British HIV Association
BHIVA

Dr Chloe Orkin

Barts Health NHS Trust, London

Dr Chloe Orkin

Barts Health NHS Trust, London

COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Dr Chloe Orkin	Dr Orkin acts in a Consultancy capacity and as a speaker at company-sponsored events for Gilead, MSD, Viiv, Jannsen,Abbvie and BMS. She has received personal grants to attend conferneces from Gilead, Viiv, Jannsen, BMS, BI and MSD and has received research grants from the same companies.
Date	**October 2014**

FIRST-LINE ART: WHERE TO NOW?

Dr Chloe Orkin

Consultant and Honorary Reader in HIV Medicine

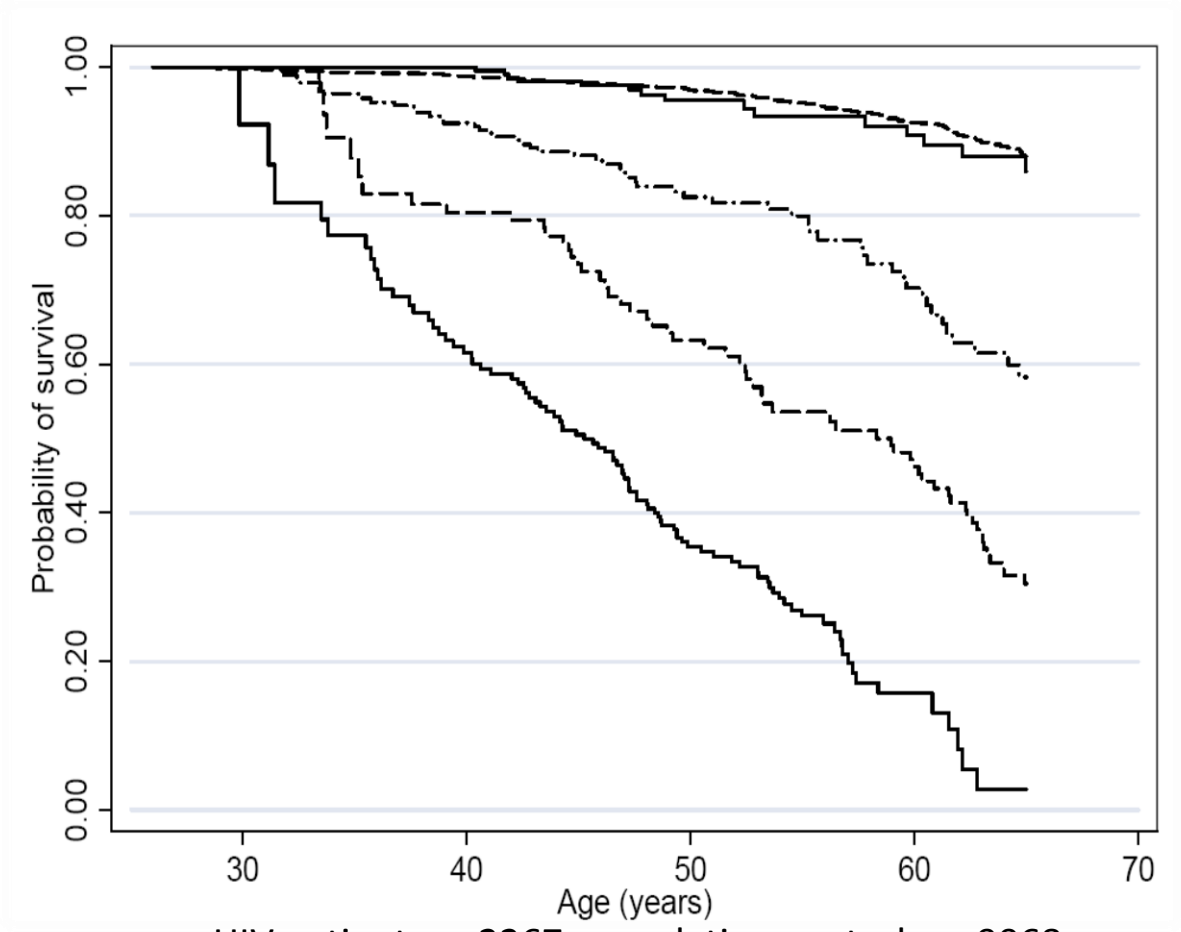
Barts Health NHS Trust

What's new since BHIVA 2013?

- Guidelines
- Backbone
- 3rd Agent
- Tolerability
- Robustness
- Durability
- STR
- Horizon scanning

Life expectancy of HIV-positive persons vs general population

Danish HIV Cohort Study



HIV patients n=2267; population controls n=9068

Population controls

HIV patients – risk (n=871)

HIV patients + risk (n=704)

HIV patients + co-morb. (n=379)

HIV patients + abuse (n=313)

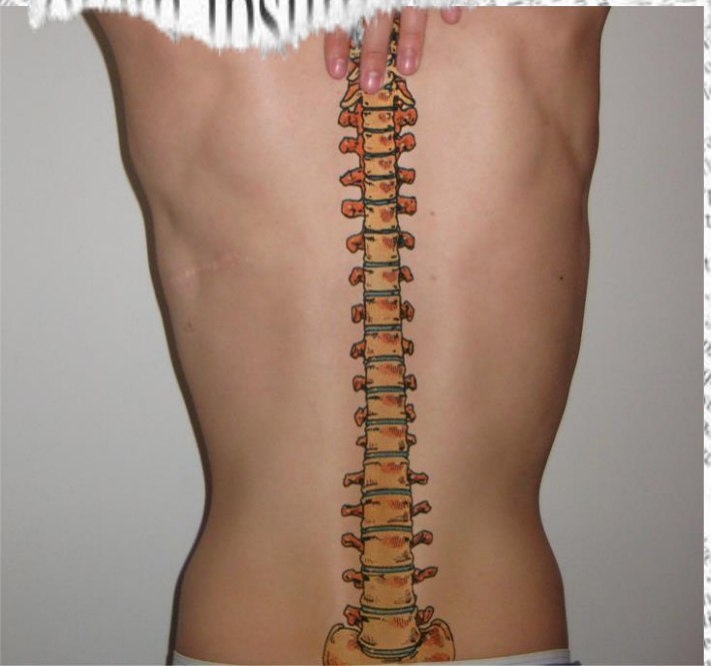
Adapted from Obel et al. PLoS One 2011. 2011;6:e22698

NEAT-001

Kivexa

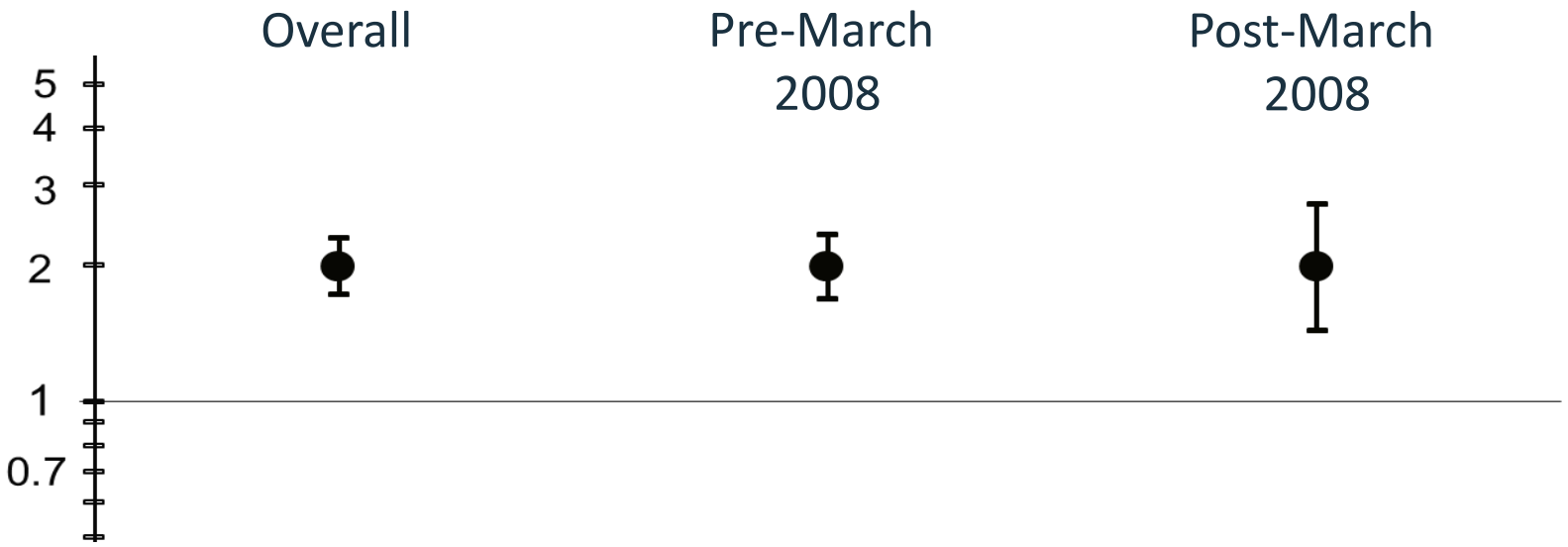
NRTI BACKBONE IN HIV TREATMENT: WILL IT REMAIN RELEVANT?

Drugs 2012 Nov 12;72(16):2051-62



Truvada

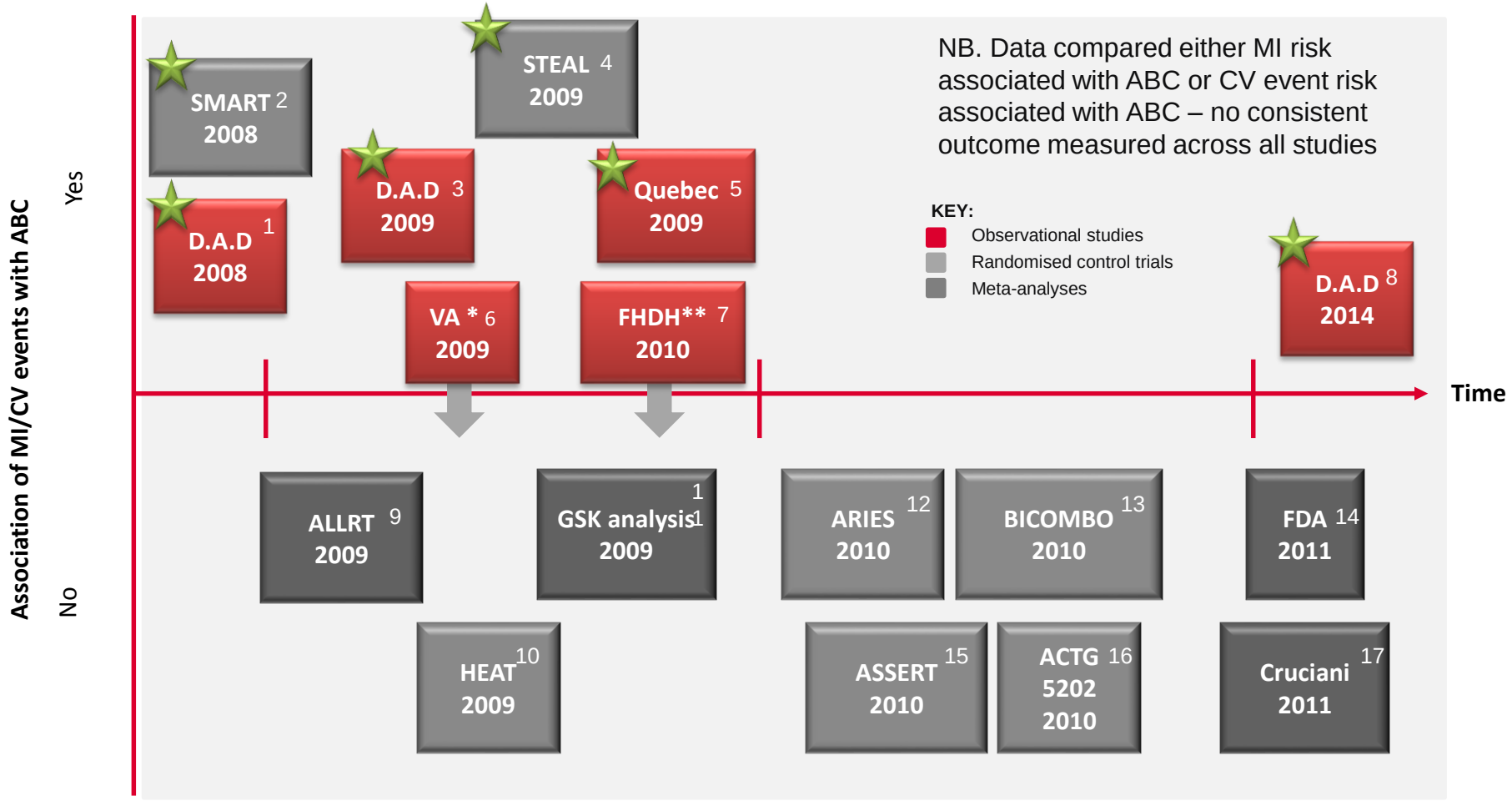
DAD data 2014: Association between current ABC use and MI risk



Not currently on ABC			
Events/PYRS	600/295642	425/169417	175/126225
Rate (95% CI)/100PYRS	0.2 (0.19,0.22)	0.25 (0.23,0.28)	0.14(o.12,0.16)
Currently on ABC			
Events/ PYRS	341/71917	247/40833	94/31084
Rate (95% CI)/100 PYRS	0.47 (0.42, 0.52)	0.61 (0.53, 0.68)	0.30 (0.24, 0.36)

Adapted from : CA Sabin et al DAD study CROI Boston 2014

Conflicting evidence on risk of MI/CV event associated with ABC treatment



***Although initial analysis identified an association between ABC and increased risk of MI, further analyses showed no association after adjustment for traditional CV risk factors and renal dysfunction.**

****Sensitivity/supportive analysis censoring cocaine or IV drug use**

1. Sabin CA *et al.*Lancet 2008;371:1417-1426. 2.SMART Study Group. AIDS 2008;22:F17-F24. 3. Lundgren JD *et al.* 16th CROI, 8th-11th Feb 2009, Montreal. LB44. 4. Martin A et al. CID 2009; 49:1591–1601. 5. Durand M *et al.* JAIDS DOI:10.1097/QAI.0b013e31821d33a5. 6.Bedimo RJ et al. 5th IAS, 19th-22nd July 2009, Cape Town, SA. MOAB202. 7. Lang S et al. Arch Intern Med 2010;170(14):1228-1238. 8. Sabin CA *et al.* 21st CROI, 3rd-6th March 2014, Boston, MA. Abstr747LB . 9. Benson C *et al.* 16th CROI, 8th-11th Feb 2009, Montreal, 721. 10. Smith KY et al. AIDS 2009, 23:1547–1556. 11. Brothers CH *et al*. J AIDS 2009;51(1):20-28. 12. Squires K *et al*. AIDS 2010, 24:2019–2027. 13.Martinez E et al. AIDS 2010; 24(3):F1-F9. 14. Ding X *et al*. J AIDS 2012;61:441–447. 15. Moyle G *et al.* Antivir Ther 2013;18(7): 905-913. 16. Moyle G. 2nd Joint Conference of BHIVA/BASHH, 20th-23rd April 2010, Manchester 17. Cruciani M *et al*. AIDS 2011; 25:1993-2004 .

BHIVA GUIDELINES 2013 (BEING RE-WRITTEN)

PREFERRED

NRTI	3rd agent
TDF and FTC	ATV/r DRV/r EFV RAL EVG/cobi

ALTERNATIVE

NRTI	3rd agent
ABC*‡ and 3TC	RPV‡ LPV/r FPV/r NVP†

*ABC is contraindicated if HLA-B*5701 positive
†NVP is contraindicated if baseline CD4 cell count is greater than 250/400 cells/mL in women/men
‡Use recommended only if baseline VL <100 000 copies/mL: RPV as a third agent, ABC/3TC as NRTI backbone

BHIVA Guidelines 2012 (updated November 2013)
HIV Medicine (2014), 15 (Suppl. 1), 1–85

DHHS, IAS-USA, EACS ON NRTI BACKBONE FOR ART-NAÏVE PATIENTS

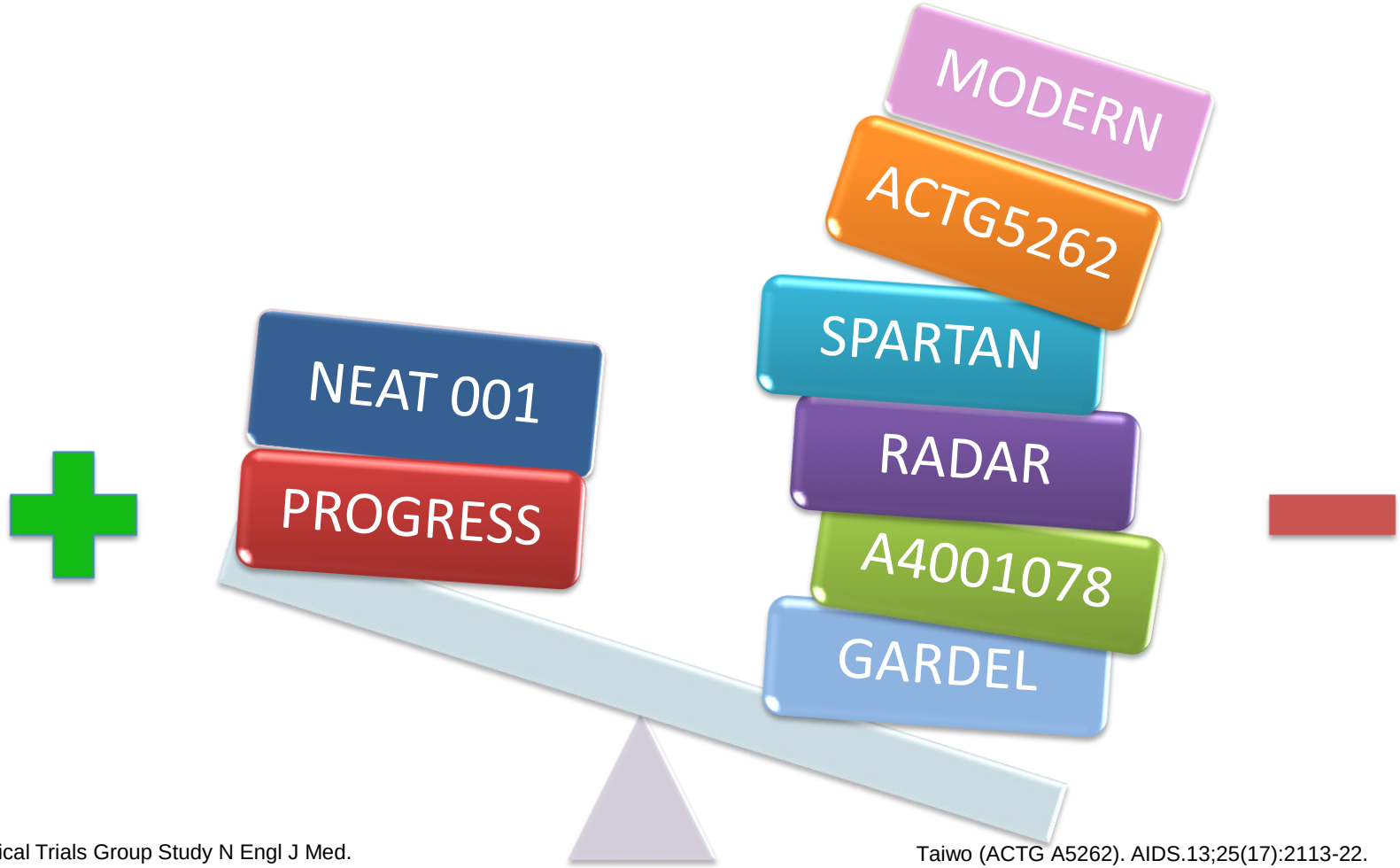
DHHS[1] (Dept. of Health and Human Services)	IAS-USA[2] (International Antiviral Society USA Panel)	EACS[3] (European AIDS Clinical Society)
NNRTI-based therapy		
EFV/TDF/FTC	**EFV** + TDF/FTC or ABC/3TC*	**EFV** or **RPV**** + TDF/FTC or ABC/3TC*** **NVP**‡ + TDF/FTC
Ritonavir-boosted PI-based therapy		
ATV/r or **DRV/r** + TDF/FTC	**ATV/r** + TDF/FTC or ABC/3TC* **DRV/r** + TDF/FTC	**ATV/r**, **DRV/r**, or **LPV/r** + TDF/FTC or ABC/3TC**
INI-based therapy		
RAL + TDF/FTC **EVG/cobi**/TDF/FTC **DTG** + ABC/3TC or TDF/FTC	**RAL** + TDF/FTC	**RAL** + TDF/FTC

*ABC/3TC only to be used in HLA-B*5701 negative patients with baseline plasma HIV-1 RNA <100,000 c/mL
**RPV: only if VL <100 000 c/mL; PPI contraindicated, H_2 antagonists to be taken 12h before or 4h after RPV
***ABC contra-indicated if HLA-B*5701 positive. Even if HLA-B*5701 negative, counselling on HSR risk still mandatory.
ABC should be used with caution in patients with a high CVD risk and/or patients with a VL > than 100,000 c/mL
‡NVP only if benefits outweigh risk

CVD, cardiovascular disease; HSR, hypersensitivity reaction
PPI, proton pump inhibitors; VL, viral load

1. DHHS Guidelines February 2013 and October 2013
2. Thompson MA, et al. JAMA 2012;308:387–402
3. EACS Guidelines Version 7.0, October 2013

NRTI-free regimes:

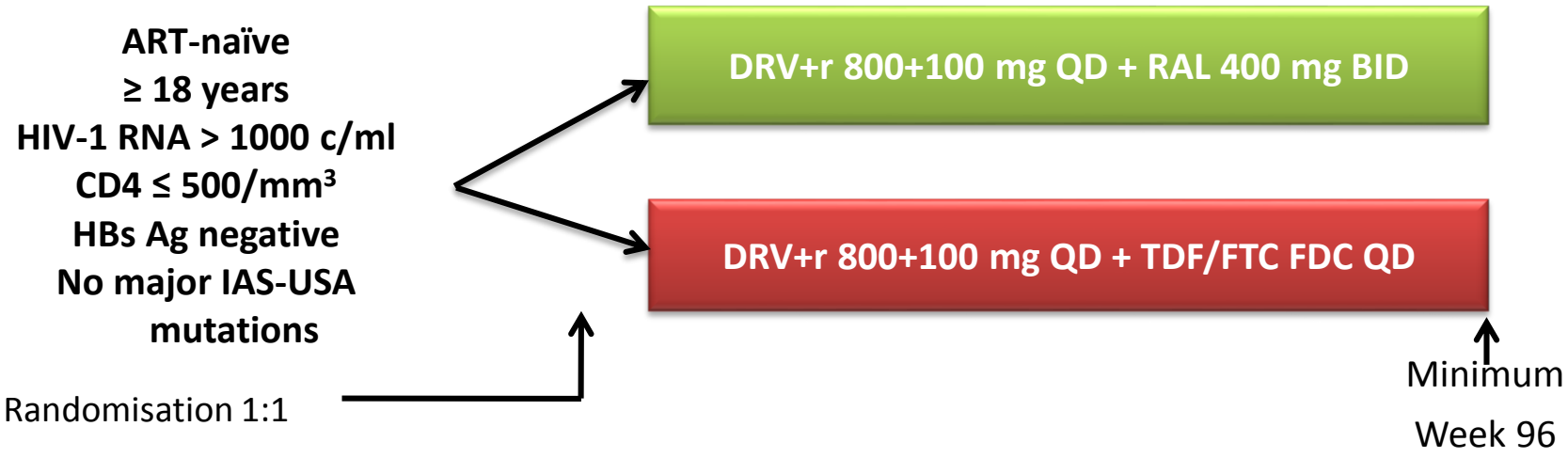


Riddler SA AIDS Clinical Trials Group Study N Engl J Med. 15;358(20):2095-106.
Kozal MJSPARTAN study results. HIV Clin Trials. 13(3):119-30.
Reynes JHIV Clin Trials. 12(5):255-67.

Taiwo (ACTG A5262). AIDS.13;25(17):2113-22.
Mills A. J Acquir Immune Defic Syndr. 1;62(2):164-70.
Mascolini M RADAR IAS June 2013, Malaysia.

NEAT 001/ANRS 143 study design

- Phase III, randomised, open-label, multicentre, parallel-group, non-inferiority, strategic trial
- 78 sites, 15 countries*



- Composite virological and clinical primary endpoint (6 components)
- Non-inferiority margin: absolute difference up to 9% for failure rate RAL vs. TDF/FTC by W96

*Austria, Belgium, Denmark, France, Germany, Great Britain, Greece, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Sweden

Adapted from Raffi F et al, NEAT 001/ANRS 143 CROI Boston 2014; Clinicaltrials.gov identifier: NCT01066962

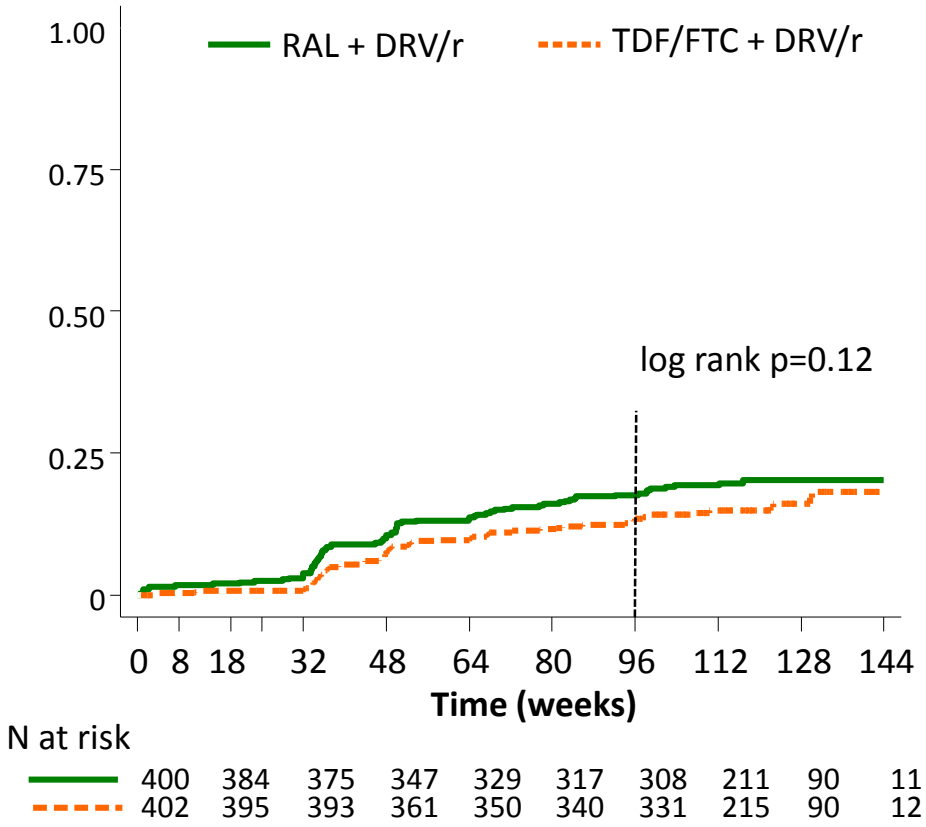
Primary analysis: Time from randomisation to primary endpoint

Primary endpoint

	RAL + DRV/r		TDF/FTC + DRV/r	
N	401		404	
N with primary endpoint	76	(19%)	61	(15%)
V1. Regimen change for insufficient response				
< 1 log_{10} c/ml HIV RNA reduction W18*	1		0	
HIV RNA ≥ 400 c/ml W24*	1		0	
V2. HIV RNA ≥ 50 c/ml at W32*	27		28	
V3. HIV RNA ≥ 50 c/ml after W32*	32		22	
C1. Death	3		1	
C2. AIDS event	5		3	
C3. SNAIDS event	7		7	

** confirmed by a subsequent measurement*

Probability of reaching primary endpoint



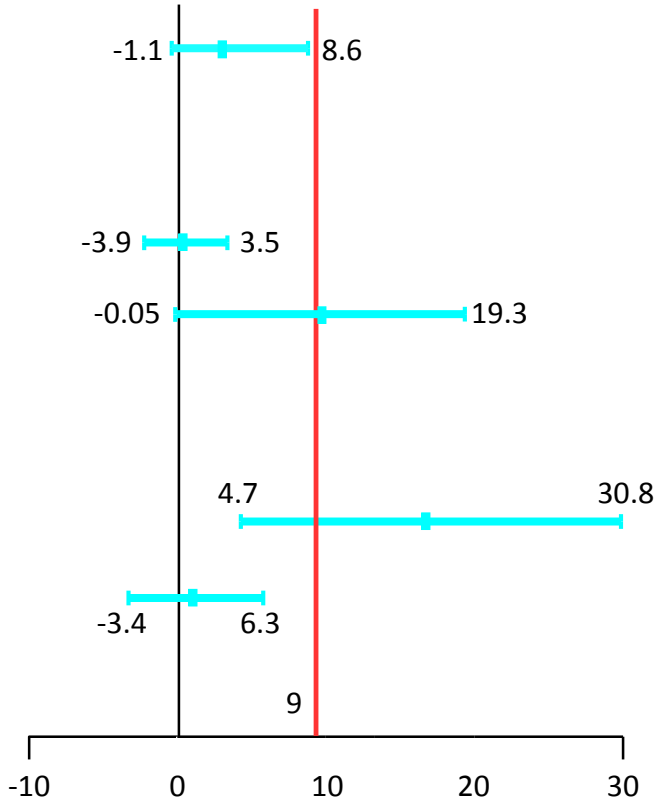
Estimated proportion reaching primary endpoint at W96
RAL: 17.4% vs TDF/FTC: 13.7%
Adjusted difference: 3.7% (95% CI: -1.1, 8.6%)

