6th Infectivology Today®

Paestum 15- 16 -17 maggio 2014

"6th INFECtivology TOday"

"Prima linea: dovremmo evitare i PI nella terapia di prima linea per i loro effetti *non desiderati*?"

Giuseppina Liuzzi

Istituto Nazionale per le Malattie Infettive

IRCCS "Lazzaro Spallanzani" Roma

Recommendations for ART Initiation

- ART is recommended for ***all*** HIV-infected ART-naive pts to reduce risk of disease progression and transmission
  - Strength of recommendation varies by CD4+ cell count and risk group (perinatal, heterosexual, other)
  - Pts should be ready to commit to ART and understand benefits and risks of therapy and importance of adherence; individual pts may elect to defer ART
- Selection of a regimen should be individualized on the basis of virologic efficacy, toxicity, pill burden, dosing frequency, drug–drug interaction potential, resistance testing results, and comorbid conditions

DHHS Guidelines. May 2014.

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

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

Individualizing First-line Therapy: Specific Circumstances

No genotype	▪ Use boosted PI
High HIV-1 RNA	▪ Caution with ABC, RPV
Renal disease	▪ Caution with TDF, ATV/RTV; monitoring complicated with COBI and DTG
Dyslipidemia	▪ RAL, DTG, RPV most lipid neutral
CV risk factors	▪ Possible association with ABC, ddI, 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

Tabella 2a – Regimi raccomandati per l'inizio della cART.

	REGIME	RACCOMANDAZIONE (FORZA/EVIDENZA)	RIFERIMENTI BIBLIOGRAFICI
Preferiti	**TDF/FTC+EFV**	[AI]	[1-9]
	ABC/3TC+EFV (se HIV-RNA < 100.000 cp/mL)	[AI]	[4-6,10]
	TDF/FTC/RPV (utilizzabile solo se HIV-RNA < 100.000 cp/mL)	[AI]	[11-13]
	TDF/FTC+ATV+r	[AI]	[6,14-18]
	ABC/3TC+ATV+r (se HIV-RNA < 100.000 cp/mL)	[AI]	[4,5]
	TDF/FTC+DRV+r	[AI]	[19-22]
	ABC/3TC+DRV+r	[AII]	[23,24]
	TDF/FTC+RAL	[AI]	[25-28]
	ABC/3TC+RAL	[AII]	[29-31]
	TDF/FTC/EVG/COBI	[AI]	[32-34]
	TDF/FTC+DTG	[AI]	[23,29,30]
	ABC/3TC+DTG	[AI]	[23,29,30,35]
Alternativi	**TDF/FTC+LPV/r**	[BI]	[7,36]
	ABC/3TC+LPV/r	[BI]	[17-22,37-40]
	TDF/FTC+NVP	[BI]	[9,14-16]

- In caso di presenza di farmacoresistenza trasmessa anche non alla classe specifica, i regimi basati su NNRTI e INI sono controindicati.
- ABC, causa HSR, è da utilizzare solo nei soggetti con negatività dell'allele HLA-B*5701.
- DRV/r è da utilizzare al dosaggio 800/100 mg QD.
- EVG/COBI da non utilizzare con e-GFR<70 ml/min/1.73m². Dati di follow-up ancora limitati sulla funzione tubulare renale.
- NVP da utilizzare nelle donne con T CD4+ < 250 cellule/µL e negli uomini con T CD4+ < 400 cellule/µL. Previste le prime due settimane di induzione a metà dosaggio. In seguito, a pieno dosaggio (400 mg/die) con la formulazione a lento rilascio (1 compressa una volta al dì).
- TDF/FTC/EVG/COBI e DTG non sono ancora disponibili per l'uso clinico in Italia/in attesa di negoziazione del prezzo da parte dell'AIFA.
- "/" = co-formulato; "+"= non co-formulato;"r"=RTV come booster.

Developed by the HHS Panel on Antiretroviral Guidelines for
Adults and Adolescents – A Working Group of the
Office of AIDS Research Advisory Council (OARAC)

What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Last updated May 1, 2014; last reviewed May 1, 2014)

Panel's Recommendations
• The optimal antiretroviral (ARV) regimen for a treatment-naive patient consists of two NRTIs in combination with a third active ARV drug from one of three drug classes: an NNRTI, a PI boosted with ritonavir, or an INSTI **(AI)**.
• The Panel recommends one of the following regimens for ART-naive patients regardless of baseline viral load or CD4 count: NNRTI-Based Regimen: • EFV/TDF/FTC[a] **(AI)** PI-Based Regimens: • ATV/r plus TDF/FTC[a] **(AI)** • DRV/r plus TDF/FTC[a] **(AI)** INSTI-Based Regimens: • DTG plus ABC/3TC[a] **(AI)**—**only** for patients who are HLA-B*5701 negative • DTG plus TDF/FTC[a] **(AI)** • EVG/cobi/TDF/FTC—**only** for patients with pre-ART CrCl >70 mL/min **(AI)** • RAL plus TDF/FTC[a] **(AI)**
• In addition to the regimens listed above, the following regimens are also recommended, **but only for patients with pre-ART plasma HIV RNA <100,000 copies/mL**: NNRTI-Based Regimens: • EFV plus ABC/3TC[a] **(AI)**—**only** for patients who are HLA-B*5701 negative • RPV/TDF/FTC[a] **(AI)**—**only** for patients with CD4 count >200 cells/mm^3 PI-Based Regimen: • ATV/r plus ABC/3TC[a] **(AI)**–**only** for patients who are HLA-B*5701 negative

Concerns Regarding NRTIs

- ABC
  - Decreased potency compared with TDF in those with high HIV-1 RNA levels (> 100,000 copies/mL) when combined with EFV and ATV + RTV
  - Variable results regarding relationship with CV events
  - Avoid in patients with positive HLA-B*5701 test
- TDF
  - Associated with greater decline in bone mineral density than ABC
  - Associated with variable decline in renal function compared with other NRTIs

Selecting the Third Drug in a First-line Regimen

Readiness for Therapy: A Key Decision Point

- Potential options
  - PI-based therapy
  - NNRTI- and RAL-based strategies
  - Simple regimen (1 pill, once daily)

- Regimens to avoid
  - Complicated regimens: frequent dosing, food requirements
  - Regimens with more adverse events: may affect adherence
  - Regimens with higher risk of resistance at failure

Which Patient for EFV?

Considerations in Favor

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

Considerations Against

- High risk of resistance at virologic failure[3]
- CNS effects[1]
- Potential for teratogenesis in early pregnancy[4]
- Drug–drug interactions with other drugs metabolized by CYP system[1]
- Increases in lipids[5]

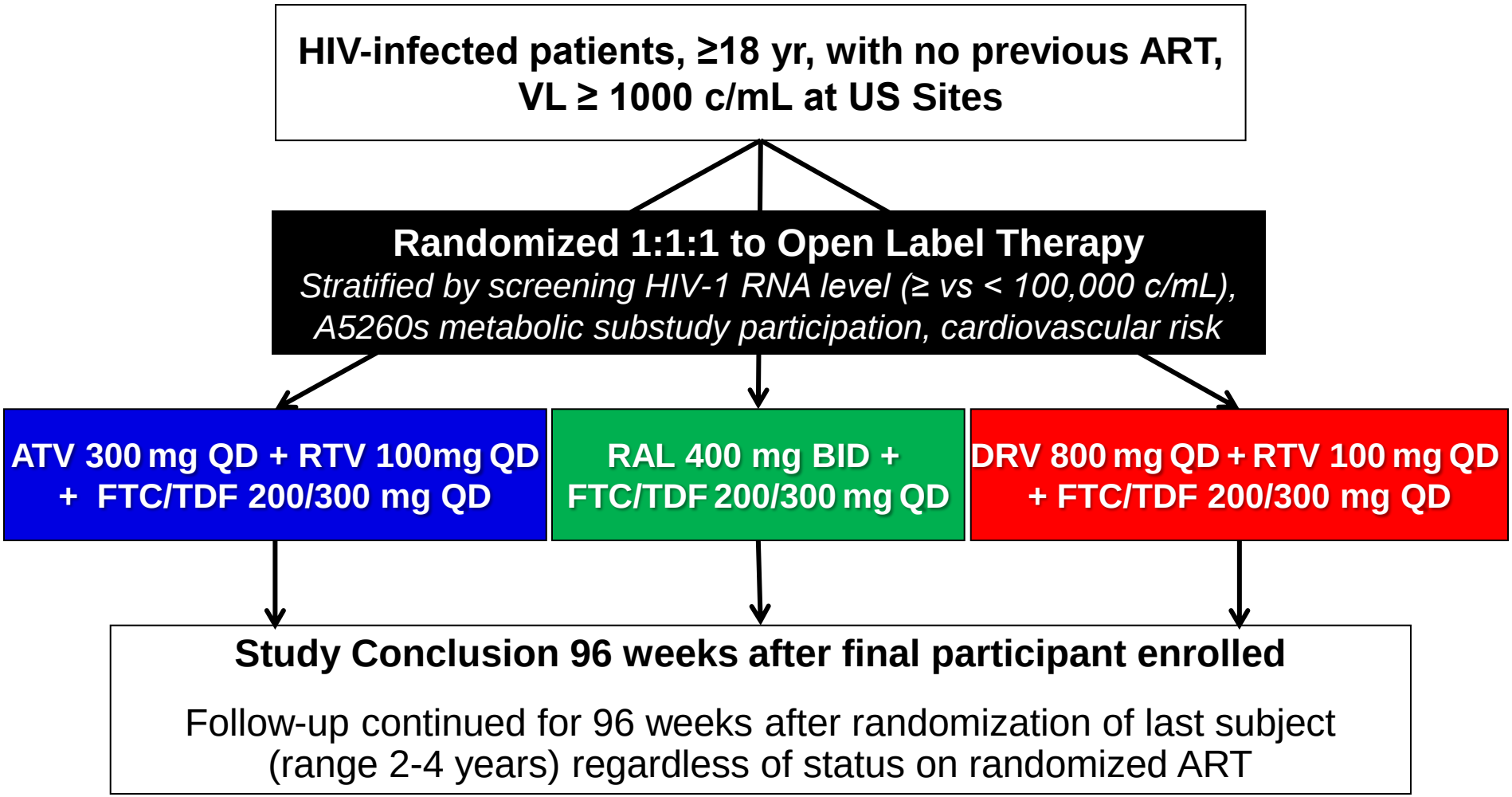
1. TDF/FTC/EFV [package insert]. 2. Ribaudo HJ, et al. J Infect Dis. 2008;197:1006-1010. 3. Gallant J, et al. N Engl J Med. 2006;354:251-260. 4. DHHS Perinatal Guidelines. July 2012. 5. Daar E, et al. Ann Intern Med. 2011;154:445-456.

