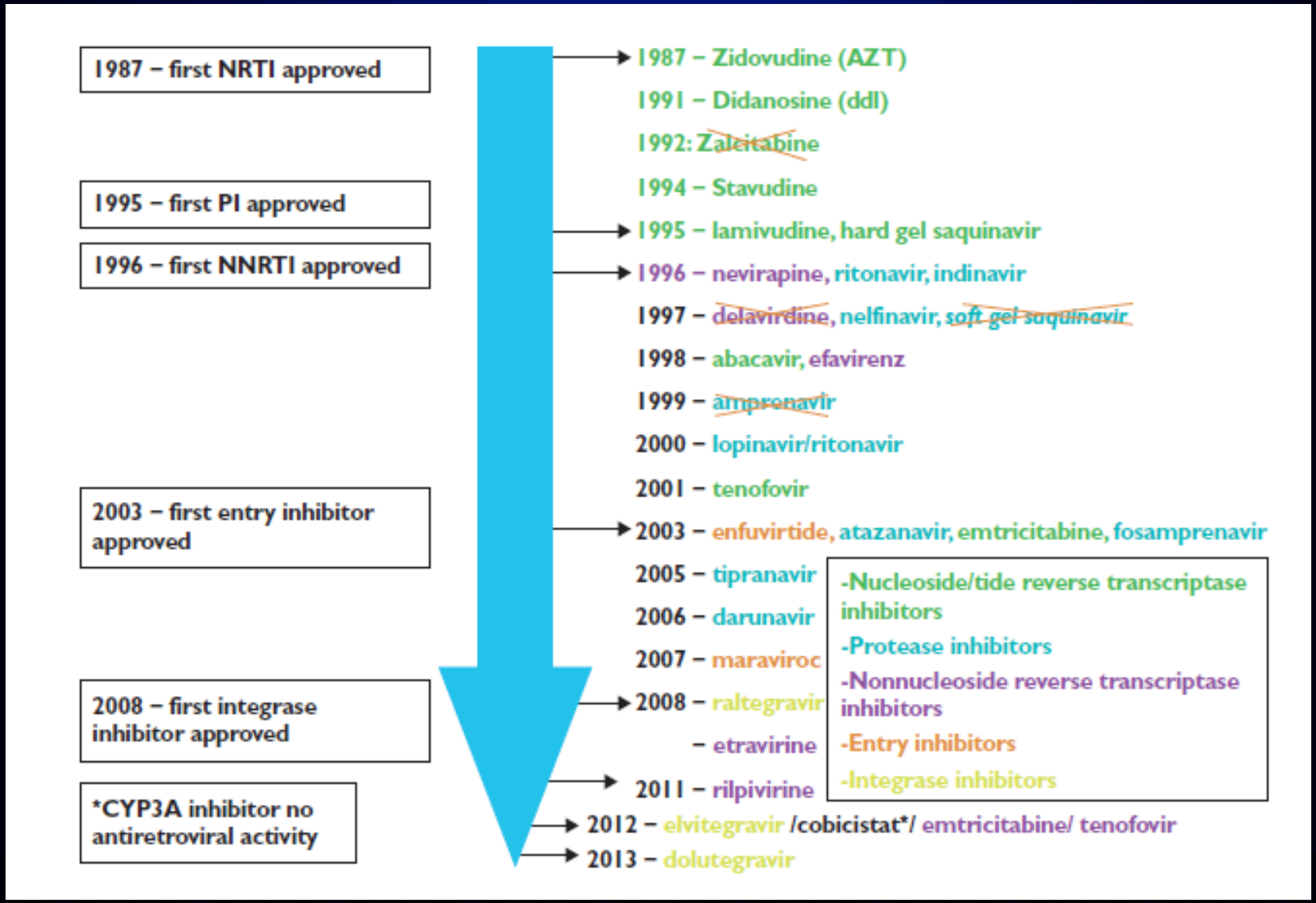
C'è un nuovo paradigma per la tollerabilità ?

Massimo Galli
Clinica delle Malattie Infettive
DIBIC L.Sacco, Università di Milano
Milano 24.9.15

Time lines of antiretroviral development



Tseng et al.Br J Clin Pharmacol 2014; 79:182-194

Cause di *switch* per *long-term toxicity*

- ~~da nucleosidici timidinici e ddI~~
- da EFV per tossicità neurologica (r… …a)
- da PI per tossicità … …a (renale,cardiovascolare)
- da AB… …enio cardiovascolare
- …da TDF per tossicità metabolica (rene-osso)

E gli inibitori dell'integrasi ?

