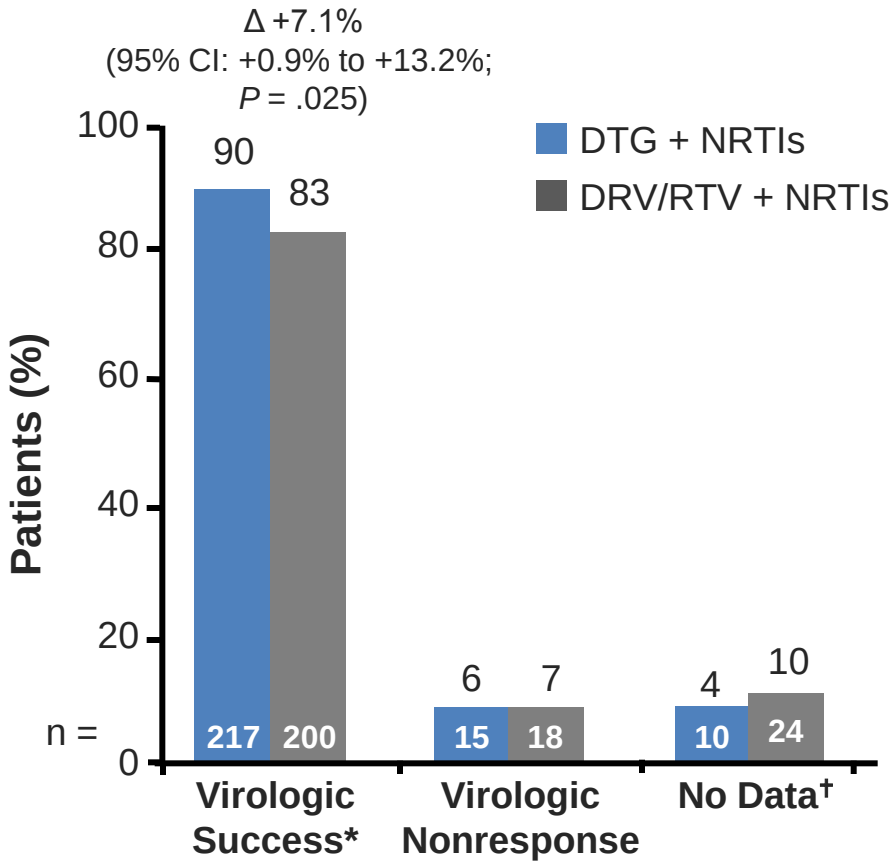


Primary endpoint: proportion with HIV-1 RNA <50 c/mL at Week 48, FDA Snapshot analysis, -12% non-inferiority (NI) margin

Secondary endpoints: antiviral activity, safety, tolerability, health outcomes and viral resistance

Feinberg et al. ICAAC 2013; Denver, CO. Abstract H-1464a.

FLAMINGO: DTG Superior to DRV/RTV + 2 NRTIs in Treatment-naive Patients at Week 48