Raffi F et al, NEAT 001/ANRS 143 CROI Boston 2014

Primary endpoint at W96 by baseline characteristics

Overall analysis: RAL + DRV/r non inferior to TDF/FTC + DRV/r

		RAL + DRV/r	TDF/FTC + DRV/r
Overall	n = 805	17.4 %	13.7 %
Baseline HIV-1 RNA			
< 100,000 c/ml	n = 530	7 %	7 %
≥ 100,000 c/ml	n = 275	36 %	27 %
			p = 0.09*
Baseline CD4+			
< 200/mm^3	n = 123	39.0 %	21.3 %
≥ 200/mm^3	n = 682	13.6 %	12.2 %
			p = 0.02*



Difference in estimated proportion (95% CI) RAL – TDF/FTC; adjusted

* Test for homogeneity

Adapted from Raffi F et al, NEAT 001/ANRS 143 CROI Boston 2014

Virological failure and resistance data

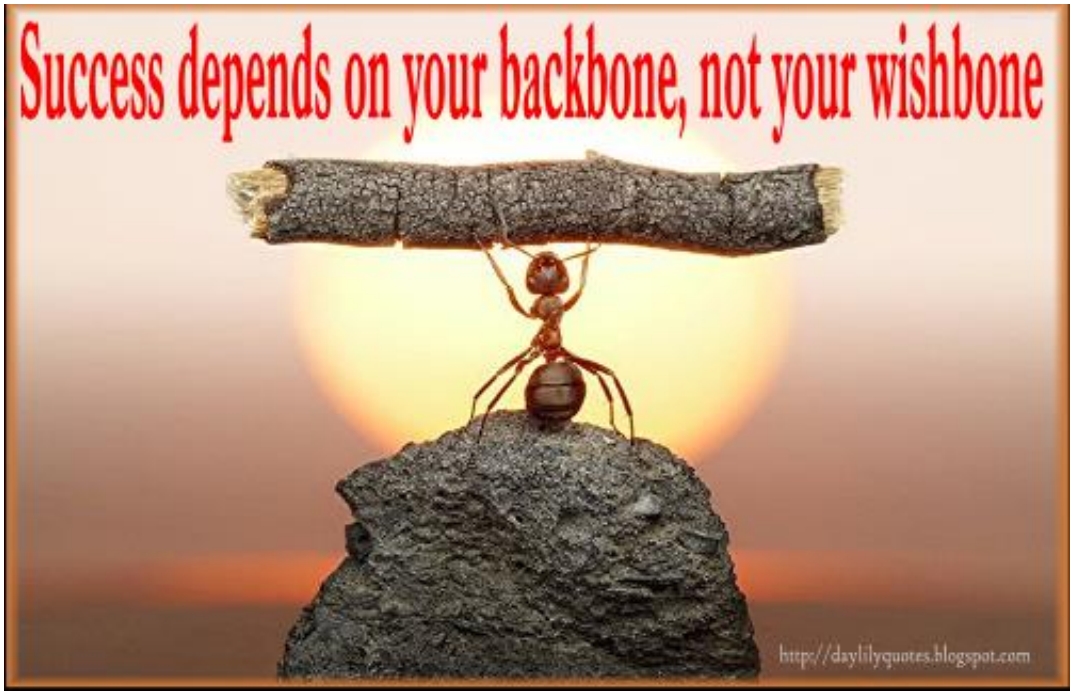
	RAL + DRV/r n=401	TDF/FTC + DRV/r n=404
Protocol-defined virological failure (PDVF), n	66	52
Number of PDVF who met criteria for genotype testing (HIV RNA > 500 copies/ml at or after W32)	33	9
Number of patients with single unconfirmed value of HIV RNA > 500 copies/ml at or after W32 (meeting criteria for genotype testing)	3	6
Genotype done, n	28/36	13/15
Major resistance mutations, n	5	0
NRTI	1 (K65R)	0
PI	0	0
INI	5 (N155H)*	-

** 1 additional patient with T97A*

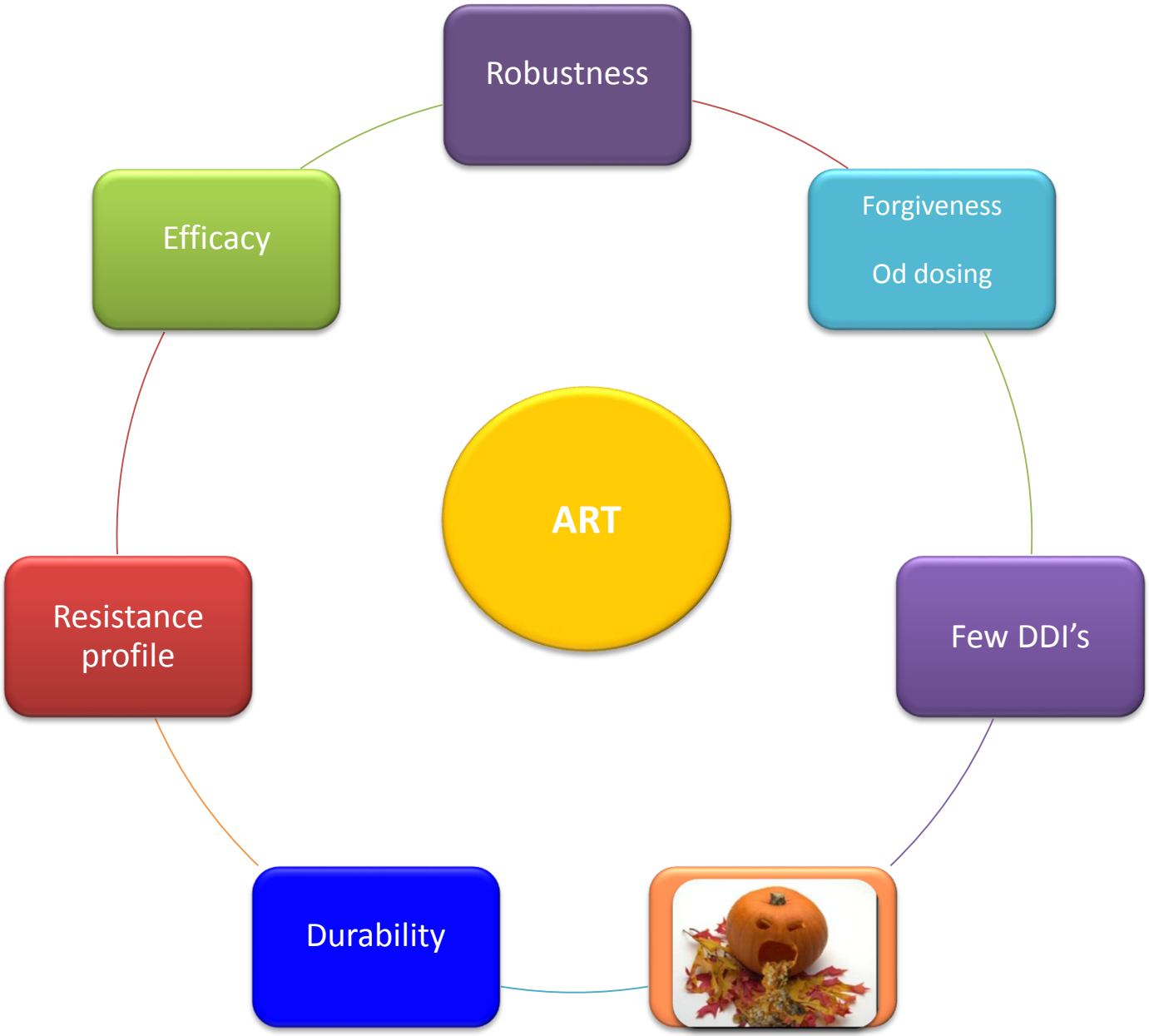
Protocol-defined virological failure change of any component of the initial randomised regimen before W32 because of confirmed insufficient virological response, defined as HIV-1 RNA reduction < 1 $\log_{10}$ copies/ml by W18 or HIV-1 RNA ≥ 400 copies/ml at W24 ; failure to achieve virological response by W32 (confirmed HIV-1 RNA ≥ 50 copies/ml at W32) ; confirmed HIV-1 RNA ≥ 50 copies/ml at any time after W32

According to the protocol, genotypic testing was carried out by local laboratories when patients had a single VL > 500 copies/ml at or after W32.

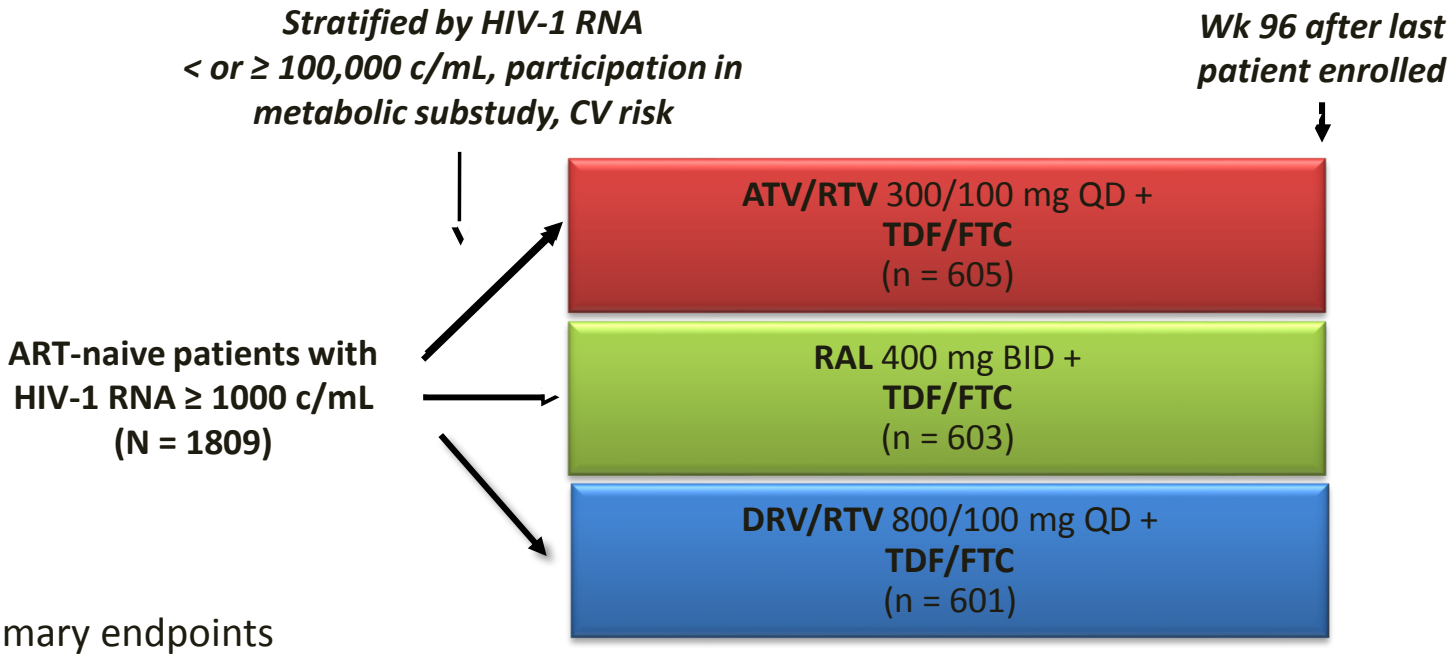
NRTI's remain



A GOOD 3RD AGENT ?



ACTG 5257: Open-Label ATV/r vs RAL vs DRV/r in 1st-line ART



- Primary endpoints
  - VF: time to HIV-1 RNA > 1000 c/mL (at Wk 16 or before Wk 24) or > 200 c/mL (at or after Wk 24)
  - TF: time to discontinuation of randomized component for toxicity
- Composite endpoint: the earlier occurrence of either VF or TF in a given participant
- Switch of regimens allowed for tolerability

Landovitz R, et al. CROI 2014. Abstract 85.

Baseline Characteristics

Characteristic		Total (N=1809)	Treatment group		
			ATV/r (N=605)	RAL (N=603)	DRV/r (N=601)
Sex	Female	**435 (24%)**	144 (24%)	148 (25%)	143 (24%)
Age (years)	Mean	**37**	38	37	38
Race/Ethnicity	White Non-His.	**615 (34%)**	212 (35%)	212 (35%)	191 (32%)
	Black Non-His.	**757 (42%)**	252 (42%)	254 (42%)	251 (42%)
	Hispanic	**390 (22%)**	125 (21%)	117 (19%)	148 (25%)

Baseline Characteristics

Characteristic		Total (N=1809)	Treatment group ATV/r (N=605)	RAL (N=603)	DRV/r (N=601)
Sex	Female	**435 (24%)**	144 (24%)	148 (25%)	143 (24%)
Age (years)	Mean	**37**	38	37	38
Race/Ethnicity	White Non-His.	**615 (34%)**	212 (35%)	212 (35%)	191 (32%)
	Black Non-His.	**757 (42%)**	252 (42%)	254 (42%)	251 (42%)
	Hispanic	**390 (22%)**	125 (21%)	117 (19%)	148 (25%)
HIV-1 RNA (log_{10} c/ml)	Median (Q1-Q3)	**4.6 (4.1-5.1)**	4.6 (4.1-5.2)	4.7 (4.1-5.1)	4.6 (4.1-5.1)
(copies/ml)	<100,000	**70%**	68%	68%	72%
	100,000-500,000	**23%**	25%	24%	22%
	>500,000	**7%**	7%	8%	6%

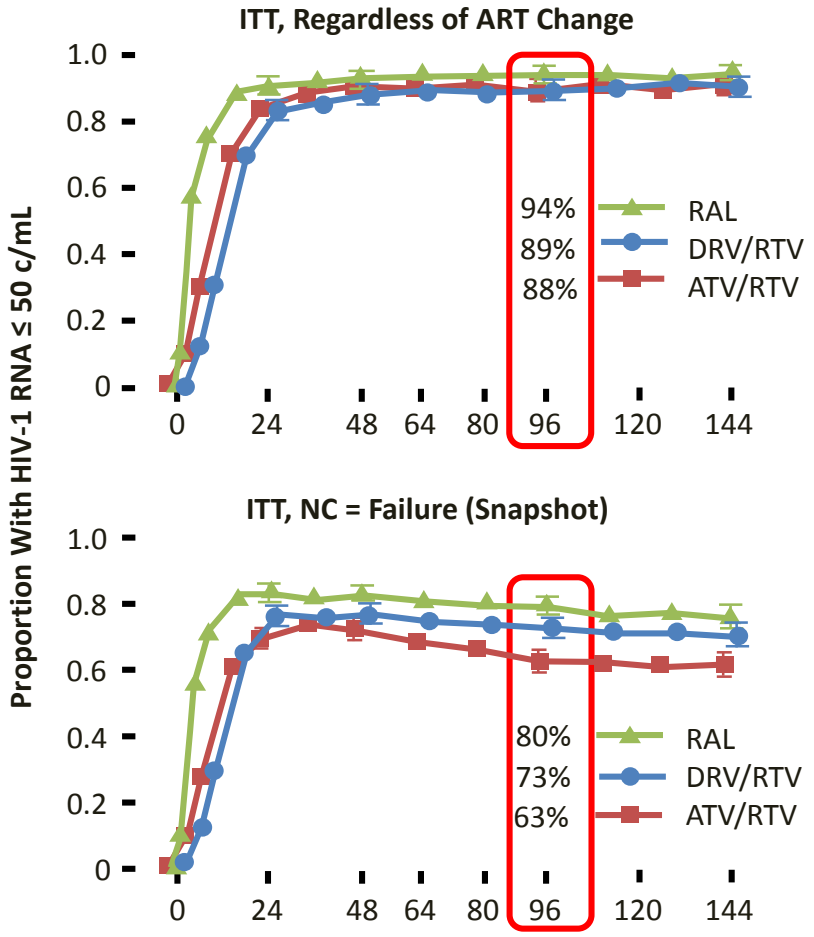
Baseline Characteristics

Characteristic		Total (N=1809)	Treatment group ATV/r (N=605)	RAL (N=603)	DRV/r (N=601)
Sex	Female	**435 (24%)**	144 (24%)	148 (25%)	143 (24%)
Age (years)	Mean	**37**	38	37	38
Race/Ethnicity	White Non-His.	**615 (34%)**	212 (35%)	212 (35%)	191 (32%)
	Black Non-His.	**757 (42%)**	252 (42%)	254 (42%)	251 (42%)
	Hispanic	**390 (22%)**	125 (21%)	117 (19%)	148 (25%)
HIV-1 RNA (log_{10} c/ml)	Median (Q1-Q3)	**4.6 (4.1-5.1)**	4.6 (4.1-5.2)	4.7 (4.1-5.1)	4.6 (4.1-5.1)
(copies/ml)	<100,000	**70%**	68%	68%	72%
	100,000-500,000	**23%**	25%	24%	22%
	>500,000	**7%**	7%	8%	6%
CD4+ cells (/mm³)	Median (Q1-Q3)	**308 (170-425)**	309 (176-422)	304 (158-427)	310 (171-424)
%	<200	**30%**	29%	31%	29%

ACTG 5257: Virologic Efficacy

- In ITT analysis ART changes allowed (per protocol), Wk 96 through Wk 144

- In ITT analysis (change = failure) (Snapshot), RAL superior to both bPI's at Wk 96 .DRV/RTV superior to ATV/RTV at Wks 96 and 144



Adapted from Landovitz R, et al. CROI 2014. Abstract 85. Reproduced with permission.

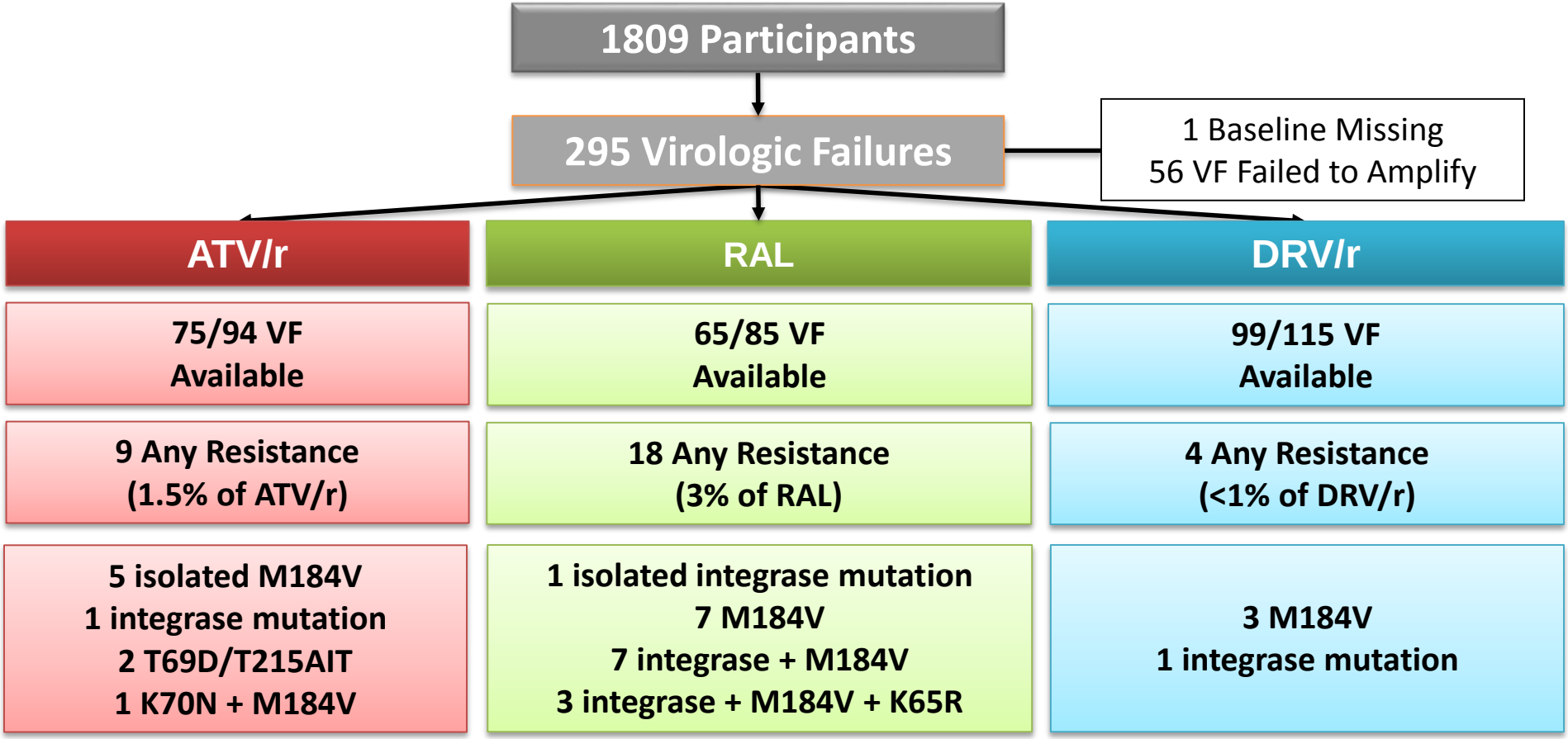
Toxicity-Associated Discontinuation of randomized ART *

	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/Hyperbilirubinaemia	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/haem (excl. LFTs)	0	0	2
Other toxicity	2	3	4

*Participants allowed to switch therapy for intolerable toxicity

Landovitz R, et al. CROI 2014. Abstract 85. Reproduced with permission.

Resistance to Study Agents



Landovitz R, et al. CROI 2014. Abstract 85. Reproduced with permission.

ACTG 5257: Primary Endpoint Analyses at Wk 96

Virologic Failure

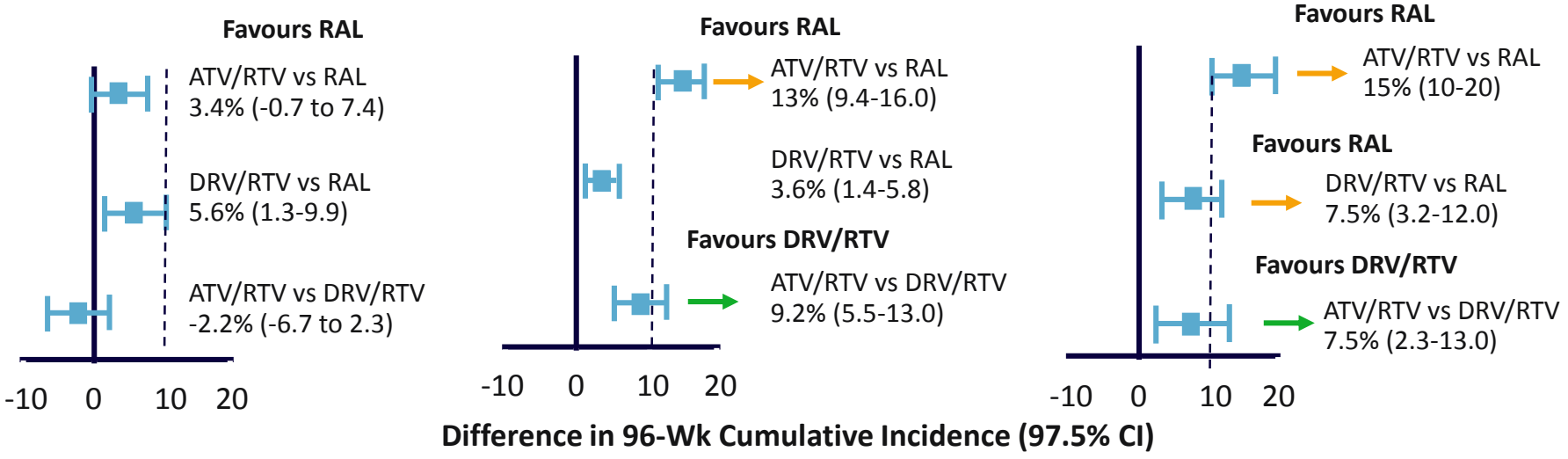
- Regimens equivalent in time to VF endpoint

Tolerability Failure

- Significantly greater treatment failure with ATV/RTV vs RAL or DRV/RTV
  - In part due to high proportion of pts with hyperbilirubinaemia

Composite Endpoint

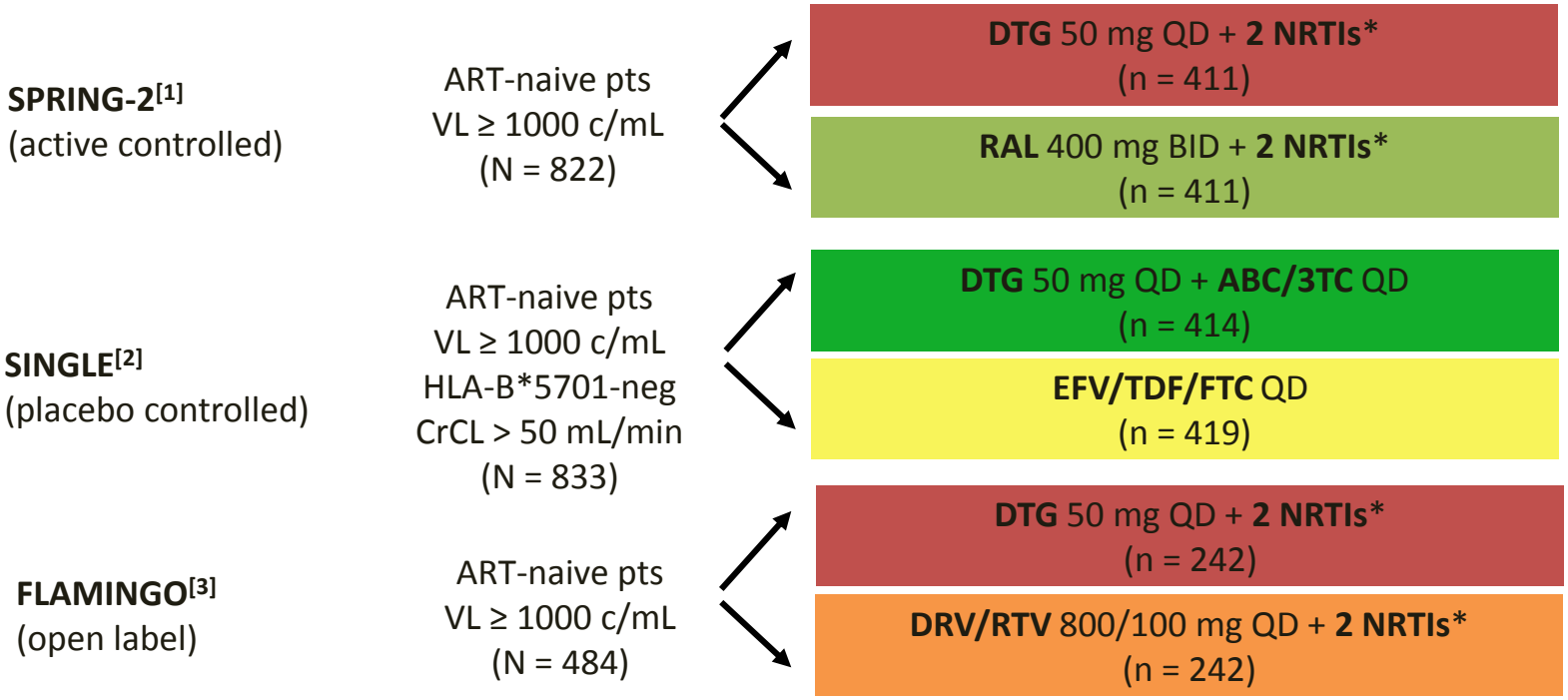
- Considering both efficacy and tolerability, RAL superior to either b PI
- DRV/RTV superior to ATV/RTV



Adapted by reformatting from: Landovitz R, et al. CROI 2014. Abstract 85..

Dolutegravir vs RAL, EFV, DRV/r

- Randomized, non-inferiority phase III studies
- Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48



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

Adapted from: 1. Raffi F, et al. Lancet. 2013;381:735-743. 2. Walmsley S, et al. N Engl J Med. 2013;369:1807-1818. 3. Feinberg J, et al. ICAAC 2013. Abstract H1464a.