Mean odds ratio (95% CrI) of AEs and discontinuation due to Aes: Dolutegravir vs other 'third' drugs.

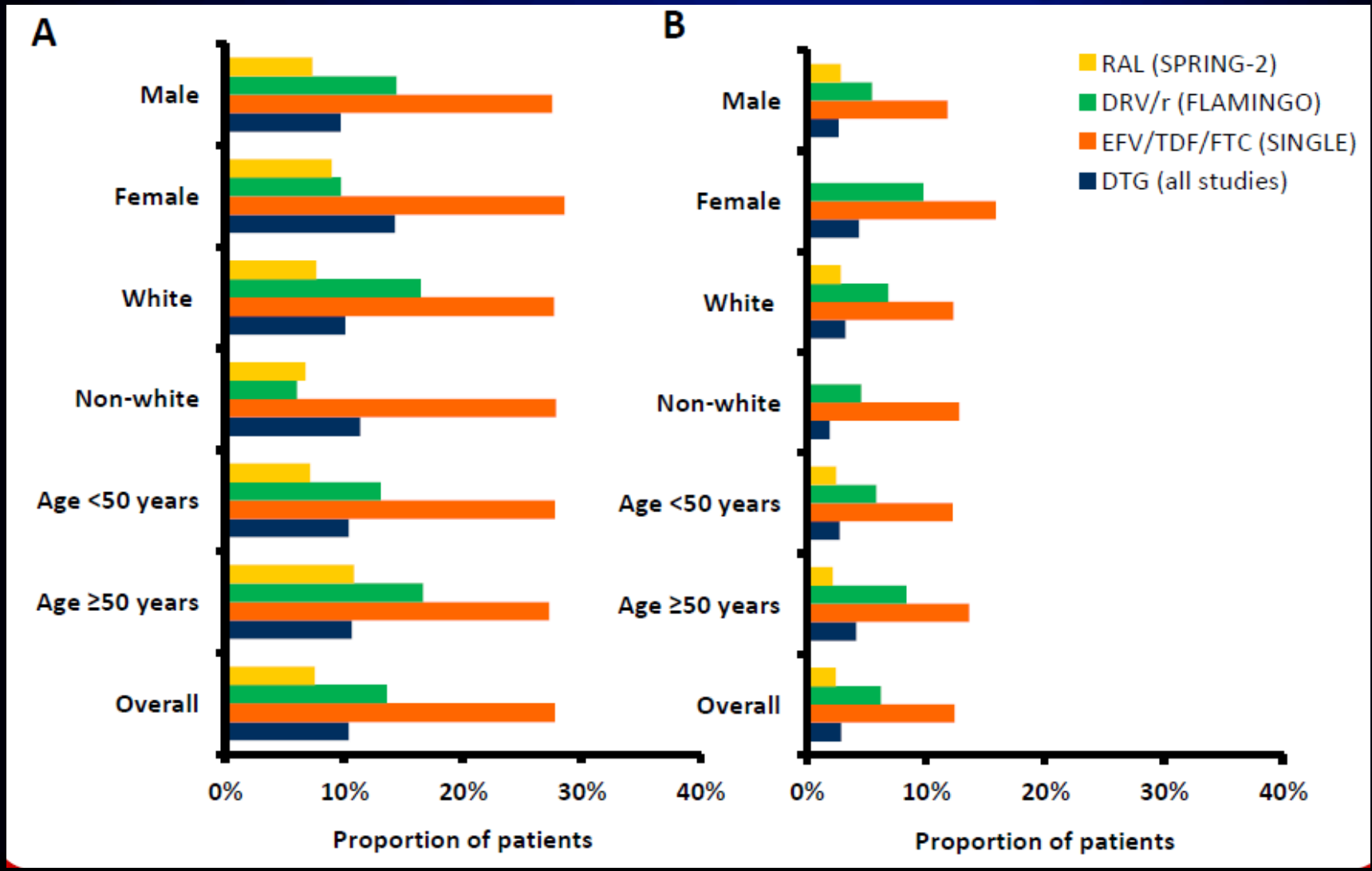
DTG compared to	Adverse Events N = 11 studies	Discontinuation due to AEs N = 18 studies
ATV/r	**0.58 (0.33, 0.94)***	**0.24 (0.10, 0.49)***
DRV/r	1.06 (0.66, 1.61)	**0.45 (0.18, 0.93)***
EFV	**0.57 (0.38, 0.81)***	**0.26 (0.14, 0.43)***
EVG/c	0.77 (0.41, 1.34)	**0.38 (0.15, 0.79)***
LPV/r	**0.54 (0.29, 0.89)***	**0.21 (0.09, 0.40)***
RAL	1.11 (0.79, 1.53)	0.87 (0.37, 1.77)
RPV	0.79 (0.44, 1.30)	0.74 (0.33, 1.42)

