EACS | HIV Summer School

EACS European AIDS Clinical Society

State of the ART of ART

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DISCLOSURES

Speaker's Bureau: Gilead

Board Member/Advisory Panel: MSD, Gilead, Janssen, ViiV, Teva

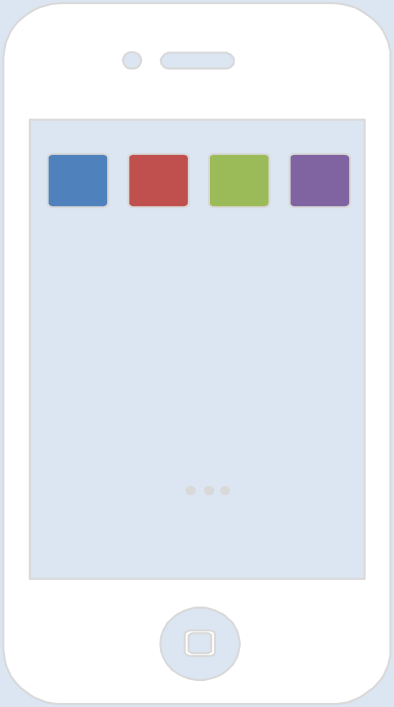
International Guidelines of ART

International Antiviral Society-USA Panel

- http://jama.jamanetwork.com/data/Journals/JAMA/935428/jsc160011.pdf
- Last update: July 2016

DHHS Panel Guidelines (USA)

- https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0
- Last update: July 2016



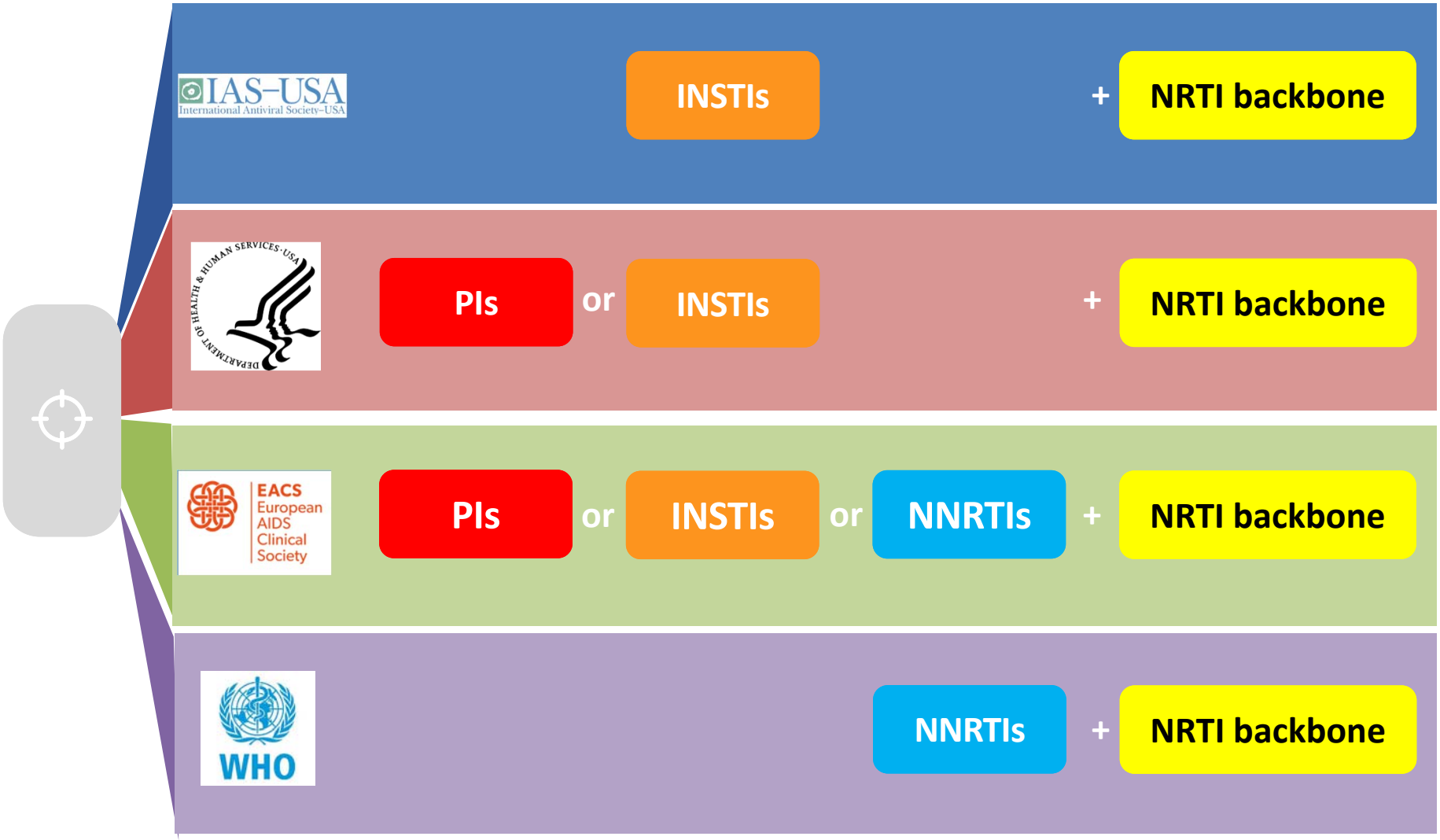
European AIDS Clinical Society Guidelines (EACS)