Efficacy and Tolerability of Atazanavir, Raltegravir, or Darunavir with FTC/TDF: ACTG A5257

Landovitz RJ, Ribaudo HJ, Ofotokun I, Wang H, Baugh BP, Leavitt RY, Rooney JF, Seekins D, Currier JS, and Lennox JL for the A5257 Study Team

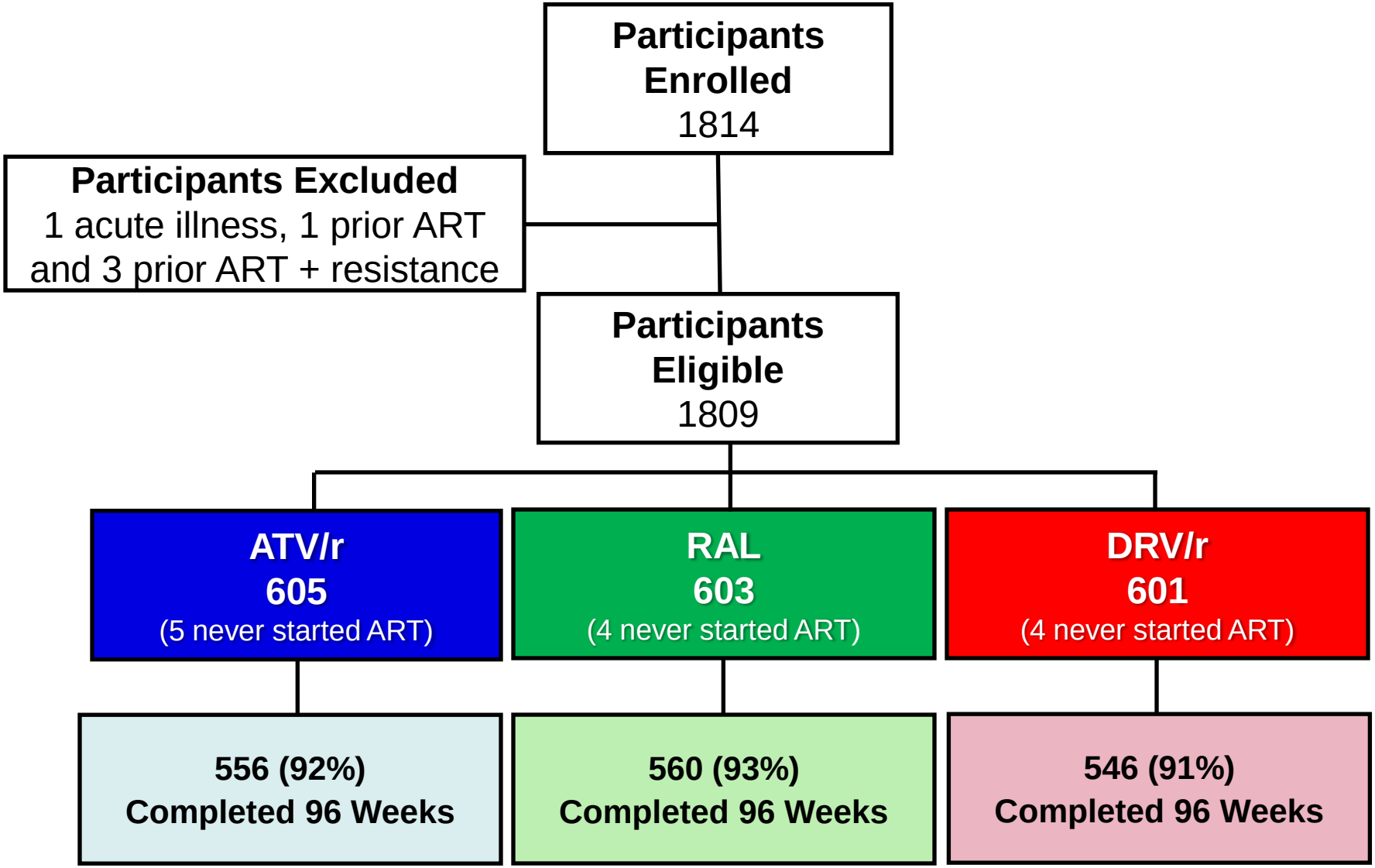
ACTG
AIDS CLINICAL TRIALS GROUP

A5257 Study Design*



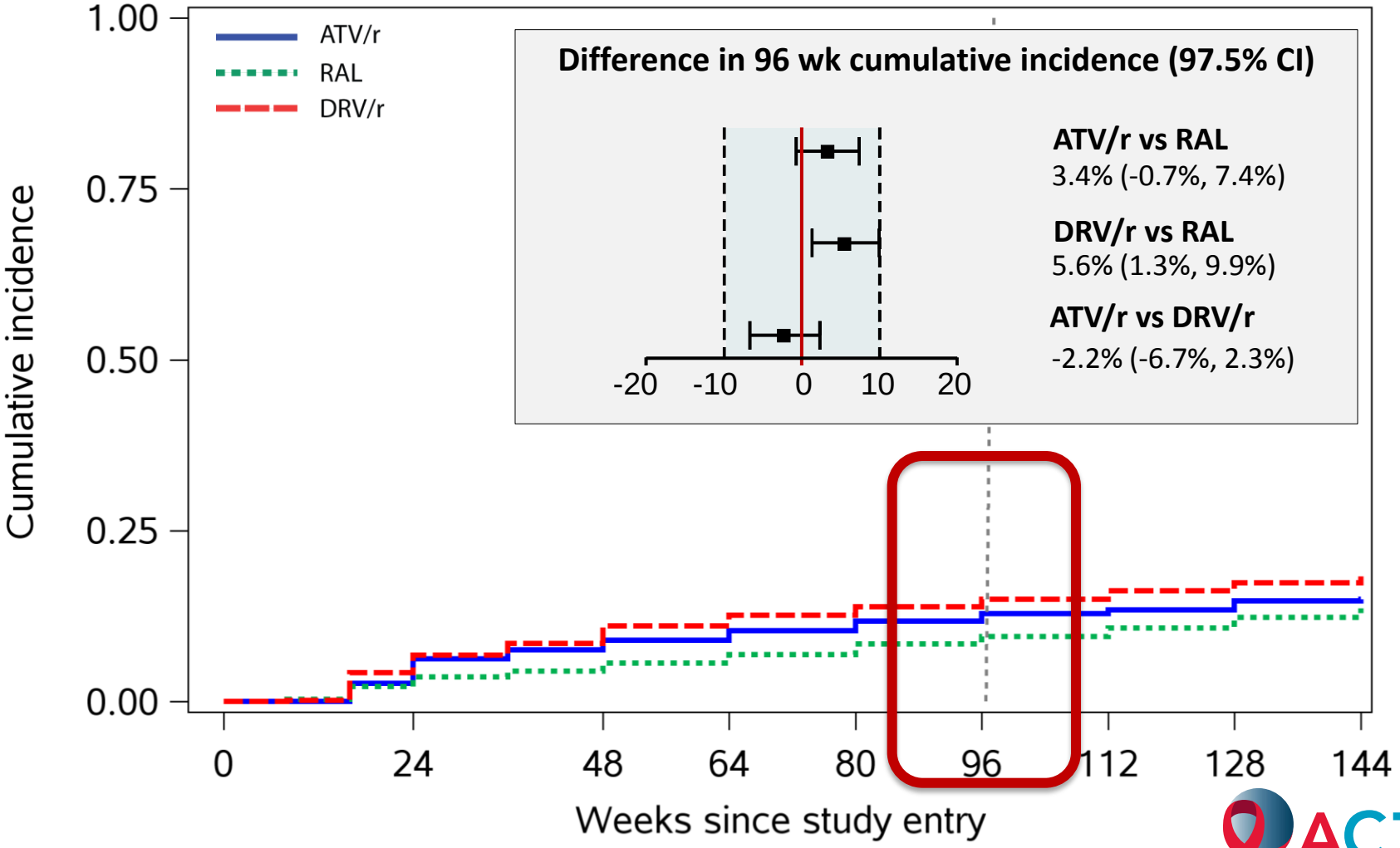
*With the exception of RTV, all ART drugs were provided by the study