*Significant comparisons are in bold with an asterisk.
doi:10.1371/journal.pone.0105653.t002

Patel et al. PLoS One. 2014;9:e105653

Dolutegravir: AEs by Treatment Subgroup.

(A) Grade 2 to 4 Drug-related AEs. (B) AEs Leading to Withdrawal



Koteff et al. 8° IAS conference, Vancouver July 2015 #TUPEB261

AAC
Journals.ASM.org

Population Pharmacokinetic Analysis and Pharmacogenetics of Raltegravir in HIV-Positive and Healthy Individuals

Mona Arab-Alameddine,[a,d] Aurélie Fayet-Mello,[a] Rubin Lubomirov,[b] Michael Neely,[e] Julia di Iulio,[b] Andrew Owen,[f] Marta Boffito,[l] Matthias Cavassini,[c] Huldrych F. Günthard,[g] Katharina Rentsch,[h] Thierry Buclin,[a] Manel Aouri,[a] Amalio Telenti,[b] Laurent Arthur Decosterd,[a] Margalida Rotger,[b] Chantal Csajka,[a,d] and the Swiss HIV Cohort Study Group

Division of Clinical Pharmacology and Toxicology, University Hospital Center and University of Lausanne, Lausanne, Switzerland[a]; Institute of Microbiology, University Hospital Center and University of Lausanne, Lausanne, Switzerland[b]; Division of Infectious Diseases, University Hospital Center and University of Lausanne, Lausanne, Switzerland[c]; School of Pharmaceutical Sciences, University of Geneva, and University of Lausanne, Geneva, Switzerland[d]; Laboratory of Applied Pharmacokinetics, University of Southern California, Los Angeles, California, USA[e]; Department of Molecular and Clinical Pharmacology, University of Liverpool, Liverpool, United Kingdom[f]; Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland[g]; Division of Laboratory Medicine, University Hospital Zurich, Zurich, Switzerland[h]; and St. Stephen's Centre, Chelsea and Westminster Foundation Trust, London, United Kingdom[l]

The objectives of this study were to characterize raltegravir (RAL) population pharmacokinetics in HIV-positive (HIV^+) and healthy individuals, identify influential factors, and search for new candidate genes involved in UDP glucuronosyltransferase (UGT)-mediated glucuronidation. The pharmacokinetic analysis was performed with NONMEM. Genetic association analysis was performed with PLINK using the relative bioavailability as the phenotype. Simulations were performed to compare once- and twice-daily regimens. A 2-compartment model with first-order absorption adequately described the data. Atazanavir, gender, and bilirubin levels influenced RAL relative bioavailability, which was 30% lower in HIV^+ than in healthy individuals. *UGT1A9*3* was the only genetic variant possibly influencing RAL pharmacokinetics. The majority of RAL pharmacokinetic variability remains unexplained by genetic and nongenetic factors. Owing to the very large variability, trough drug levels might be very low under the standard dosing regimen, raising the question of a potential relevance of therapeutic drug monitoring of RAL in some situations.