- http://www.eacsociety.org/files/guidelines_8.1-english.pdf
- Available in English and in other 11 European languages.
- Last update: October 2016

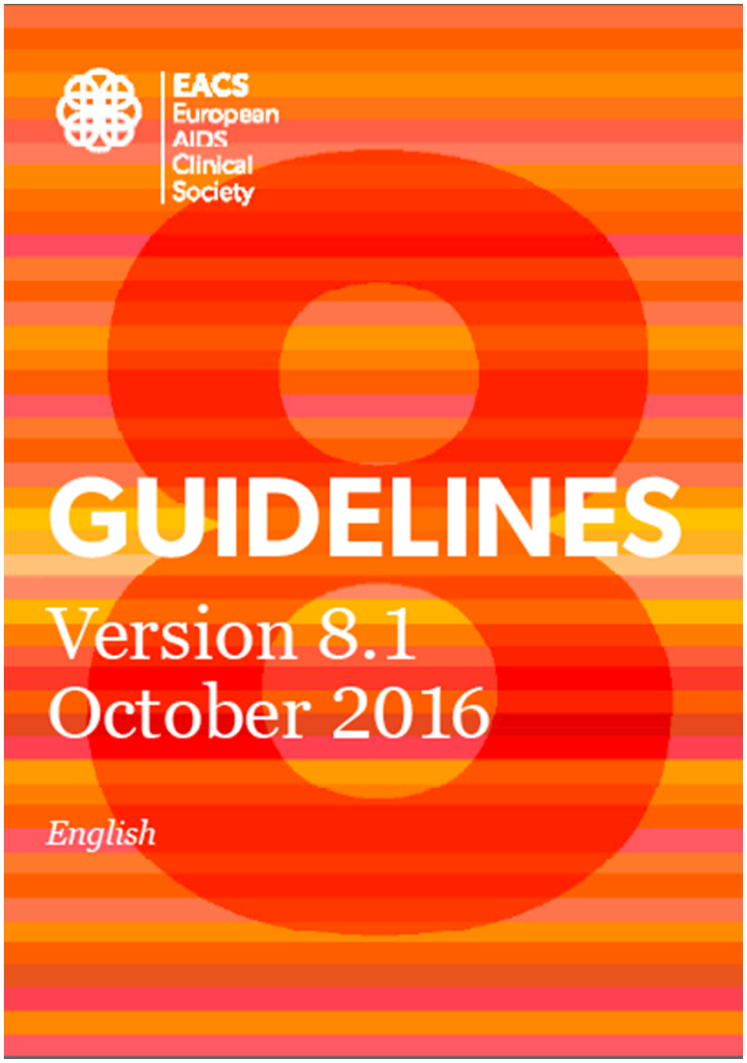
World Health Organization (WHO)

- http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf
- Last update: June 2016