ACTG AIDS CLINICAL TRIALS GROUP



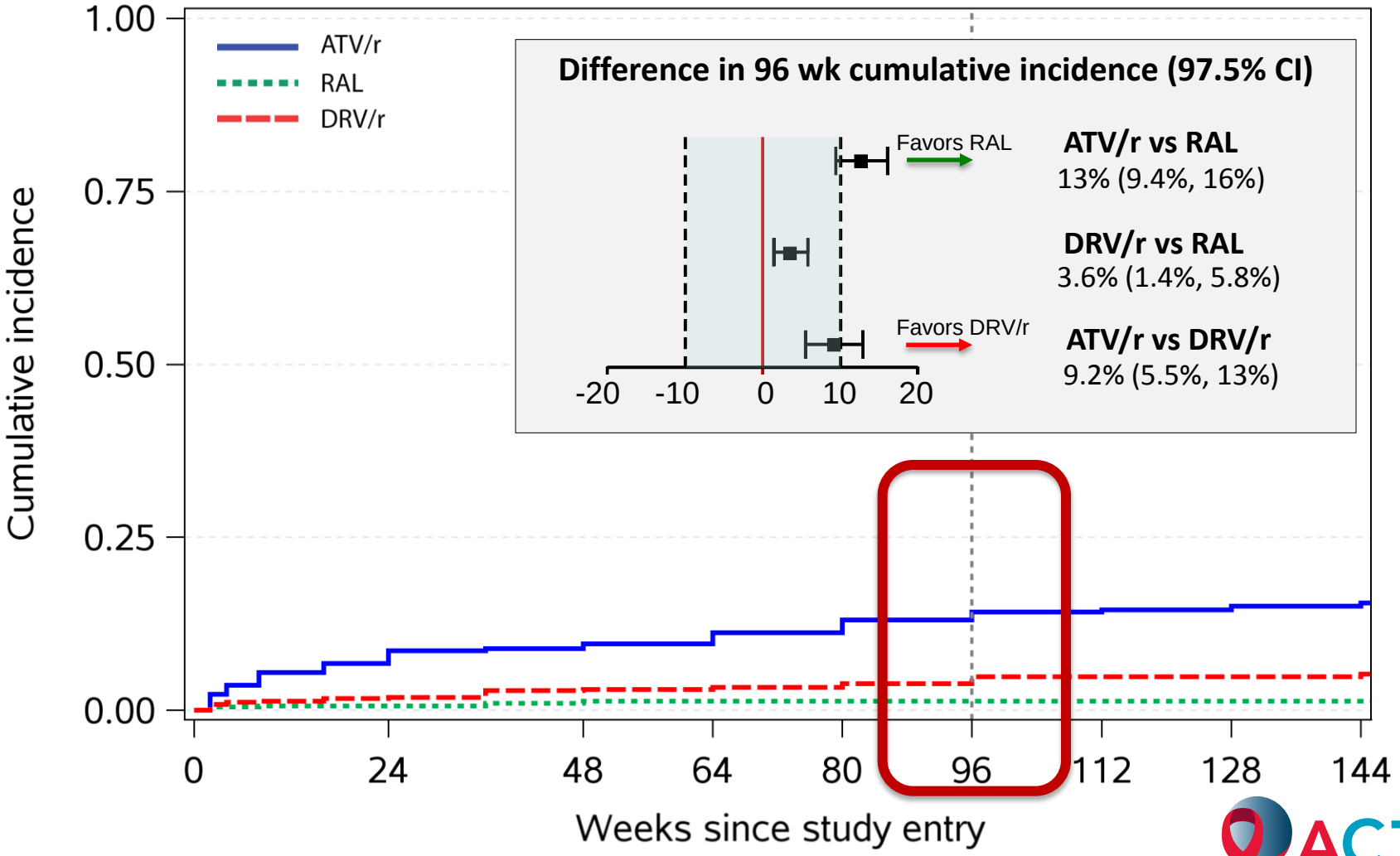
ACTG
AIDS CLINICAL TRIALS GROUP

Cumulative Incidence of Virologic Failure



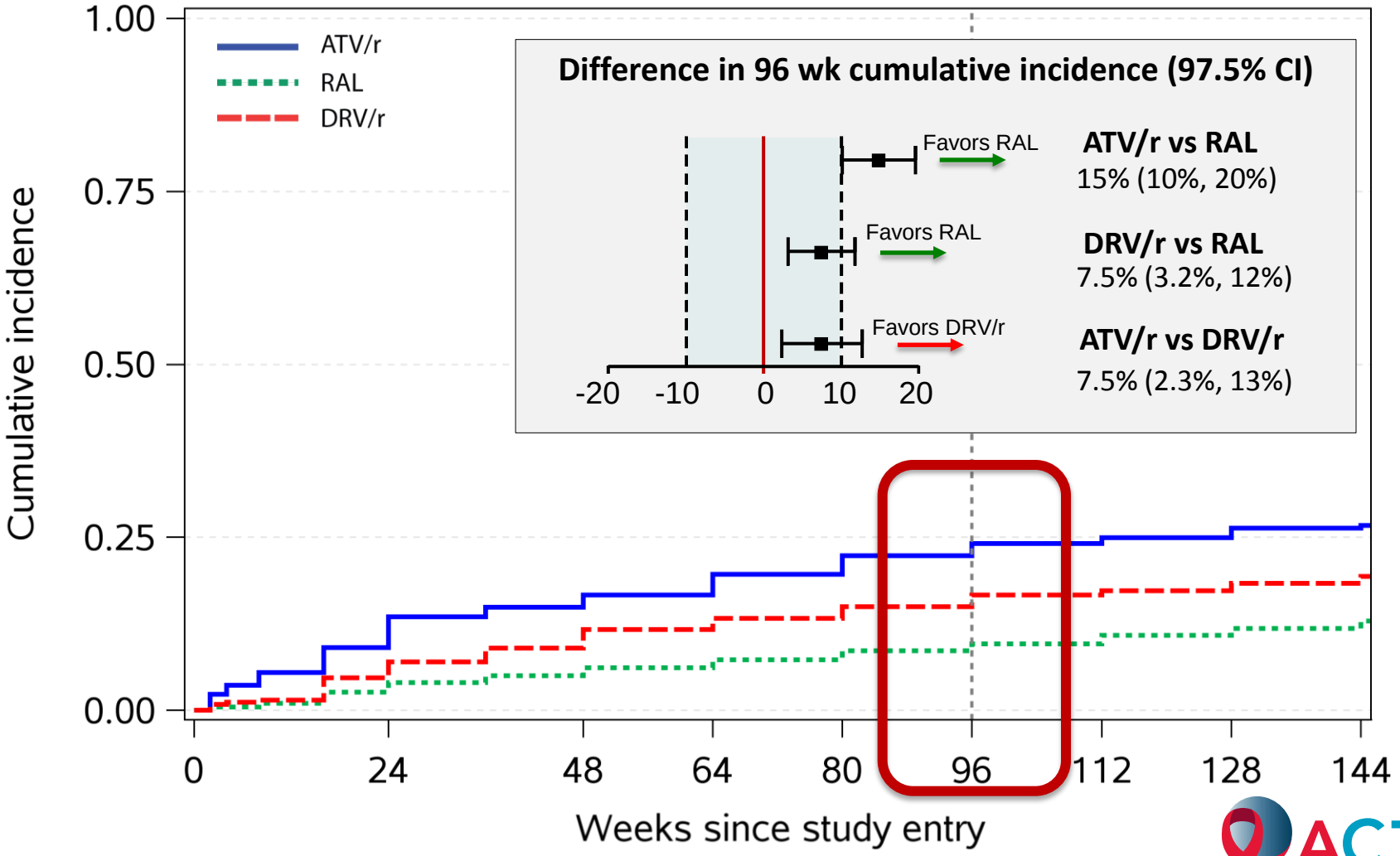
ACTG
AIDS CLINICAL TRIALS GROUP

Cumulative Incidence of Tolerability Failure



ACTG
AIDS CLINICAL TRIALS GROUP

Cumulative Incidence of Virologic or Tolerability Failure



**Consistent results seen with TLOVR at a 200 copies/ml threshold*

ACTG AIDS CLINICAL TRIALS GROUP

Tolerability Failure

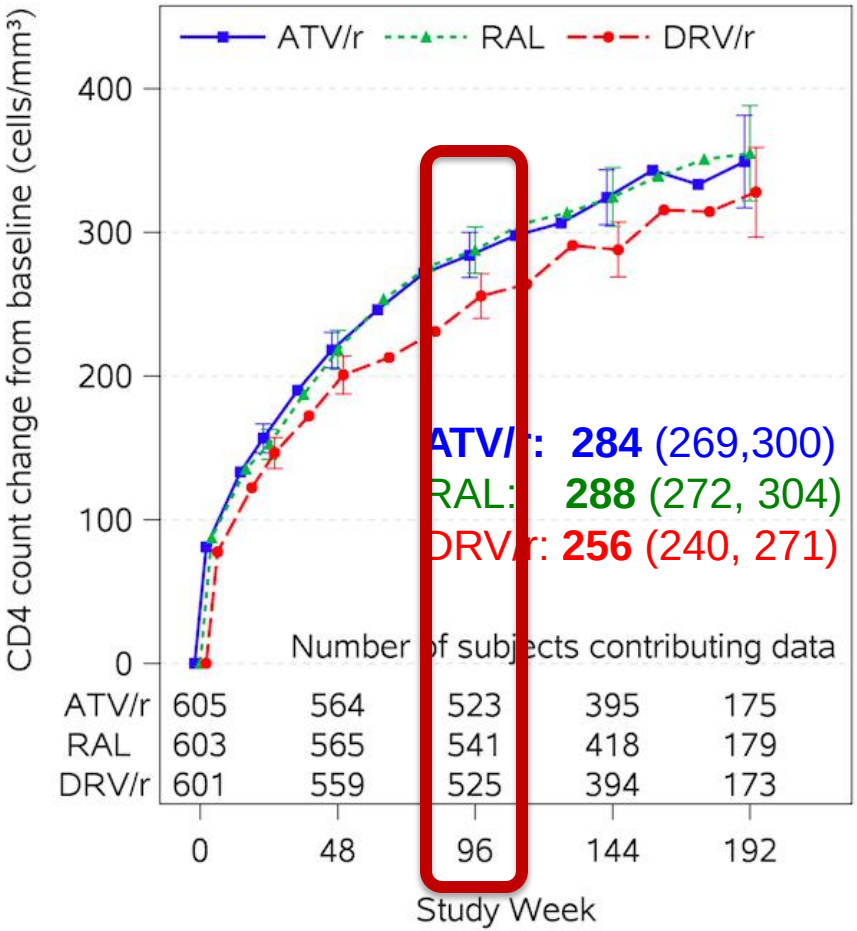
Toxicity Associated Discontinuation of randomized ART *

	ATV/r (N=605)	RAL (N=603)	DRV/r (N=601)
Any toxicity discontinuation	**95 (16%)**	**8 (1%)**	**32 (5%)**
Gastrointestinal toxicity	25	2	14
Jaundice/Hyperbilirubinemia	47	0	0
Other hepatic toxicity	4	1	5
Skin toxicity	7	2	5
Metabolic toxicity	6	0	2
Renal toxicity (all nephrolithiasis)	4	0	0
Abnormal chem/heme (excl. LFTs)	0	0	2
Other toxicity	2	3	4

*Participants allowed to switch therapy for intolerable toxicity

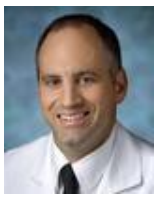
Additional Clinical Outcomes

Mean change in CD4 count from baseline

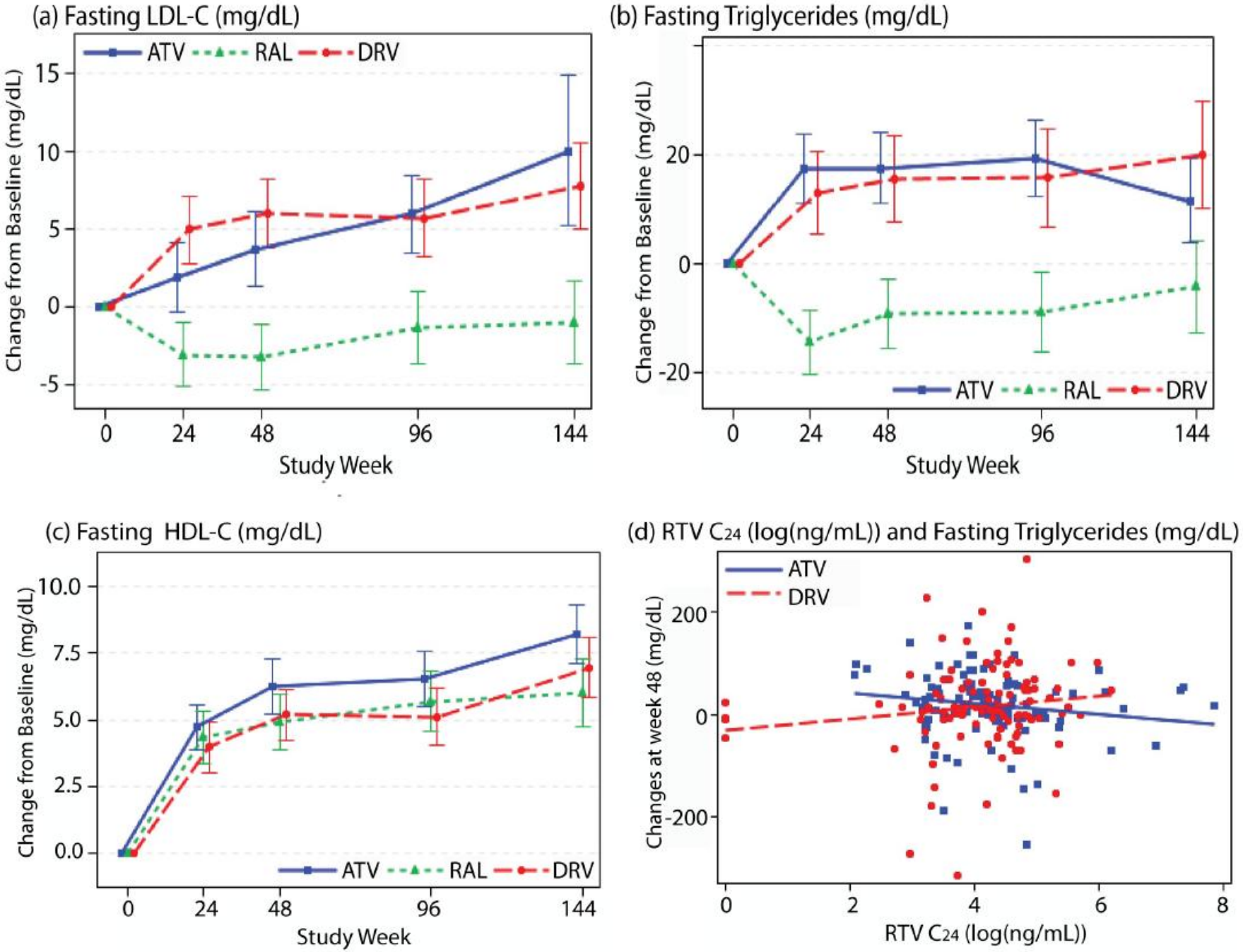


Lipid and Bone Changes

- Both PI/r arms had greater increases in LDL and triglycerides than the RAL-arm ($p<0.001$)
- Lipids: Poster 746 (Ofotokun *et al*)
- Bone: Poster 779LB (Brown *et al)*



ACTG AIDS CLINICAL TRIALS GROUP


(a) Fasting LDL-C (mg/dL)
ATV
RAL
DRV
Change from Baseline (mg/dL)
15
10
5
0
-5
0
24
48
96
144
Study Week
(b) Fasting Triglycerides (mg/dL)
Change from Baseline (mg/dL)
20
0
-20
ATV
RAL
DRV
0
24
48
96
144
Study Week
(c) Fasting HDL-C (mg/dL)
Change from Baseline (mg/dL)
10.0
7.5
5.0
2.5
0.0
ATV
RAL
DRV
0
24
48
96
144
Study Week
(d) RTV C24 (log(ng/mL)) and Fasting Triglycerides (mg/dL)
ATV
DRV
Changes at week 48 (mg/dL)
200
0
-200
0
2
4
6
8
RTV C24 (log(ng/mL))