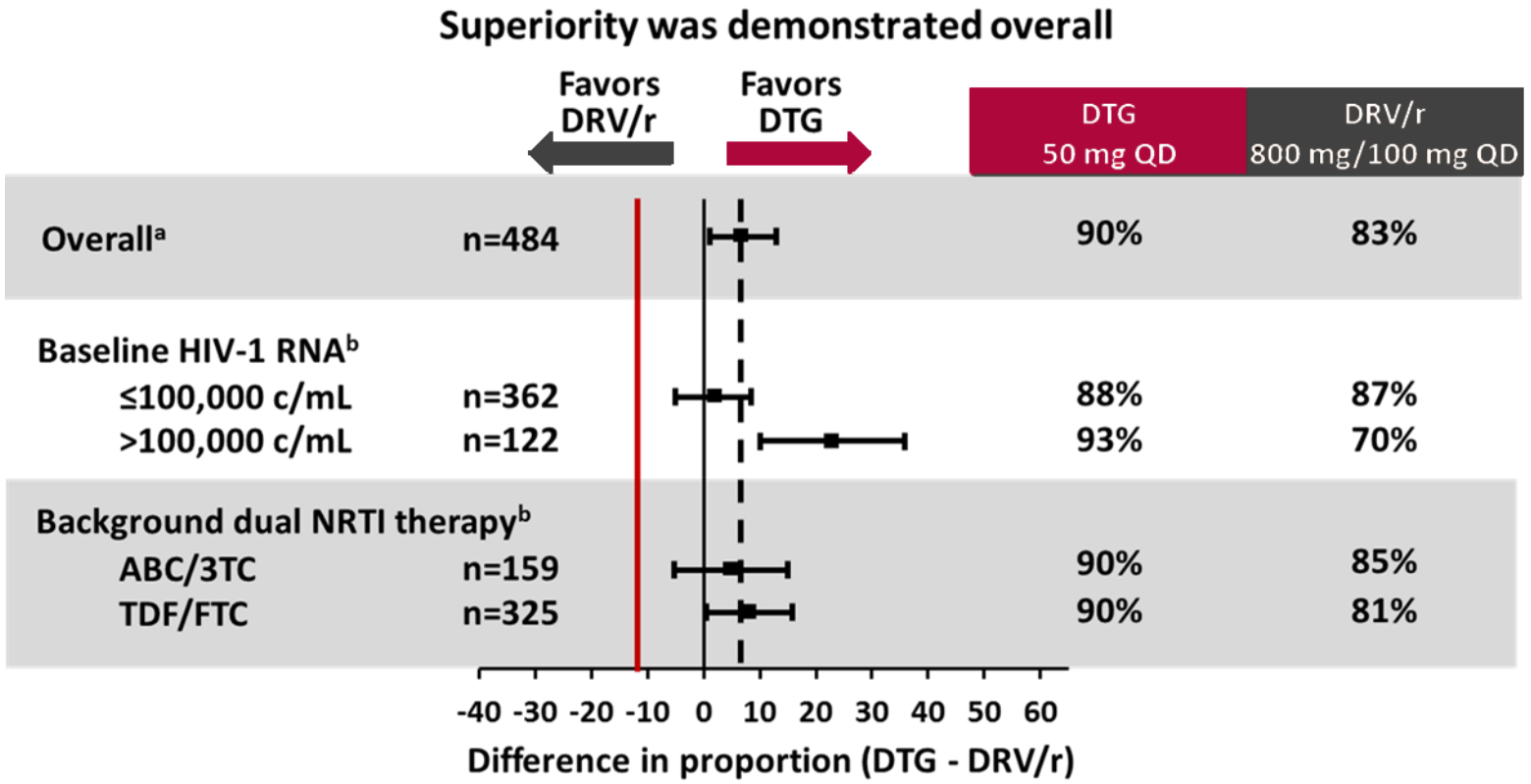


- **2 pts (<1%) in each arm met criteria for virologic failure**
  - No patients with resistance in either arm
- **Similar increase in CD4+ cell count at Week 48:**
  - +210 cells/mm^3 in each arm

*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm
†Discontinued for AE, death, or missing data.

Feinberg J, et al. ICAAC 2013. Abstract H-1464a.

Snapshot by Randomization Strata at Week 48

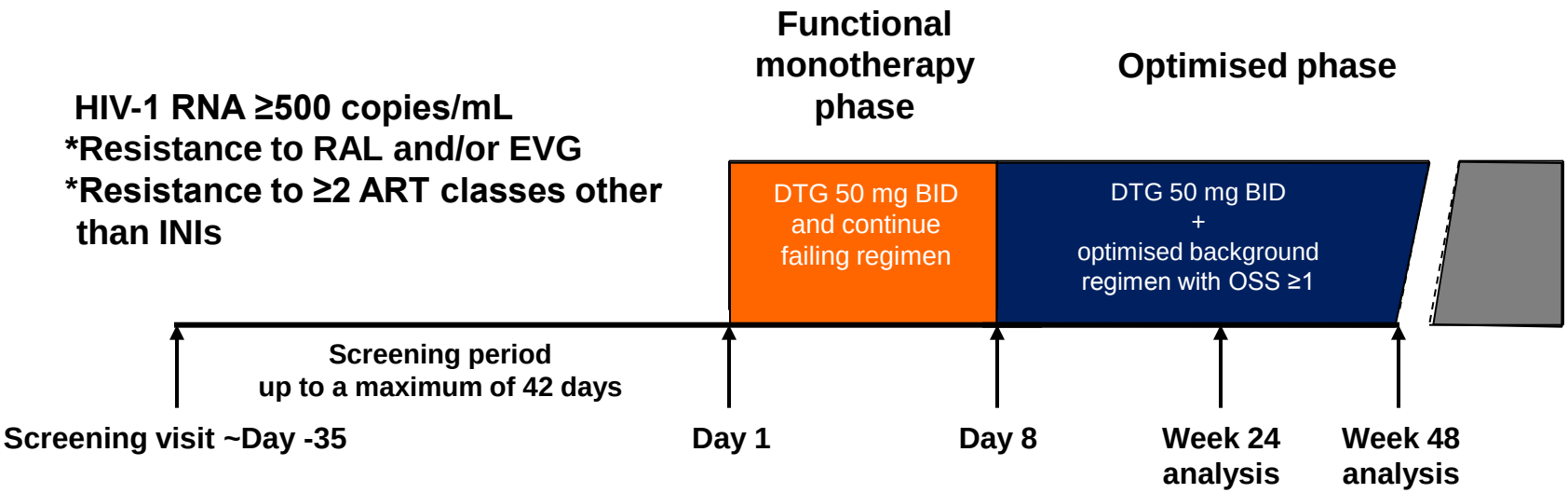


[a] Adjusted difference (DTG - DRV/r) based on Cochran-Mantel-Haenszel stratified analysis adjusting for baseline HIV-1 RNA and background dual NRTI therapy

[b] Unadjusted differences support non-inferiority of DTG vs DRV/r within baseline HIV-1 RNA and background dual NRTI strata.

Feinberg et al. ICAAC 2013; Denver, CO. Abstract H-1464a.

Study Design



*Screening or documented historical evidence.