Overview of Clinical Guidelines and First-Line Antiretroviral Treatment Options

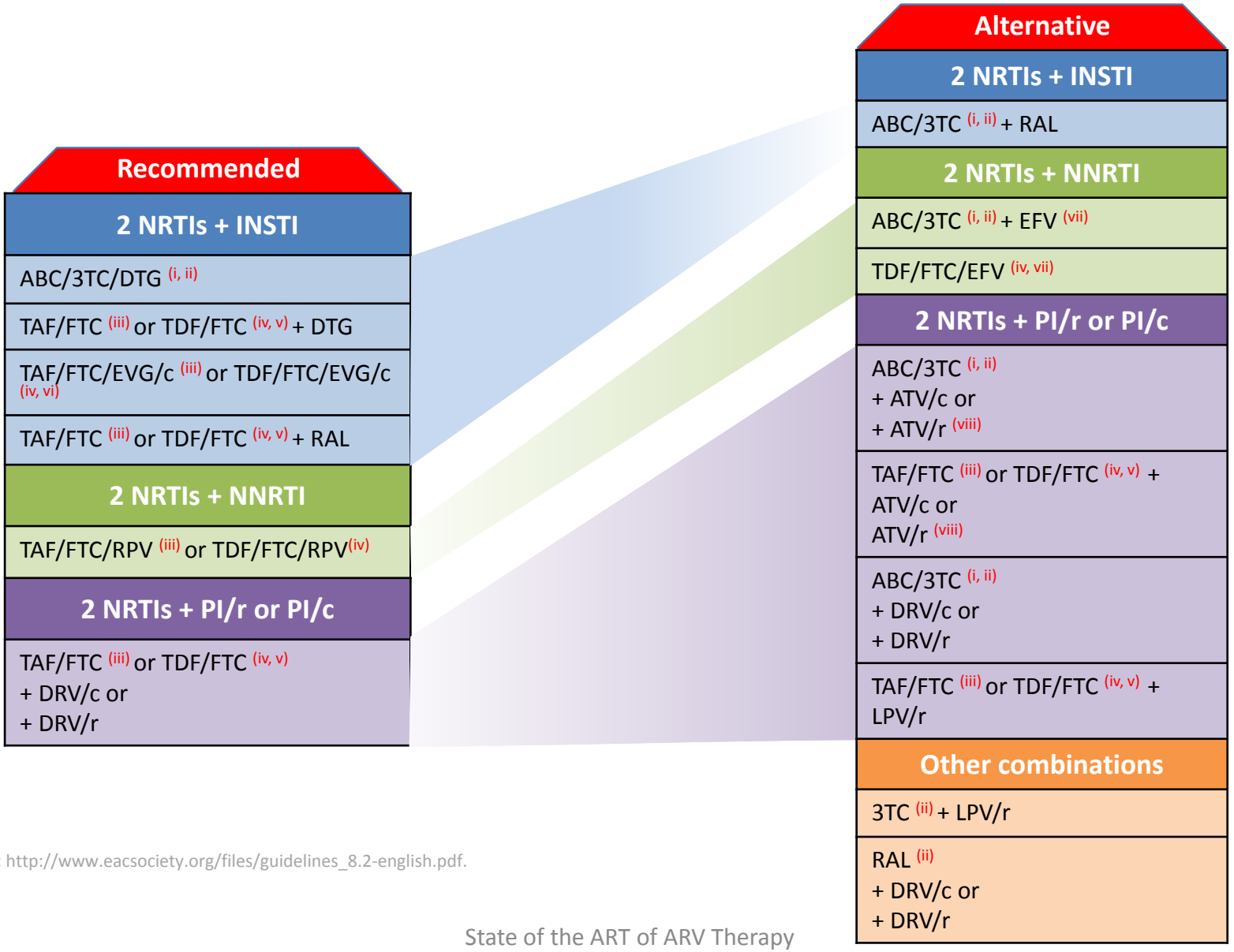