779LB Bone Density Changes After Antiretroviral Initiation With Protease Inhibitors or Raltegravir

Todd Brown[1], Carlee Moser[2], Judith Currier[3], Heather Ribaudo[2], Jennifer Rothenberg[4], Michael Dube[5], Robert Murphy[6], James Stein[7], Grace McComsey[8]

[1]Johns Hopkins University, Baltimore, MD, United States, [2]Harvard University, Boston, MA, United States, [3]UCLA, Los Angeles, CA, United States, [4]Social & Scientific Systems, Silver Spring, MD, United States, [5]University of Southern California, Los Angeles, CA, United States, [6]Northwestern University, Chicago, IL, United States, [7]University of Wisconsin, Madison, WI, United States, [8]Case Western Reserve University, Cleveland, OH, United States

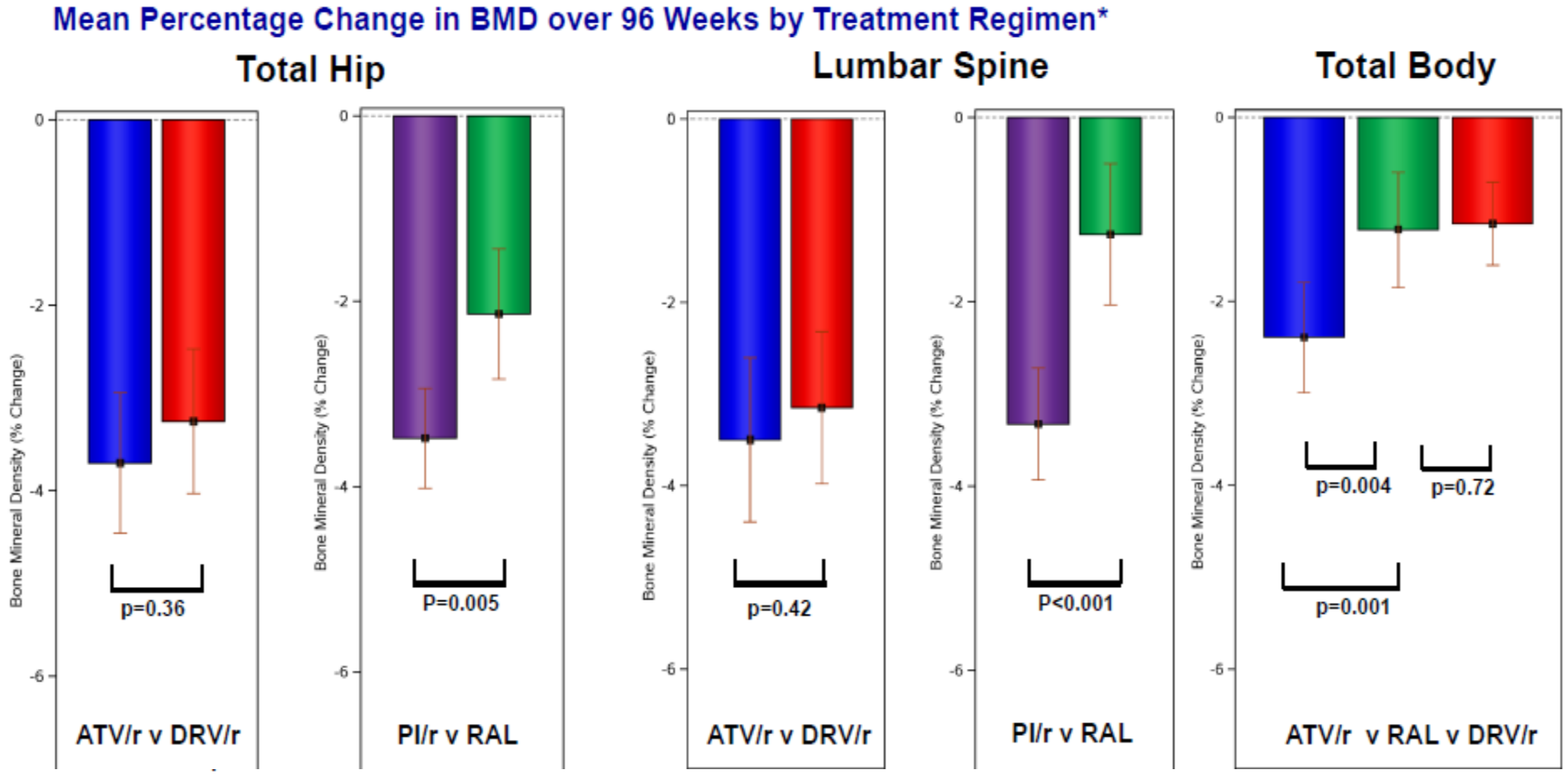
Background: The initiation of antiretroviral therapy (ART) leads to a 2-6% loss of bone mineral density (BMD) over 48-96 weeks which depends in part on the specific medications used. The effect of integrase inhibitors on BMD with ART initiation and how it compares to the changes seen with protease inhibitors (PIs) have not been clearly established.

Methodology: We compared the percentage change in BMD at the lumbar spine, total hip, and total body over 96 weeks in HIV-infected treatment-naive participants randomized equally to open labeled Tenofovir Disoproxil Fumarate-Emtricitabine (TDF/FTC) plus Atazanavir-Ritonavir (ATV/r), Darunavir-Ritonavir (DRV/r), or Raltegravir (RAL) in a substudy of AIDS Clinical Trials Group A5257 (N= 1809) with randomization stratified by substudy participation. BMD was measured using standardized dual-energy x-ray absorptiometry (DXA) and centrally read. We used linear regression with reverse Helmert contrasts to compare the 96-week percentage change in BMD in the two PI arms (ATV/r vs DRV/r) and, if no difference was found, the BMD changes in the combined PI arms were compared to those in the RAL arm. Primary analyses were intent-to-treat, adjusted for the stratification factors of baseline cardiometabolic risk and HIV-1 RNA.

Results: Three hundred and twenty eight participants were randomized and had baseline DXA scans. At baseline, 90% were male and 44% were white, non-Hispanic; the median HIV-1 RNA load was 4.55 $\log_{10}$ copies/mL; age was 37 years; CD4 count was 349 cells/μL. At week 96, the mean percentage changes from baseline in spine and hip were statistically significant in all arms ($p>0.001$) and similar in the PI arms (Spine: ATV/r -4.0% v DRV/r -3.6%, $p=0.42$; Hip: ATV/r -3.9% v DRV/r -3.4%, $p=0.36$), but were greater in the combined PI arms than the RAL arm (Spine: -3.8% v -1.8%, $p<0.001$; Hip -3.7% v -2.4%, $p=0.005$). The percentage changes in total body BMD were small, but statistically significant in all of the arms ($p<0.001$ for all), but the magnitude of the change was greater with ATV/r than DRV/r (-2.9% v -1.6%, $p=0.001$) or RAL (v -1.7%, $p=0.004$), but not different between the DRV/r and RAL arms ($p=0.72$). As-treated analyses led to similar results.

Conclusions: In ART-naïve, HIV-infected individuals initiating ART with TDF/FTC, 96 week BMD losses at the lumbar spine and total hip were similar with the PIs, ATV/r and DRV/r, whereas the integrase inhibitor, RAL, had significantly less BMD loss at these sites than the combined PIs arms. In contrast, total body BMD loss was slightly greater with ATV/r than DRV/r.

BONE RESULTS



- All of the treatment arms showed a statistically significant loss of BMD over 96 weeks at all of the sites (p<0.001)
- At the hip and the spine, the mean percentage BMD changes over 96 weeks were not different in the PI arms
  - Hip: ATV/r -3.9% v DRV/r -3.4%, p=0.36; Spine: ATV/r -4.0% v DRV/r -3.6%, p=0.42
- At the hip and the spine, the loss of BMD was greater in the combined PI arms than the RAL arm
  - Hip -3.7% v -2.4%, p=0.005;Spine: -3.8% v -1.8%, p<0.001

- Total body BMD loss was greater with ATV/r than DRV/r (-2.9% v -1.6%, p=0.001) and greater with ATV/r than RAL (-2.9% v -1.7%, p=0.004)

Conclusions

- **ATV/r, RAL, and DRV/r were equivalent for virologic efficacy**
- **ATV/r was less well tolerated than DRV/r or RAL**
  - Largely due to cosmetic hyperbilirubinemia
- **RAL was superior to both PI/r regimens for combined tolerability and virologic efficacy**
  - DRV/r was superior to ATV/r
- **VF with resistance was rare**
  - More frequently observed with RAL
- **Analyses are ongoing to evaluate:**
  - Cardiovascular, metabolic, skeletal, fat, inflammatory biomarkers, behavior, adherence, and key subgroup differences

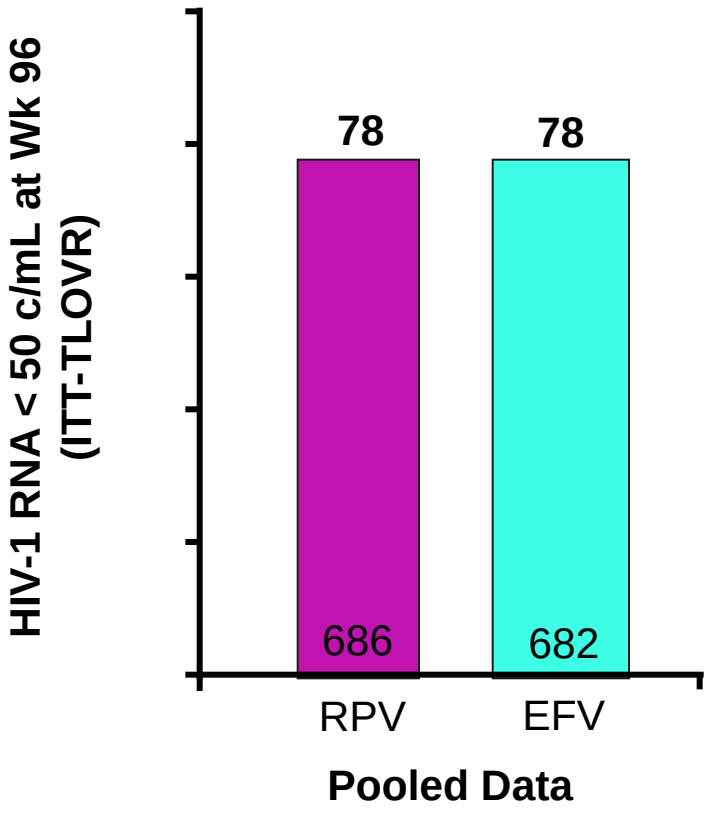
ACTG
AIDS CLINICAL TRIALS GROUP

Guidelines for Initial Therapy: Time for a Change?

- In 2009, DHHS listed 4 regimens as “preferred”; no changes since
- Since then, several new agents have been approved: RPV, EVG/COBI, DTG
- What do the clinical trials of these agents show?