Baseline characteristics

Characteristic	Total (N=833)	Total N=822)	Total (N=484)
Median age, years	35	37	34
Female, %	16	14	15
African-American/African heritage, %	24	11	23
Baseline HIV-1 RNA			
Median (log10 c/mL)	4.68	4.55	4.49
>100,000 c/mL, %	32	28	25
Median CD4 cell count, cells/mm^3	338		
<200, %	14	13	10

Adapted from . Raffi F, et al. Lancet. 2013;381:735-743
Walmsley S, et al. N Engl J Med 2013;369:1807–18;Supplementary appendix
Feinberg J, et al. ICAAC 2013. Abstract H1464a

Tolerability

- DTG vs RAL[1,2]
  - Adverse events similar between arms

DTG vs EFV[3]

  - CNS events and rash more common with EFV; insomnia more frequent with DTG

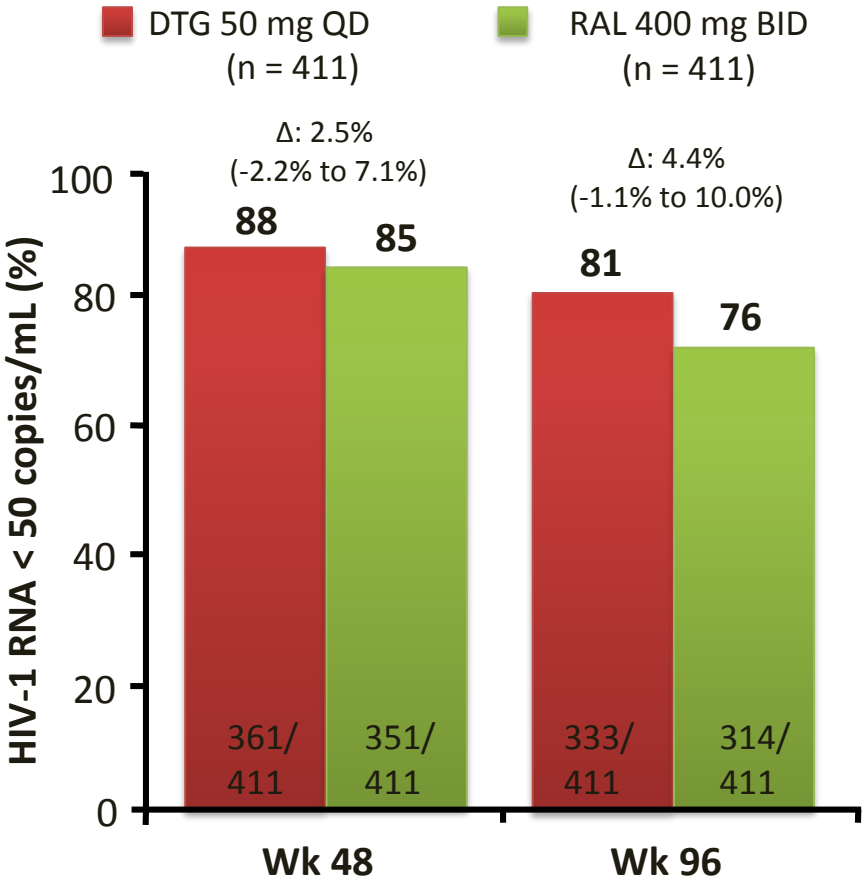
DTG vs DRV/RTV[4]

  - More diarrhea with DRV/RTV; more headache with DTG

- DTG associated with small, rapid increase in serum creatinine in first 4 wks : remained stable through Wk 48 (mean change from baseline: +0.11 mg/dL; range: -0.60 to 0.62 mg/dL)[5]
  - Rise in creatinine related to inhibition of tubular secretion of creatinine by DTG
  - No drug-related discontinuations due to renal adverse events

1. Raffi F, et al. Lancet. 2013;381:735-743. 2. Raffi F, et al. IAS 2013. Abstract TULBPE17.
3. Walmsley S, et al. N Engl J Med. 2013;369:1807-1818. 4. Feinberg J, et al. ICAAC 2013. Abstract H1464a. 5. Dolutegravir [package insert].

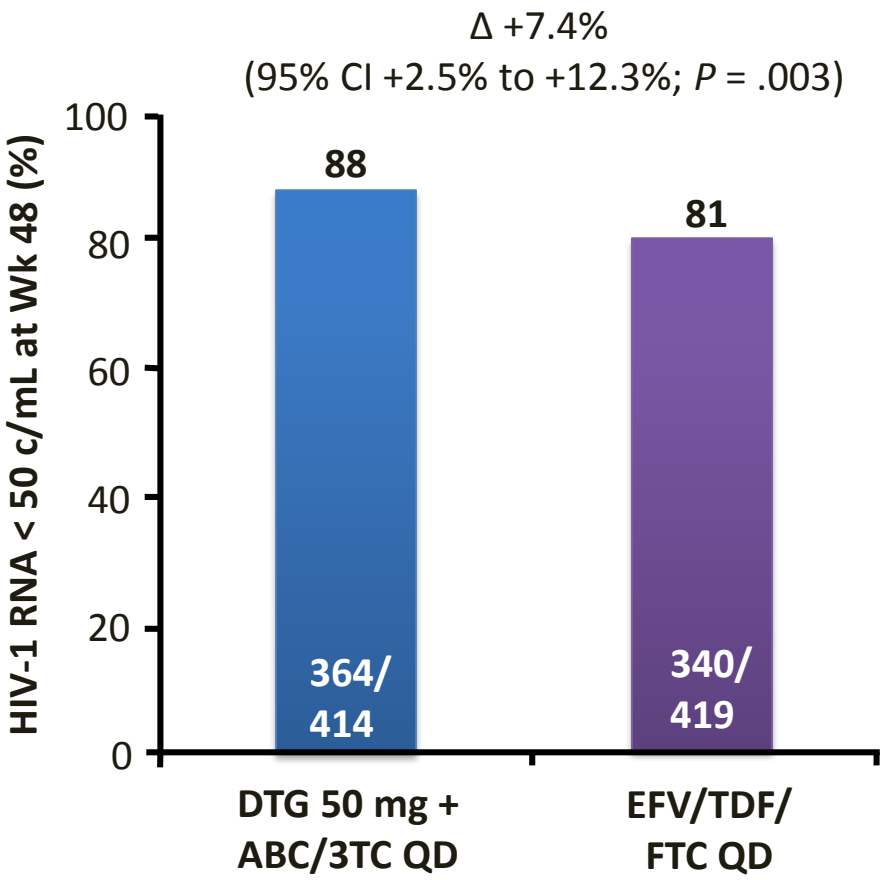
SPRING-2: DTG vs RAL + 2 NRTIs Wk 48 &96



- DTG non-inferior to RAL at Wk 48[] and Wk 96[2]
- 2% treatment-related study d/c: in each arm (Wk 96)
- VF at Wk 96[2]: 5% DTG vs 7% RAL arm
- Similar CD4+ cell count increase at Wk 96

Adapted from: . Raffi F, et al. Lancet. 2013;381:735-743. 2. Raffi F, et al. IAS 2013. Abstract TULBPE17.

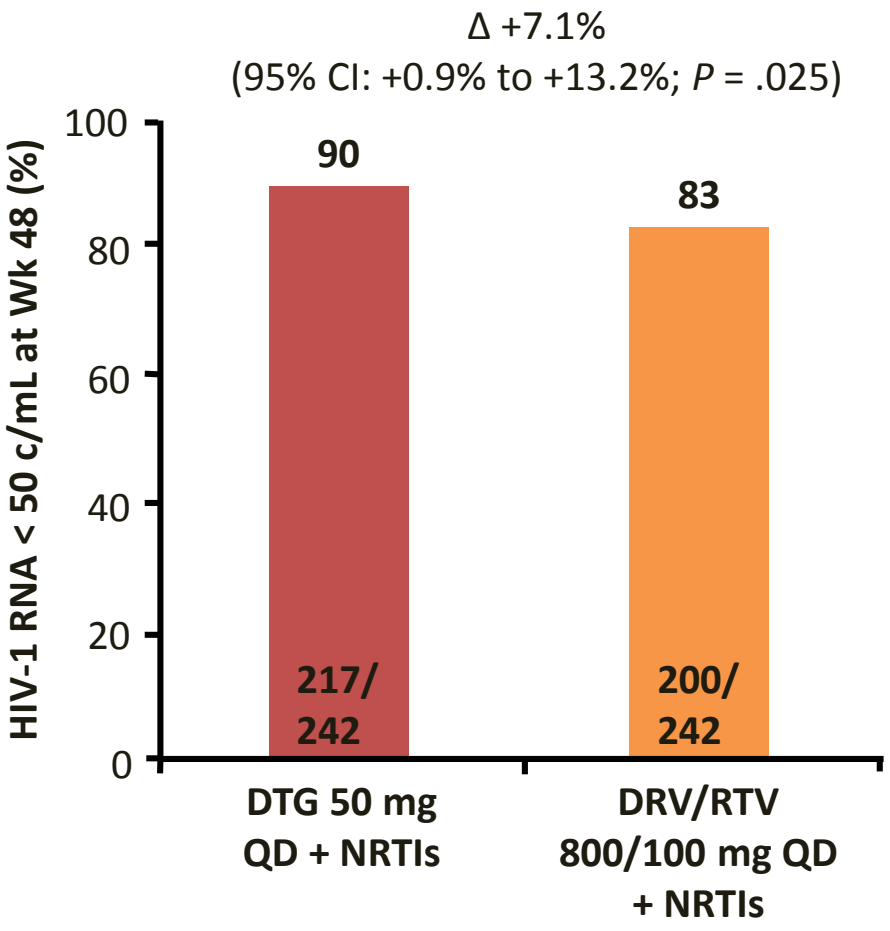
SINGLE: DTG + ABC/3TC vs EFV/TDF/FTC Wk 48 data



- DTG superior to EFV at Wk 48
- Treatment-related study d/c:
  2% DTG vs 10% EFV
- VF at Wk 48: 4% DTG and 4% EFV arm
- CD4+ cell count increase at
  Wk 48 greater with DTG:
  - +267 cells/mm^3 (DTG) vs +208 cells/mm^3 (EFV)
    (P < .001)

Adapted from Walmsley S, et al. N Engl J Med. 2013;369:1807-1818.

FLAMINGO: DTG vs DRV/r + 2 NRTIs at Wk 48



- DTG superior to DRV/RTV at Wk 48
- Treatment-related study d/c: 2% DTG vs 4% DRV/r
- VF at Wk 48: < 1% (n = 2) in each arm
- Similar CD4+ cell count increase at Wk 48

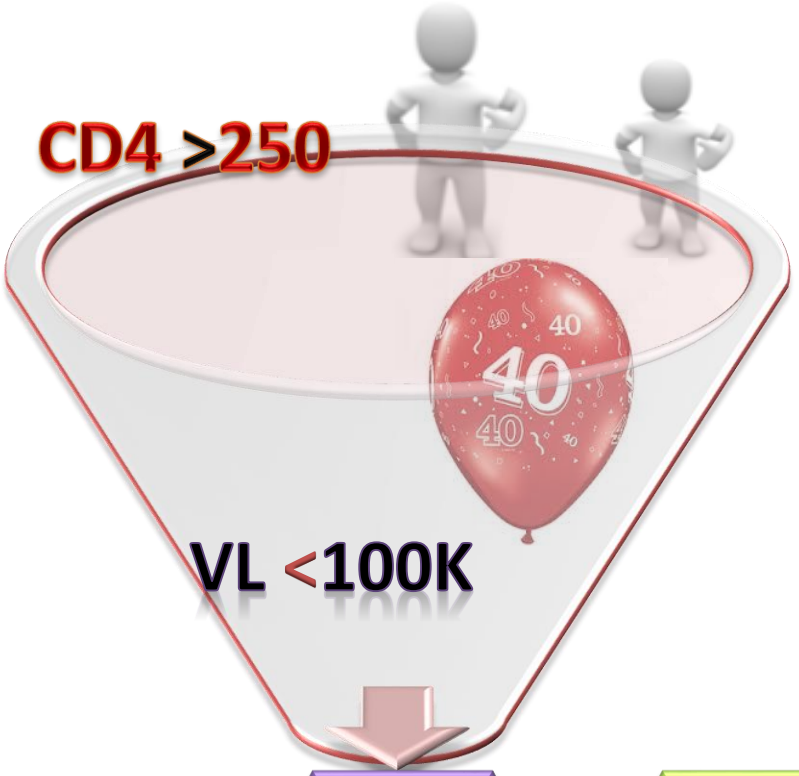
Adapted from Feinberg J, et al. ICAAC 2013. Abstract H1464a.

Resistance Summary

- DTG vs RAL[1,2]
  - 0 pts with resistance in DTG arm
  - 1 pt with INSTI-R and 4 pts with NRTI-R with RAL at Wk 48; no additional resistance by Wk 96
- DTG vs EFV[3]
  - 0 pts with resistance in DTG arm
  - 1 pt with NRTI and 4 with NNRTI resistance in EFV arm
- DTG vs DRV/RTV[4]
  - No pts with resistance in either arm

1. Raffi F, et al. Lancet. 2013;381:735-743. 2. Raffi F, et al. IAS 2013. Abstract TULBPE17. 3. Walmsley S, et al. N Engl J Med. 2013;369:1807-1818. 4. Feinberg J, et al. ICAAC 2013. Abstract H1464a.

Who are our study subjects?



ACTG 5257

Rilpivirine
ECHO/THRIVE

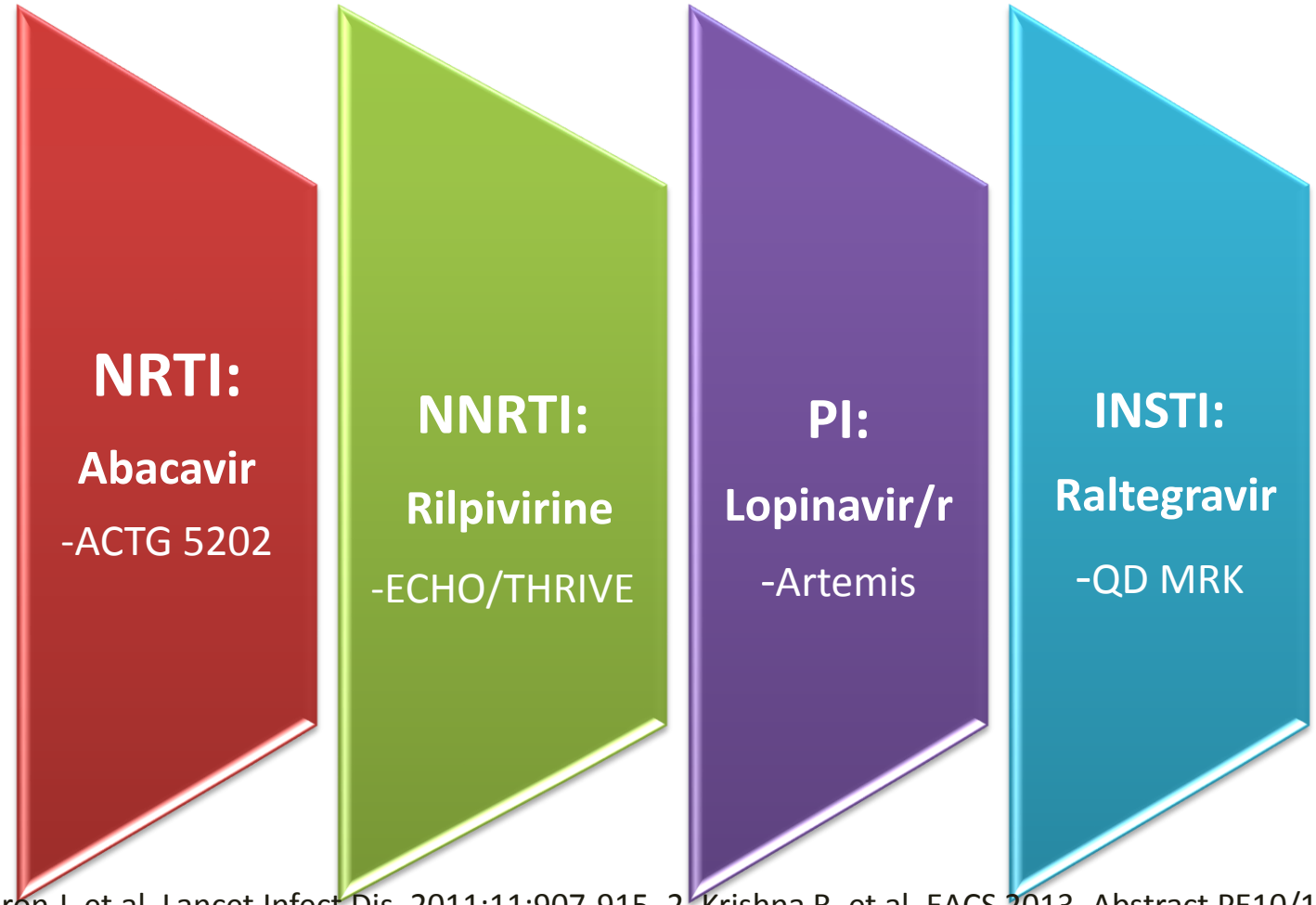
DTG
Single/Flamingo
/Sailing

RAL/DRV/r
NEAT 001

TDF/FTC/ELVI/c
0102/3

Robustness:

High Baseline VL > 100,000c/ml affects performance of **all** drug classes



1. QDMRK: Eron J, et al. Lancet Infect Dis. 2011;11:907-915. 2. Krishna R, et al. EACS 2013, Abstract PE10/17.
2. ACTG 5202: Daar E, et al. Ann Intern Med. 2011;154:445-456.
3. Artemis: Ortiz R, et al. AIDS. 2008;22:1389-1397. 2. Mills A, et al. AIDS. 2009;23:1679-1688.
4. ECHO/THRIVE: Rimsky L, et al. J Acquir Immune Defic Syndr 2012;59:39–4

DHHS Guidelines May 2014

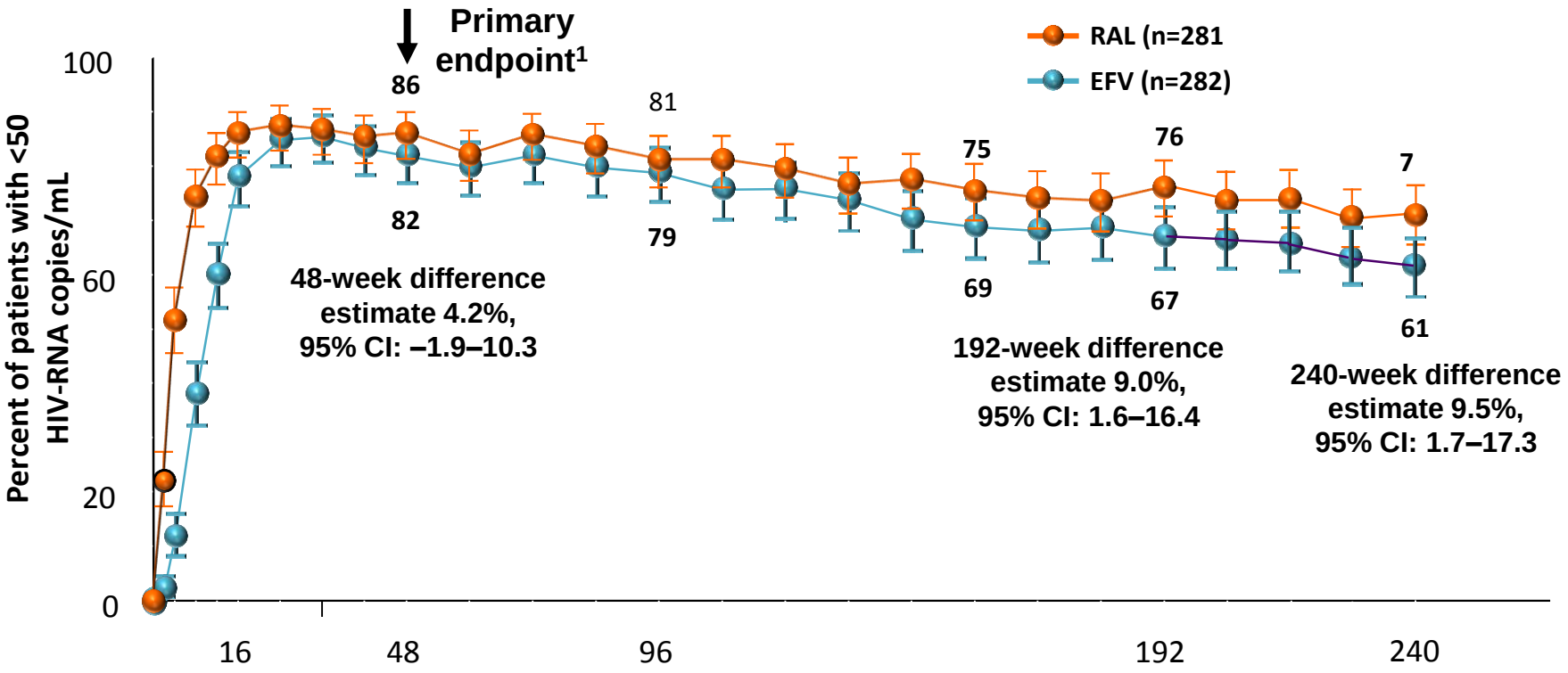
	For All Pts, Regardless of BL VL or CD4+ Count	Only for Pts With Pre-ART VL < 100,000 c/mL
NNRTI	▪ EFV/TDF/FTC	▪ EFV + ABC/3TC* ▪ RPV/TDF/FTC†
Boosted PI	▪ ATV/RTV + TDF/FTC ▪ DRV/RTV + TDF/FTC	▪ ATV/RTV + ABC/3TC*
INSTI	▪ RAL + TDF/FTC ▪ EVG/COBI/TDF/FTC ▪ DTG + ABC/3TC* ▪ DTG + TDF/FTC	

*Only for pts who are HLA-B*5701 negative. †Only for those with CD4+ cell counts > 200 cells/mm^3.

- If initiating ART in a pt with acute/early HIV before resistance test results are available, use a boosted PI plus NRTIs due to slow emergence of PI resistance and uncommon transmitted resistance

DHHS Guidelines. May 2014.

STARTMRK:
EFV vs RAL through 240 weeks (NC=F)



	DC due to AEs (%)
RAL (n=281)	5%
EFV (n=282)	10%

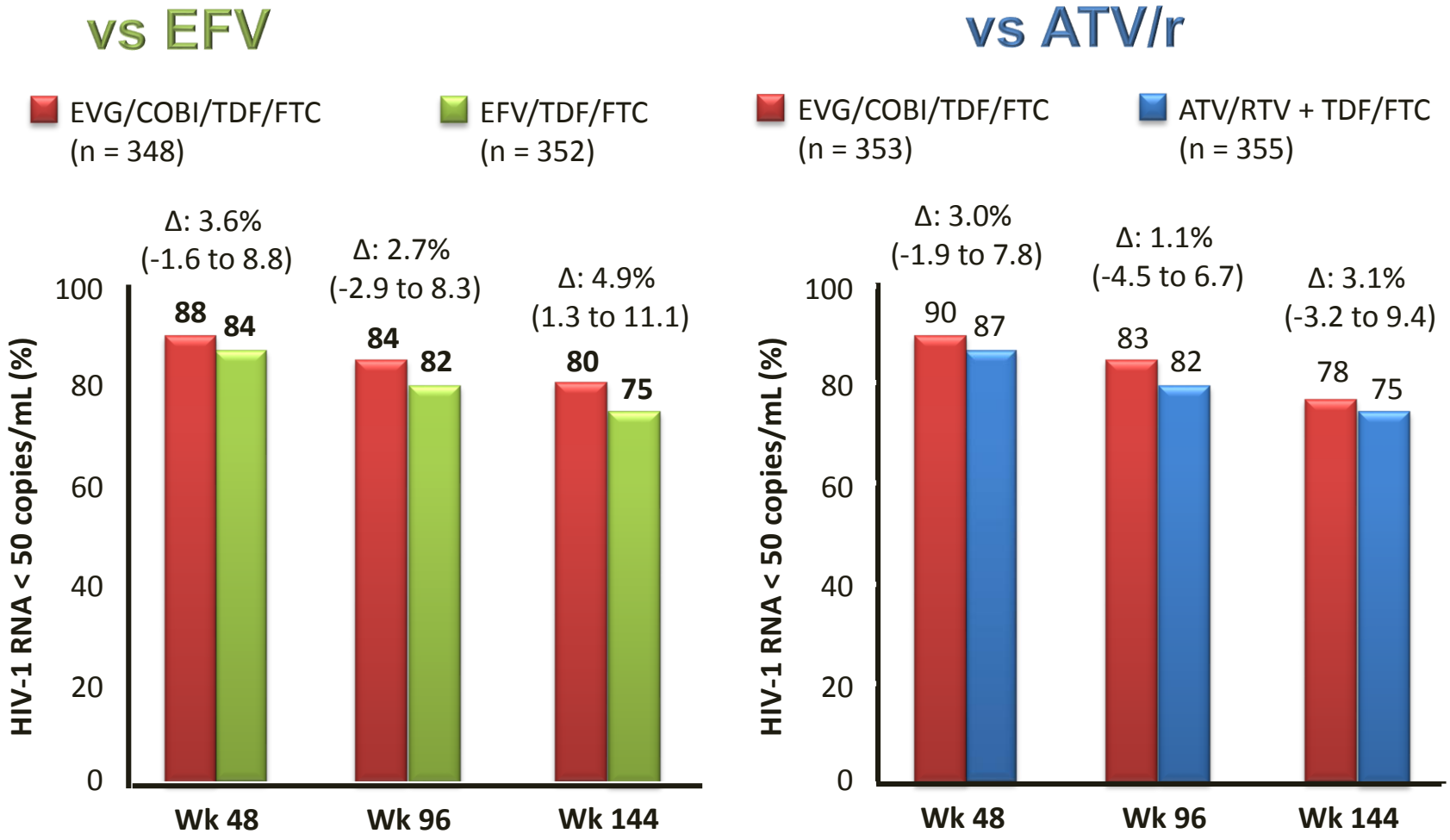
No. of virologic failures with resistance data	RAL or EFV resistance alone	RAL or EFV resistance + NRTI resistance	NRTI resistance alone
RAL (n=23)	1	3	3
EFV (n=20)	7	3	2

NC=F: non-completer=failure; *HIV-RNA <50 copies/mL

Adapted from Rockstroh JK, et al. 19th AIDS; 2012 July 22–27. Washington DC, USA. Poster LBE19.

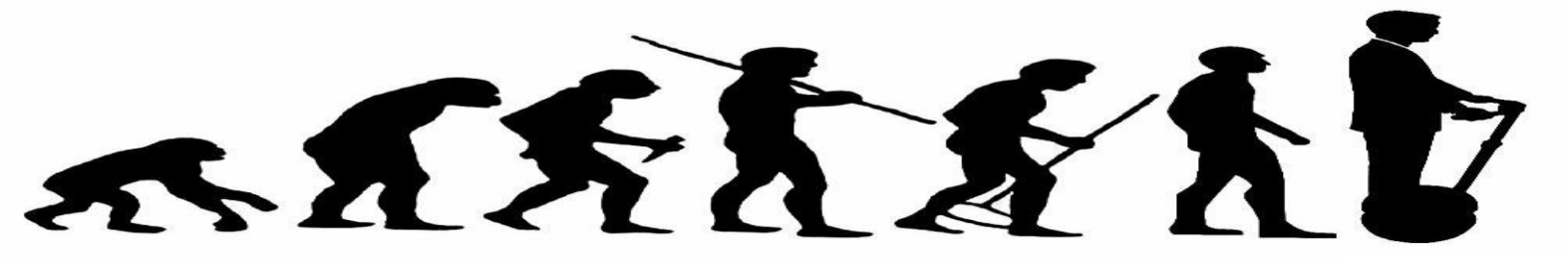
Durability:

EVG/COBI/TDF/FTC Non-inferior Through Week 144



Adapted from: 1. Sax PE, et al. Lancet. 2012;379:2439-2448. 2. Zolopa A, et al. J Acquir Immune Defic Syndr. 2013;63:96-100. 3. Wohl D, et al. ICAAC 2013. Abstract H-672a. 4. De Jesus E, et al. Lancet. 2012;379:2429-2438. 5. Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;62:483-486. 6. Clumeck N, et al. EACS 2013. Abstract LBPS7/2.