EACS Guidelines



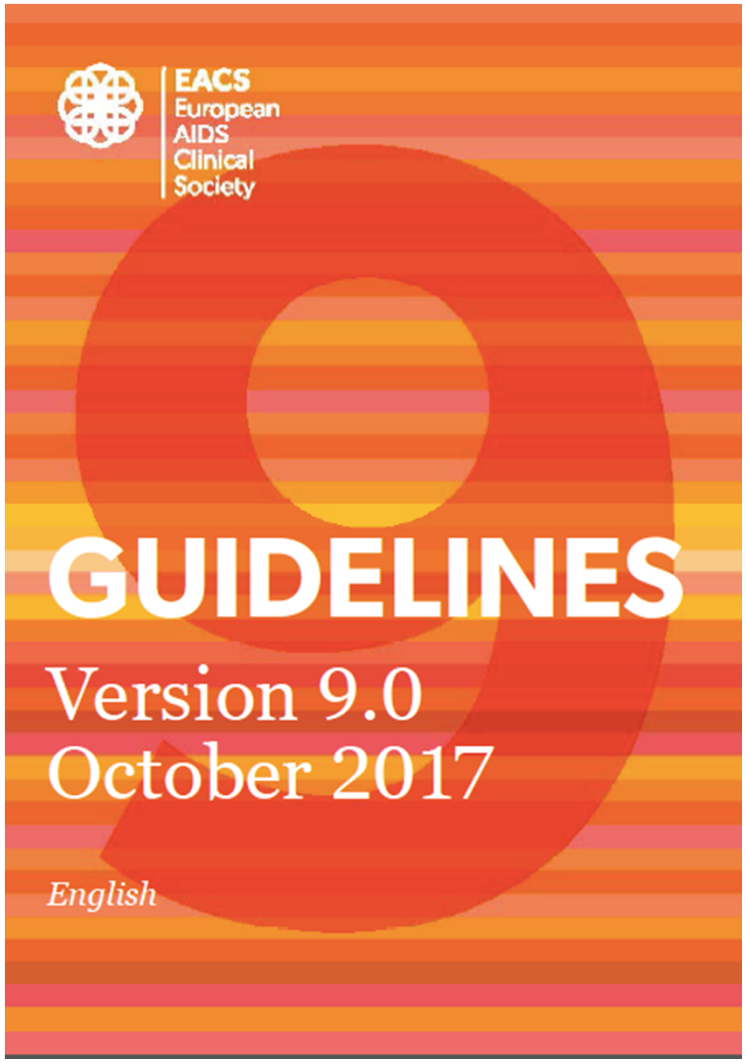
http://www.eacsociety.org/files/guidelines_8.2-english.pdf.