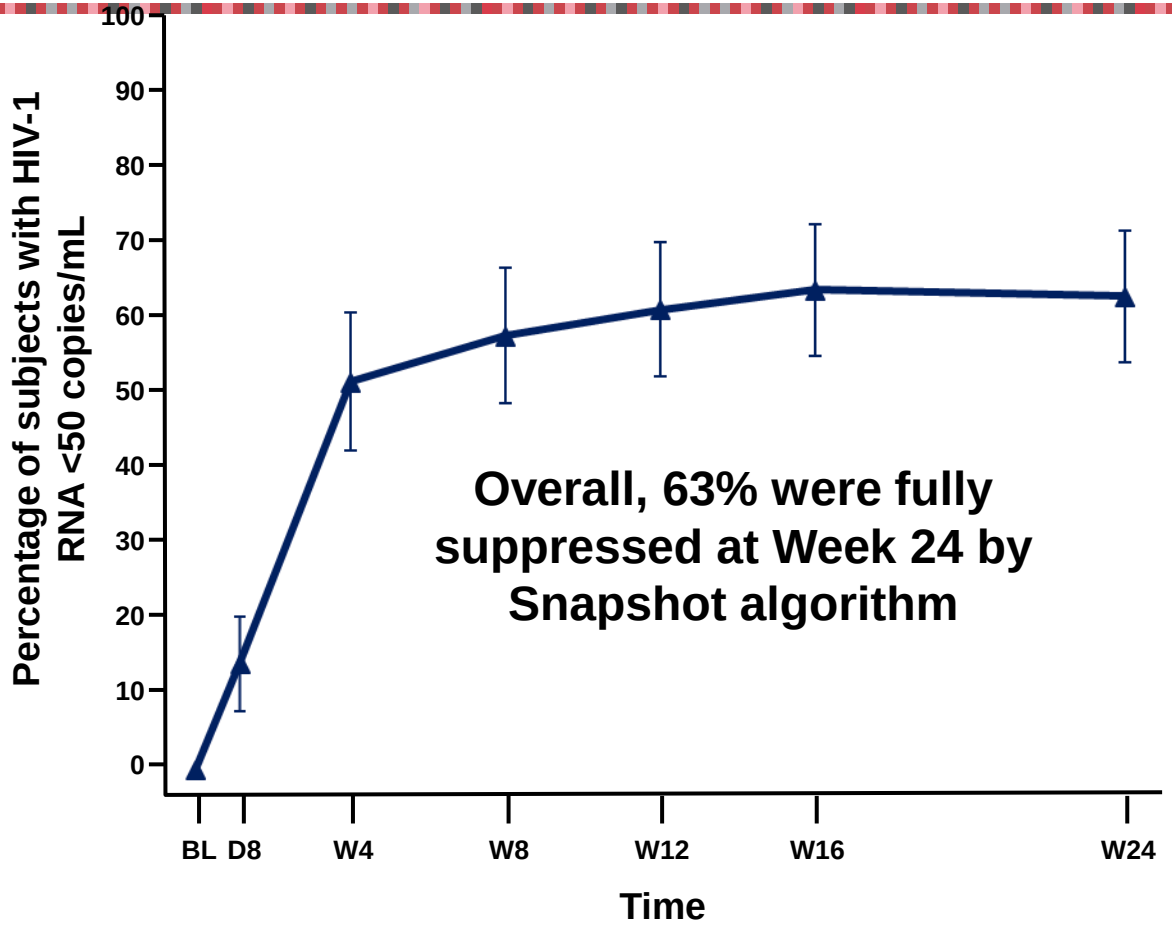
OSS (overall susceptibility score) determined by Monogram Biosciences

Nichols, G. et al. HIV11, Glasgow, UK; 11-15 November 2012 ; Oral # O232.

Day 8 and Week 24 Efficacy Endpoints

VIKING-3

- **Day 8 change from BL: -1.43 log_{10} copies/mL, *P*<0.001**
  - 95% CI, -1.52 to -1.34 (ITT-E, N=183)
- **Week 24 by Snapshot (MSDF): 72/114 (63%) <50 copies/mL**
  - 37/114 (32%) were virologic non-responders
    - 6/114 (5%) changed OBR
  - Only 5/114 (4%) were non-responders for discontinuation due to AEs



Week 24 population (N=114) was those subjects who had opportunity to reach Week 24 at time of data cut-off

Nichols, G. et al. HIV11, Glasgow, UK; 11-15 November 2012 ; Oral # O232.

Week 24 Response by Mutation Category and OBR Overall Susceptibility Score (OSS)

	HIV-1 RNA <50 copies/mL at Week 24 (Snapshot) (N=101)			
Derived IN mutation group*	OSS=0	OSS=1	OSS≥2	Total
No Q148,** n (%)	2/2 (100)	24/29 (83)	31/41 (76)	57 (79)
Q148 + 1,† n (%)	2/2 (100)	3/7 (43)	4/11 (36)	9 (45)
Q148 +≥ 2,† n (%)	1/2 (50)	0/7 (0)	0	1 (11)

* Virus from the ≥2 primary mutations group was re-categorized to the Q148+ or No Q148 groups as appropriate
**143, 155, 66, 92, historical resistance evidence only. †G140A/C/S, E138A/K/T, L74I

- **In multivariate analyses of baseline factors on Week 24 response rates, the presence of Q148 + ≥2 mutations and increasing DTG FC were highly correlated with fewer subjects achieving <50 copies/mL (*P*≤0.001)**
- **Increasing OBR activity score did not impact response**
  - In patients with OSS=1, the most common active ARVs were TDF, T20, MVC and ETR
  - Overall, only 23% (28/114) received a PI/r as the fully active ARV in OBR
  - In most cases, the 2nd and 3rd active ARV was an NRTI

Nichols, G. et al. HIV11, Glasgow, UK; 11-15 November 2012 ; Oral # O232.