Antimicr Agents Chemother. 2012; 56: 2959-2966

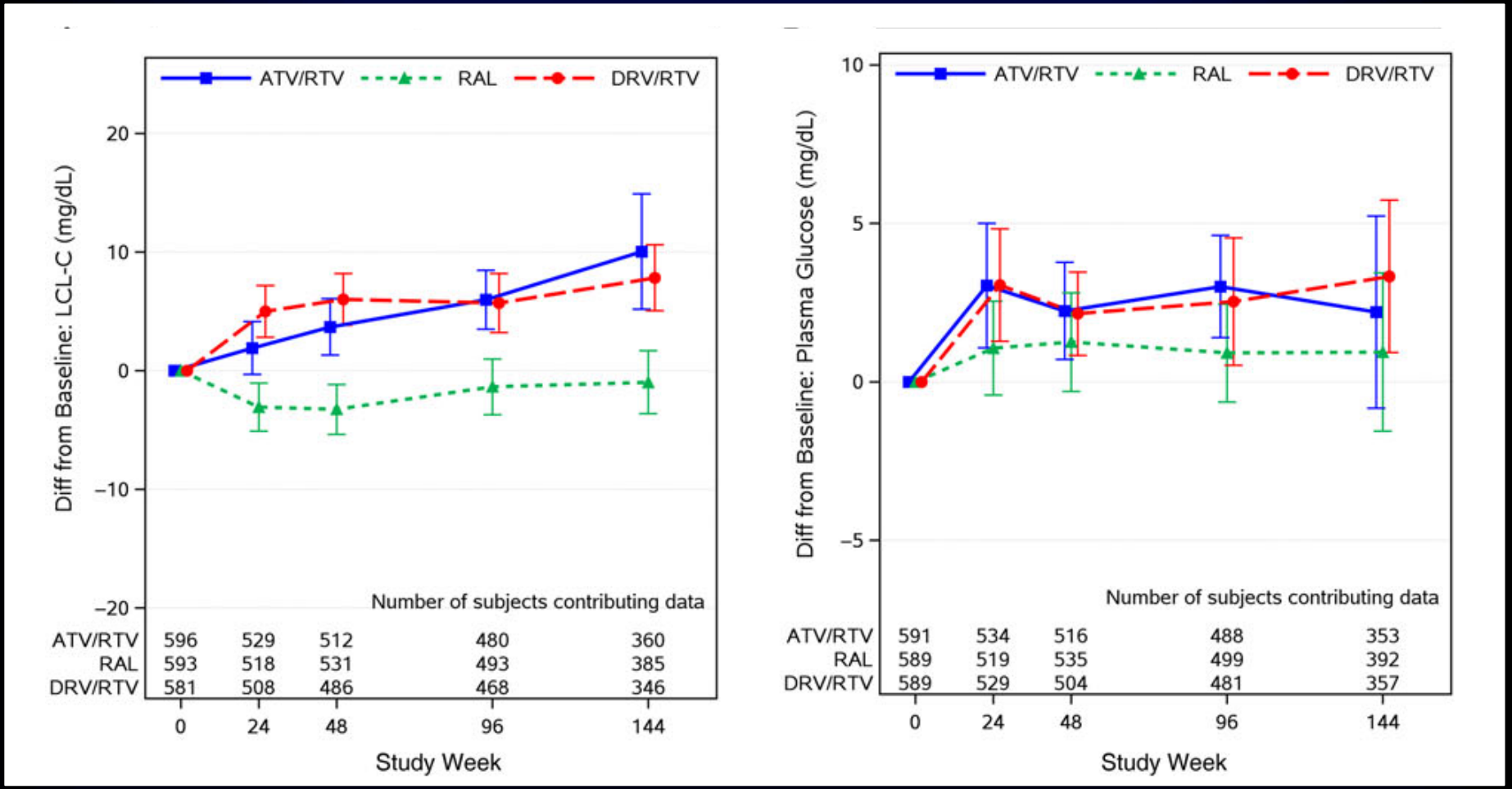
Tolerability Failure – ARDENT

Toxicity Associated Discontinuation of randomized ART*