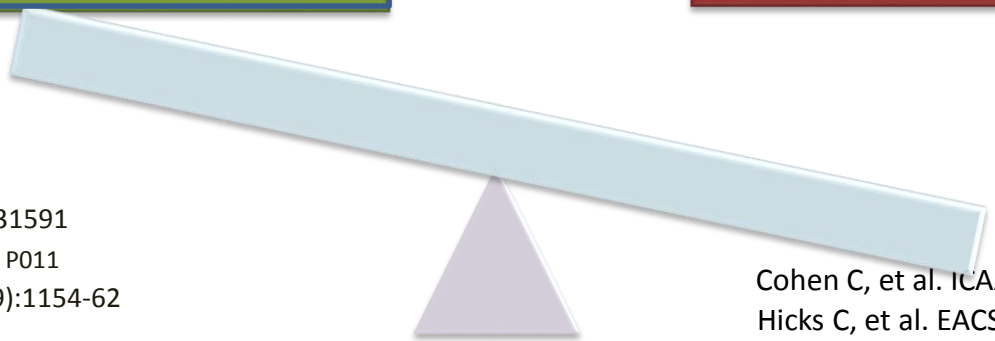
STR (single tablet regimen)



Potential Benefits and Limitations of an STR

- Approved STRs combine components of preferred or alternative ARVs
  - High virologic response rates especially in adherent patients
- Avoids risk of partial regimen adherence
  - Pharmacy dispensing error
  - Pt preference to miss select pills
- US Medicaid data set has reported better adherence
- Patients prefer the simplicity

- Friction between costs for medications vs. generic components
- Cannot dose adjust ARV components
  - e.g. pts with renal dysfunction
- No PI inhibitor based regimen available yet in the UK
  - PI has highest barrier to resistance of all initial regimens
- No randomized study of any STR vs. multi-tablet regimen to assess actual benefits
- Patients who need three or more pills a day may feel less prepared to take these regimes



Sax P, et al. PLoS ONE 2012;7(2):e31591

Fabbiani, et al. HIV-11 2012; Glasgow. P011

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

Vera J, et al. HIV-11 2012; Glasgow. P5

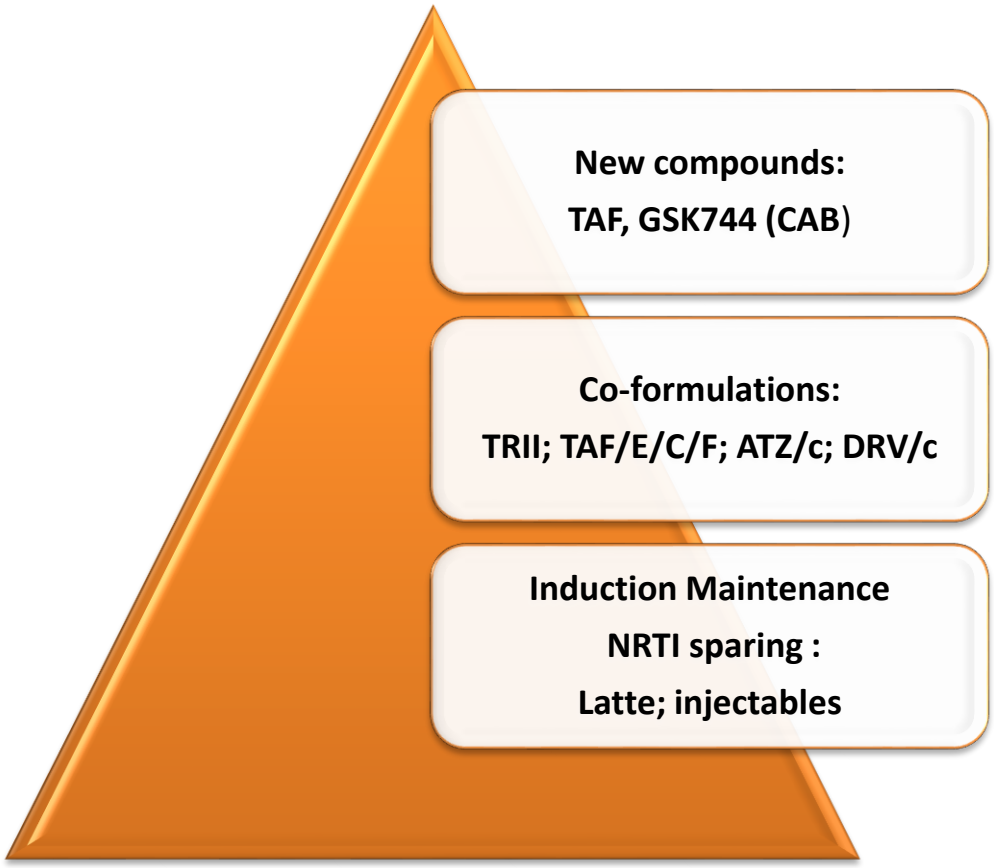
Cohen C, et al. ICAAC 2012; San Francisco, CA. #H-211

Hicks C, et al. EACS 2007. Madrid. Poster P5.7/01

572 Tri GSI GSI 123

Images not to scale http://i-base.info

Horizon Scanning



We need more studies enrolling…

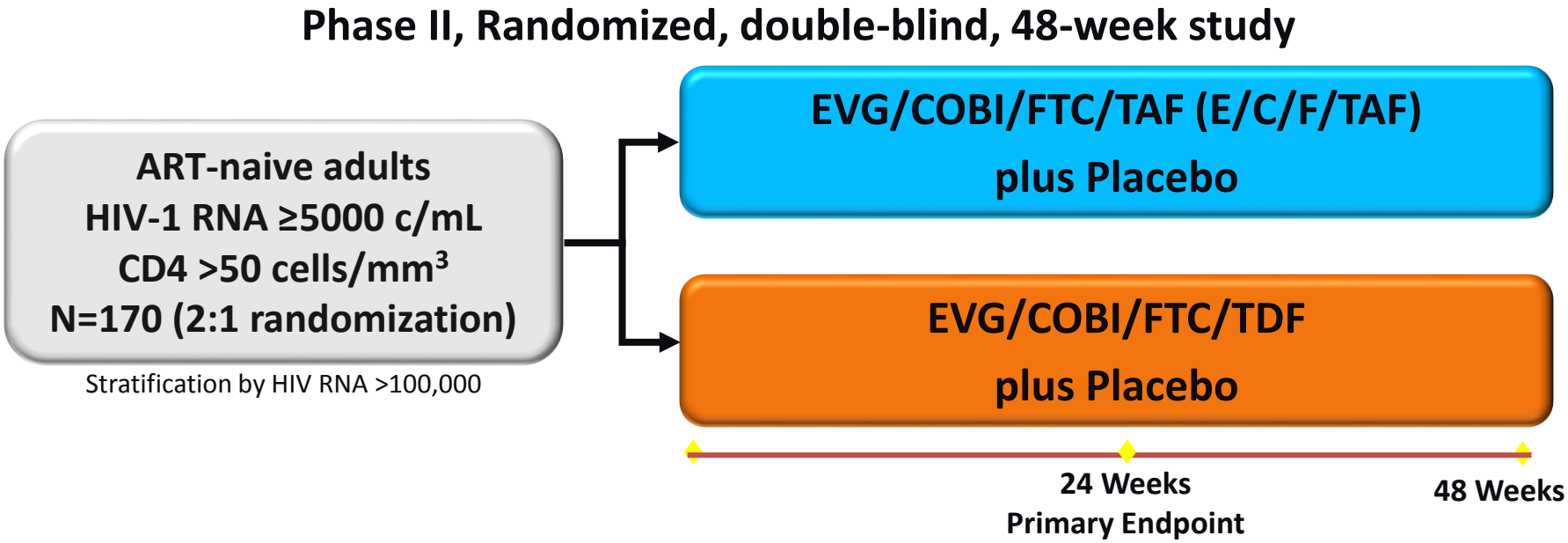
CD4 < 250

VL > 100K

Sick people

- 5164 like studies
- Waves: TAF QUAD
- RAL/DRV/r NEAT 001
- ACTG 5257
- ARIA: DTG

GS-292-102: TAF vs. TDF as E/C/F/TAF STR component

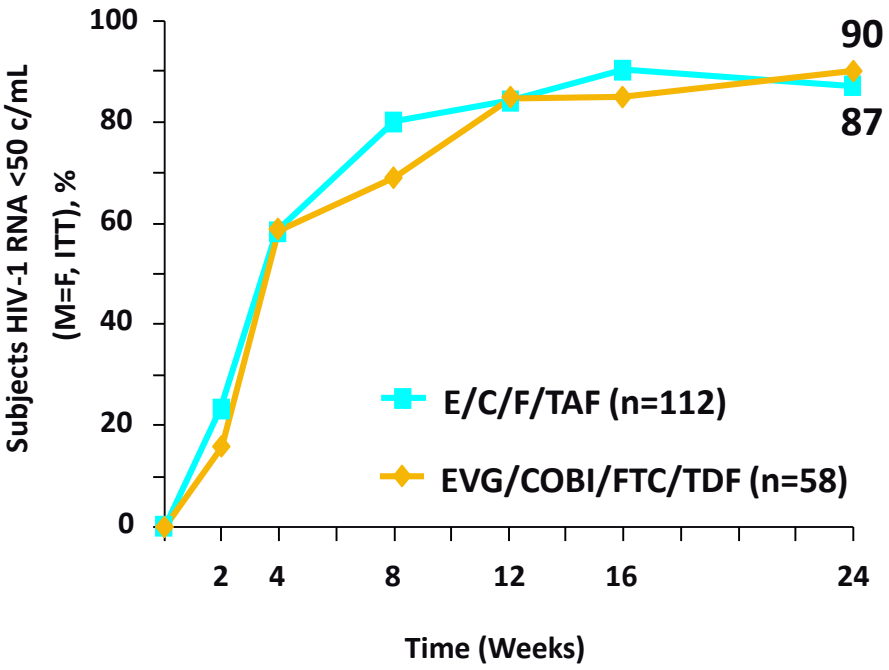


- Primary objective
  - To evaluate the efficacy of the E/C/F/TAF single-tablet regimen vs. EVG/COBI/FTC/TDF
    - Primary endpoint: HIV-1 RNA <50 c/mL at Week 24

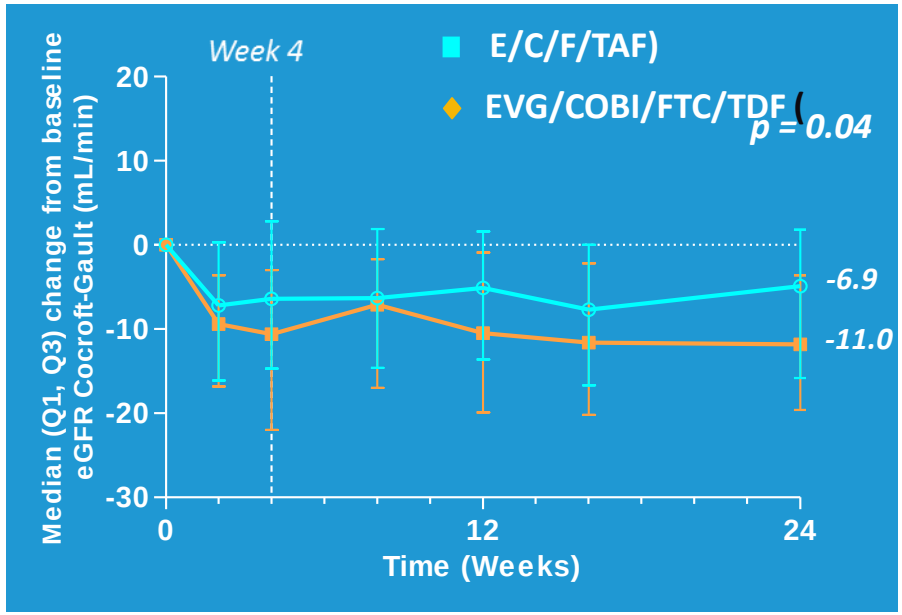
1. Zolopa A, et al. CROI 2013; Atlanta, GA. Oral #99LB.

TAF Phase II: GS-292-102
Week 24 Results – Efficacy and GFR

Virological suppression at 24 weeks



Median Estimated GFR Change from Baseline (Cockcroft-Gault)

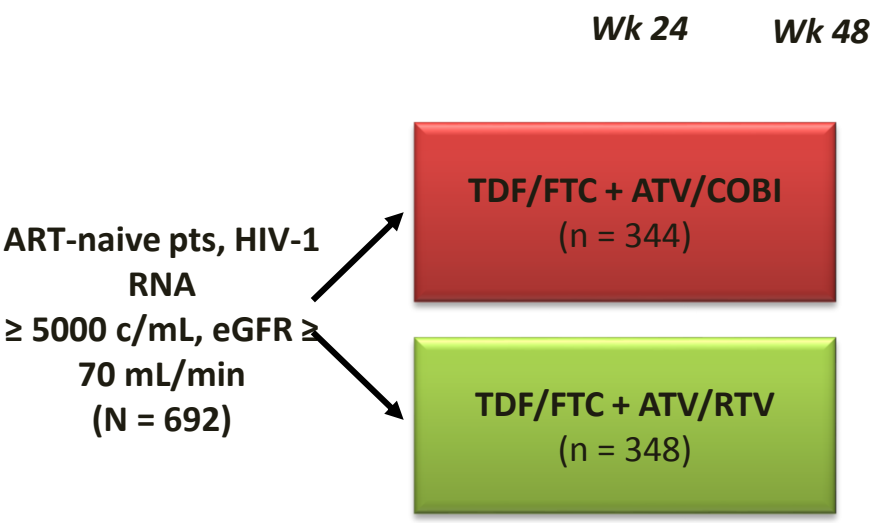


- No renal AEs or discontinuation occurred
- No cases of proximal renal tubulopathy seen

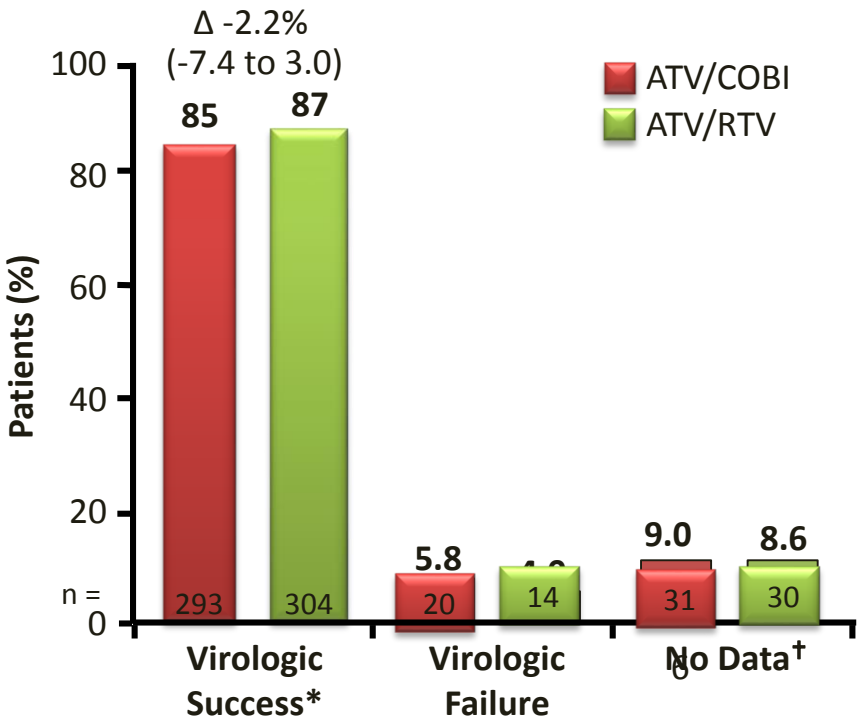
Adapted from : Zolopa A, et al. CROI 2013; Atlanta, GA. Oral #99LB

ATV/COBI + TDF/FTC vs ATV/RTV + TDF/FTC Wk 48: non-inferior

- Randomized, double-blind, phase III trial in ART-naive patients
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 48



- Coformulation of ATV and COBI being considered for approval by FDA

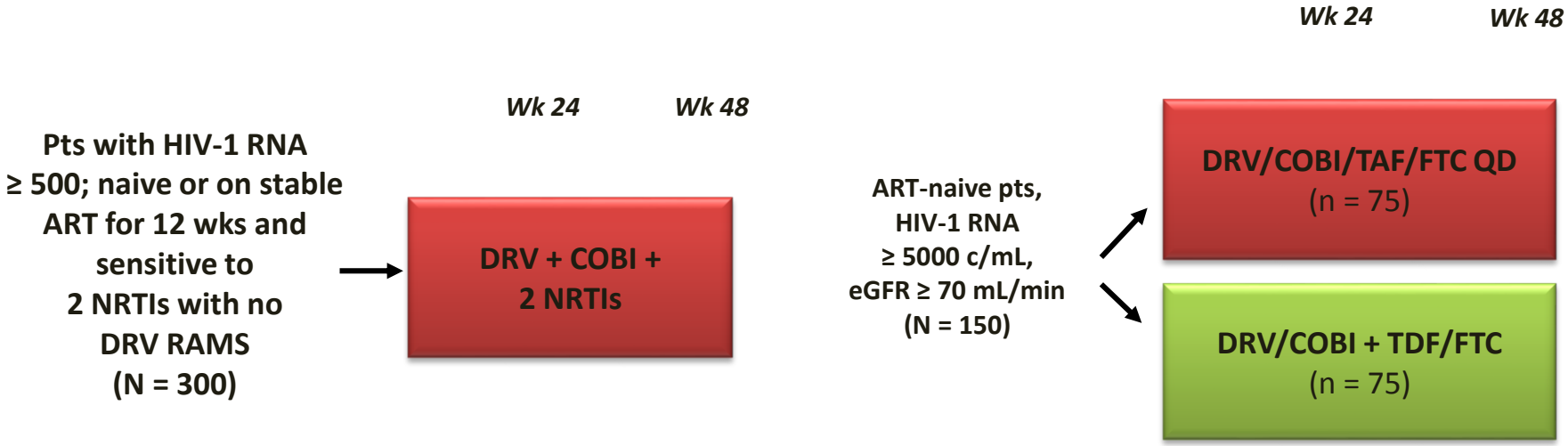


*HIV-1 RNA < 50 c/mL as defined by FDA Snapshot algorithm
†Discontinued for AE, death, or missing data.

Adapted from: Gallant JE, et al. J Infect Dis. 2013;208:32-39.

Ongoing Studies of COBI-Boosted DRV Plus 2 NRTIs

- Phase IIIb study in tx-naive tx-exp'd pts with no DRV RAMs[1]
  - Primary endpoint: grade 3 or grade 4 AEs by Wk 24
  - Secondary endpoints: HIV-1 RNA at Wk 24 and Wk 48
- Randomized, double-blind phase II trial[2]
  - Primary endpoint: HIV-1 RNA < 50 copies/mL at Wk 24

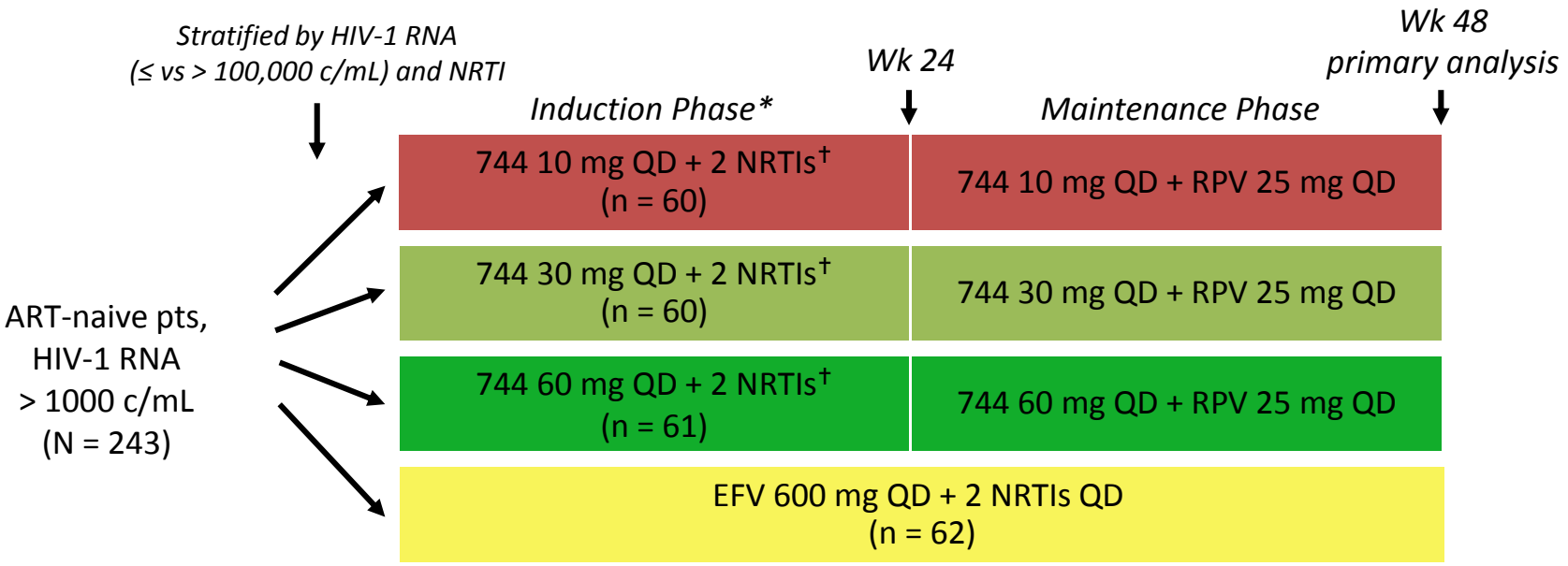


- Coformulation of DRV and COBI being considered for approval by FDA

1. ClinicalTrials.gov. NCT01440569. 2. ClinicalTrials.gov. NCT01565850.

LATTE: GSK1265744 ART for Naive Pts: Results of 24-Wk Induction

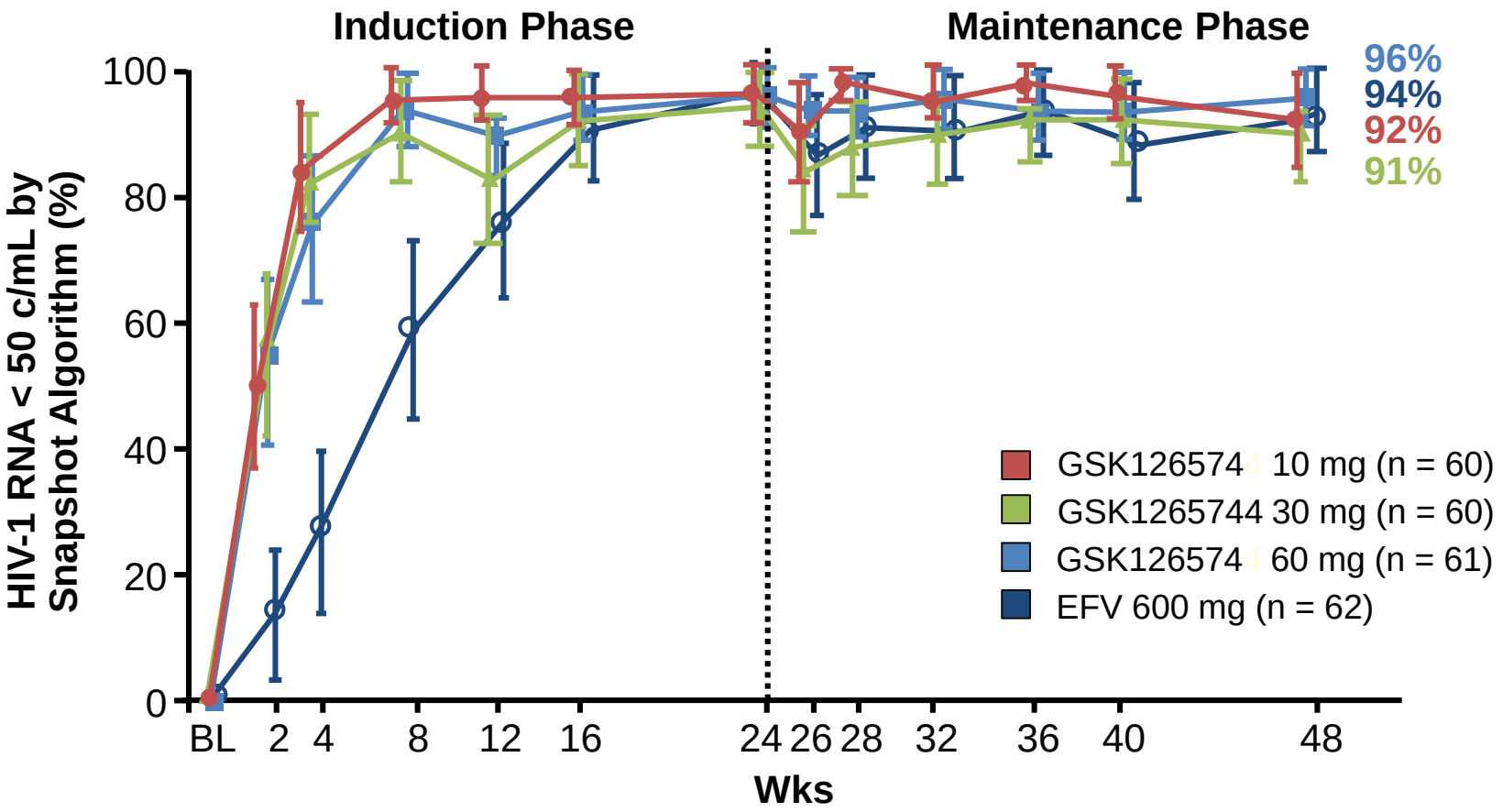
- GSK1265744 (744), DTG analogue with long half-life, oral or injectable formulations
- Randomized, dose-ranging phase IIb study of oral formulation
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48



*Pts with HIV-1 RNA < 50 c/mL at Wk 24 continued to maintenance phase.
†TDF/FTC or ABC/3TC.

Margolis D, et al. EACS 2013. Abstract PS7/1. Margolis D, et al. CROI 2014. Abstract 91LB.

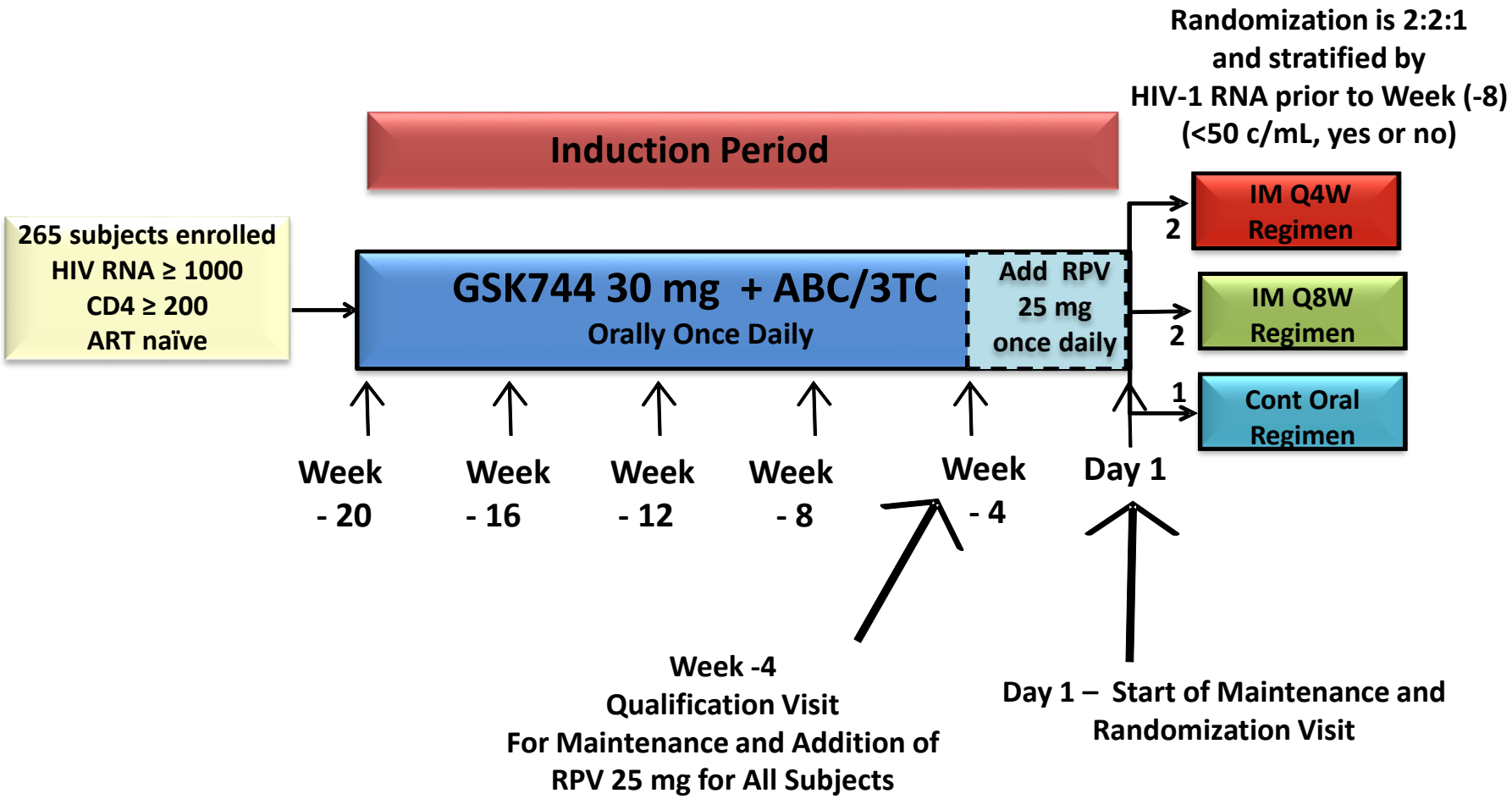
LATTE: GSK1265744 ART for Naive Pts: Results of 24-Wk Induction
Virologic Success During Induction and Maintenance Phases



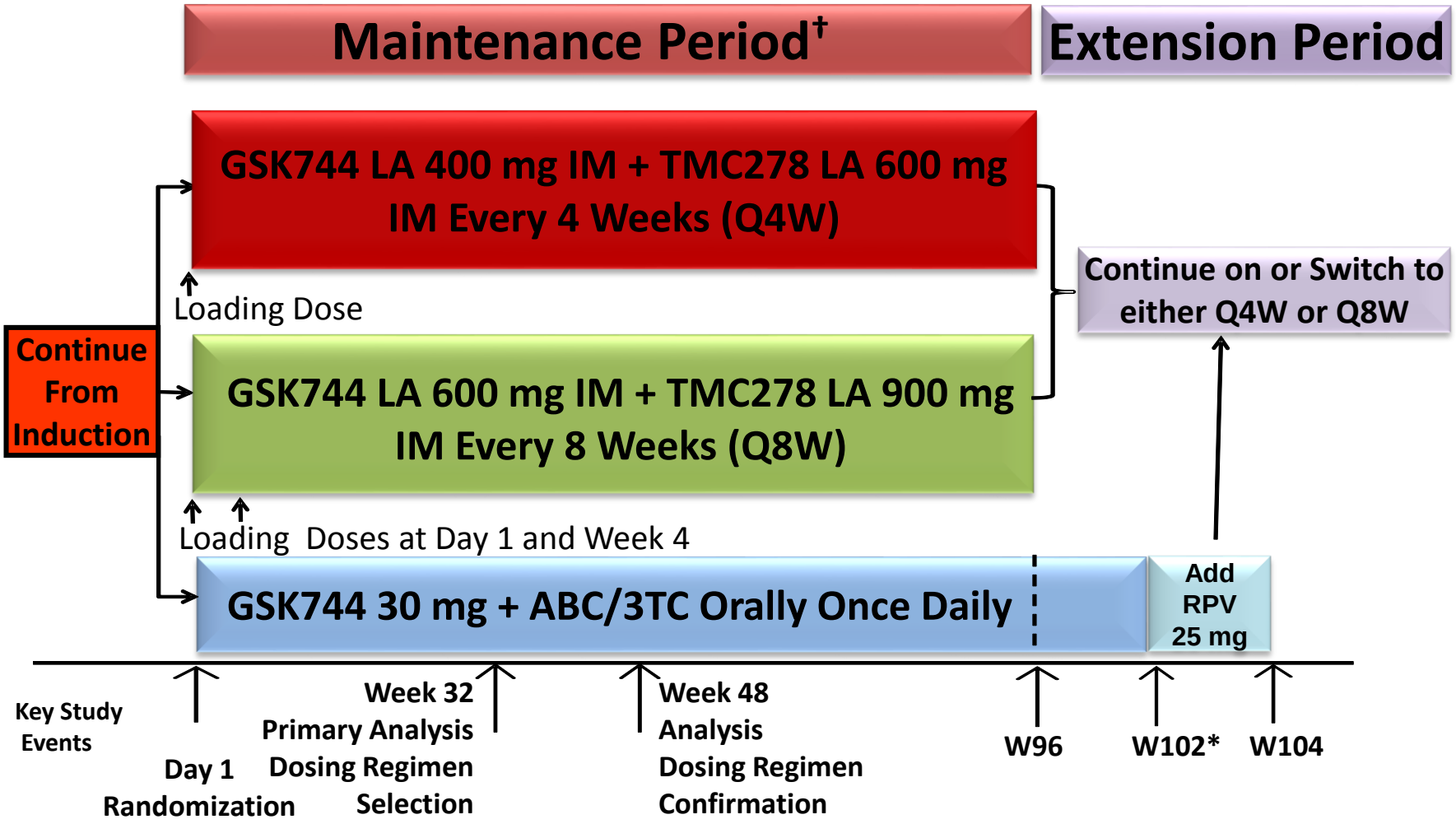
- 2 pts with PDVF during maintenance; both with INSTI mutations at BL

Margolis D, et al. EACS 2013. Abstract PS7/1. Margolis D, et al. CROI 2014. Abstract 91LB

LATTE-2: Study Design – Induction



LATTE-2: Study Design – Maintenance and Extension



†Subjects who WD after at least 1 IM dose enter Long Term Follow Up Period

*If eligible

Generics & new drugs/formulations: An evolving competitive landscape

EU patent expiration (approx.)