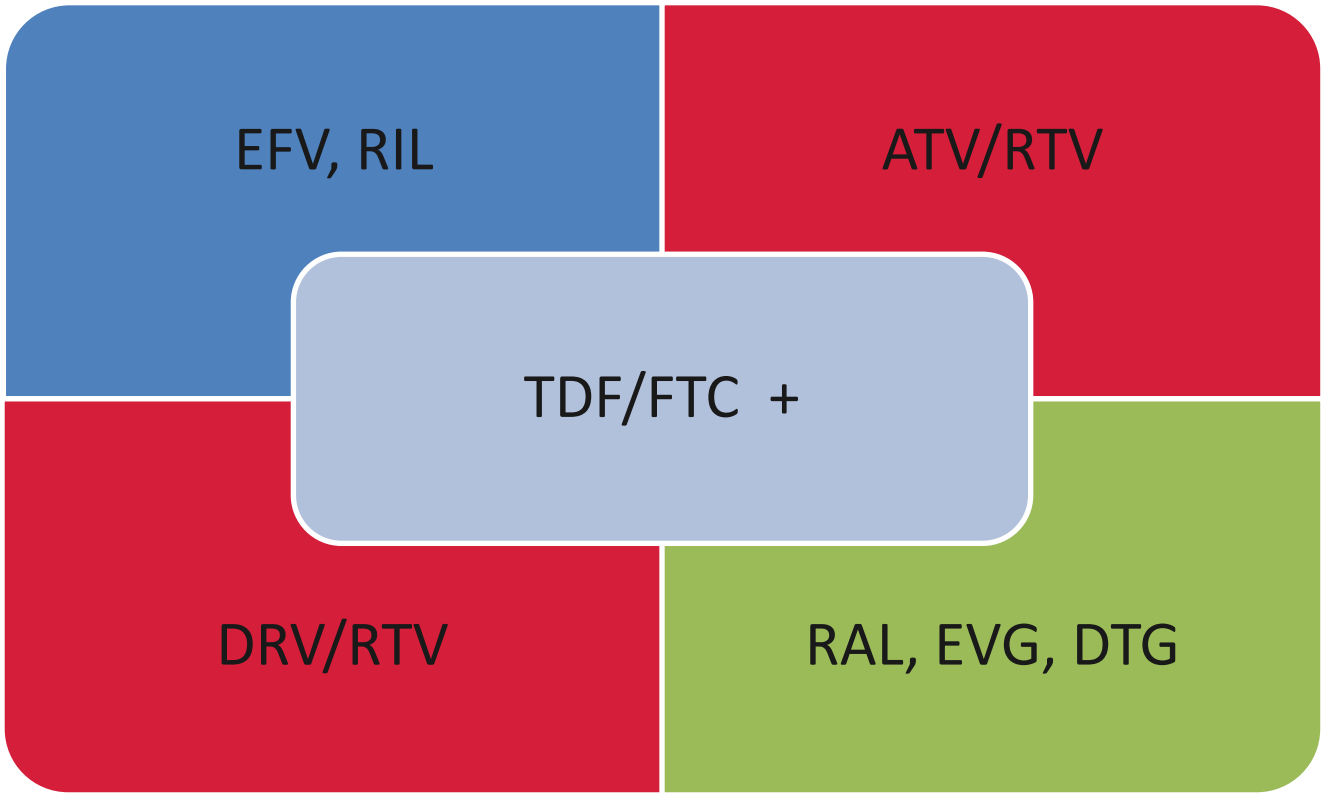
Dolutegravir
Efficacy Studies

- **High rate of success in naïve patients**
  - Superior to EFV and DRV/r. Non inferior to RAL
- **Good tolerability**
  - Impact on creatinine clearance/serum creatinine
- **High genetic barrier**
  - No development of resistance after failure in naïve patients
  - High rate of success in deep salvage therapy
- **Convenient (STR)**
  - No significant interactions