Characteristics	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

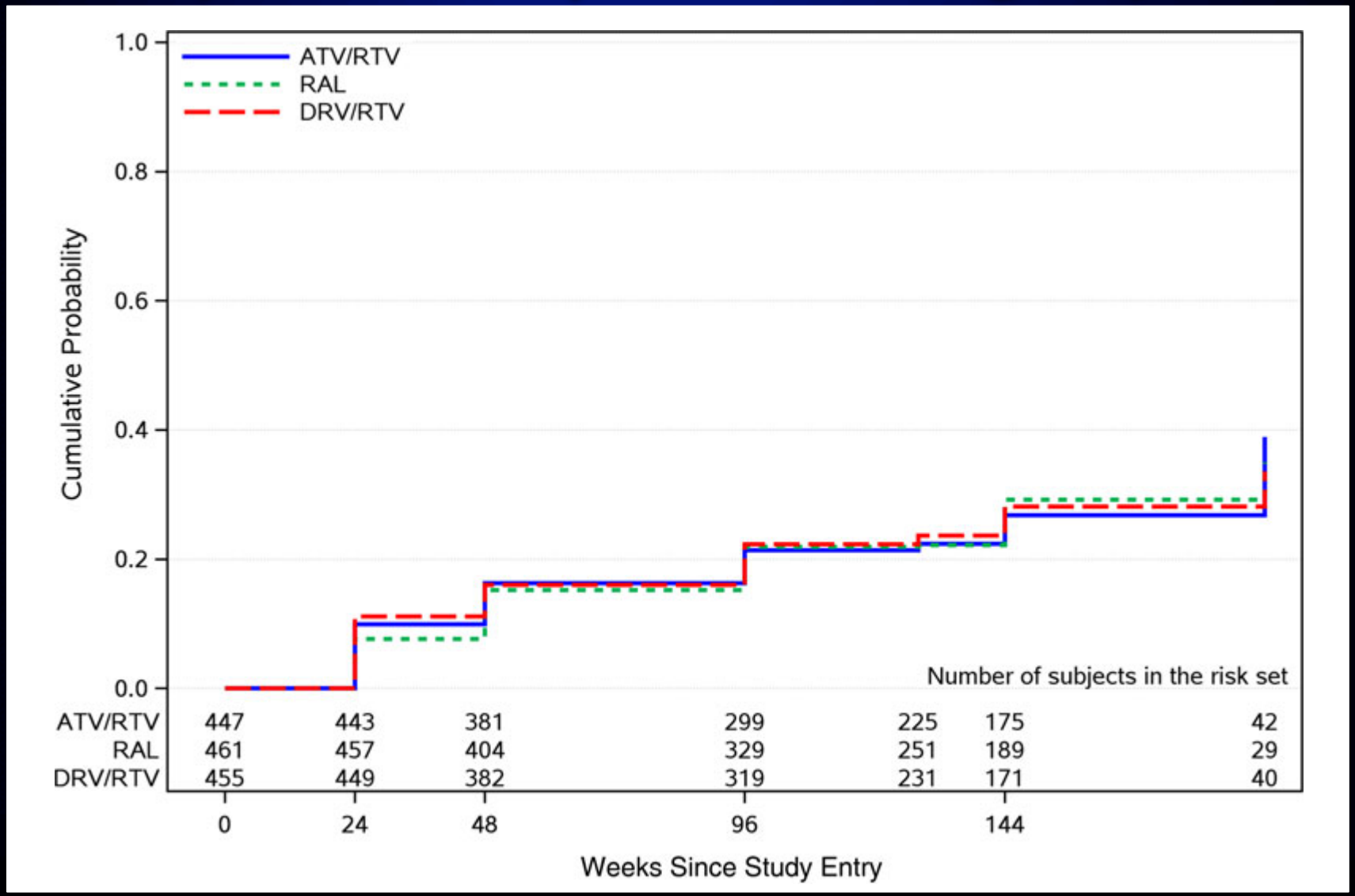
* Participants allowed to switch therapy for intolerable toxicity