Current Preferred Regimens	
NRTIs	**Third Agent**
TDF/FTC +	EFV
	ATV/RTV
	DRV/RTV
	RAL

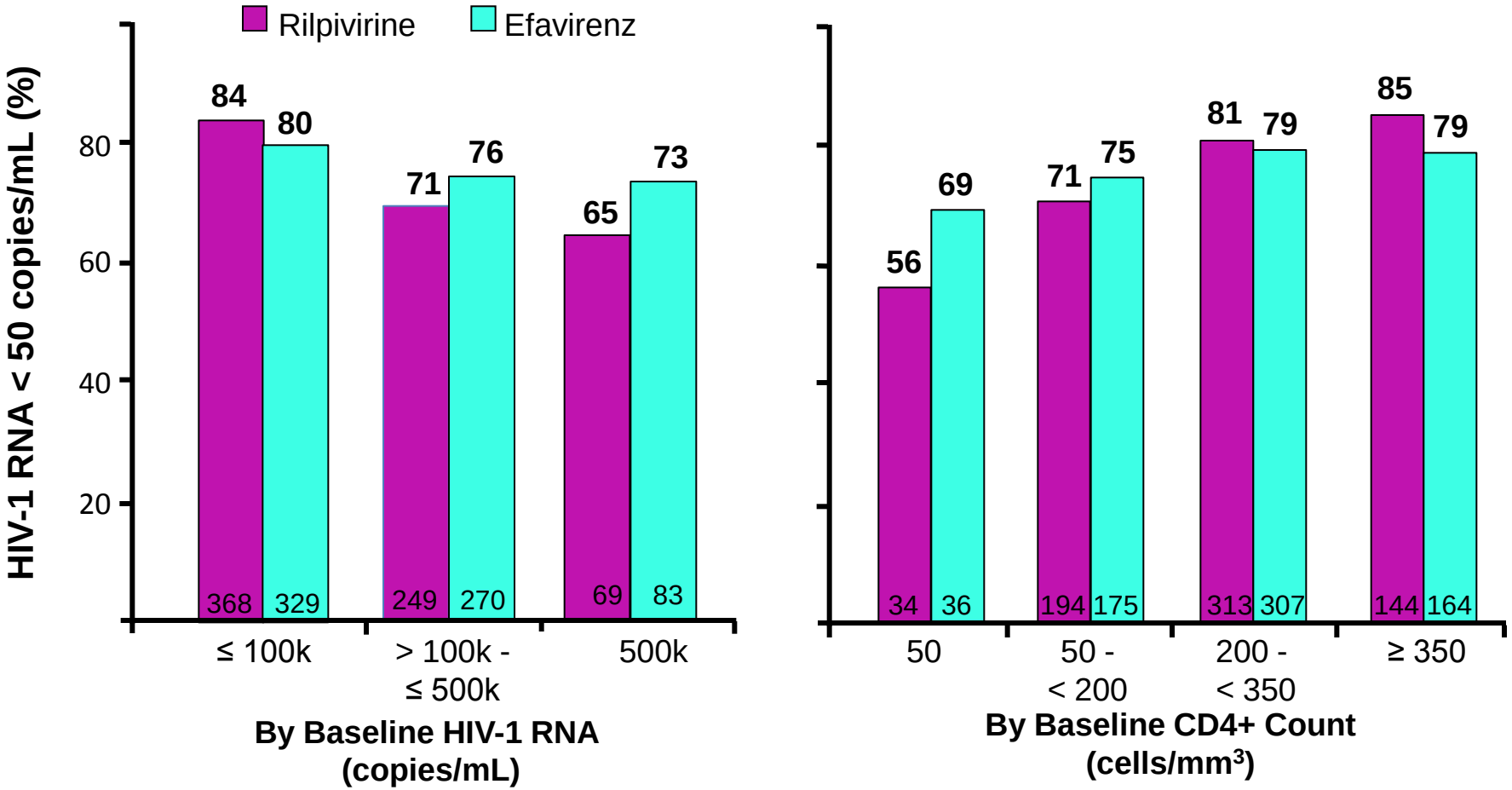
ECHO/THRIVE: Rilpivirine Noninferior to Efavirenz Through Wk 96



- More virologic failures with RPV vs EFV: 14% vs 8%
  - Difference due to more failures between Wks 0-48; failures comparable between arms from Wks 48-96
  - Development of NRTI mutations more common with RPV vs EFV
  - E138K mutation with RPV → cross-resistance with ETR
- Discontinuation for AEs more common with EFV vs RPV: 9% vs 4%

Cohen CJ, et al. AIDS. 2013;27:939-950.

ECHO/THRIVE Post Hoc Analysis: Wk 96 Efficacy by Baseline VL and CD4+ Count



Cohen CJ, et al. AIDS. 2013;27:939-950.

Pooled ECHO/THRIVE Analysis: Wk 96 Safety

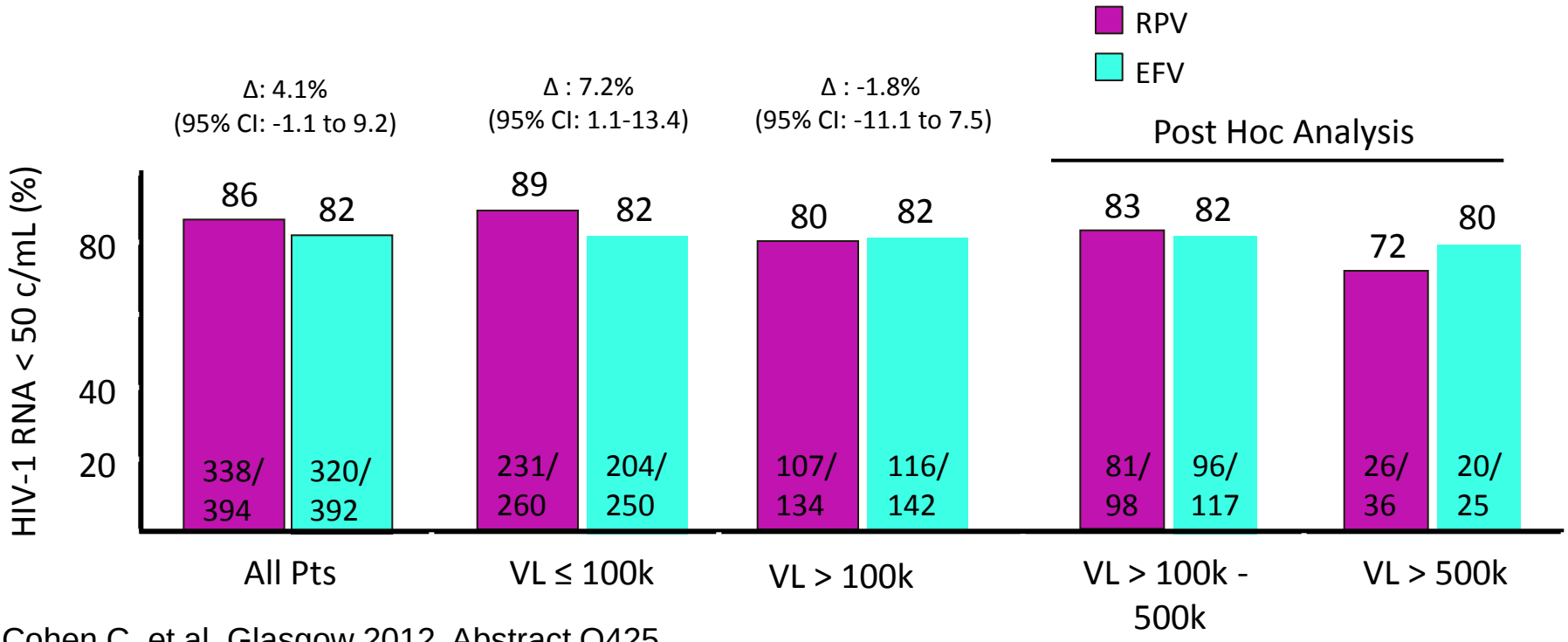
Adverse Event, %	Rilpivirine (n = 686)	Efavirenz (n = 682)
Most common adverse events of interest		
▪Any neurologic	17	38*
• Dizziness	8	27*
▪Any psychiatric	16	24*
• Abnormal dreams/nightmares	8	13†
▪Rash (any type)	4	15*
Grade 2-4 laboratory abnormality		
▪Total cholesterol	7	22*
▪LDL-C	7	18*
▪AST	6	10
▪ALT	6	11

*P < .0001 vs rilpivirine.
†P = .0039 vs rilpivirine.

Cohen CJ, et al. AIDS. 2013;27:939-950

Open-Label STaR Trial: RPV/TDF/FTC Non inferior to EFV/TDF/FTC at Wk 48

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



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

Summary of Results From Phase III Studies of RPV vs EFV

- More virologic failures, especially with HIV-1 RNA > 100k[1,2]
  - Difference reduced in open-label study, suggesting importance of adherence, food effect[2]
  - DHHS: **RPV is not recommended** in patients with pretreatment HIV-1 RNA > 100,000 copies/mL; higher rate of virologic failures reported in patients with pre-ART CD4+ count < 200 cells/mm^3 who were treated with RPV + 2 NRTIs[3]
- RPV resistance mutation (E138K) causes cross-resistance with ETR[1,2]
- Fewer drug discontinuations with RPV than EFV[1,2]
  - Fewer rash, CNS events; better lipids[1,2]

1. Cohen CJ, et al. AIDS. 2013;27:939-950. 2. Cohen C, et al. Glasgow 2012. Abstract O425.
3. DHHS Guidelines. February 2013.

Which Patient for RPV?

Considerations in Favor

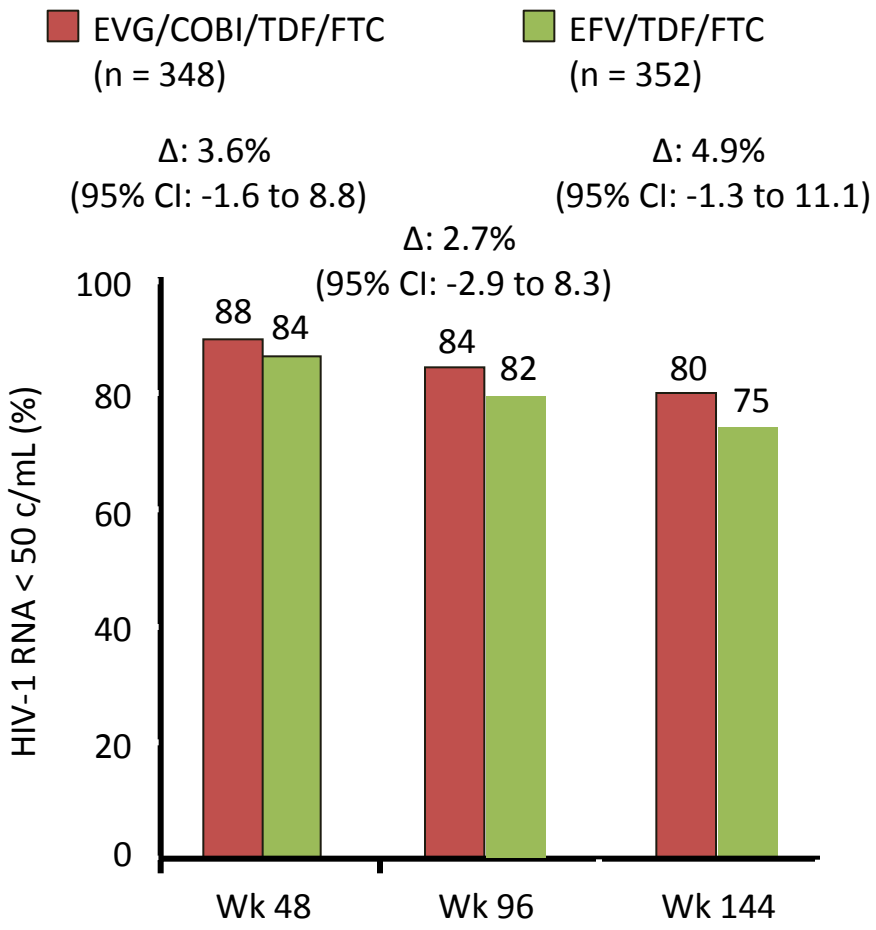
- Coformulated/1 pill daily
- Superior vs EFV at lower VL[1]
- Fewer CNS adverse events than EFV[2]

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].