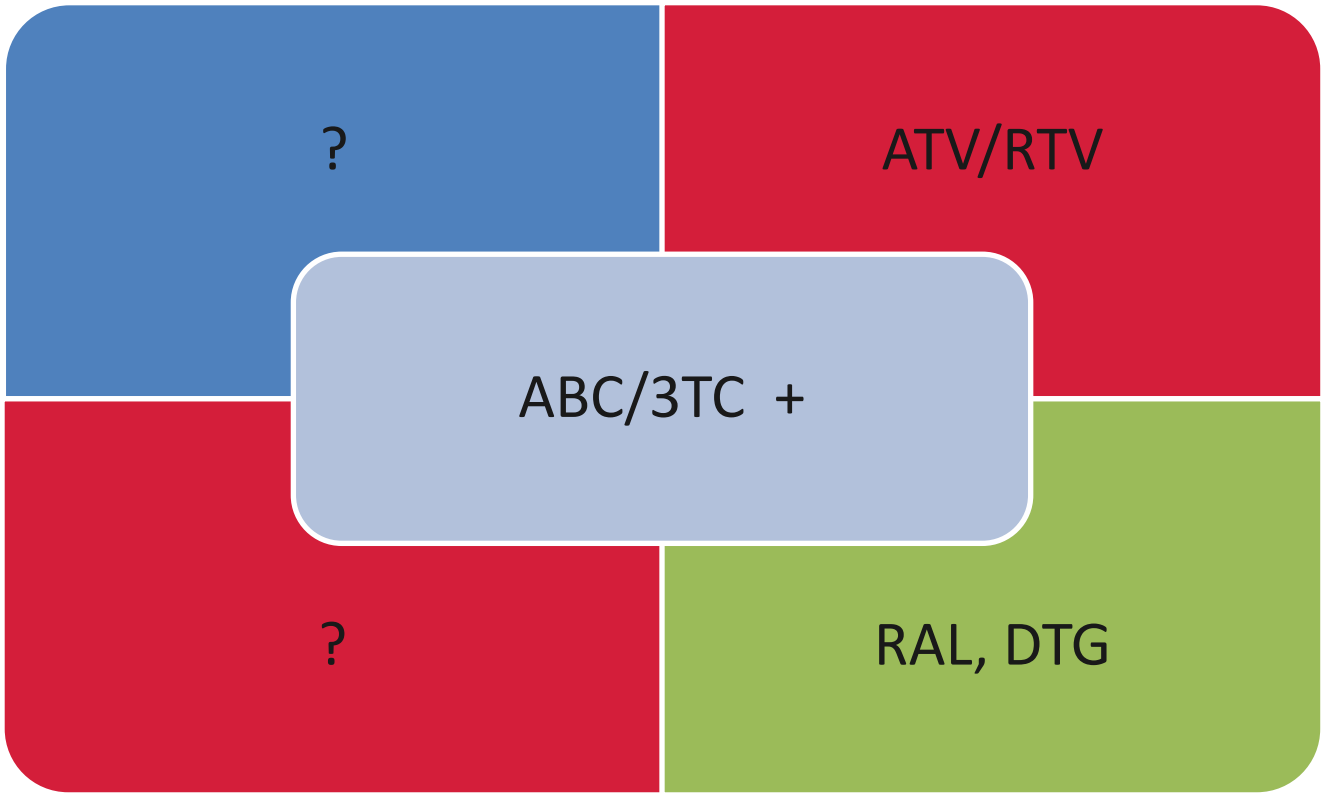
New drugs
Will they have an impact on .....?

- Virological efficacy
  - Probably not
- Resistance
  - Dolutegravir
- Tolerability
  - Rilpivirine, Dolutegravir
- Long term toxicity
  - No
- Convenience
  - New STR (Rilpivirine, Elvitegravir/c, Dolutegravir)
- Cost
  - Certainly not

Initial Regimen: Recommended/Preferred Agents



Initial Regimen: Recommended/Preferred Agents



Which Patient for EFV?

Considerations in Favor

- Effective across HIV-1 RNA, CD4+ strata[2]
- Most experience of all NNRTIs
- Most experience of all preferred drugs
- Coformulation; 1 pill QD[1]

Considerations Against

- CNS effects[1]
- High risk of resistance at virologic failure[3]
- Drug–drug interactions with other drugs metabolized by CYP system[1]
- ? Potential for teratogenesis in early pregnancy[4]

1. TDF/FTC/EFV [package insert]. 2. Ribaudo HJ, et al. J Infect Dis. 2008;197:1006-1010. 3. Gallant J, et al. N Engl J Med. 2006;354:251-260. 4. DHHS Perinatal Guidelines. July 2012. 5. Daar E, et al. Ann Intern Med. 2011;154:445-456

Which Patient for Boosted PIs?

Considerations in Favor

- Effective across HIV-1 RNA, CD4+ strata[1,2]
- Little/no emergence of resistance at VF[1,2]
- Low risk for new resistance to develop in those with transmitted resistance
- Preferred agents in pregnancy (ATV/RTV, LPV/RTV)[3]

Considerations Against

- Drug–drug interactions with other drugs metabolized by CYP system[5,6]
- Concerns about renal function (greatest concern when combined with TDF)[1,4]
- Variable lipid effects[1,2]
- No coformulations with NRTIs

1. Molina JM, et al. Lancet. 2008;372:646-655. 2. Ortiz R, et al. AIDS. 2008;22:1389-1397. 3. DHHS Perinatal Guidelines. July 2012. 4. Mocroft A, et al. AIDS. 2010;24:1667-1678. 5. Atazanavir [package insert]. 6. Darunavir [package insert].

Which Patient for RAL?

Considerations in Favor

- Effective across HIV-1 RNA, CD4+ strata[1]
- Few adverse events[1]
- Few drug–drug interactions[2]
- Limited effects on lipids[3]

Considerations Against

- No coformulations with NRTIs
- Twice-daily dosing[2,4]
- High risk of resistance at VF[3]

1. Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;63:77-85. 2. Raltegravir [package insert].
3. Lennox J, et al. Lancet. 2009;374:796-806. 4. Eron JJ Jr, et al. Lancet Infect Dis. 2011;11:907-915.

And what about new drugs?

Which Patient for RPV?

Considerations in Favor

- Superior vs EFV at lower VL[1]
- Fewer CNS adverse events than EFV[2]
- Coformulated/1 pill daily

Considerations Against

- Less effective at high BL VL[2] (not recommended at high VL and low CD4+)[3]
- Food requirement[4]
- Restricted use with PPIs or H2 blockers[4]
- High risk of resistance and cross-resistance with other NNRTIs at VF[2]

1. Cohen C, et al. Glasgow 2012. Abstract O425. 2. Cohen C, et al. AIDS. 2013;27:939-950.
3. DHHS Guidelines. February 2013. 4. TDF/FTC/RPV [package insert].