TDF?

DRV

RTV

LPV/r

2000 | 2001 | 2015 | 2016

LPV/RTV

Single

3TC[4]

OBI

(2017?)[2]

New drugs

Dolutegravir

GSK744

TAF

Cobicistat

www.clinicaltrials.gov and:
1. http://www.aidsmeds.com/articles/hiv_complera_gilead_1667_20970.shtml; 2. http://investors.gilead.com/phoenix.zhtml?c=69964&p=irol-newsArticle_pf&id=1580287; 3. http://www.viivhealthcare.com/media-room/press-releases/2011-02-03.aspx; 4. http://www.presseportal.de/pm/21683/2079912/abbott-confirms-long-term-commitment-to-hiv-care-with-the-planned-development-of-new-formulations; 5. http://www.gilead.com/pr_1596378. All accessed April 2013.

Going Viral
Universal testing for HIV/Hep B/Hep C

- Universal Testing for HIV, Hepatitis B and Hepatitis C
- 13th -20th October 2014
- 9 Emergency Department sites across England

Barts Health NHS Trust

NHS

British HIV Association BHIVA

NPL

Public Health England

BASHH

THE HEPATITIS C TRUST

BASL British Association for the Study of the Liver

Thank you!

Back-up slides

EVG/COBI/TDF/FTC Resistance Through Week 144

- EVG/COBI vs EFV [1-3]

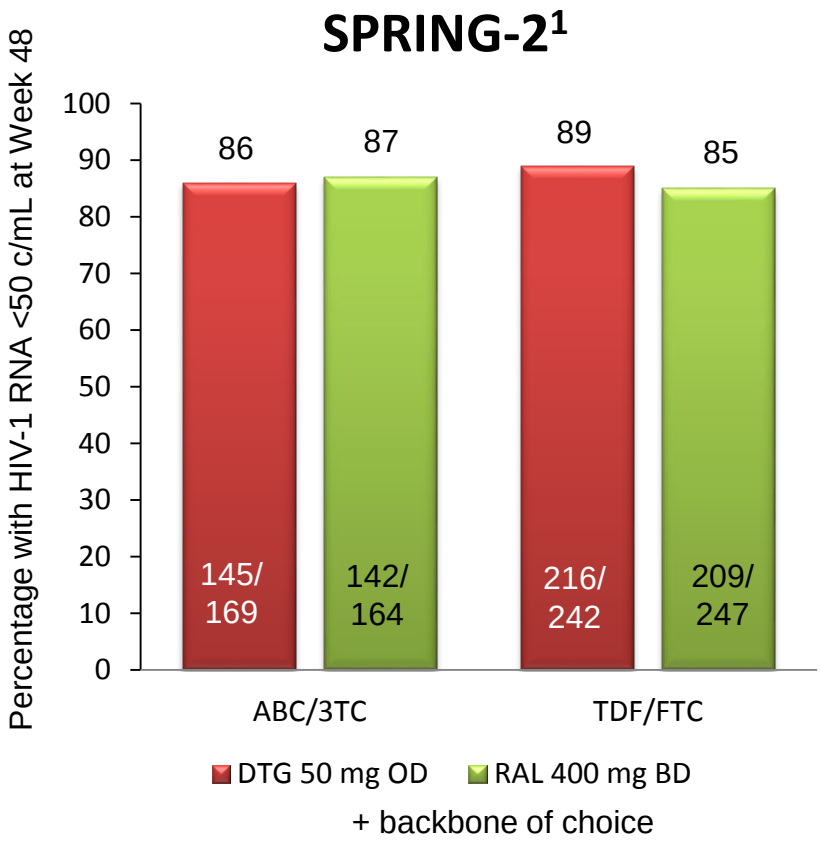
	EVG/COBI (n = 348)			EFV (n = 352)		
Wk	**48**	**96**	**144**	**48**	**96**	**144**
Resistance at VF, n	8	+2	+0	8	+2	+4
INSTI RAMs, n	7	+2	+0			
NNRTI RAMs, n				8	+2	+4
NRTI RAMs, n	8	+2	+0	2	+1	+1

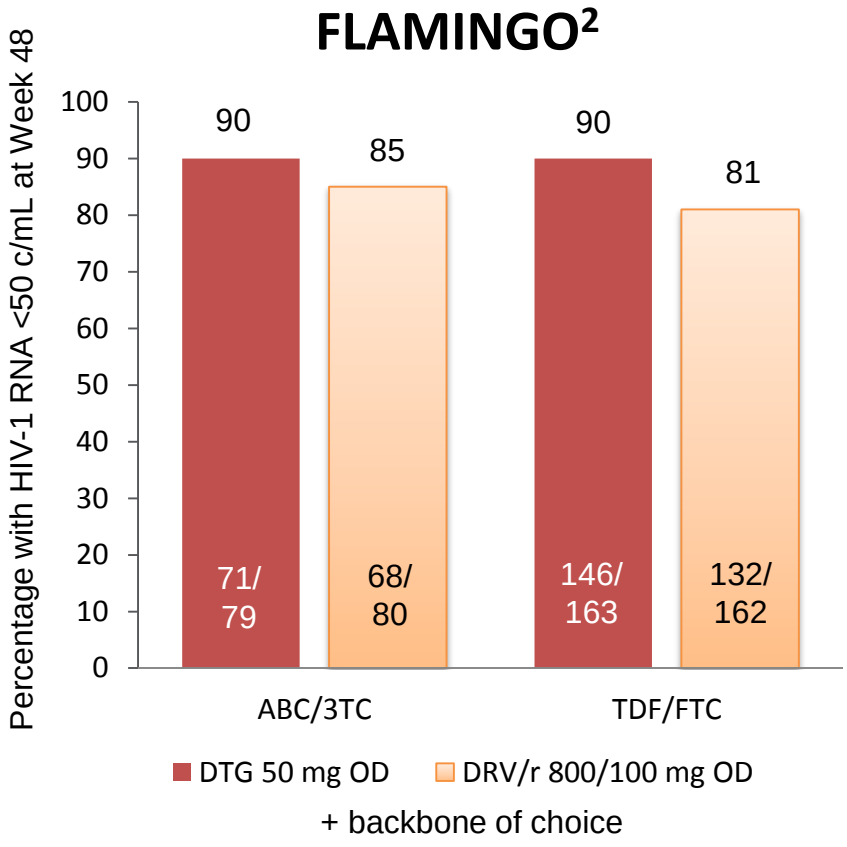
- EVG/COBI vs ATV/ [4-6]

	EVG/COBI (n = 353)			ATV/RTV (n = 355)		
Wk	**48**	**96**	**144**	**48**	**96**	**144**
Resistance at VF, n	5	+1	+2	0	+0	+2
INSTI RAMS, n	4	0	+1			
PI RAMs, n				0	+0	+0
NRTI RAMs, n	3	+1	+2	0	0	+2

Adapted from: 1. Sax PE, et al. Lancet. 2012;379:2439-2448. 2. Zolopa A, et al. J Acquir Immune Defic Syndr. 2013;63:96-100. 3. Wohl D, et al. ICAAC 2013. Abstract H-672a. 4. De Jesus E, et al. Lancet. 2012;379:2429-2438. 5. Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;62:483-486.
6. Clumeck N, et al. EACS 2013. Abstract LBPS7/2

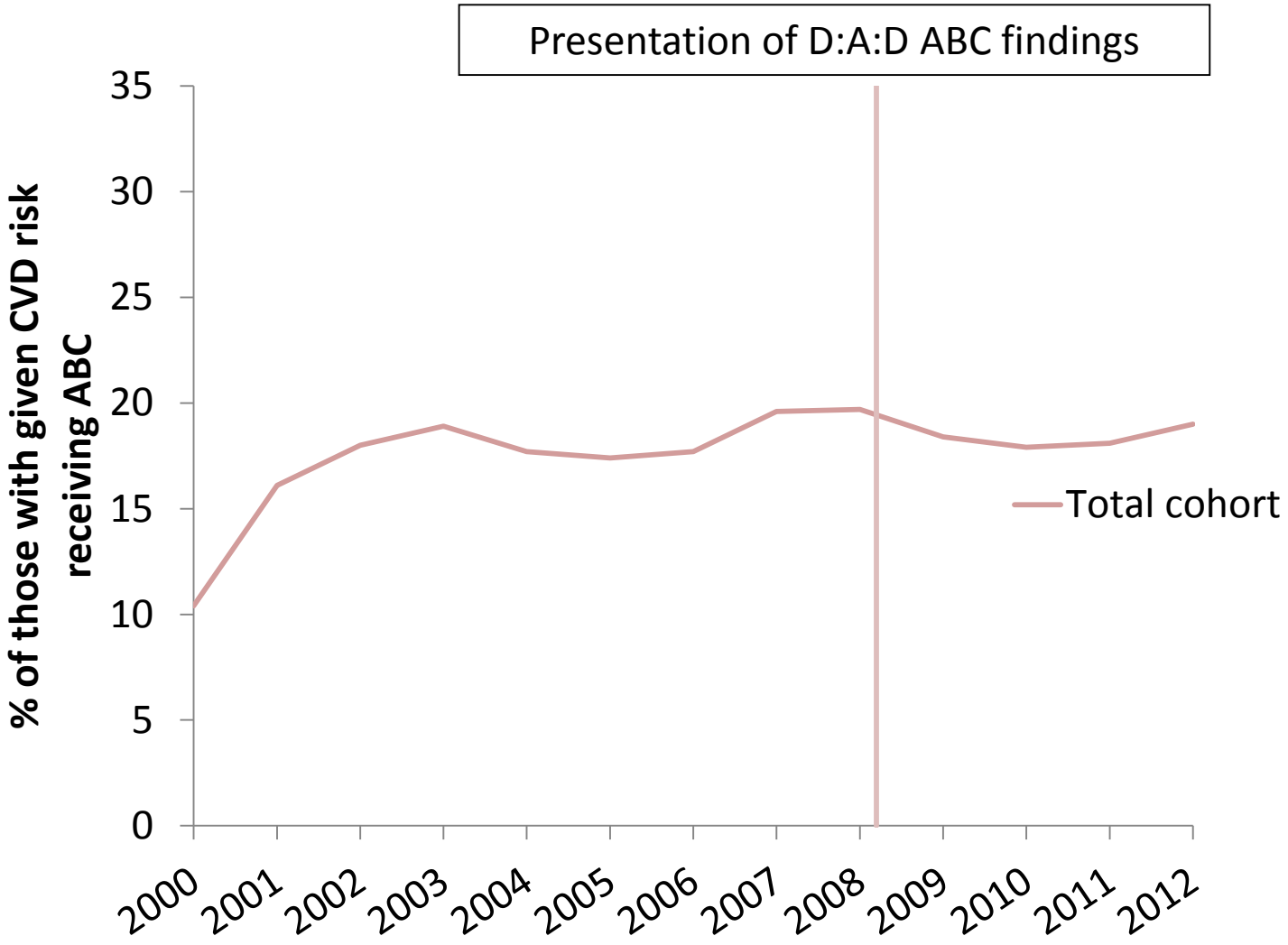
SPRING-2 and FLAMINGO: Virologic response by NRTI backbone at Week 48





1. Adapted from Raffi F et al. Lancet 2013;381:735–43
2. Adapted from Feinberg J et al. Slides presented at ICAAC Sept 10-13, 2013 Abstract H-1464a

DAD Results 2014 : Use of ABC in cohort over time



CA Sabin et al DAD study CROI Boston 2014

Association between 10-year CVD risk and ABC initiation

10-year CVD risk	ABC initiations/ Total ART initiations	% (95% CI)	aOR (95% CI)
Pre-March 2008			
Low/unknown	1251/9213	13.6 (12.8, 14.3)	1
Moderate/high	111/648	17.1 (13.9, 20.3)	1.14 (0.90, 1.44)
Post-March 2008			
Low/unknown	326/4282	7.6 (6.8, 8.4)	1
Moderate/high	33/622	5.3 (3.5, 7.1)	0.74 (0.48, 1.13)
Interaction *P*-value			0.007

Association between 10-year CVD risk and ABC discontinuation

10-year CVD risk	Discounts/ PYRS	Rate (95% CI) /100 PYRS	aRR (95% CI)
Suppressed/low viral load			
Pre-March 2008			
Low/unknown	2045/16506	12.4 (11.9, 12.9)	1
Moderate/high	562/5465	10.3 (9.4, 11.1)	1.04 (0.93, 1.16)
Post-March 2008			
Low/unknown	1403/13950	10.1 (9.5, 10.6)	1
Moderate/high	880/6560	13.4 (12.5, 14.3)	1.49 (1.34, 1.65)
Interaction *P*-value			0.0001

Association between 10-year CVD risk and ABC discontinuation

10-year CVD risk	Discounts/ PYRS	Rate (95% CI) /100 PYRS	aRR (95% CI)
Non-suppressed viral load			
Pre-March 2008			
Low/unknown	2966/7766	38.2 (36.8, 39.6)	1
Moderate/high	662/2041	32.4 (29.9, 34.9)	0.99 (0.90, 1.09)
Post-March 2008			
Low/unknown	622/2297	27.1 (25.0, 29.2)	1
Moderate/high	236/921	25.6 (22.4, 28.9)	1.23 (1.02, 1.48)
Interaction *P*-value			0.07

Association between current ABC use and MI risk

- 941 MI events, rate 0.26 [95% CI 0.24-0.27] /100 PYRS
- Current ABC use associated with a 98% increase in MI rate (aRR 1.98 [1.72-2.29])

Association between current ABC use and MI risk

- 941 MI events, rate 0.26 [95% CI 0.24-0.27] /100 PYRS
- Current ABC use associated with a 98% increase in MI rate (aRR 1.98 [1.72-2.29])

	Pre-March 2008	Post-March 2008
Events	672	269
PYRS	210,250	157,309
Rate (95% CI)	0.32 (0.30, 0.34)	0.17 (0.15, 0.19)

Association between current ABC use and MI risk

- 941 MI events, rate 0.26 [95% CI 0.24-0.27] /100 PYRS
- Current ABC use was associated with a 98% increase in MI rate (aRR 1.98 [1.72-2.29])

	Pre-March 2008	**Post-March 2008**
Events	672	269
PYRS	210,250	157,309
Rate (95% CI)	0.32 (0.30, 0.34)	0.17 (0.15, 0.19)
RR (current ABC vs. no ABC)	**1.97**	**1.97**
95% CI	(1.68, 2.33)	(1.43, 2.72)
P-value for interaction		0.74

Association between current ABC use and MI risk

Conclusions

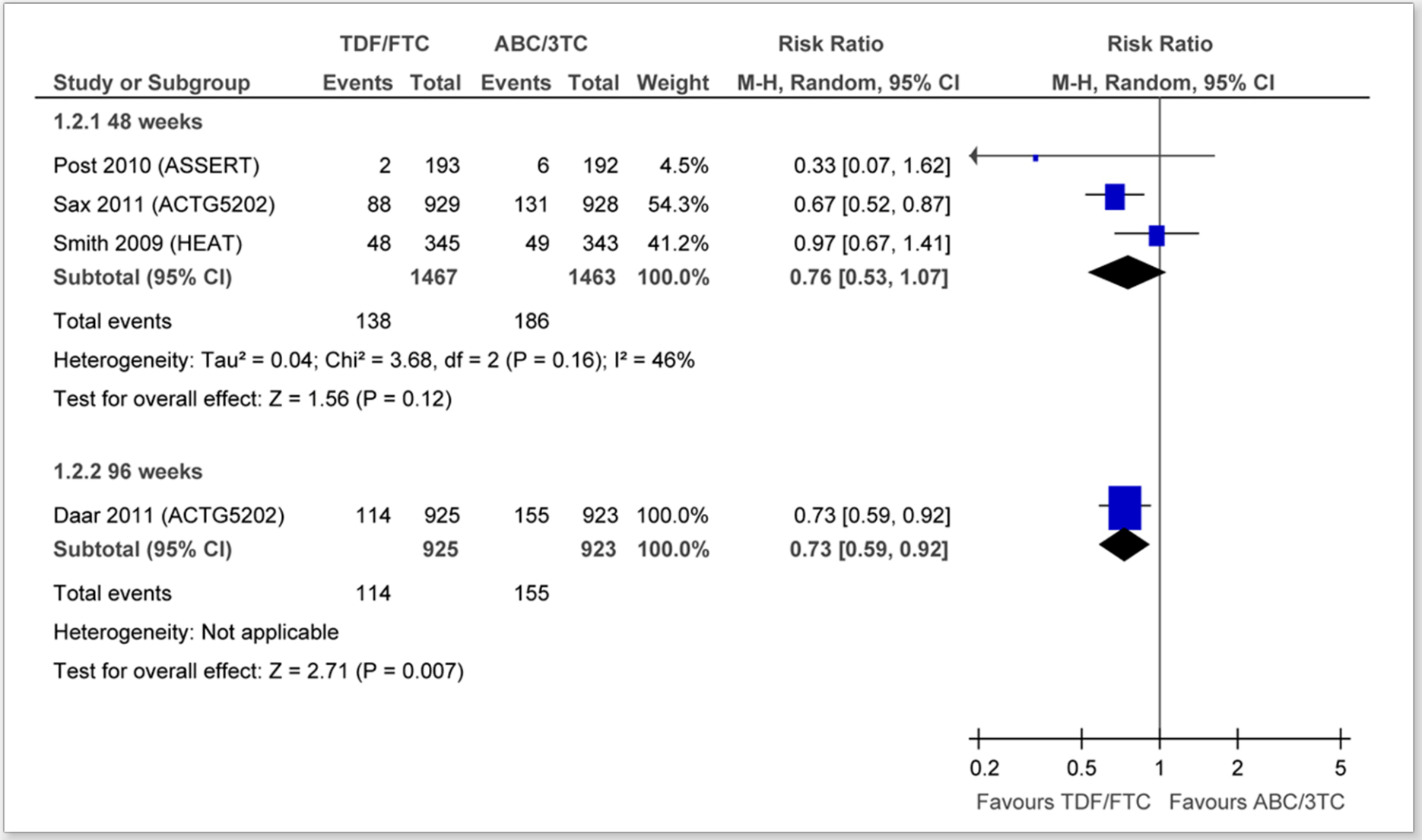
- Clear that there has been some channelling of ABC away from those at higher CVD risk since 2008
- Despite this, we continue to see a strong association between current ABC use and MI risk
- Whilst confounding can never be ruled out in any cohort study, any channelling bias would now be expected to be much weaker (or even to act in the opposite direction)
- Thus, our findings continue to argue against channelling bias as an explanation for our findings

NRTI-free regimes:

- **MODERN Study Stopped: An NRTI-Sparing, Two-Drug Initial Regimen Disappoints Again**
- And for the record, here's a list of NRTI-sparing studies that gave "meh" results at best:
- **ACTG 5142 — LPV/r + EFV vs NRTIs + EFV vs NRTIs vs LPV/r.**
  LPV/r + EFV had high rates of hyperlipidemia; regimen was also cumbersome with lots of GI side effects.
- **SPARTAN — ATV + RAL vs ATV/r + TDF/FTC.**
  More treatment failure, more jaundice in the ATV + RAL arm.
- **PROGRESS — LPV/r + RAL vs. LPV/r + TDF/FTC.**
  Comparable success rates, but baseline HIV RNA low in the study population; 3 pill, twice-daily regimen.
- **ACTG 5262 — Single-arm study of DRV/r + RAL.**
  Unexpectedly high rates of virologic failure (with resistance), especially among those with HIV RNA > 100k at baseline.
- **A4001078 — ATV/r + MVC vs ATV/r + TDF/FTC**
  Only 75% virologic suppression rate in ATV/r + MVC arm, with more hyperbilirubinemia than the control group; study not fully powered.
- **RADAR — DRV/r + RAL vs. DRV/r + TDF/FTC.**
  63% suppression rate in the RAL arm, vs 84% for TDF/FTC; study not fully powered.
- Regardless, HIV clinicians and researchers eagerly await the result of two completed but not yet presented clinical trials — the fully-powered NEAT study comparing RAL to TDF/FTC (both with DRV/r), and the GARDEL study, comparing 3TC to NRTI/3TC (both with LPV/r).

- – See more at: http://blogs.jwatch.org/hiv-id-observations/index.php/modern-study-stopped-an-nrti-sparing-two-drug-initial-regimen-disappoints-again/2013/10/14/#sthash.EV4U3cCZ.dpuf

CVS debate 2014



Adapted from BHIVA APPENDIX 3 Grade tables; www.bhiva.org; accessed November 2012

Systematic reviews/meta-analyses

Study name	n	Increased risk of CV Events and abacavir?	Results (study methodologies and primary endpoints varied)
ACTG 5001/ALLRT	3,207	No	Retrospective review of five ACTG trials identified a total of 36 MIs and 56 serious CV events. There was no association between recent abacavir use and an increased risk of CV events. Adj HR = 1.0 CI 95% 0.4 - 2.9, p = 0.98.
GSK analysis	14,174	No	Retrospective review of 52 clinical trials identified 23 coronary artery disorders in adults receiving abacavir compared with 20 in those not receiving abacavir; there were 11 MIs in those who received abacavir compared with 7 in those who did not. There was no association between abacavir use and an increased risk of CV events RR 0.81 CI 95% 0.38 - 1.75.
Cruciani meta-analysis	9,233	No	No increased risk for MI in abacavir-containing cART (risk ratio [RR] 0.73 [95%CI 0.39–1.35]) when compared to non-abacavir-containing cART.
FDA meta-analysis	9,868	No	Retrospective review of 26 studies identified MI in 24/5,028 patients receiving abacavir compared with 22/4,840 receiving non-abacavir-containing therapy. There was no association between recent abacavir use and an increased risk of CV events. No significant difference in risk of MI detected between the 2 groups (difference 0.008%, 95% CI -0.26, 0.27)

Benson C *et al.* 16th CROI, 8th-11th Feb 2009, Montreal, 721. Brothers CH *et al*. J Acquir Immune Defic Syndr 2009;51(1):20-28. Cruciani M *et al.* AIDS 2011; e-publication ahead of print. Ding X *et al.* 18th CROI. Boston, MA. 27 February–2 March, 2011; Abstract 808.

Randomised Controlled Trial Data

Study name	n	Increased risk of CV Events and abacavir?	Results (study methodologies and primary endpoints varied)
STEAL	357	Yes	Randomised 96 week trial comparing viral suppression with Kivexa and TDF/FTC reported nine serious CV events, one in the TDF/FTC arm and eight in the Kivexa arm. HR (TDF/ABC) 0.13 CI 95% 0.02 - 0.98, p = 0.046.
HEAT	688	No	Randomised 96 week trial comparing markers of inflammation and endothelial activation after initiation of Kivexa and TDF/FTC reported six CV-related events, four in the TDF/FTC arm and two in the Kivexa arm. Analysis unavailable
ARIES	515	No	Phase IIIb, randomised open-label non-inferiority study in naive patients comparing the efficacy of Kivexa and atazanavir with or without ritonavir.
ASSERT	380	No	Open-label randomised controlled trial comparing the eGFR in patients receiving Truvada and Kivexa.
BiCombo	80	No	Retrospective sub-study of BICOMBO RCT, using stored plasma. ABC/3TC did not lead to significant changes in markers of inflammation, endothelial dysfunction, insulin resistance or hypercoagulability vs TDF/FTC.
ACTG5202	1,857	No	Rate of Vascular Events (coronary artery disease, infarct, ischemia, angina, cerebrovascular accident, transient ischemic attack or peripheral vascular disease)/1000 Patient-Years was 1.4 and 2.5 in the ABC/3TC and TDF/FTC arms, respectively

Martin A et a.l Clinical Infectious Diseases 2009; 49:1591–1601. Smith KY et al. AIDS 2009;23:1547-1556. Squires KE et al. AIDS 2010; 24:2019–2027. Post F et al. J Acquir Immune Defic Syndr 2010;55(1):49-57. Data on file, HIVDOF070,ViiV Healthcare. Martinez E et al. AIDS 2010, 24*:F1–F9.* Moyle G. 2nd Joint Conference of BHIVA/BASHH, 20th-23rd April 2010, Manchester.

Observational/case control studies

The D:A:D study initially suggested a potential association between recent ABC use and an increased risk of MI. Studies such as the VA, FHDH and Partners (John Hopkins) which controlled for additional risk factors such as chronic kidney disease and illicit drug use, did not find the same association.

Cohort/study	Design	MI Event ascertainment	Subjects in cohort/ study, n	Events associated with ABC, n	Association with ABC
D:A:D	Prospective observational cohort	Prospective, pre-defined MI	33,347	192	Yes
SMART	RCT observational	Prospective, pre-defined MI	2,752	19	Yes
US VA clinical case registry	Retrospective observational cohort	Retrospective, MI identified via ICD-9	19,424	23	No*
Quebec Public Health Insurance Database(RAMQ)	Case control in observational cohort	Retrospective, MI identified via ICD-9	N/A	45	Yes
Danish HIV cohort study	Prospective observational cohort	Prospective, MI hospitalisation identified via ICD-8/10	2,952	36	Yes
FHDH	Case control in observational study	Prospectively reported MI, retrospectively validated via ICD-10	N/A	127	No**
"Partners HealthCare System" clinical care data registry	Retrospective observational registry-based cohort	Retrospective, MI identified via ICD-9- CM codes	6,517	–†	No¶

* After adjustment for traditional CV risk factors and renal dysfunction

** Sensitivity/supportive analysis censoring cocaine or IV drug use

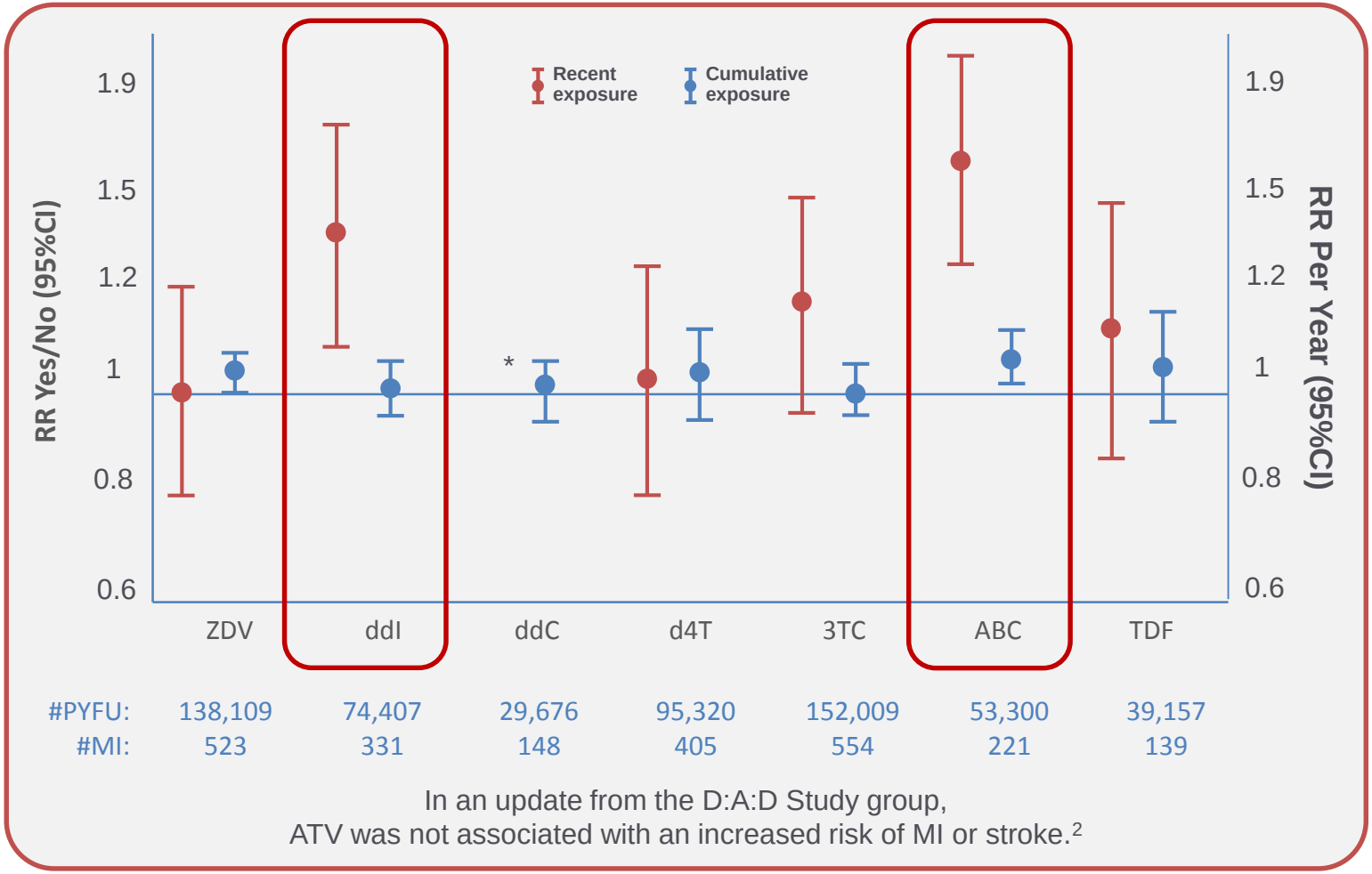
¶ After adjustment for renal dysfunction and CD4 cell count

† Information not available

* Recent analysis of VA cohort demonstrated an association between ABC and increased risk of atherosclerotic events

D:A:D Study Group. Lancet. Published online April 2nd 2008 DOI:10.1016/50140-6736(08)60423-7. SMART/INSIGHT & D:A:D Study Groups. AIDS 2008;22:F17-F24. Bedimo R *et al.* 5th IAS , 19th-22nd July 2009,Cape Town, SA. MOAB202. Durand M *et al.* 5th IAS, 19th-22nd July 2009,Cape Town, SA. TUPEB175. Obel N *et al.* HIV Med 2010;11:130-136. Lang S *et al.* Arch Intern Med. 2010;170(14):1228-1238. Triant VA *et al.* JAIDS 2010;55:615–619

Largest observational cohort demonstrating an association between ABC and MI risk: D:A:D[1]



*Not shown (low number of patients currently on ddC)

1. Adapted from Lundgren J, et al. CROI 2009, abstract 44
2. d'Arminio Monforte A et al. CROI 2012, poster 823

Is There Continued Evidence for an Association Between Abacavir and Myocardial Infarction Risk?