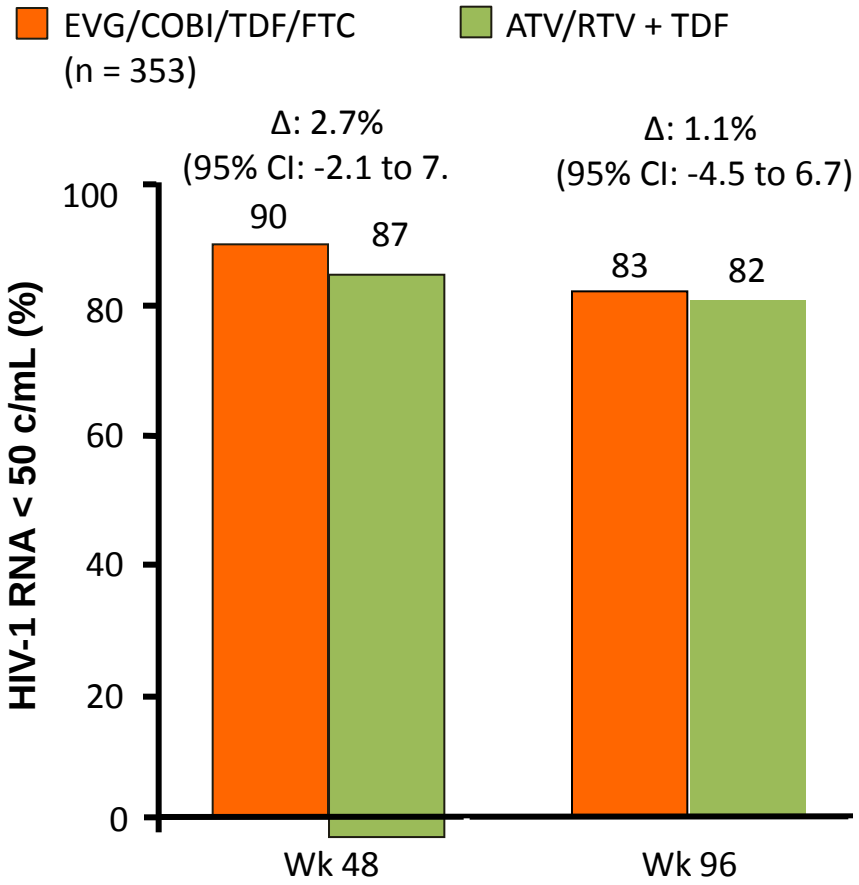
Elvitegravir/Cobicistat/TDF/FTC Noninferior to Efavirenz/TDF/FTC Through Wk 144



- Results consistent across subgroups: BL HIV-1 RNA, CD4+ count, age, sex, race
- Resistance at VF detected in 8 pts per arm through Wk 48, plus 2 additional pts per arm through Wk 96—rates similar btwn arms; no additional pts on EVG/COBI developed resistance after Wk 96
  - In those on EVG/COBI, 9/10 pts had primary integrase and 10/10 had NRTI resistance mutations
  - In those on EFV, 10/10 had NNRTI and 3/10 had NRTI resistance mutations

Zolopa A, et al. J Acquir Immune Defic Syndr. 2013;63:96-100. Sax PE, et al. Lancet. 2012;379:2439-2448. Wohl D, et al. ICAAC 2013. Abstract H-672a.

EVG/COBI/TDF/FTC Non inferior to ATV/RTV + TDF/FTC Through Wk 96



- Results consistent across subgroups: BL HIV-1 RNA, CD4+ count, adherence, age, sex, race
- 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
  - 5/6 had primary integrase and 5/6 had NRTI resistance mutations

Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;62:483-486.
De Jesus E, et al. Lancet. 2012;379:2429-2438.

Adverse Events With EVG/COBI/TDF/FTC vs ATV/RTV + TDF/FTC

Adverse Events > 10% in Either Group

	EVG/COBI/ TDF/FTC (n = 353)	ATV/RTV + TDF/FTC (n = 355)
Diarrhea	22	27
Nausea	20	19
Upper respiratory infection	15	16
Headache	15	12
Fatigue	14	13
Ocular icterus	1	14

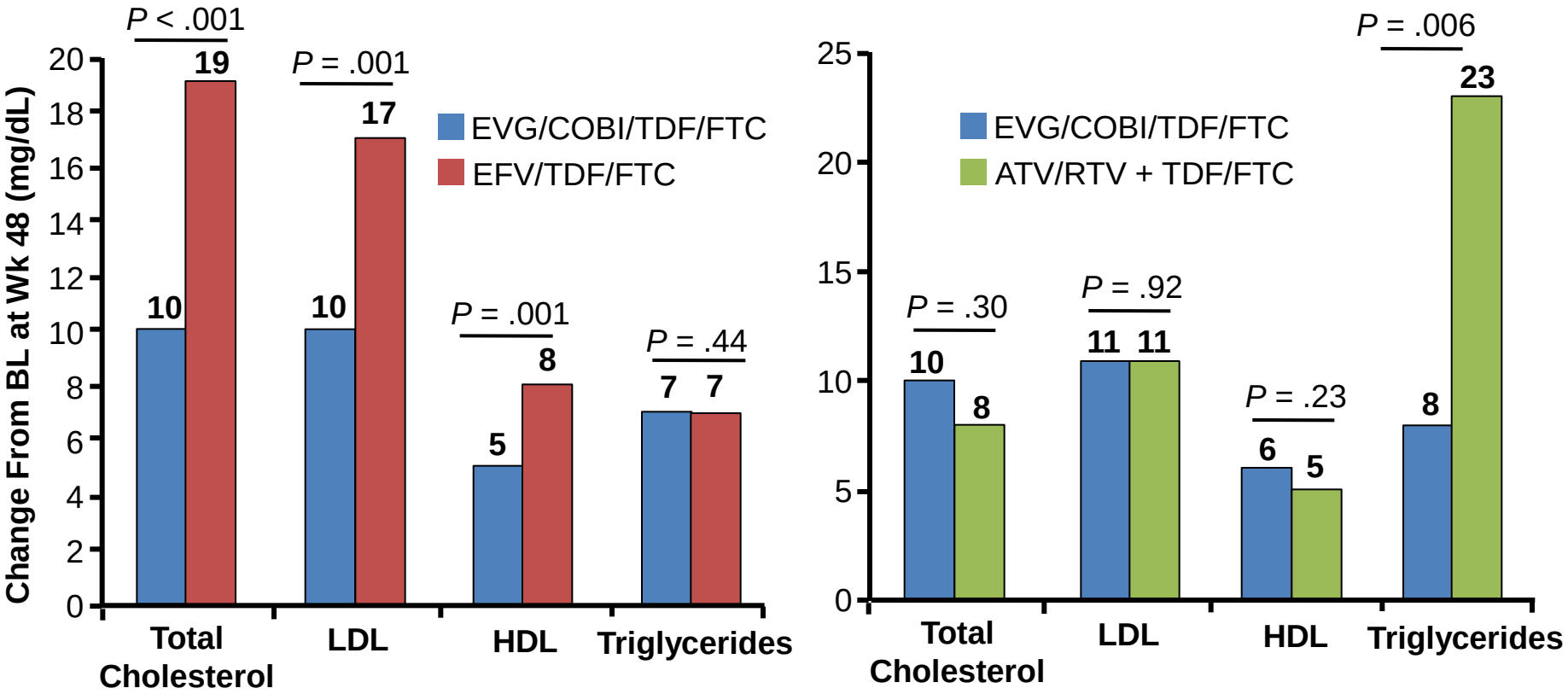
Overall Discontinuation Rate

	EVG/COBI/ TDF/FTC (n = 353)	ATV/RTV + TDF/FTC (n = 355)
Overall	4	5
Diarrhea	1	< 1
Nausea	< 1	1
Vomiting	< 1	1
Ocular icterus	0	1
Jaundice	0	1
Drug eruption	0	1

Discontinuation rates due to renal adverse events were identical in both arms (0.3%)

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

EVG/COBI/TDF/FTC vs EFV or ATV/RTV: Lipid Changes



Conclusion: Whereas some lipid fractions better with EVG/COBI/TDF/FTC than EFV or ATV/RTV, overall differences were modest and unlikely to be of clinical significance

Sax P, et al. Lancet. 2012;379:2439-2448. DeJesus E, et al. Lancet. 2012;379:2429-2438.
Sax P, et al. CROI 2012. Abstract 101.

EVG/COBI/TDF/FTC vs EFV/TDF/FTC: Common Adverse Events

Treatment Emergent Adverse Events in ≥ 10% of Subjects, %	EVG/COBI/TDF/FTC (n = 348)	EFV/TDF/FTC (n = 352)
Diarrhea	23	19
Nausea*	**21**	**14**
Abnormal dreams†	**15**	**27**
Upper respiratory infection	14	11
Headache	14	10
Fatigue	11	13
Insomnia*	**9**	**14**
Depression	9	11
Dizziness†	**7**	**24**
Rash‡	**6**	**12**

*$P < .05$
†$P < .001$
‡$P = .009$

Sax P, et al. Lancet. 2012;379:2439-2448.

Summary of Results From Tx-Naïve Phase III Studies of EVG/COBI/TDF/FTC

- Virologic outcomes noninferior to EFV/TDF/FTC and ATV/RTV + TDF/FTC
  - Activity sustained in high VL stratum
- 2% failed with resistance, usually to both NRTIs and EVG
- Adverse events
  - vs EFV: fewer CNS, rash events; better lipids; more nausea
  - vs ATV/RTV: less jaundice
- Small, rapid increase in serum creatinine related to inhibition of tubular secretion of creatinine
- 5 pts (0.7% of total) developed tubulopathy, likely from TDF

Which Patient for TDF/FTC/EVG/COBI?

Considerations in Favor

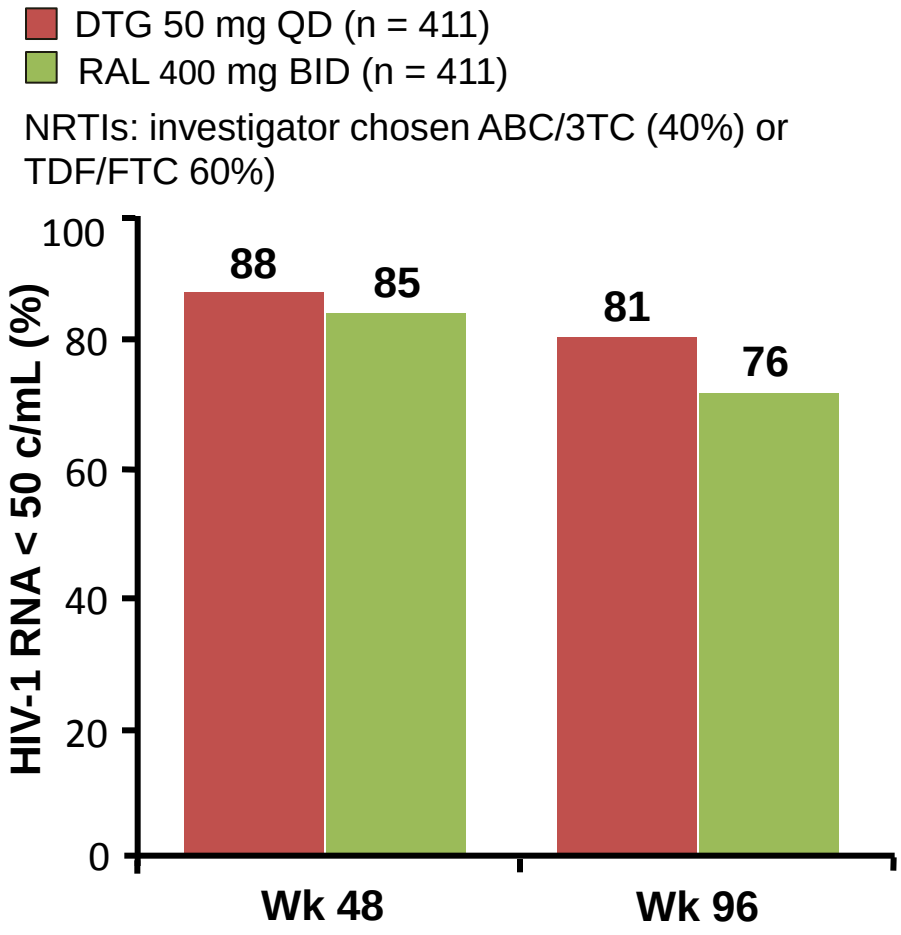
- Coformulated/1 pill dally
- Once-daily INSTI regimen
- Noninferior to EFV and ATV/RTV across HIV-1 RNA, CD4+ strata[1,2]
- Fewer CNS AEs than EFV[1]

Considerations Against

- Includes pharmacologic booster
- High risk of resistance at VF[1-4]
- Cross resistance with RAL[5]
- Drug–drug interactions[6]
- 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].