Which Patient for TDF/FTC/EVG/COBI?

Considerations in Favor

- Coformulated/1 pill dally
- Once-daily INSTI regimen
- Noninferior to EFV and ATV/RTV across HIV-1 RNA, $CD4+$ strata[1,2]

Considerations Against

- Includes pharmacologic booster
- Drug–drug interactions[6]
- High risk of resistance at VF[1-4]
- Cross resistance with RAL[5]
- Concerns about monitoring renal function with COBI[6]

1. Zolopa A, et al. J Acquir Immune Defic Syndr. 2013;63:96-100. 2. Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;62:483-486. 3. Sax PE, et al. Lancet. 2012;379:2439-2448. 4. DeJesus E, et al. Lancet. 2012;379:2429-2438. 5. DeJesus E, et al. IAS 2007. Abstract TUPEB032. 6. TDF/FTC/EVG/COBI [package insert].

Tabella 3 – Preferenze dei farmaci nei regimi raccomandati (preferiti e alternativi), all'interno delle classi principali (NRTI, NNRTI, IP/r, INI) e in rapporto a specifiche condizioni.

CONDIZIONI	NRTI *backbone*		NNRTI		IP/r		INI	
	1° scelta	2° scelta	1° scelta	2° scelta	1° scelta	2° scelta	1° scelta	2° scelta
Dislipidemia/ Rischio cardiovascolare	TDF/FTC	ABC/3TC	NVP RPV	EFV	ATV+r DRV+r	LPV/r	DTG EVG/COBI RAL	
Insufficienza renale	ABC/3TC	TDF/FTC	EFV NVP RPV		DRV+r	ATV+r LPV/r	DTG RAL	
Problematiche gastrointestinali	ABC/3TC TDF/FTC		EFV NVP RPV		ATV+r DRV+r	LPV/r	DTG EVG/COBI RAL	

Uso contraccettivi orali	ABC/3TC TDF/FTC		RPV	EFV NVP	ATV/r	DRV+r LPV/r	DTG RAL	EVG/COBI
Uso concomitante PPI (Inibitori di Pompa Protonica)	ABC/3TC TDF/FTC		EFV NVP		DRV+r LPV/r	ATV+r	DTG EVG/COBI RAL	
Terapia sostitutiva con metadone	ABC/3TC TDF/FTC		RPV	EFV NVP	ATV+r DRV+r	LPV/r	DTG RAL	EVG/COBI
Alto grado di interazioni farmacologiche	ABC/3TC TDF/FTC			EFV NVP RPV		ATV+r DRV+r LPV/r	DTG RAL	EVG/COBI
Necessità di miglioramento dell'aderenza/riduzione del *pill burden*	ABC/3TC TDF/FTC		EFV NVP RPV		ATV+r; DRV+r	LPV/r	DTG EVG/COBI	RAL
Co-trattamento con farmaci anti-HCV	TDF/FTC	ABC/3TC	RPV	EFV NVP	ATV+r	DRV+r LPV/r	DTG RAL	EVG/COBI
Co-trattamento con farmaci Tubercolari	ABC/3TC TDF/FTC		EFV	NVP RPV		ATV+r DRV+r LPV/r	RAL	DTG EVG/COBI
Disturbi cognitivi sintomatici (MND, HAD)	ABC/3TC	TDF/FTC	NVP	EFV RPV	DRV+r LPV/r	ATV+r	DTG RAL	EVG/COBI
Disturbi psichiatrici maggiori	ABC/3TC TDF/FTC		NVP RPV	EFV	ATV+r DRV+r LPV/r		DTG EVG/COBI	RAL
Osteoporosi	ABC/3TC	TDF/FTC	EFV NVP	RPV	ATV+r DRV+r	LPV/r	RAL	DTG EVG/COBI
Gravidanza	ABC/3TC TDF/FTC		NVP	EFV RPV	ATV+r LPV/r	DRV+r	RAL	DTG EVG/COBI

- Il criterio principale della prima/seconda scelta si basa su dati da studi randomizzati o osservazioni. Per i farmaci in cui le evidenze non sono considerate sufficienti o per i quali vi siano evidenze contrarie, si è scelto di indicarli come seconda scelta.
- ATV+r rispetto a DRV+r ha dati comparabili sulla dislipidemia. ATV+r /non è associato ad un aumentato rischio di malattie cardio e cerebrovascolari, mentre per DRV+r non si dispongono di osservazioni sufficienti al riguardo.
- EVG/COBI è considerato e valutato solo nella co-formulazione comprendente TDF/FTC/EVG/COBI.
- TDF/FTC/EVG/COBI non deve essere utilizzato con e-GFR<70 ml/min/1.73m^2).
- La valutazione come 2° scelta di ATV+r e LPV/r nell'insufficienza renale è riferita soprattutto ai regimi comprendenti TDF/FTC come backbone nucleos(t)idico.
- Per il grado delle interazioni farmacologiche tra i farmaci si richiama alle schede tecniche e/o alle indicazioni presenti nella relativa parte delle LG.
- La valutazione della scelta nei pazienti con co-trattamento con farmaci anti-HCV è basata sulle interazioni con DAA di prima generazione e con ribavirina.
- La valutazione della scelta nei pazienti con Tubercolosi è basata sulla compatibilità dei farmaci antiretrovirali con rifampicina o rifabutina in base al profilo di interazione.
- La co-somministrazione di ATV+r con PPI non è raccomandata; quella con RPV è controindicata.
- La co-somministrazione di ATV+r e contraccettivi orali è compatibile utilizzando dosi di etinil-estradiolo pari o superiori a 35 mcg.
- Osteoporosi definita da criterio OMS con DXA e/o anamnesi per fratture osteoporotiche da trauma minimo.
- "/" = co-formulato; "+"= non co-formulato;"r"=RTV come booster.