EACS Guidelines



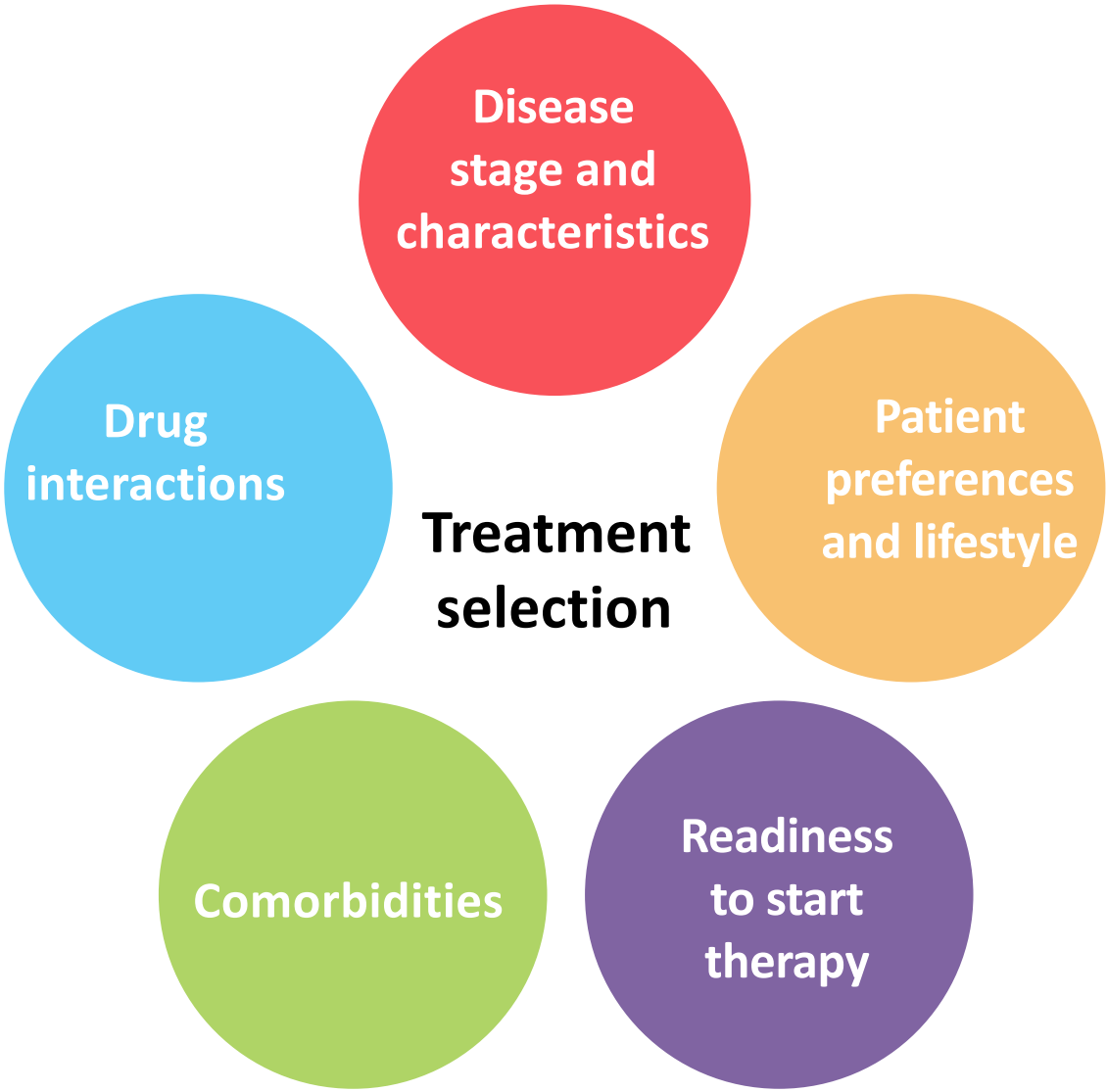
Source: http://www.eacsociety.org/files/guidelines_8.2-english.pdf.

EACS Guidelines



http://www.eacsociety.org/files/guidelines_8.2-english.pdf.

Key Factors to Consider When Choosing an Initial Antiretroviral Regimen



NRTIs: Drug Characteristics

	ABC[a]	TDF	TAF	FTC	3TC
Toxicity	• HSR if HLA-B*5701+ • Possible increased risk of CV events • Increased lipids	• Increased risk of renal toxicity • Decreased BMD	• No signature toxicity	• No signature toxicity	• No signature toxicity
Drug interactions	• Almost none relevant	• Increased TDF levels with ritonavir • Decreased ATV levels	• Reduce dose with ritonavir or cobicistat • Rifampicin	• Almost none relevant	• Almost none relevant
Hepatitis B	Not active	Active	Active	Active	Active
Resistance	Low barrier	Low barrier	Low barrier	Low barrier	Low barrier

[a] In the preferred regimen of DTG/ABC/3TC.