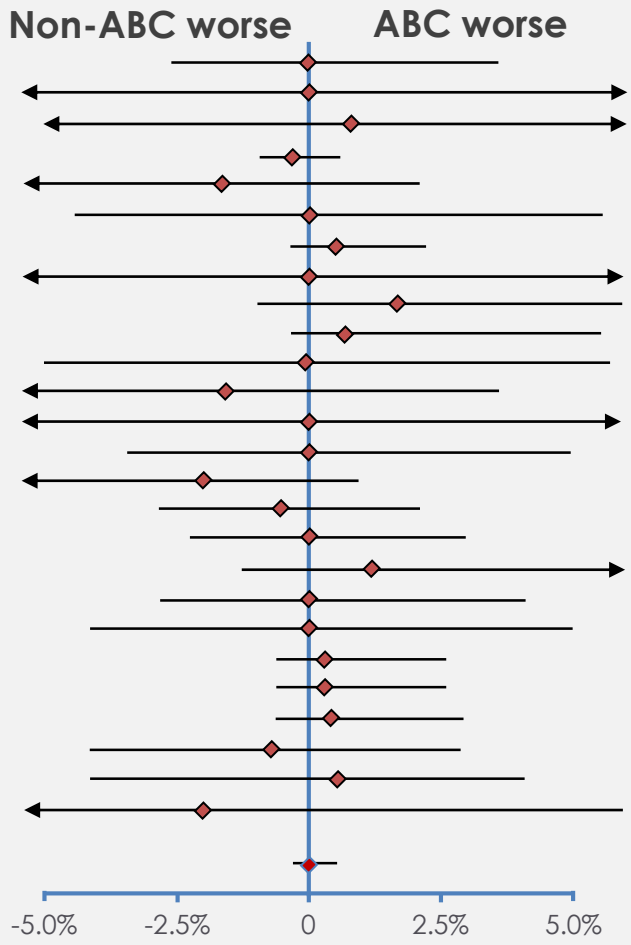
C.A. Sabin,[1] P. Reiss,[2] L. Ryom,[3] S. de Wit,[4] O. Kirk,[3] R. Weber,[5]
C. Pradier,[6] F. Dabis,[7] A.N. Phillips,[1] J.D. Lundgren,[3]
for the D:A:D study group

Adapted from Sabin et al. CROI 2014; Boston, MA. Poster 747LB.

FDA meta-analysis of RCTs did not show an association between ABC and MI

26 studies -

- ABC:
  24 MI events in
  5,028 patients
- Non ABC:
  22 MI events
  in 4,840 patients



Risk difference (95% CI)
0 (–2.73, 2.87)
0 (–13.79, 6.38)
0.79 (–4.77, 6.54)
–0.32 (–1.08, 0.33)
–1.64 (–6.17, 1.64)
0 (–4.49, 4.13)
0.53 (–0.75, 1.5)
0 (–7.01, 8.34)
1.68 (–1.27, 5.17)
0.67 (–0.55, 4.04)
–0.06 (–5.23, 4.9)
–1.57 (–5.61, 3.38)
0 (–9.09, 7.08)
0 (–3.79, 3.88)
–1.97 (–5.9, 0.58)
–0.52 (–3.12, 1.55)
0 (–2.42, 2.4)
1.18 (–1.14, 7.08)
0 (–3.15, 3.11)
0 (–4.35, 4.19)
0.29 (–0.86, 1.75)
0.31 (–0.91, 1.86)
0.38 (–1.13, 2.29)
–0.71 (–4.27, 2.21)
0.64 (–4.21, 3.6)
–2 (–11.05, 5.37)
0.01 (–0.26, 0.27)

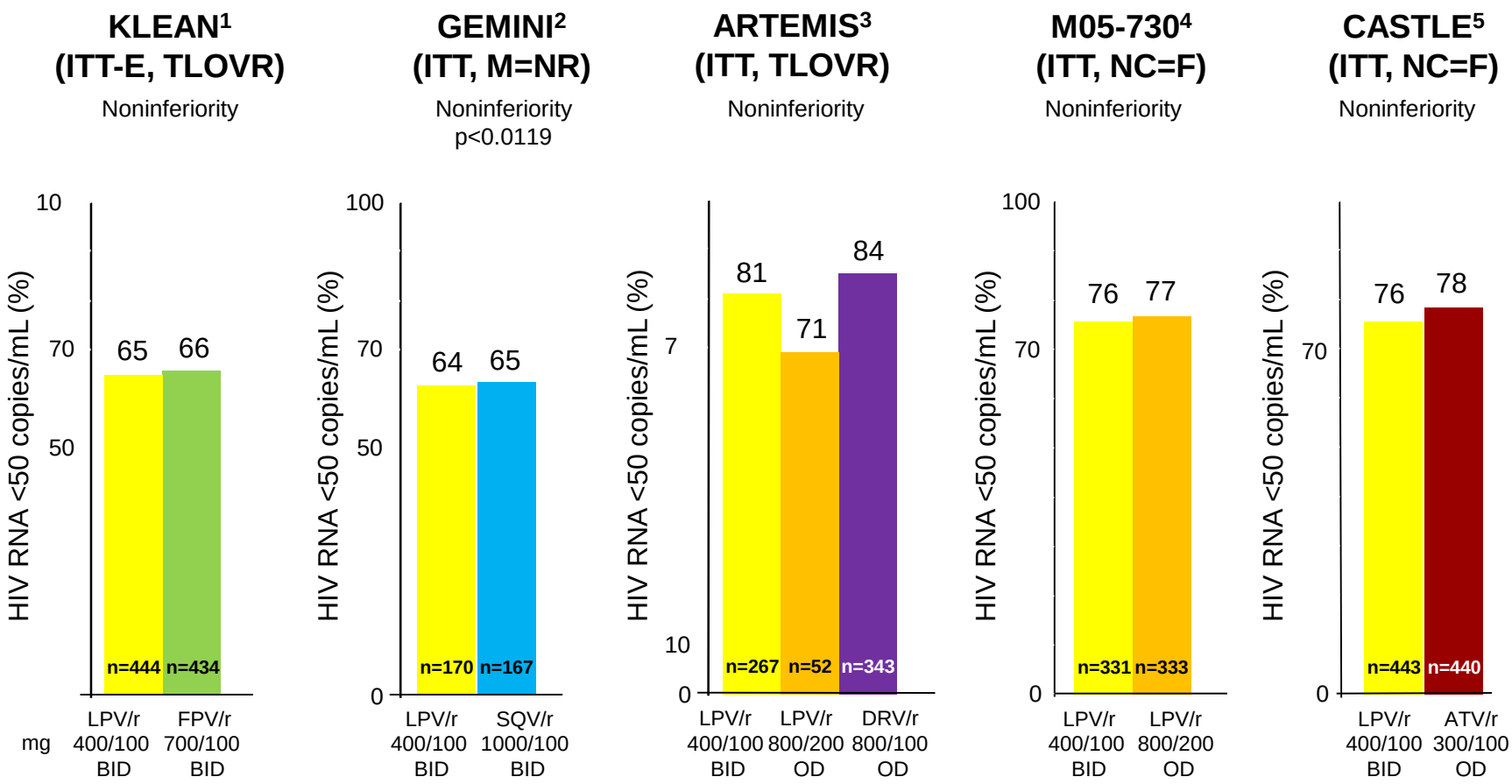
Adapted from Ding X et al. J Acquir Immune Defic Syndr 2012;61:441–447.

BHIVA guidelines
Cardiovascular Disease

- No RCT has been powered to assess the CVD risk associated with the use of individual ARVs and a history of CVD may be an exclusion criteria.
- Avoid abacavir (2C), fosamprenavir/ritonavir (2C) and lopinavir/ritonavir(2C) in patients with a high CVD risk, if acceptable alternative antiretroviral drugs are available
- Modifiable risk factors should be addressed in all patients with high CVD risk
- A meta-analysis of all RCTs where ABC was assigned randomly found no association with MI, but the event rate in the population was low; the extent to which these findings can be extrapolated to a population with high CVD risk is unknown

BHIVA Guidelines 2012 (updated November 2013) HIV Medicine 2014;15(Suppl. 1):1–85.

Boosted PIs: efficacy across the board

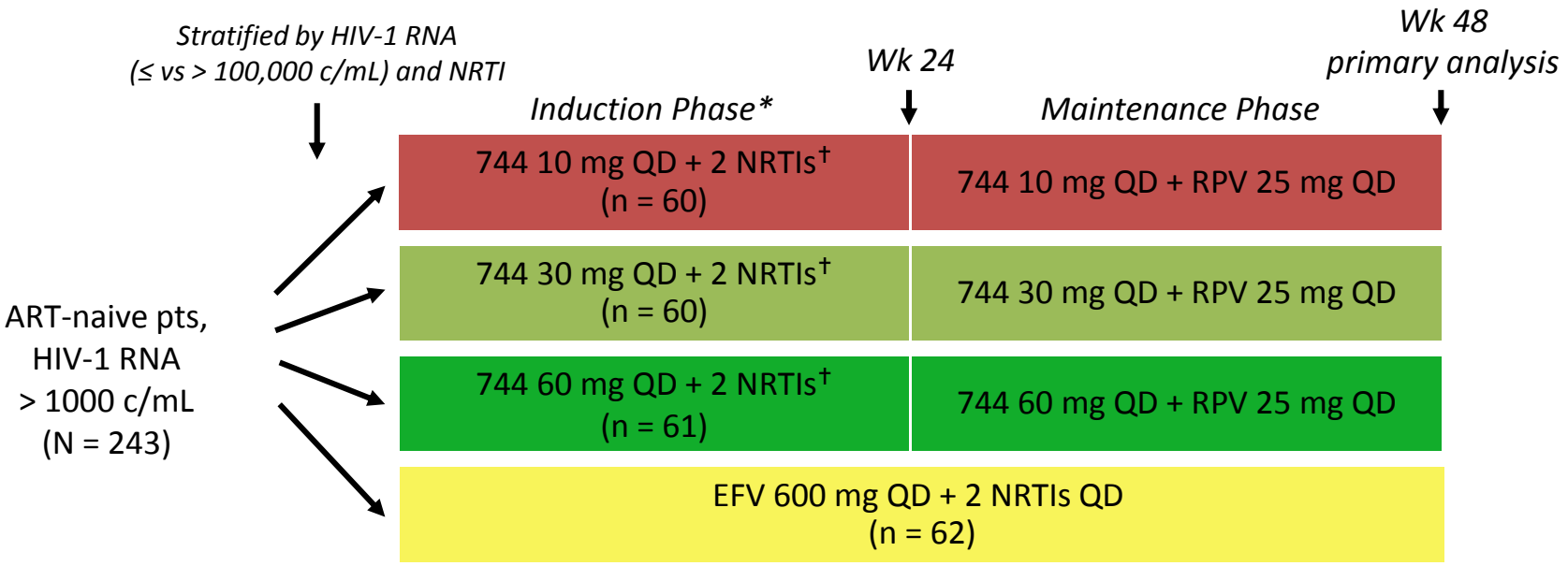


Data in figures are from different studies and cannot be compared directly
ITT-E, intent-to-treat exposed

Created from: 1. Eron J, et al. Lancet 2006;368:476–482. 2. Walmsley S, et al. 11th EACS 2007 October 24–27; Madrid, Spain. Abstract PS1/4. 3. De Jesus E, et al. 47th ICAAC; 2007 September 17–20; Chicago, USA. Abstract LBA H-718b. 4. Gathe J, et al. 15th CROI; 2008 February 3–6; Boston, USA. Abstract 775. 5. Molina J, et al. 15th CROI; 2008 February 3–6. Presentation 37.

LATTE: GSK1265744 ART for Naive Pts: Results of 24-Wk Induction

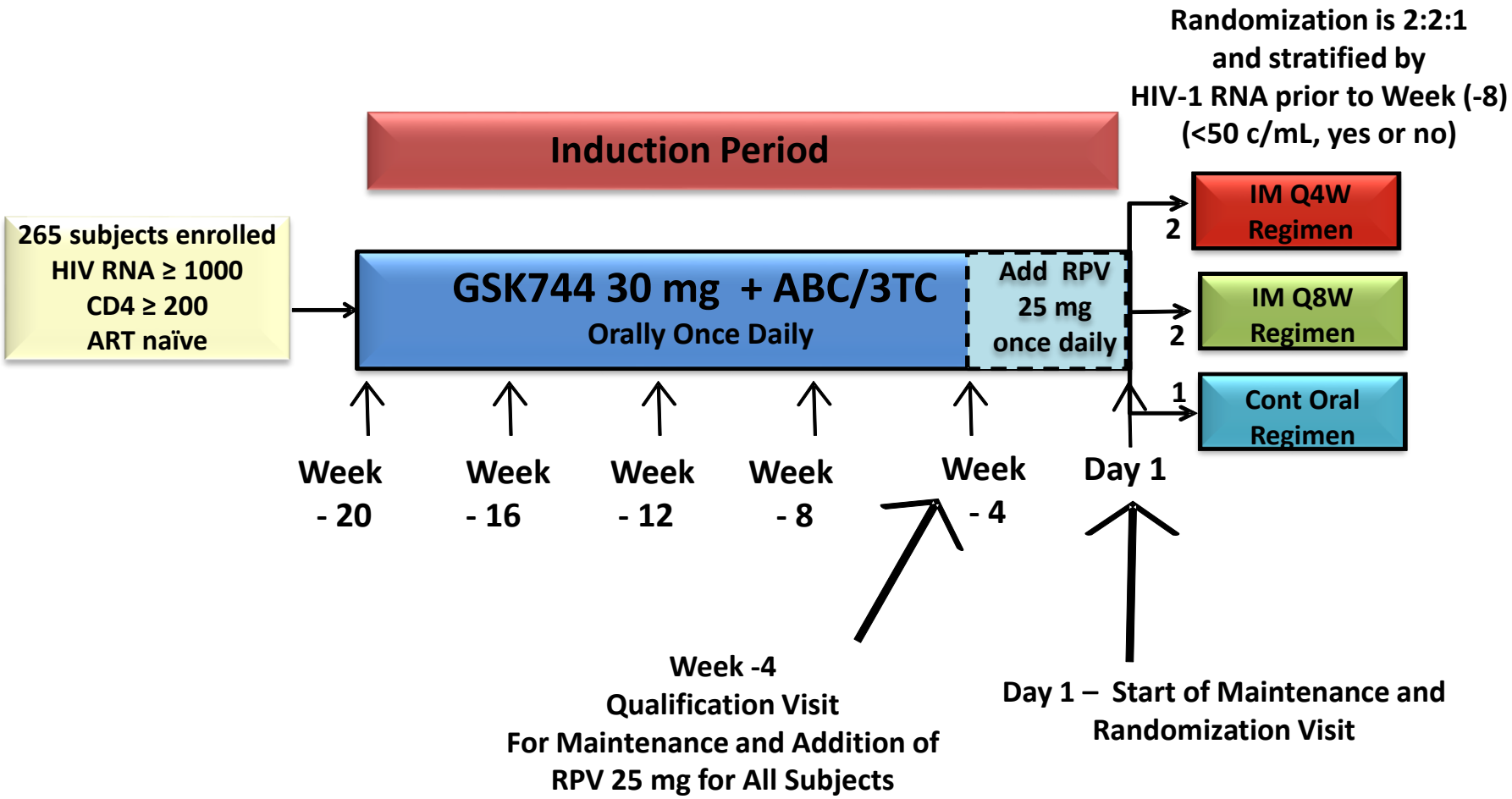
- GSK1265744 (744), DTG analogue with long half-life, oral or injectable formulations
- Randomized, dose-ranging phase IIb study of oral formulation
- Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48



*Pts with HIV-1 RNA < 50 c/mL at Wk 24 continued to maintenance phase.
†TDF/FTC or ABC/3TC.

Margolis D, et al. EACS 2013. Abstract PS7/1. Margolis D, et al. CROI 2014. Abstract 91LB.

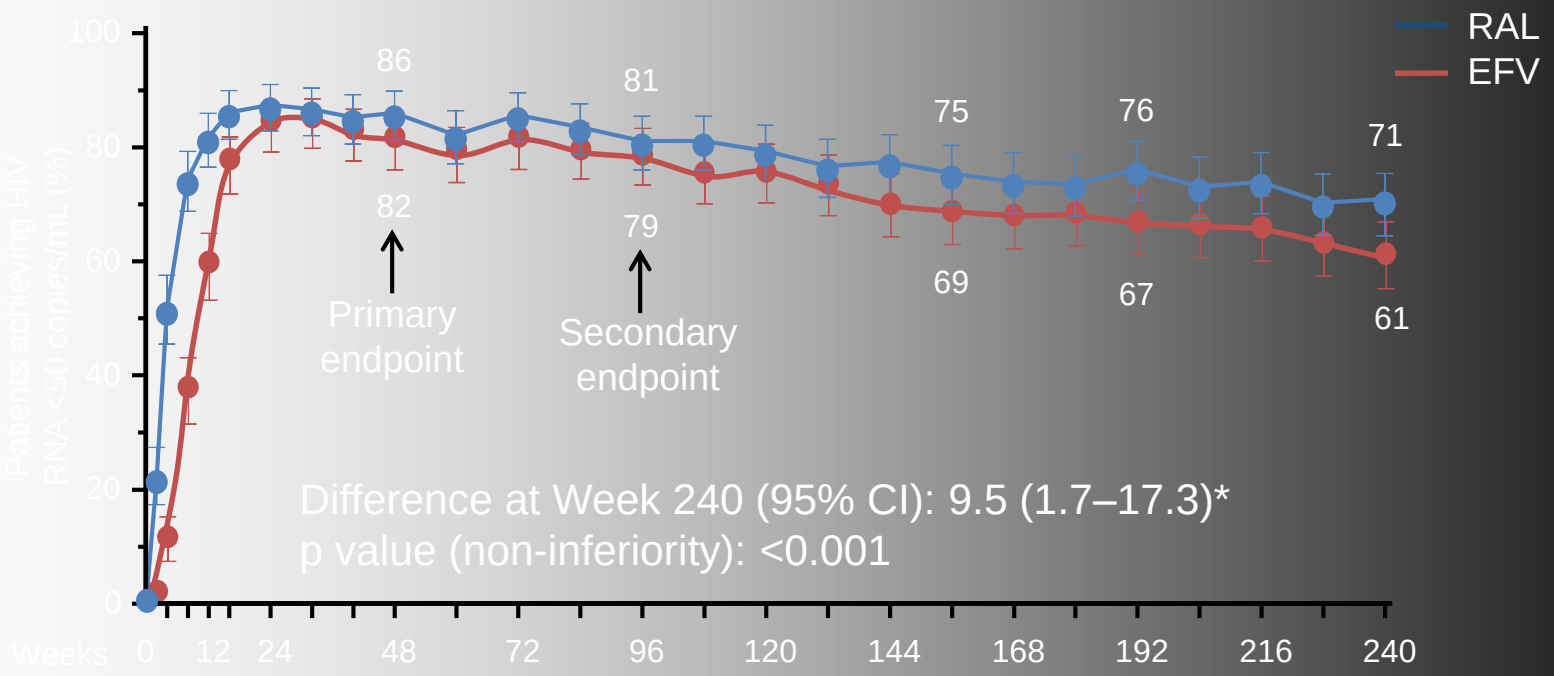
LATTE-2: Study Design – Induction



New benchmark comparator: Durability vs EFV?

- **STARTMRK: RAL vs EFV in naïve patients – 5-year outcomes**

Proportion of patients with HIV RNA <50 copies/mL (ITT, NC=F)



Number of contributing patients

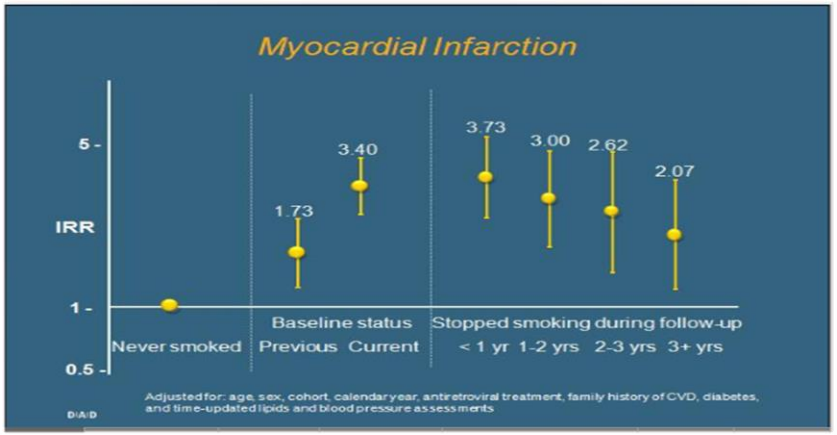
RAL 400 mg BID	281	278	279	280	281	281	277	280	281	281	277	279
600 mg at night ON	282	282	282	281	282	282	281	281	282	282	282	279

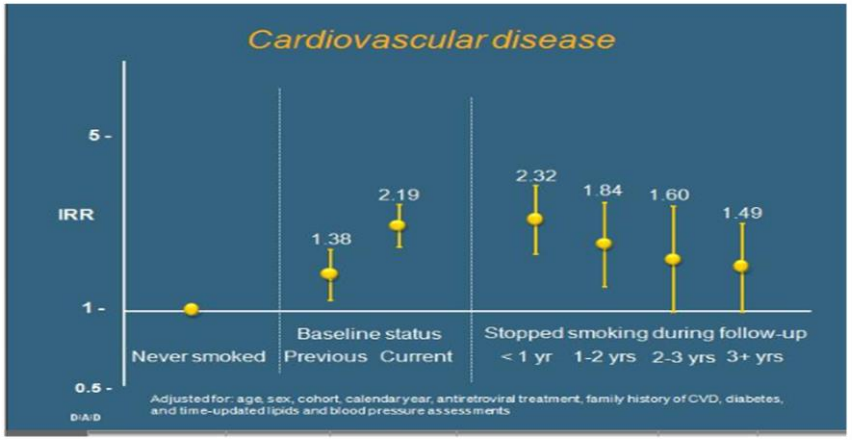
- Week 240 CD4 count (cells/mm^3) change: RAL +374 vs EFV +312
- Difference (95% CI): 62 (22–102)

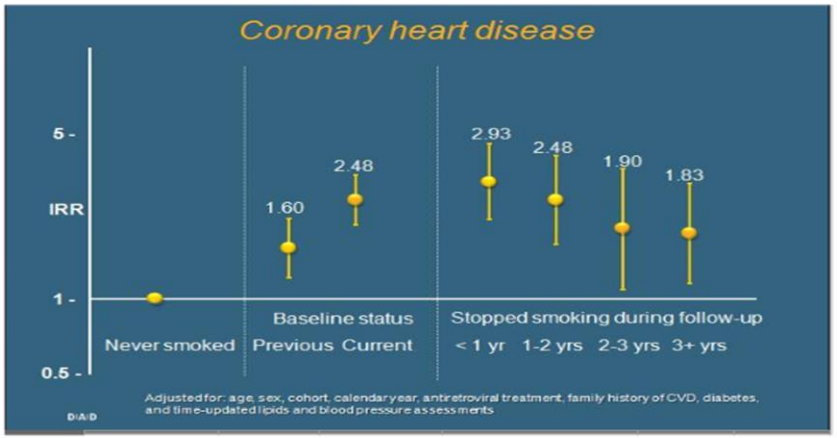
Adapted from Rockstroh J, *et al*. IAC 2012. Poster LBPE19.

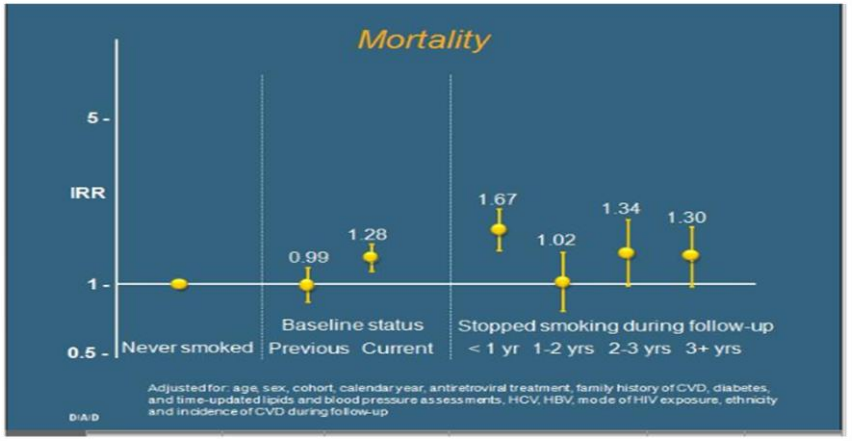
Potential clinical benefits for smoking cessation in HIV patients

- >27,500 HIV-positive patients in the D:A:D study
- Rates of CVD before and after smoking cessation



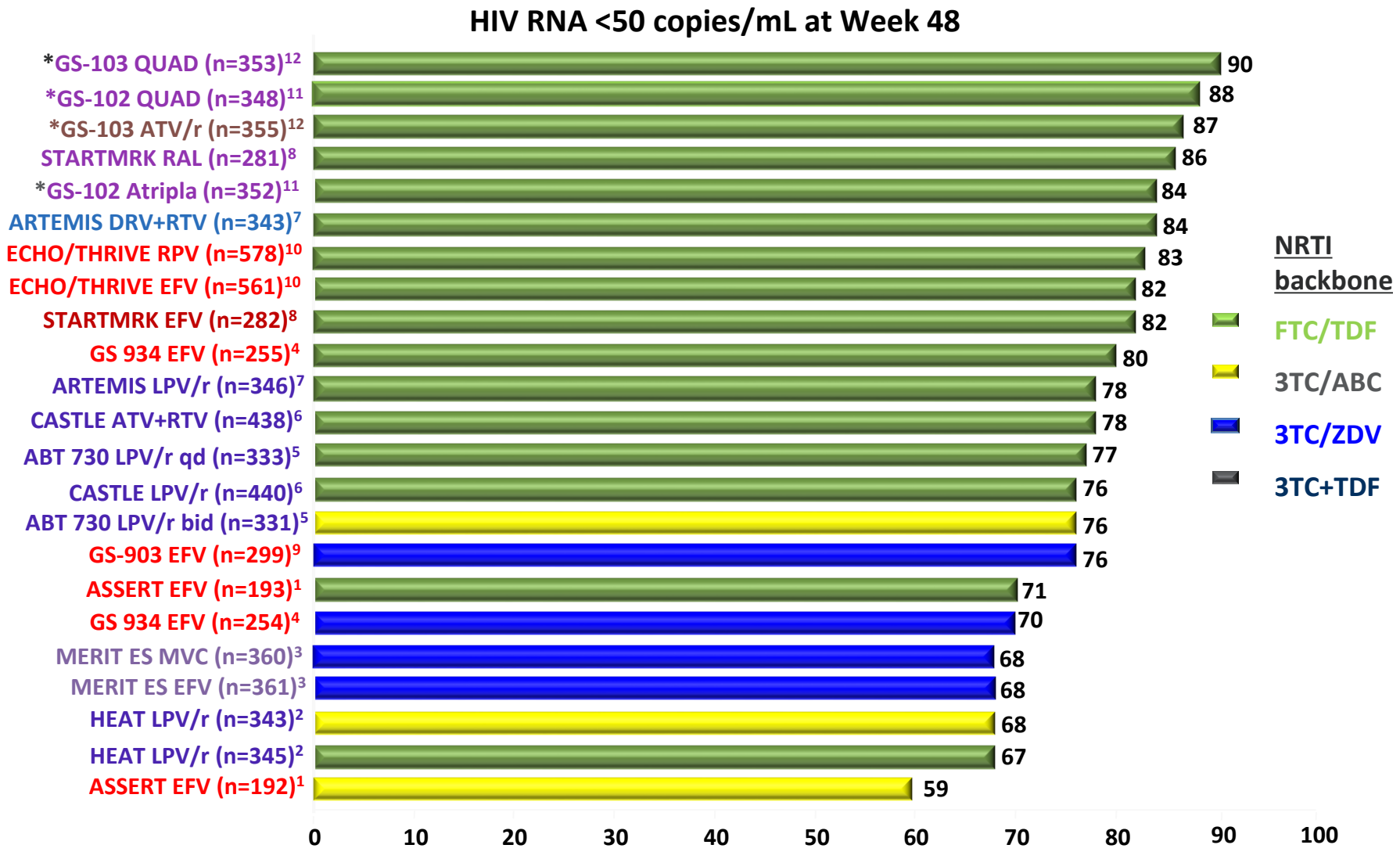






Adapted from Petoumenos K, et al. 17th CROI; 2010 Feb 16–19; San Francisco, USA. Oral abstract paper 124.