Individualizing First-line Therapy: Specific Circumstances

Circumstance	Agents
No genotype	▪ Use boosted PI
High HIV-1 RNA	▪ Caution with RPV, ABC?,
Renal disease	▪ Caution with TDF; monitoring complicated with COBI
Dyslipidemia	▪ RAL, RPV most lipid neutral
CV risk factors	▪ Possible association with ABC, LPV/RTV ▪ No data for DRV/RTV, INSTIs, MVC
Pregnancy	▪ Preferred: ZDV/3TC + NVP, LPV/RTV, or ATV/RTV ▪ EFV can be used after first 5-6 wks
Chronic HBV infection	▪ Preferred TDF + 3TC or FTC ▪ Alternative is entecavir
Decreased BMD	▪ Caution with TDF
Concerns about CNS effects	▪ Caution with EFV for at least first mo

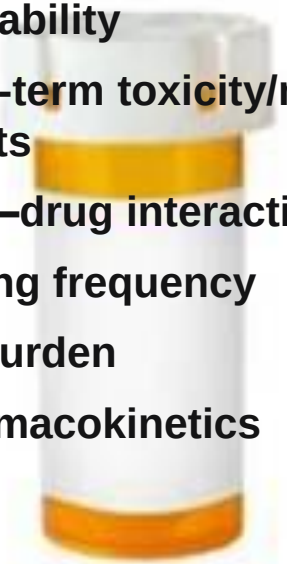
Considerations When Selecting First-line Antiretroviral Therapy

Patient/Viral Factors

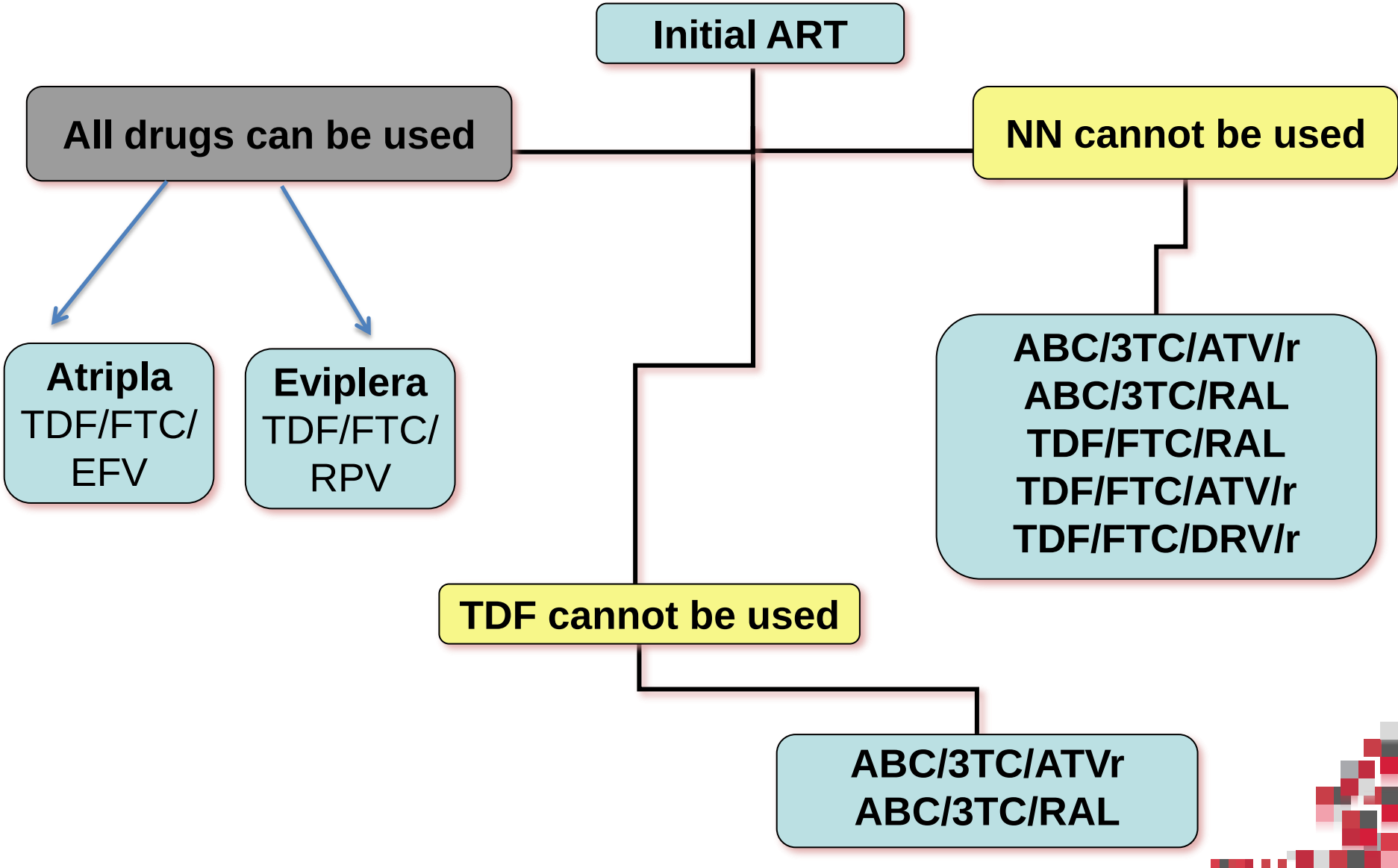
- **Baseline CD4+ cell count/ HIV-1 RNA level**
- **Age**
- **Sex**
- **Occupation (eg, work schedule)**
- **Comorbid conditions (eg, CV risk, renal abnormalities)**
- **Plans for pregnancy**
- **Access to care**
- **Concurrent medications**
- **Adherence to other medications**
- **Genetics (eg, HLA-B*5701)**
- **Viral tropism**