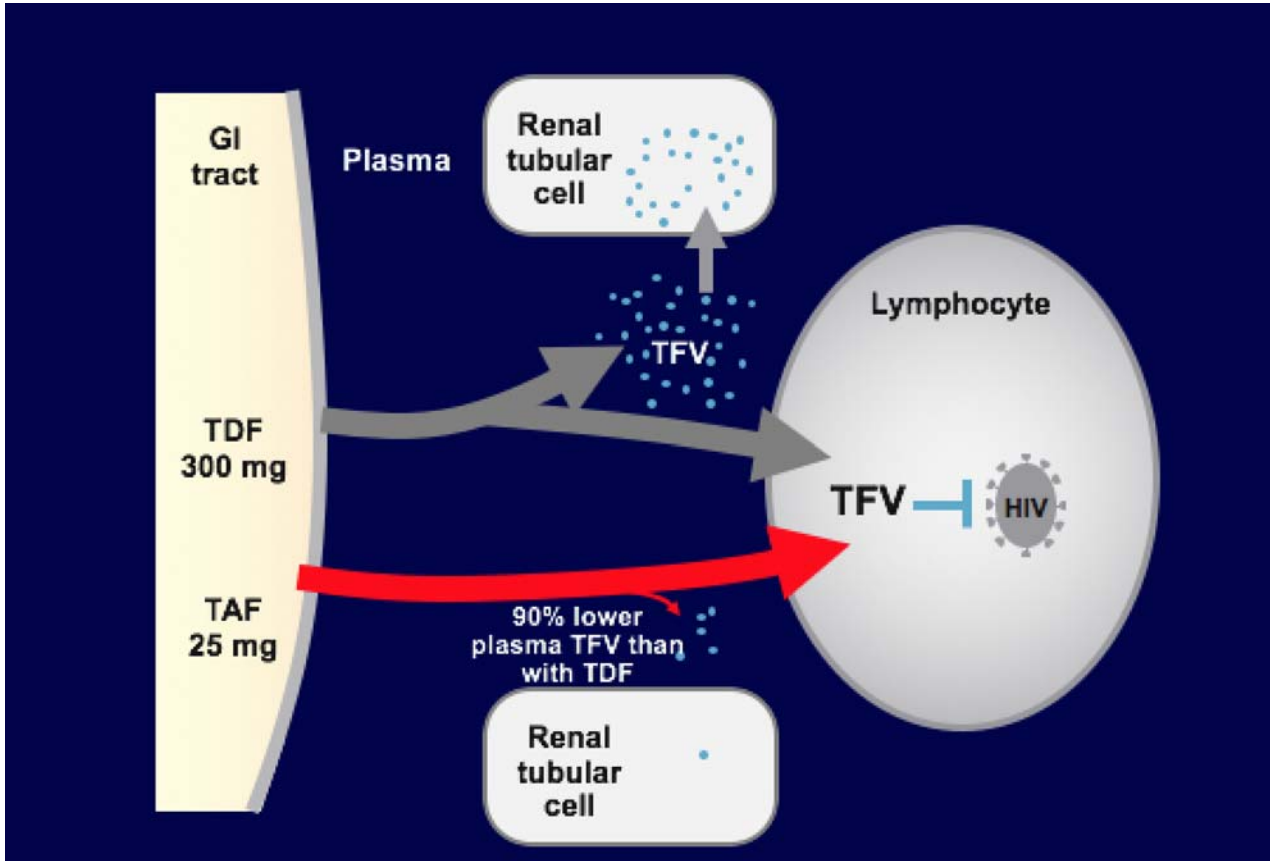
Source: 1. JR Arribas, oral communication, April 2017.
2. EACS. http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Published January 2017. Accessed April 13, 2017.
3. US DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Updated July 2016. Accessed April 13, 2017.
4. Günthard HF et al. JAMA. 2016;316:191-210.
5. WHO. http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf. Published June 2016. Accessed April 13, 2017.

Summary of Key Analyses Addressing Risk of MI With ABC

Study	Study Design	Age, Yrs (Range)	Event (n)	Pts, N	ABC CV Effect	Time on ABC, Mos	Risk of MI (95% CI)
D:A:D[1]	Cohort	40 (35-47)	MI, validated (387)	22,625	Yes	≥ 6	2.04 (1.66-2.51)
D:A:D 2015[2]	Cohort	39 (33-46)	MI (493)	32,663	Yes	Current	1.47 (1.26-1.71)
SMART[3]	RCT	45 (39-51)	MI, validated (19)	2752	Yes	Current	4.3 (1.4-13.0)
STEAL[4]	RCT	45.7 ± 8.8	MI (4)	357	Yes	96	2.79* (1.76-4.43)
QPHID[5]	CC	47 (22-67)	MI (125)	7053	Yes	Any	1.79 (1.16-2.76)
Danish[6]	Cohort	39 (33-47)	MI (67)	2952	Yes	> 6	2.00 (1.07-3.76)
VA (Choi)[7]	Cohort	46	CVD event (501)	10,931	Yes	Recent	1.64 (0.88-3.08)
Swiss[8]	Cohort	NR	CVD event (365)	11,856	Yes	Recent	4.06† (2.24-7.34)
MAGNIFICENT[9]	CC	50 (22-85.5)	CVD event (571)	1875	Yes	Current	1.56 (1.17-2.07)
NA-ACCORD[10]	Cohort	NR	MI, validated (301)	16,733	Yes	Recent	1.33
FHDH[11]	CC	47 (41-54)	MI (289)	74,958	No	< 12/recent	1.27‡ (0.64-2.49)
ALLRT/ACTG[12]	Cohort	37 (26-51)	MI (36)	5056	No	72	0.6 (0.3-1.4)
VA[13]	Cohort	46	MI (278)	19,424	No	Per 12	1.18 (0.92-1.50)
FDA[14]	MA of RCTs	36-42	MI (46)	9868	No	19	1.02 (0.56-1.84)
NA-ACCORD[10]	Cohort	NR	MI, validated (301)	16,733	No	Recent	1.33