SPRING-2: Dolutegravir QD Non inferior to Raltegravir BID Through Wk 96



- DTG non inferior to RAL at Wk 48[1] and Wk 96[2]
- Adverse events and discontinuation rates similar
- No resistance at VF with DTG vs 1 subject with integrase resistance and 4 with NRTI resistance in RAL group

Raffi F, et al. Lancet. 2013;381:735-743. Raffi F, et al. IAS 2013. Abstract TULBPE17.

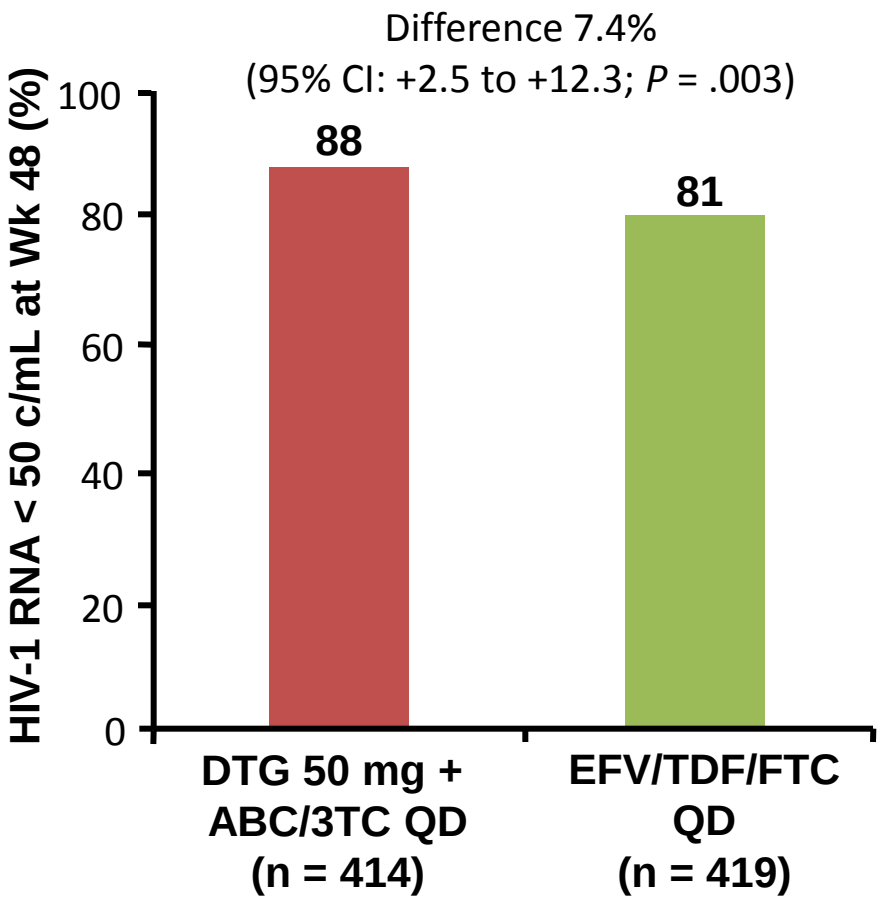
SPRING-2: Wk 48 Safety and Tolerability

Outcome	Dolutegravir 50 mg QD (n = 411)	Raltegravir 400 mg BID (n = 411)
Treatment-emergent adverse events, %		
▪ Nausea	14	13
▪ Headache	12	12
▪ Nasopharyngitis	11	12
▪ Diarrhea	11	11
Serious adverse events, %	7	8
Withdrawals due to adverse events, %	2	2
Mean change in creatinine clearance, mL/min	-15.5	-5.4
Median change in lipids, mg/dL		
▪ Total cholesterol	+4	+8
▪ Triglycerides	+1	+6

All patients received either TDF/FTC or ABC/3TC.

Raffi F, et al. IAC 2012. Abstract ThLBB04.

SINGLE: DTG + ABC/3TC Superior to EFV/TDF/FTC at Wk 48



- DTG superior to EFV at Wk 48 primary efficacy endpoint
- 4% on each arm with protocol-defined VF
- Among pts with VF in EFV arm, 1 pt with NRTI and 4 with NNRTI resistance vs 0 pts with resistance in DTG arm
- Treatment-related study discontinuation in 10% on EFV vs 2% on DTG
- CNS events and rash more common with EFV

Walmsley S, et al. ICAAC 2012. Abstract H-556b.

SINGLE Study: Wk 48 Safety and Tolerability

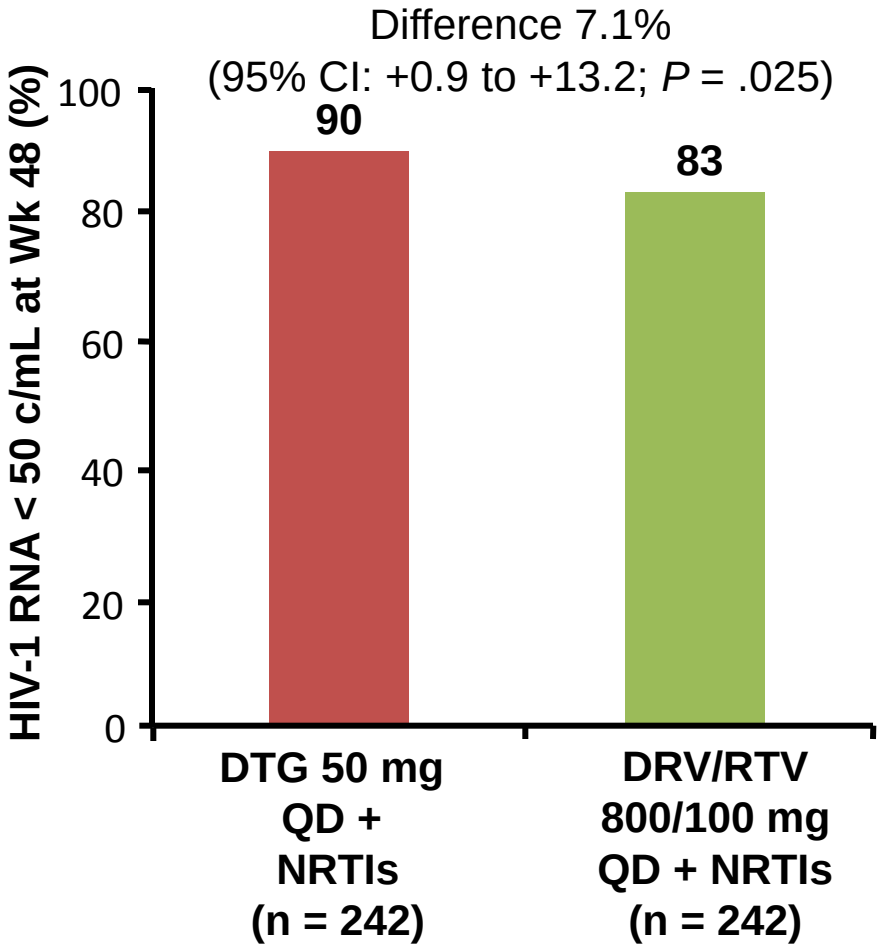
Outcome, %	DTG 50 mg + ABC/3TC QD (n = 414)	EFV/TDF/FTC QD (n = 419)
Treatment-emergent adverse events		
▪ Dizziness	9	35*
▪ Headache	13	13
▪ Somnolence	2	5
▪ Insomnia	15†	10
▪ Abnormal dreams	7	17*
Serious adverse events	< 1	2
Withdrawals due to adverse events	2	10
Liver changes		
▪ ALT > 3 x ULN	1	4
▪ Total bilirubin > 1.5 ULN	< 1	< 1
▪ Alkaline phosphatase > 1.5 x ULN	< 1	5

*$P < .001$

†$P = .029$

Walmsley S, et al. ICAAC 2012. Abstract H-556b.

FLAMINGO: DTG + NRTIs Superior to DRV/RTV + NRTIs at Wk 48



- DTG superior to DRV/RTV (both with TDF/FTC or ABC/3TC) at Wk 48 primary efficacy endpoint
- VF: 2 pts (1%) on each arm
- No treatment-emergent resistance in either arm
- Treatment-related study discontinuation in 1% of DTG pts and 4% of DRV/RTV pts
- More diarrhea with DRV/RTV; more headache with DTG

Feinberg J, et al. ICAAC 2013. Abstract H1464a.

Summary of Results From Tx-Naïve Phase III Studies of DTG

- DTG + NRTIs noninferior to RAL + NRTIs; superior to DRV/RTV + NRTIs; DTG + ABC/3TC superior to EFV/TDF/FTC
  - More drug discontinuations in EFV and DRV/RTV arms
- No DTG resistance mutations as yet detected with virologic failure
- DTG well tolerated with low rates of study drug discontinuation
  - Fewer CNS and rash events compared with EFV
  - Less diarrhea than DRV/RTV
- Small rapid increase in serum creatinine related to inhibition of tubular secretion of creatinine
  - No drug-related renal events

Which Patient for DTG?