Benchmark for efficacy? Cross-study comparison of treatment-naïve trials

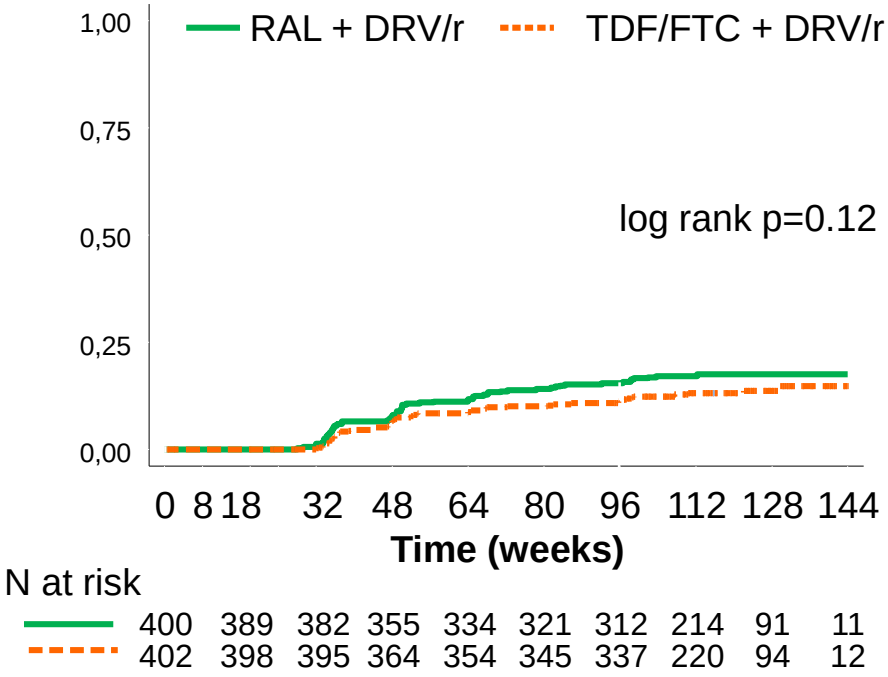


This slide depicts data from multiple studies published from 2004 to 2012 and cannot be compared directly.
**Studies involve investigational drugs not approved for use in the UK.*

1. Post FA, *et al. JAIDS* 2010;55:49–57; 2. Smith KY, *et al. AIDS* 2009;23:1547–56; 3. Cooper DA, *et al. J Infect Dis*. 2010;201:803–13; 4. Gallant JE, *et al. NEJM* 2006;354:251–60; 5. Gathe J, *et al. JAIDS* 2009;50:474–81; 6. Molina JM, *et al. Lancet* 2008;372:646–55; 7. Ortiz R, *et al. AIDS* 2008;22:1389–97; 8. Lennox JL, *et al. Lancet* 2009;374:796–806; 9. Gallant JE, *et al. JAMA* 2004;292:191–201; 10. Cohen CJ, *et al. JAIDS* 2012;60:33–42; 11. Sax P, *et al. Lancet* 2012;379:2439–48; 12. DeJesus E, *et al. Lancet* 2012;379:2429–38.

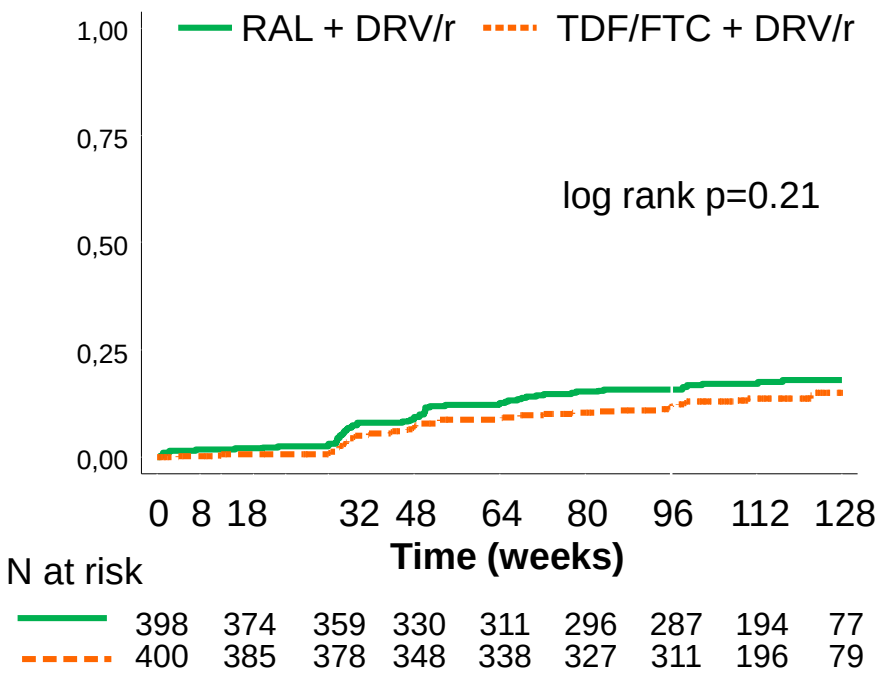
Primary endpoint: Sensitivity/secondary analysis

Sensitivity analysis : Time to virological failure as measured by virological components in primary endpoint



Estimated proportion reaching endpoint at W96
RAL: 15.4% vs TDF/FTC: 11.8%
Adjusted difference: 3.6% (95% CI: - 0.8, 8.1%)

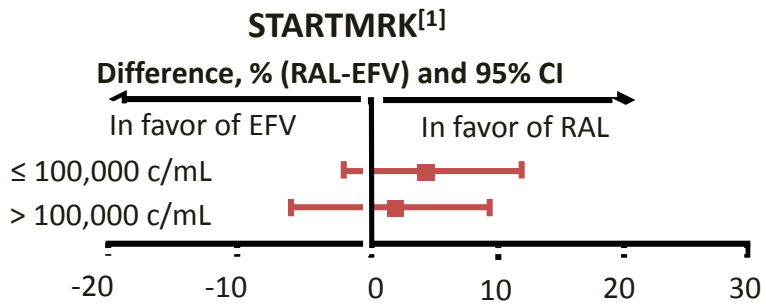
Secondary analysis : Time to primary endpoint with the addition of discontinuation of any component of randomised regimen for any reason as an endpoint

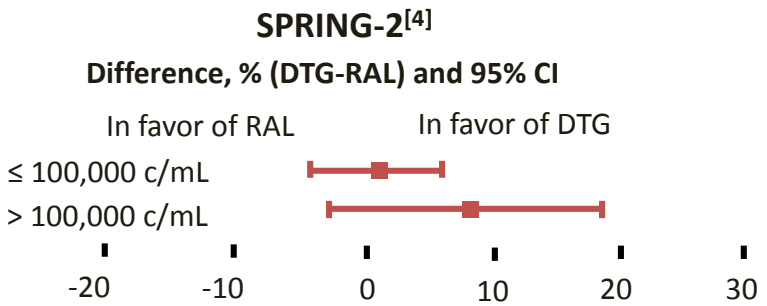


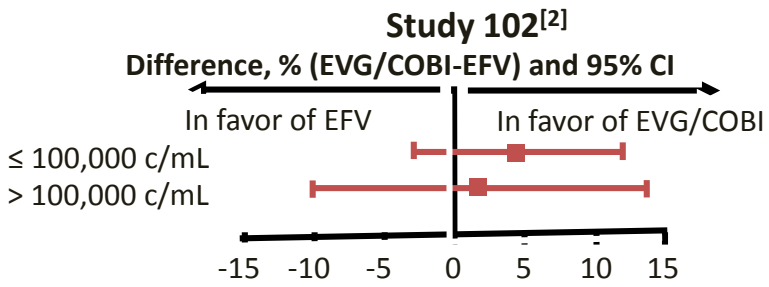
Estimated proportion reaching endpoint at W96
RAL: 22.8% vs TDF/FTC: 19.5%
Adjusted difference : 3.3% (95% CI: - 1.9, 8.4%)

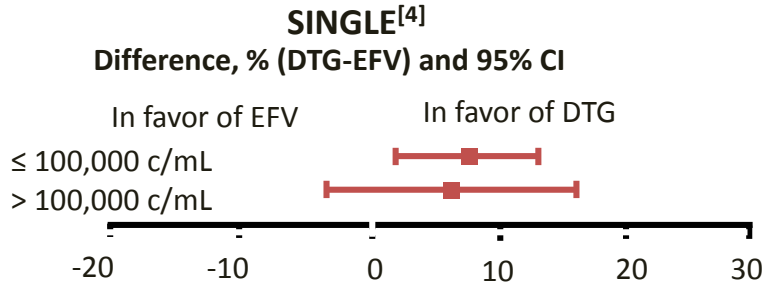
Raffi F et al, NEAT 001/ANRS 143 CROI Boston 2014

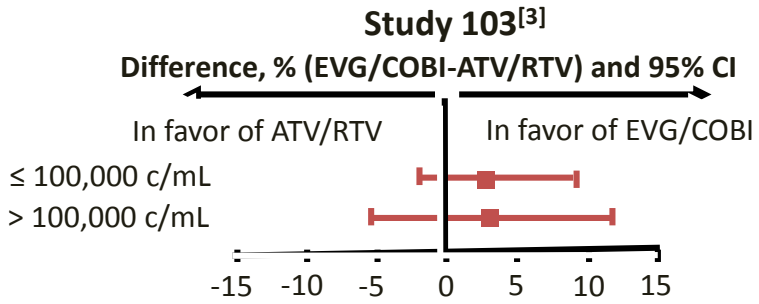
Virologic Suppression at Wk 48 by Baseline HIV-1 RNA

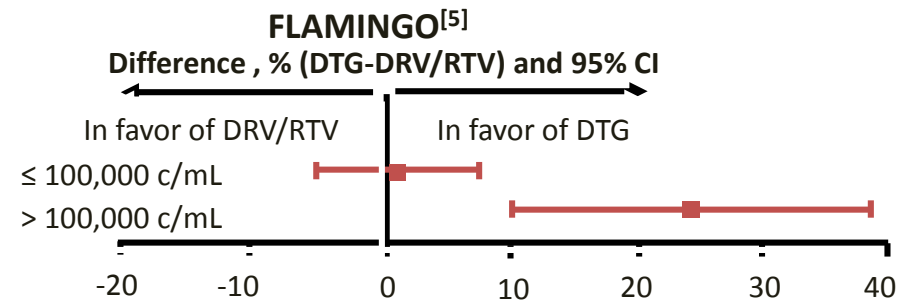








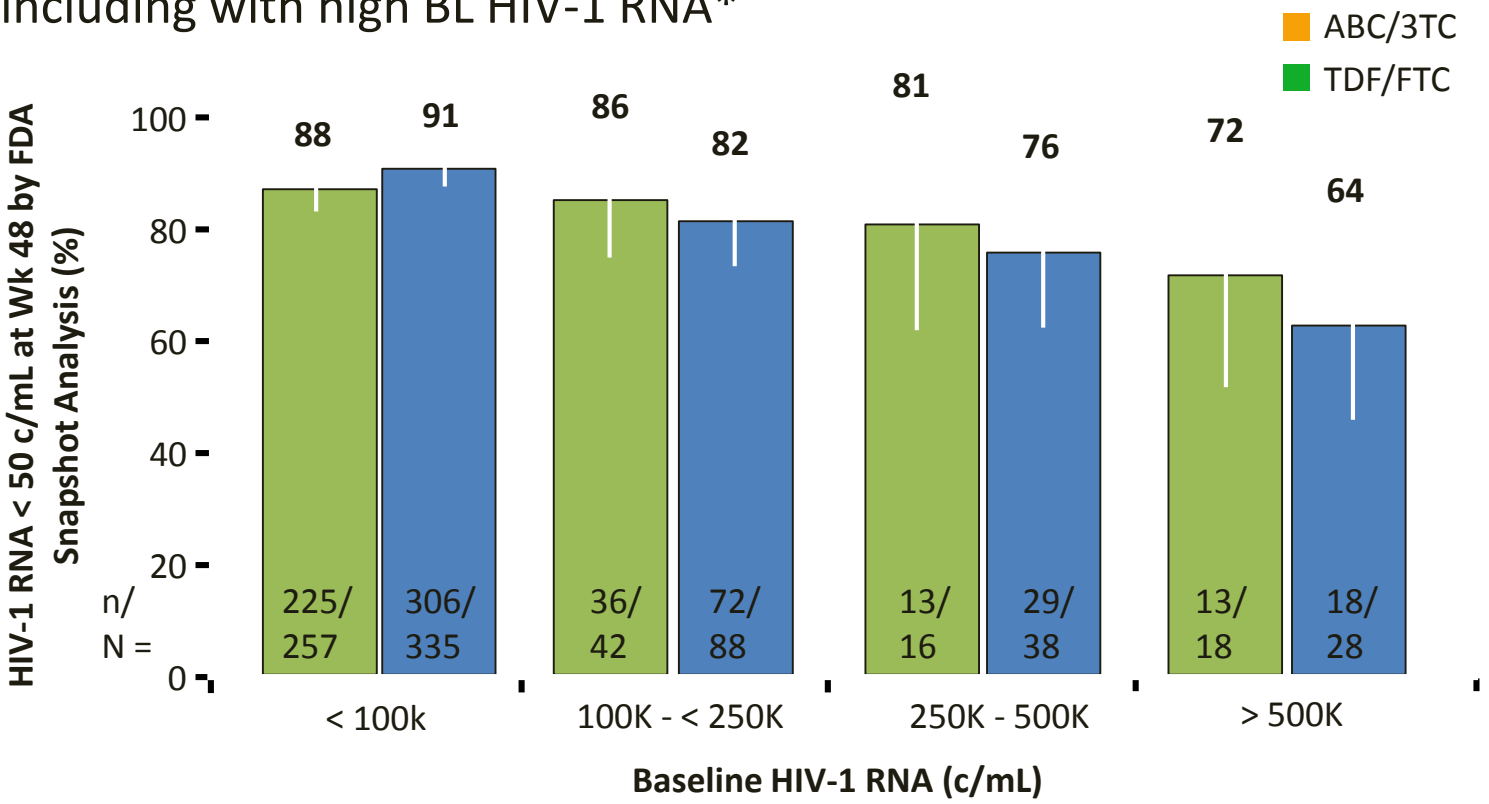




1. Lennox J, et al. Lancet. 2009;374:796-806. 2. Sax PE, et al. Lancet. 2012;379:2439-2448. 3. DeJesus E, et al. Lancet. 2012;379:2429-2438. 4. Brinson C, et al. CROI 2013. Abstract 554. 5. Feinberg J, et al. ICAAC 2013. Abstract H1464a.

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*



*Pooled data from both INSTIs.

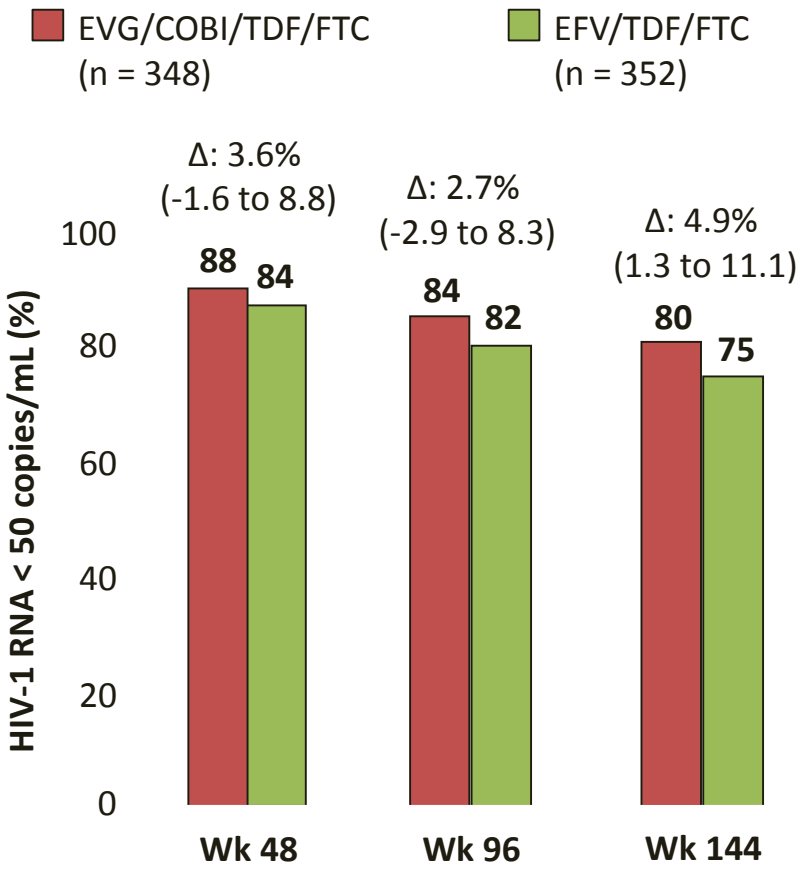
Eron J, et al. Glasgow 2012. Abstract P204.

Resistance Summary

- DTG vs RAL[1,2]
  - 0 pts with resistance in DTG arm
  - 1 pt with INSTI-R and 4 pts with NRTI-R with RAL at Wk 48; no additional resistance by Wk 96
- DTG vs EFV[3]
  - 0 pts with resistance in DTG arm
  - 1 pt with NRTI and 4 with NNRTI resistance in EFV arm
- DTG vs DRV/RTV[4]

1. Raffi F, et al. Lancet. 2013;381:735-743. 2. Raffi F, et al. IAS 2013. Abstract TULBPE17. 3. Walmsley S, et al. N Engl J Med. 2013;369:1807-1818. 4. Feinberg J, et al. ICAAC 2013. Abstract H1464a.

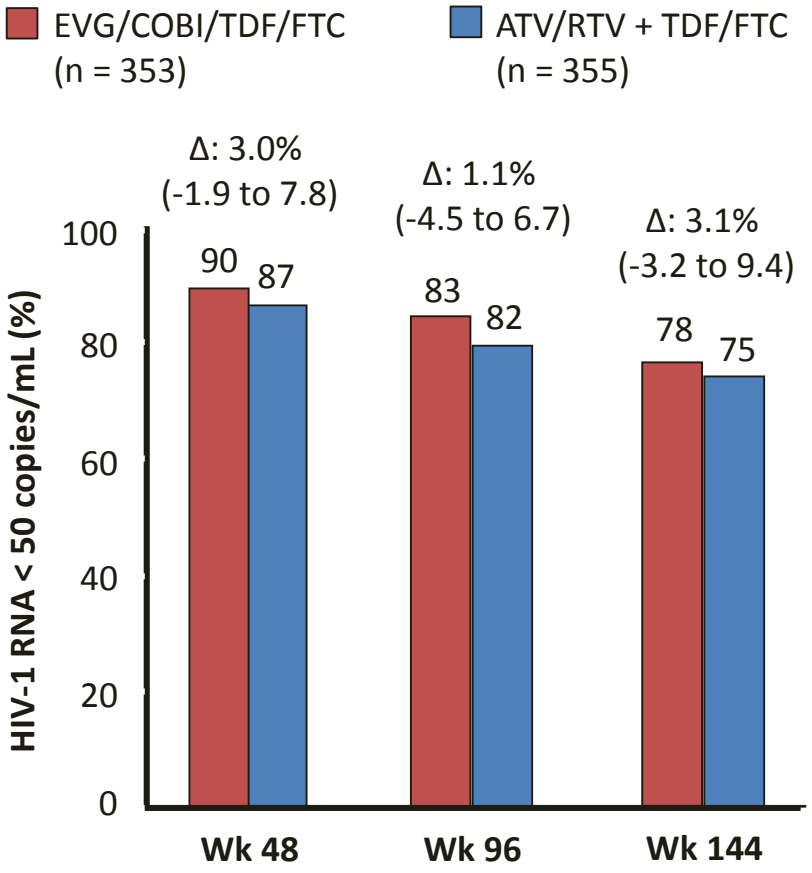
EVG/COBI/TDF/FTC Noninferior to EFV/TDF/FTC Through Wk 144



- EVG/COBI arm noninferior to EFV arm at Wk 48 primary endpoint[1] and through Wk 144[2,3]
  - Results consistent across subgroups: BL HIV-1 RNA, CD4+ cell count, age, sex, race
    - Treatment-related study d/c: 6% in EVG/COBI arm vs 7% in EFV arm at Wk 144
- VF: 7% in EVG/COBI arm and 10% in EFV arm at Wk 144
- Similar CD4+ cell count increase at Wk 144:
  - +321 cells/mm^3 (EVG/COBI) vs +300 cells/mm^3 (EFV)

1. Sax PE, et al. Lancet. 2012;379:2439-2448. 2. Zolopa A, et al. J Acquir Immune Defic Syndr. 2013;63:96-100. 3. Wohl D, et al. ICAAC 2013. Abstract H-672a.

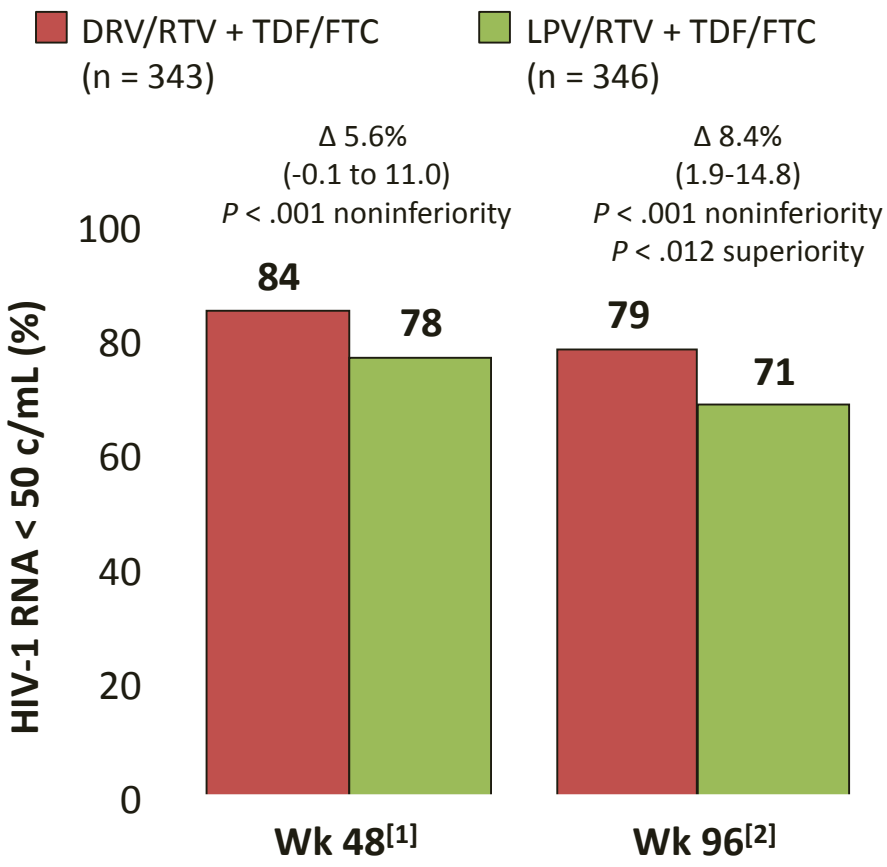
EVG/COBI/TDF/FTC Noninferior to ATV/RTV + TDF/FTC Through Wk 144



- EVG/COBI arm noninferior to ATV/RTV arm at Wk 48 primary endpoint[1] and through Wk 144[2,3]
  - Results consistent across subgroups: BL HIV-1 RNA, CD4+ count, adherence, age, sex, race
- Treatment-related study d/c:
  6% in EVG/COBI arm vs
  9% in ATV/RTV arm at Wk 144
- VF: 8% in EVG/COBI arm vs
  7% in ATV/RTV arm at Wk 144
- Similar CD4+ cell count increase at Wk 144: +280 cells/mm^3 (EVG/COBI) vs +293 cells/mm^3 (ATV/RTV)

1. De Jesus E, et al. Lancet. 2012;379:2429-2438. 2. Rockstroh J, et al. J Acquir Immune Defic Syndr. 2013;62:483-486. 3. Clumeck N, et al. EACS 2013. Abstract LBPS7/2.

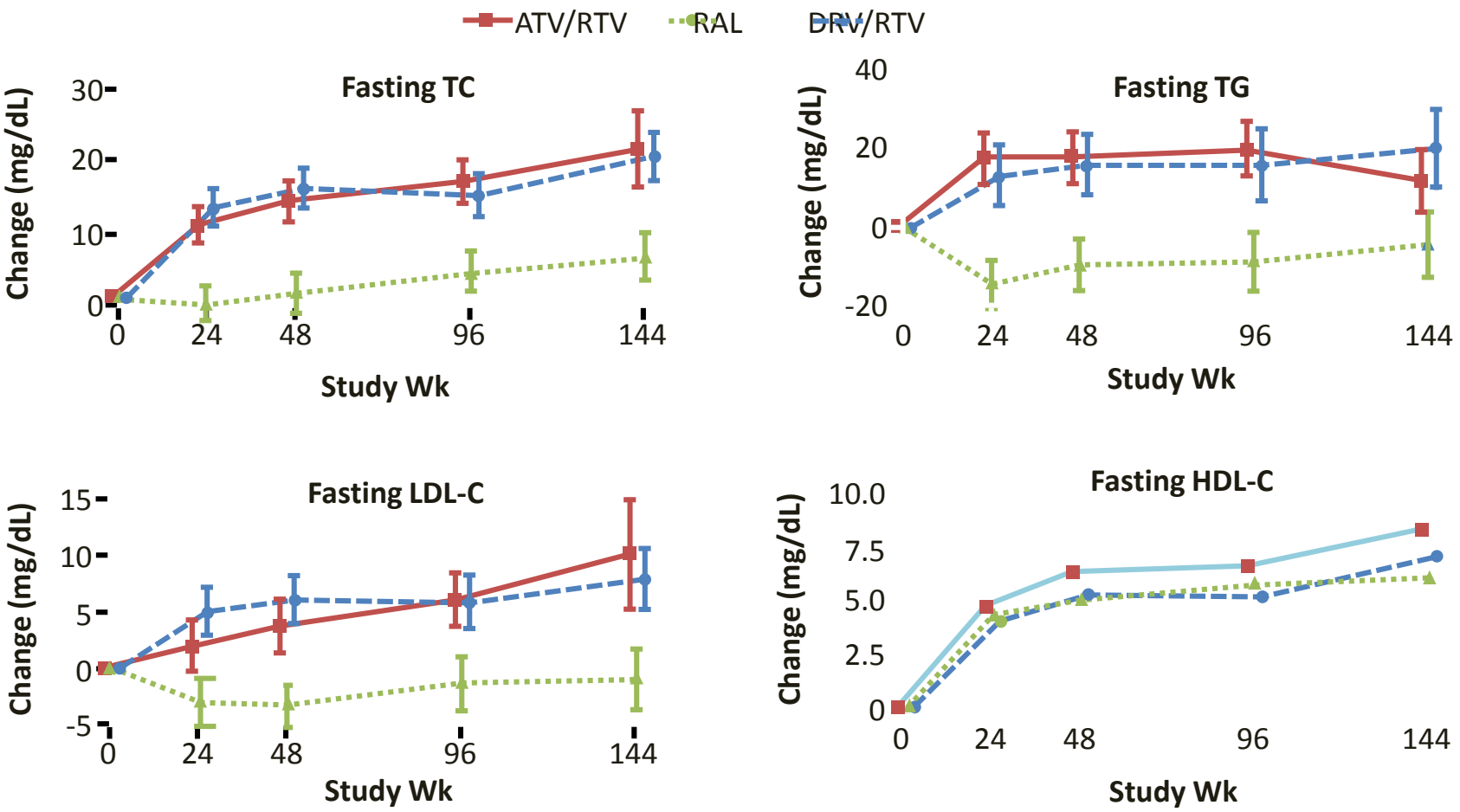
ARTEMIS: DRV/RTV vs LPV/RTV in Naive Pts Through 96 Weeks



- DRV/RTV noninferior to LPV/RTV at Wk 48; superior at Wk 96
  - Efficacy results better in DRV/RTV arm among those with BL VL > 100K (*P* = .023) c/mL and CD4+ < 200 (*P* = .009)
- VF in 1% of DRV/RTV arm vs 2% of LPV/RTV by Wk 96
  - No major PI mutations in either arm at Wk 96; NRTI mutations in 2 pts in DRV/RTV arm vs 5 in LPV/RTV arm
- Treatment-related study d/c:
  4% in DRV/RTV arm vs
  9% in LPV/RTV arm at Wk 96
- CD4+ count increase at Wk 96:
  +171 (DRV/RTV) vs +188 (LPV/RTV)
- Significantly smaller mean change in TC and TG at Wk 48 with DRV/RTV

1. Ortiz R, et al. AIDS. 2008;22:1389-1397. 2. Mills A, et al. AIDS. 2009;23:1679-1688.

ACTG 5257: Mean Change From BL in Fasting Lipids



Ofotokun I, et al. CROI 2014. Abstract 746.