Antiretroviral Drug Factors

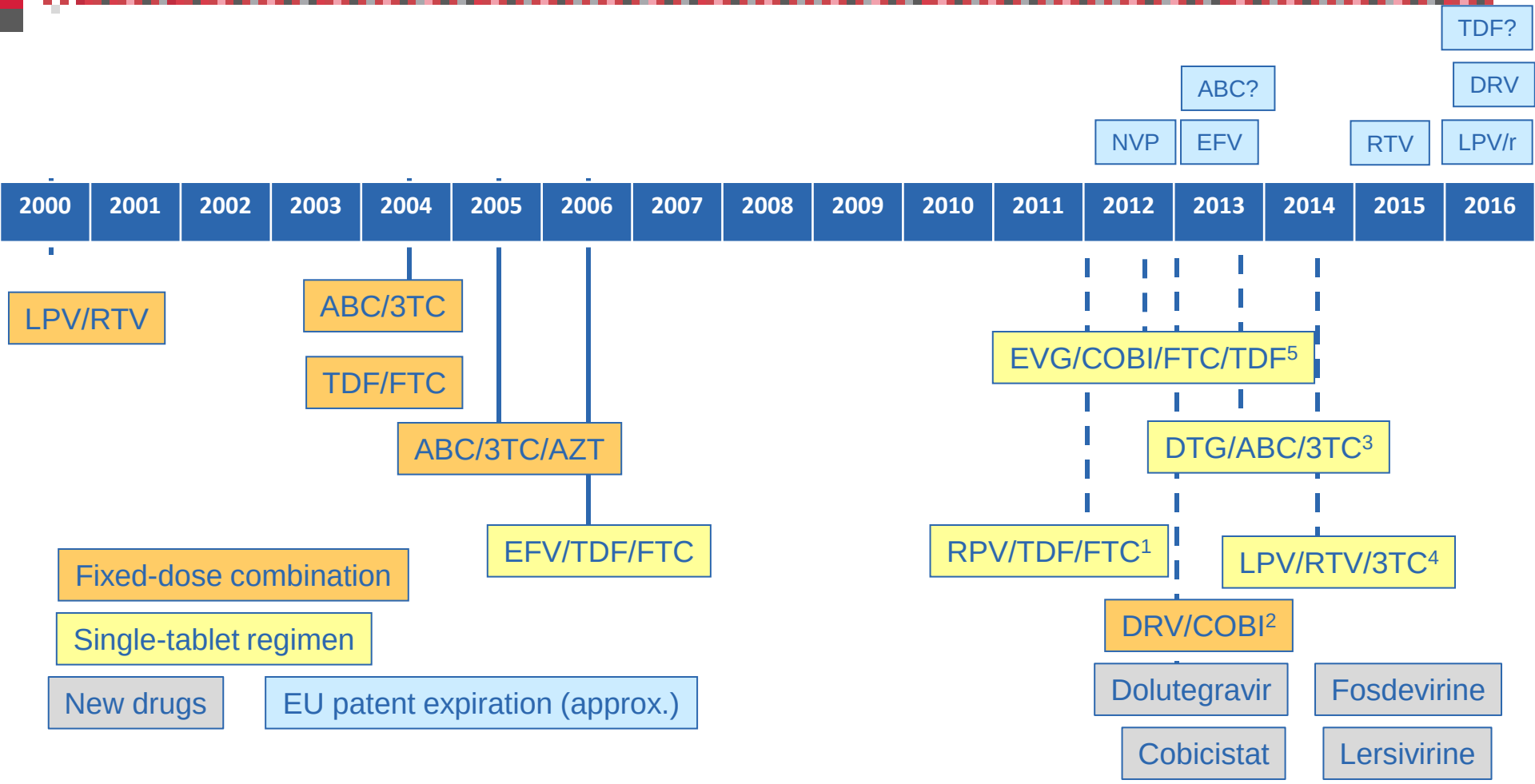
- **Efficacy**
- **Baseline drug resistance**
- **Tolerability**
- **Long-term toxicity/metabolic effects**
- **Drug–drug interactions**
- **Dosing frequency**
- **Pill burden**
- **Pharmacokinetics**
- **Cost**



Proposed Algorithm for Initial ART



Generic Drugs



Grazie!