ACTG 5257: Mean changes from baseline in metabolic outcomes



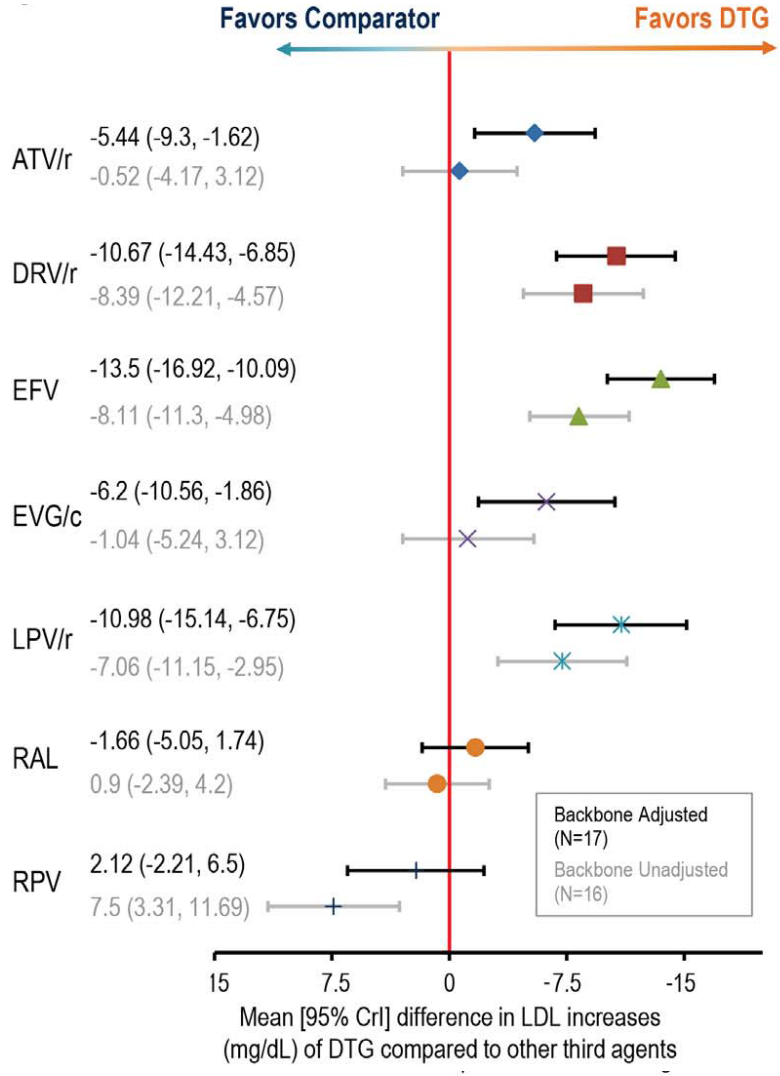
Ofotokun et al.CID 2015;60:1842–51

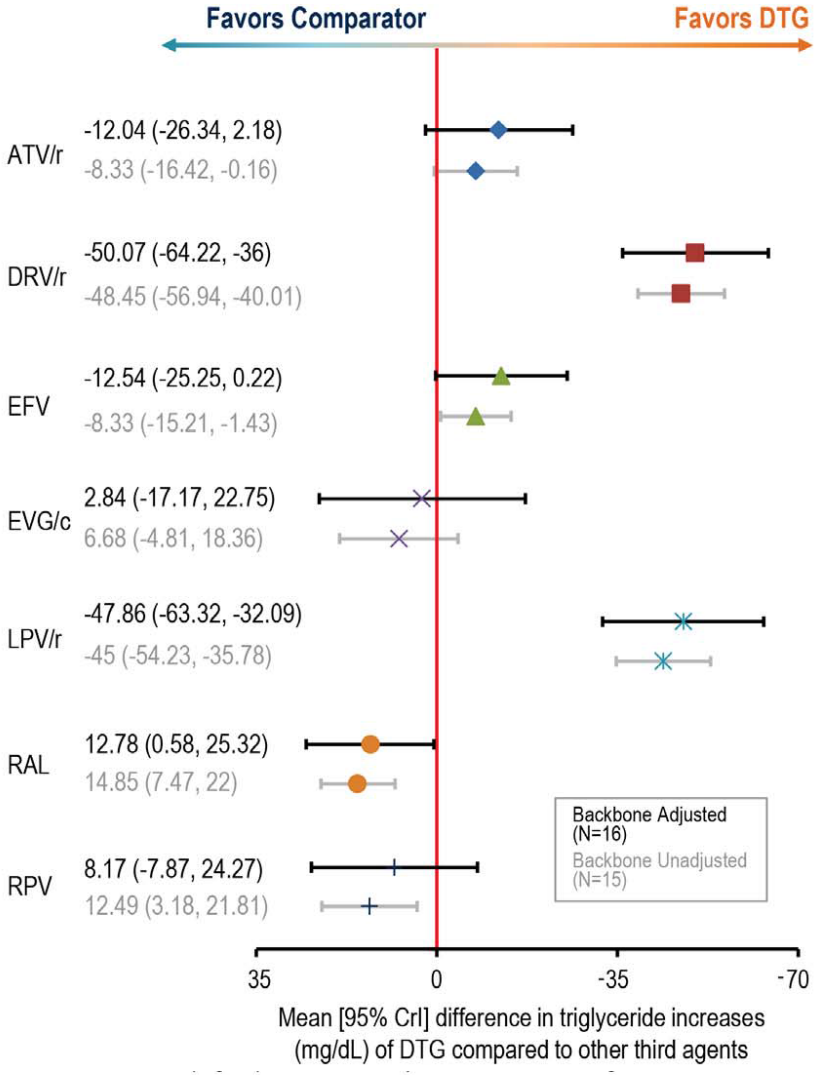
Cumulative probability of metabolic syndrome, by treatment group.



Ofotokun et al.CID 2015;60:1842-51

Relative changes in metabolic parameters for dolutegravir versus third agents of interest





Patel et al.PLoS ONE 2014; 9: e105653.

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