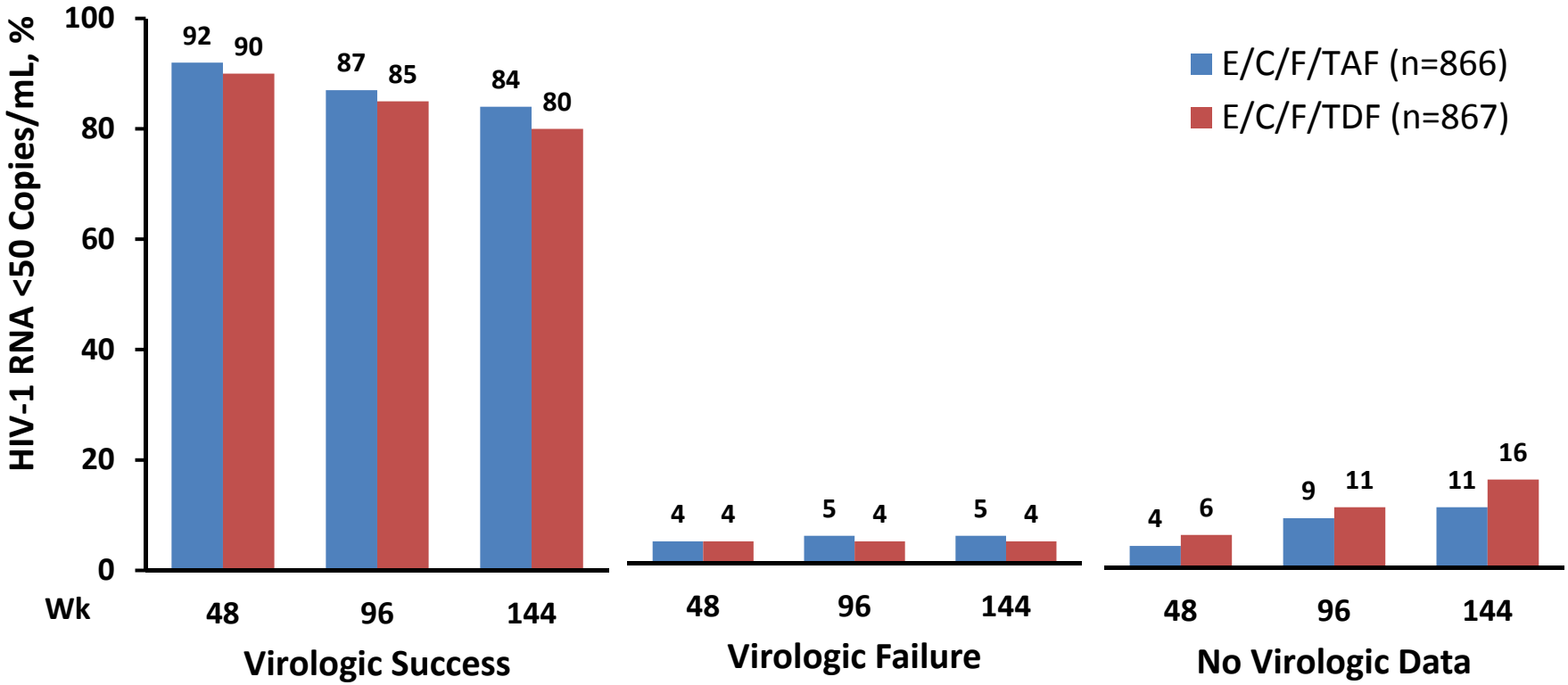
Source: 1. Friis-Moller N, et al. Eur J Cardiovasc Prev Rehabil. 2010;17:491-501.
2. Friis-Moller N, et al. Eur J Prev Cardiol. 2015;[Epub ahead of print].
3. SMART/INSIGHT Study Group. AIDS. 2008;22:F17-F24.
4. Martin A, et al. Clin Infect Dis. 2009;49:1591-1601.
5. Durand M, et al. J Acquir Immune Defic Syndr. 2011;57:245-253.
6. Obel N, et al. HIV Med. 2010;11:130-136.
7. Choi AI, et al. AIDS. 2011;25:1289-1298.
8. Young J, et al. J Acquir Immune Defic Syndr. 2015;69:413-421.
9. Rotger M, et al. Clin Infect Dis. 2013;57:112-121.
10. Palella F, et al. CROI 2015. Abstract 749LB.
11. Lang S, et al. Arch Intern Med. 2010;170:1228-1238.
12. Ribaudo HJ, et al. Clin Infect Dis. 2011;52:929-940.
13. Bedimo RJ, et al. Clin Infect Dis. 2011;53:84-91.
14. Ding X, et al. J Acquir Immune Defic Syndr. 2012;61:441-447.