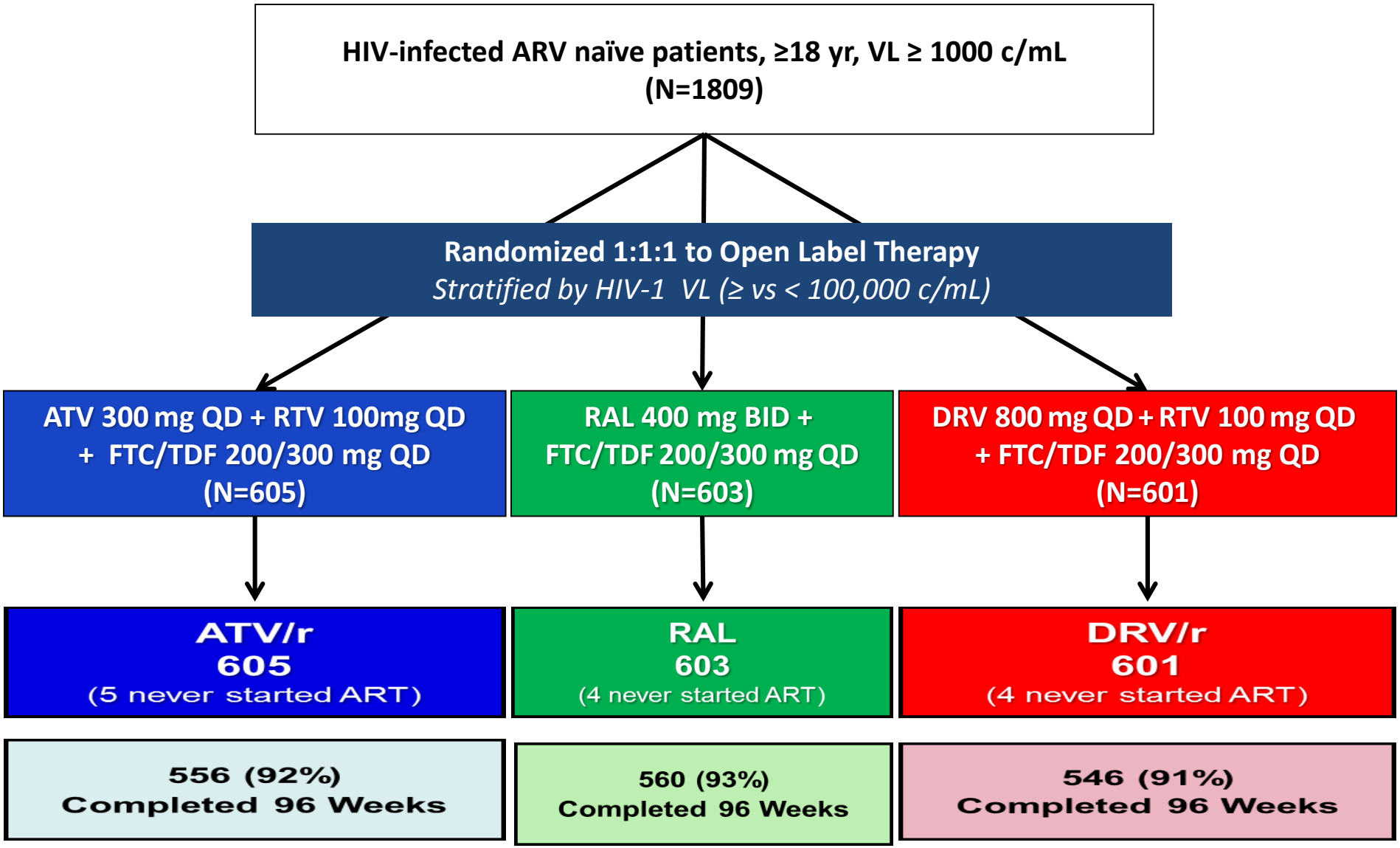
PI Resistance Rare at VF in First-line Studies of Boosted PIs

Study	n	PI	Wk	Genotypes	Major PI Mutations
CASTLE[1]	440 443	ATV/RTV LPV/RTV	96	26 26	1 0
ACTG 5202[2]	463 465	ATV/RTV	96	83 57	1 0
Study 103[3]	355	ATV/RTV	144	NR	0
ARTEMIS[4]	343 346	DRV/RTV LPV/RTV	96	31 46	0 0
FLAMINGO[5]	242	DRV/RTV	48	NR	0
ACTG 5257[6]	605 601	ATV/RTV DRV/RTV	96	75 99	0 0

- Among 4303 pts in these trials, only 2 pts developed major PI mutations at initial VF

1. Molina JM, et al. Lancet. 2008;372:646-655. 2. Daar ES, et al. Ann Intern Med. 2011;154:445-456.
3. Clumeck N, et al. EACS 2013. Abstract LBPS7/2. 4. Mills A, et al. AIDS. 2009;23:1679-1688.
5. Clotet B, et al. Lancet. 2014;[Epub ahead of print]. 6. Landovitz R, et al. CROI 2014. Abstract 85.

A5257 Study Design: 96 week F/U*



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

Adapted from Landowitz et al

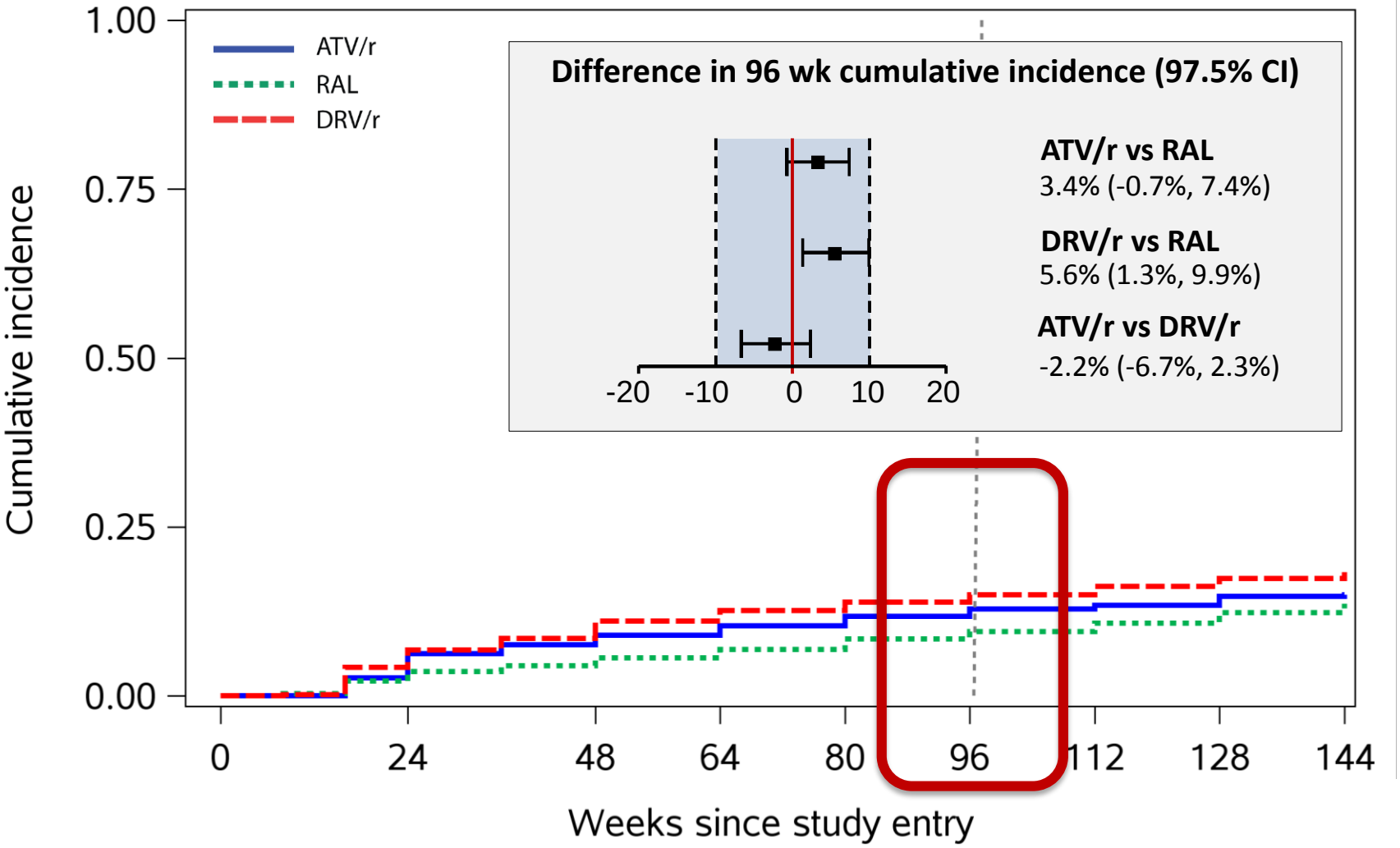
Landovitz RJ, CROI 2014, Boston

Study Design

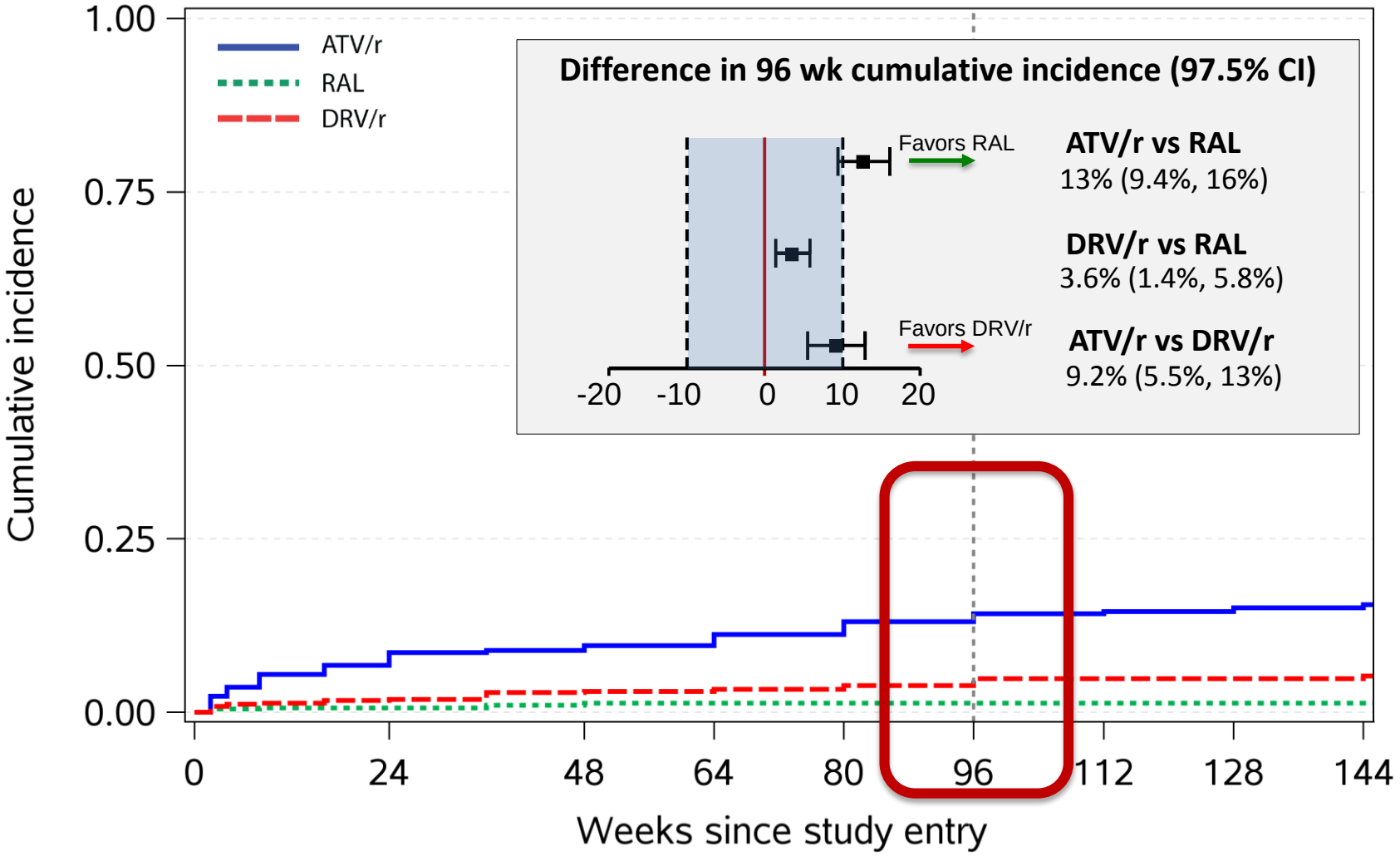
- Hypothesis
  - FTC/TDF with ATV/r, RAL, or DRV/r will be equivalent in terms of virologic efficacy and tolerability over 96 weeks
- Primary Endpoints*
  - Time to HIV-1 RNA >1000 c/mL wk 16 to before wk 24, or >200 c/mL at or after wk 24 (VF)
  - Time to discontinuation of randomized component for toxicity (TF)
- Pre-planned Composite Endpoint
  - The earlier occurrence of either VF or TF in a given participant

** Time measured from date of study entry/randomization*

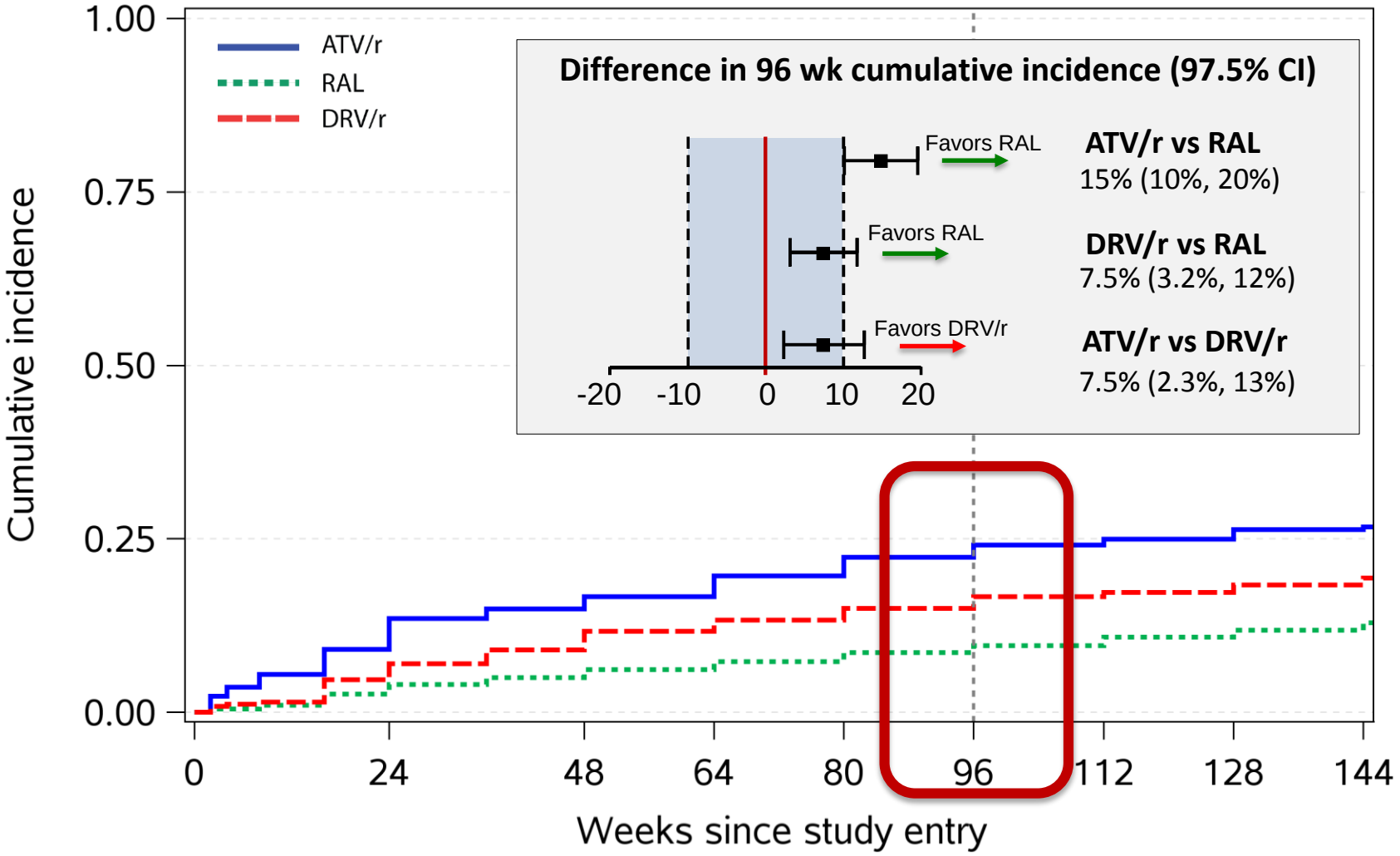
Cumulative Incidence of Virologic Failure



Cumulative Incidence of Tolerability Failure

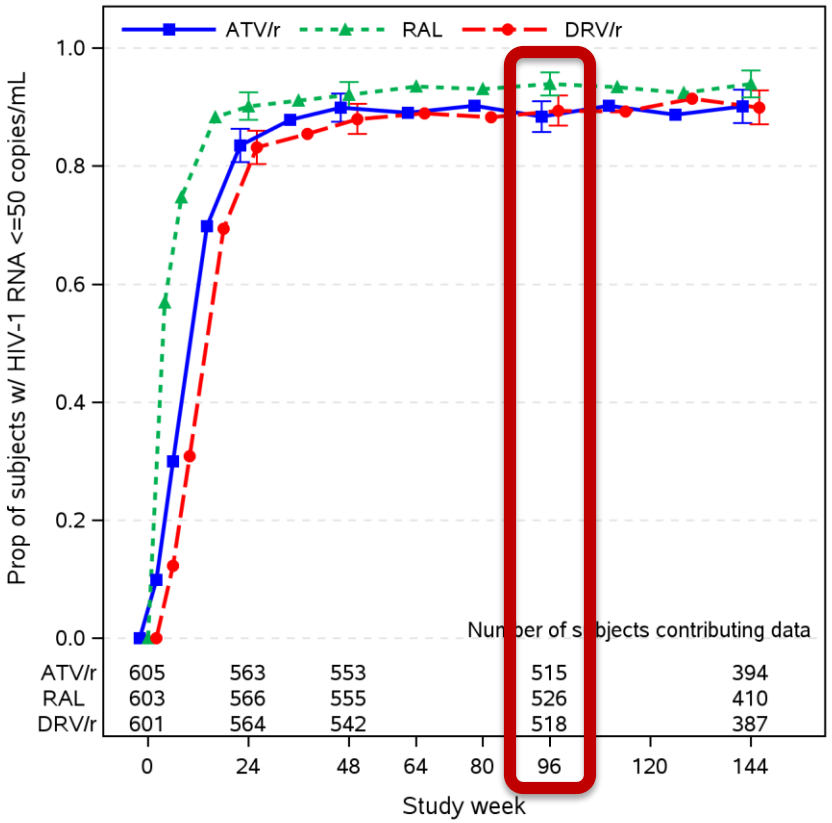


Cumulative Incidence of Virologic or Tolerability Failure

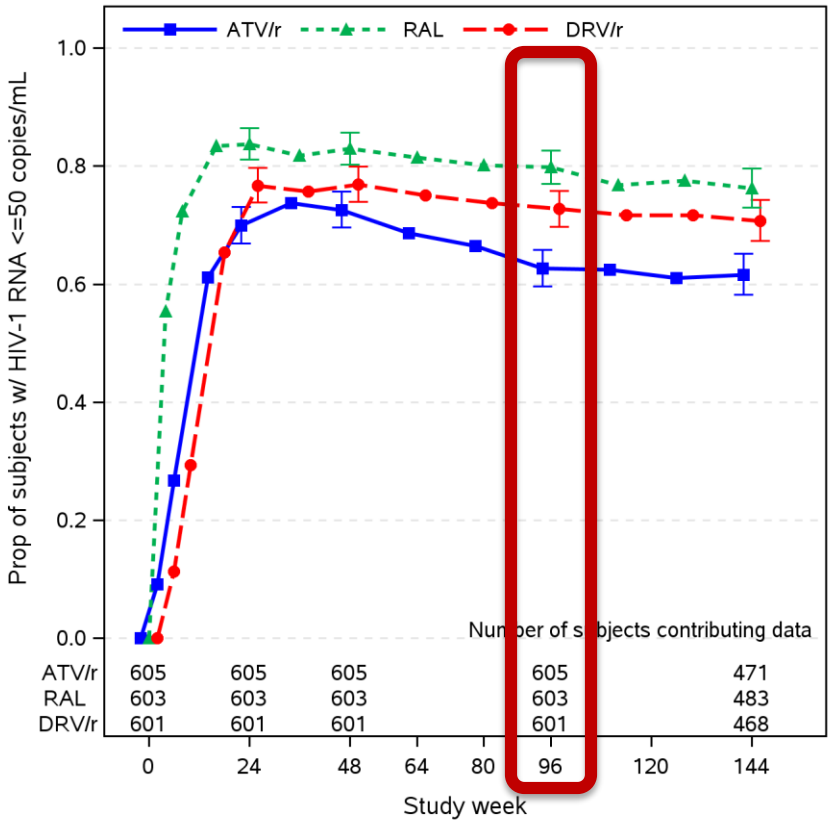


Proportion VL ≤50 copies/mL

ITT, regardless of ART change



ITT, off-ART=failure (SNAPSHOT)



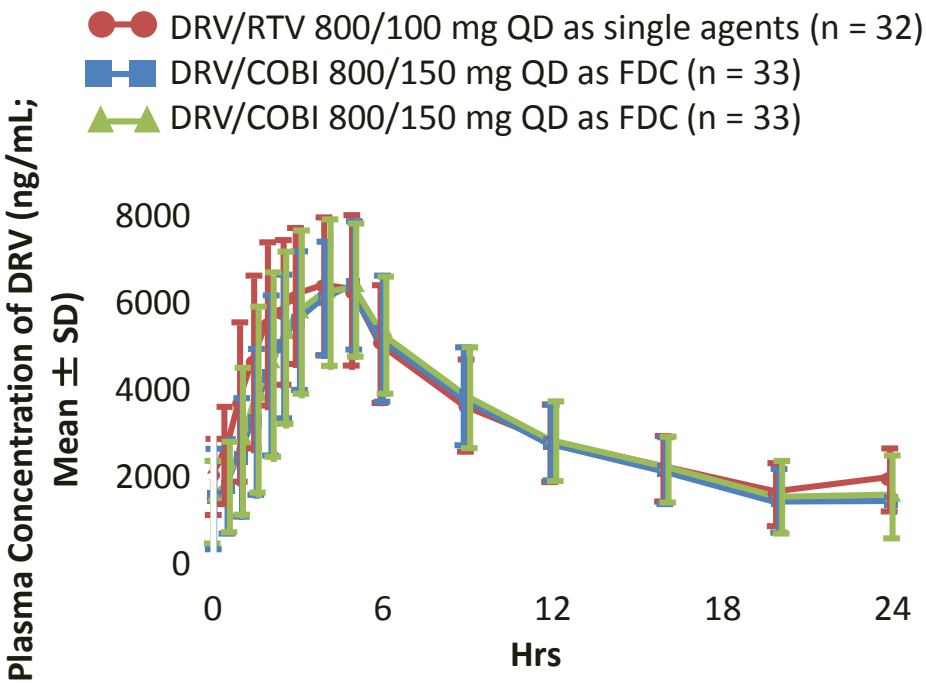
	24	48	96	144
ATV/r	83%	90%	**88%**	90%
RAL	90%	92%	**94%**	94%
DRV/r	83%	88%	**89%**	90%

	24	48	96	144
ATV/r	70%	73%	**63%**	62%
RAL	84%	83%	**80%**	76%
DRV/r	77%	77%	**73%**	71%

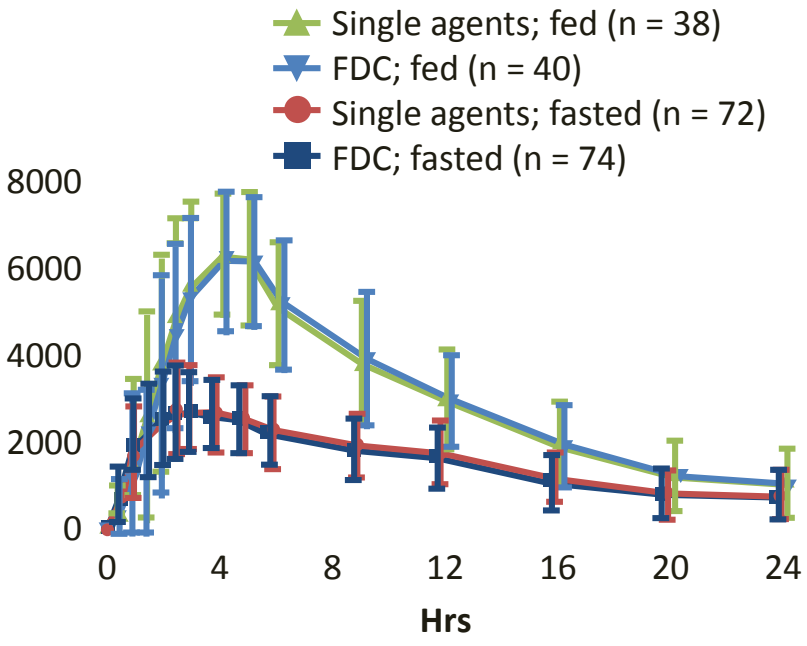
DRV/COBI FDC Bioequivalent to DRV + RTV and to DRV + COBI

- PK analyses in healthy subjects

DRV Concentration When Administered as DRV + RTV or as DRV/COBI Coformulation[1]



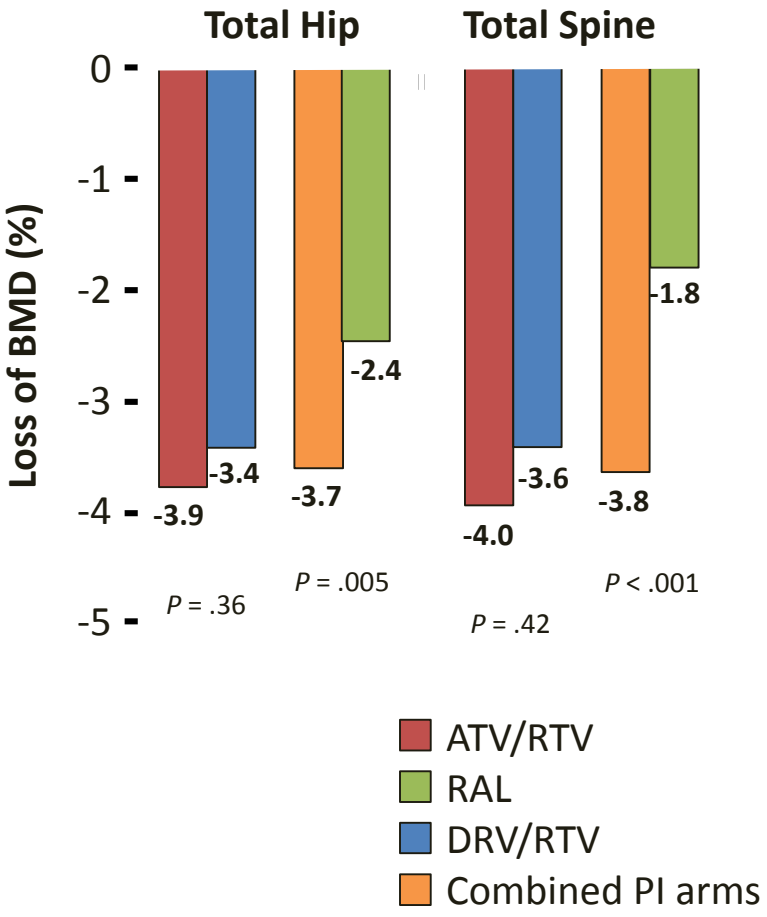
DRV Concentration When DRV and COBI Administered as Single Agents or as Coformulation[2]



1. Kakuda TN, et al. Clin Pharmacol. 2012. Abstract O_20.
2. Kakuda TN, et al. IAS 2013. Abstract MOPE029.

ACTG 5257: Loss of BMD With First-line Boosted PI vs RAL

- All arms associated with significant loss of BMD through Wk 96 (P < .001)
- At hip and spine, similar loss of BMD in the PI arms
  - Significantly greater loss in the combined PI arms than in the RAL arm



Brown T, et al. CROI 2014. Abstract 779LB. Reproduced with permission.

Horizon Scanning

- New compounds: TAF MSD? Gilead
- More co-formulation Single-tablet regimens: TRII; TAF QUAD ; ATV/COBI; DRV/COBI;DRV/COBI/TAF/FTC
- ? Initiation/ maintenance: NRTI-sparing combinations : ? INSTI+NNRTI or INSTI+NNRTI
- Injectable preps : Rilpivirine containing; gold-based preparations