Considerations in Favor

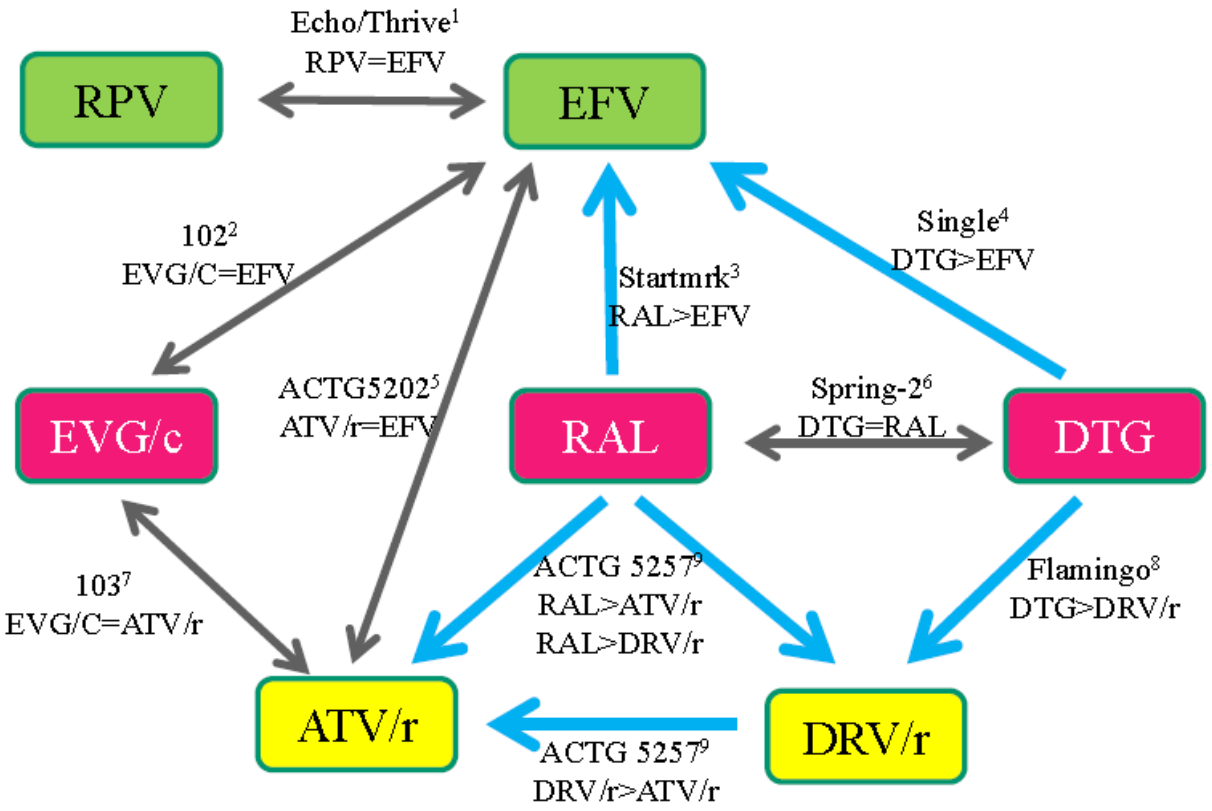
- Once-daily INSTI without boosting
- Superior efficacy vs EFV and DRV/RTV[1,2]
- Potentially less resistance at VF[1,3]
- Effective at high VL with both ABC/3TC and TDF/FTC[3]
- Well tolerated[1-3]
- Few drug–drug interactions[4]

Considerations Against

- Not yet available as coformulation
- Concerns about monitoring renal function[4]
- No guideline recommendation at this time

1. Walmsley S, et al. ICAAC 2012. Abstract H-556b. 2. Feinberg J, et al. ICAAC 2013. Abstract H-1464a. 3. Raffi F, et al. Lancet. 2013;381:735-743. 4. Dolutegravir [package insert].

Increasing evidence for integrase inhibitors in ART-naive patients



1. Cohen CJ et al. JAIDS 2012; 60 (1): 33-42 ; 2. Sax PE et al. Lancet 2012; 379: 2439–48; Rockstroh JK et al. JAIDS 2013; 63 (1); 4. Walmsley SL et al. N Engl J Med 2013; 369:1807-1818; 5. Daar ES, et al. Ann Intern Med 2011;154:445–56; 6. Raffi F et al. Lancet. 2013 Mar 2;381(9868):735-43; 7. DeJesus E, et al. Lancet 2012;379:2429–38; 8. Feinberg J et al. 52 ICAAC, September 9-12, 2012, H-1464a; 9. Landovitz RJ et al. CROI 2014. Abstract 85.

Potential Benefits of New Treatment Options for HIV

Rilpivirine	Elvitegravir/Cobicistat	Dolutegravir
▪ Smallest single-tablet regimen ▪ Fewer CNS and rash events vs EFV ▪ Better lipids than EFV ▪ Superior to EFV if HIV-1 RNA < 100k	▪ Single-tablet regimen ▪ Maintains comparable virologic activity to EFV, ATV across low and high HIV-1 RNA ▪ Fewer CNS and rash events vs EFV ▪ Better lipids than EFV, comparable to ATV/RTV ▪ Less jaundice than ATV/RTV	▪ Superior to EFV/TDF/FTC and DRV/RTV ▪ Maintains at least comparable virologic activity to EFV, RAL, DRV/RTV across low and high HIV-1 RNA ▪ Fewer CNS and rash events vs EFV ▪ Better lipids than EFV ▪ No resistance detected with virologic failure ▪ Fewer drug–drug interactions than boosted PIs, EVG/COBI

Lipid Comparisons in Clinical Trials

ARV	Comparisons
RPV[1]	vs EFV at Wk 48 ▪ **Smaller changes in TC, HDL-C, LDL-C, TG** (all *P* < .0001)
COBI[2]	vs RTV at Wk 48 when combined with ATV ▪ Similar changes in lipids in all fractions
EVG/COBI TDF/FTC[3-5]	vs EFV at Wk 48 ▪ Smaller changes in TC (*P* < .001), HDL-C, LDL-C (both *P* = .001) ▪ Similar changes in TG between arms vs ATV/RTV at Wk 48 ▪ Similar changes in TC, HDL-C, LDL-C ▪ Smaller change in TG (*P* = .006)
DTG[6]	vs RAL at Wk 48 ▪ **Similar small changes in lipids in all fractions** vs EFV at Wk 48 ▪ Smaller changes in TC, HDL-C, LDL-C

1. Cohen C, et al. AIDS. 2013;27:939-950. 2. Gallant J, et al. J Infect Dis. 2013;208:32-39. 3. Sax P, et al. Lancet. 2012;379:2439-2448.
4. DeJesus E, et al. Lancet. 2012;379: 2429-2438. 5. Sax P, et al. CROI 2012. Abstract 101.
6. Dolutegravir [package insert].

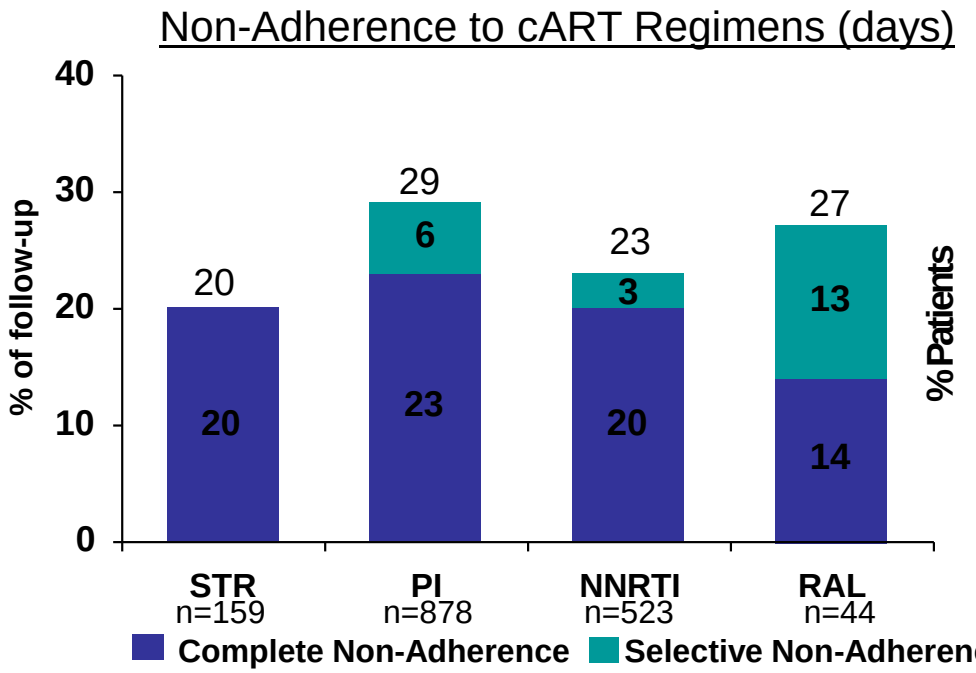
Drug–Drug Interactions With BOC and TVR

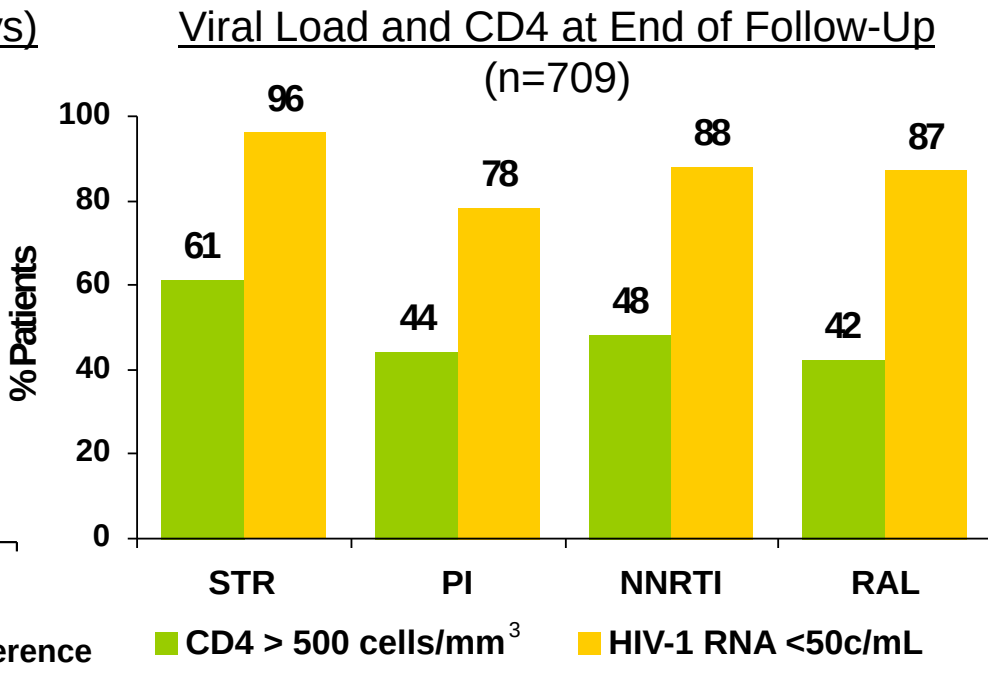
Antiretroviral	Interactions With Boceprevir	Interactions With Telaprevir
RPV[1,2]	No clinically relevant interactions	No clinically relevant interactions
EVG/COBI TDF/FTC[3]	No data	No clinically relevant interactions
DTG[4]	No clinically relevant interactions	No clinically relevant interactions
ATV/RTV[5]	Coadministration not recommended	Coadministration not recommended
DRV/RTV[5]	Coadministration not recommended	Coadministration not recommended
EFV[5]	Coadministration not recommended	Increase TVR dose to 1125 mg q8h
RAL[5]	No clinically relevant interactions	No clinically relevant interactions

1. Rhee E, et al. CROI 2013. Abstract 537. 2. Rilpivirine [package insert]. 3. Custodio J, et al. ICAAC 2013. Abstract A-1576. 4. Dolutegravir [package insert]. 5. DHHS Adult Guidelines. February 2013.

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

Evaluation of outcomes in observational, retrospective cohort of 1,604 HIV+ pts (2008-2010)





STR was associated with higher adherence vs. multi-pill regimens and with greater rates of virologic suppression and CD4 > 500 cells/mm^3

Antinori A, et al. HIV-11 2012; Glasgow. P14

What's Available as Fixed-Dose Combinations, and What's Coming?

Available Now

- Efavirenz/tenofovir DF/ emtricitabine
- Rilpivirine/tenofovir DF/ emtricitabine
- Elvitegravir/cobicistat/ tenofovir DF/emtricitabine

Future Options

- Darunavir/cobicistat
  - Darunavir/cobicistat/ emtricitabine/tenofovir alafenamide (GS-7340)
- Atazanavir/cobicistat
- Dolutegravir/abacavir/ lamivudine
  - Dolutegravir will be initially available as single tablet, not fixed-dose combination

Conclusions

- Currently many simple and easy-to-administer first-line antiretroviral regimens
- The decision as to which regimen to select first is based upon efficacy, safety, and select characteristics
  - Concerns regarding adherence
  - Virologic characteristic (eg, baseline HIV-1 RNA, drug resistance)
  - Comorbid conditions (eg, cardiovascular disease, hepatitis coinfection, renal disease)