TAF vs TDF: Mechanism of Action



Source: Arribas JR, et al. CROI 2017. Abstract 453.
Sax PE, et al. Lancet. 2015;385:2606-2615.
Wohl D, et al. J Acquir Immune Defic Syndr. 2016;72:58-64

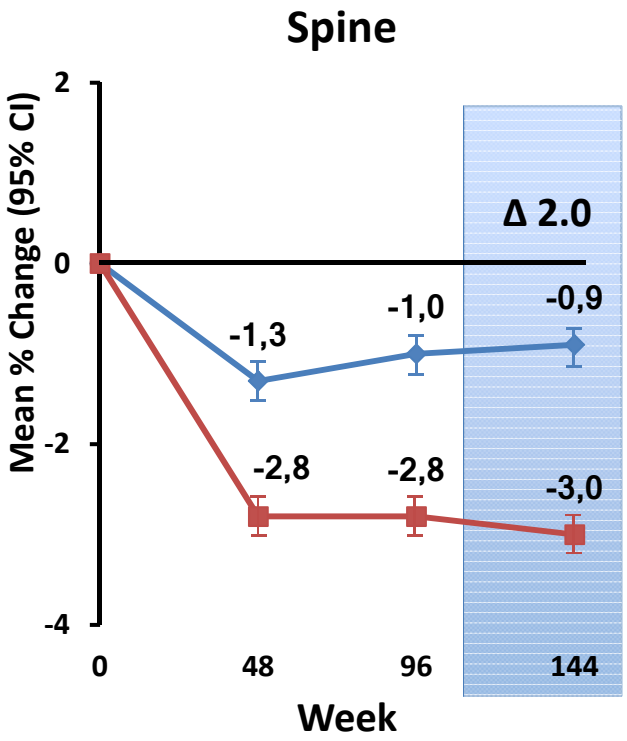
TAF vs TDF (FTC/EVG/c) in Naïves: 144 Weeks



At Week 144, E/C/F/TAF was superior to E/C/F/TDF in efficacy difference at both <50 copies/mL; 4.2% (95% CI 0.6%, 7.8%; p=0.02) and <20 copies/mL: 5.4% (95% CI 1.5%, 9.2%; p=0.01)

Source: Arribas J, et al. 24th CROI; Seattle, WA; February 13-16, 2017. Abst. 453.

TAF vs TDF (FTC/EVG/c) in Naïves: Bone and Renal Endpoints



Renal AE D/C, n	E/C/F/TAF n=866	E/C/F/TDF n=867
Total	**0**	**12**
Proximal renal tubulopathy	0	4
Increased creatinine/decreased eFGR	0	3
Renal failure	0	2
Nephropathy	0	1
Proteinuria	0	1
Bladder spasm	0	1

6 patients discontinued due to decrease in BMD

Source: Arribas J, et al. 24th CROI; Seattle, WA; February 13-16, 2017. Abst. 453.

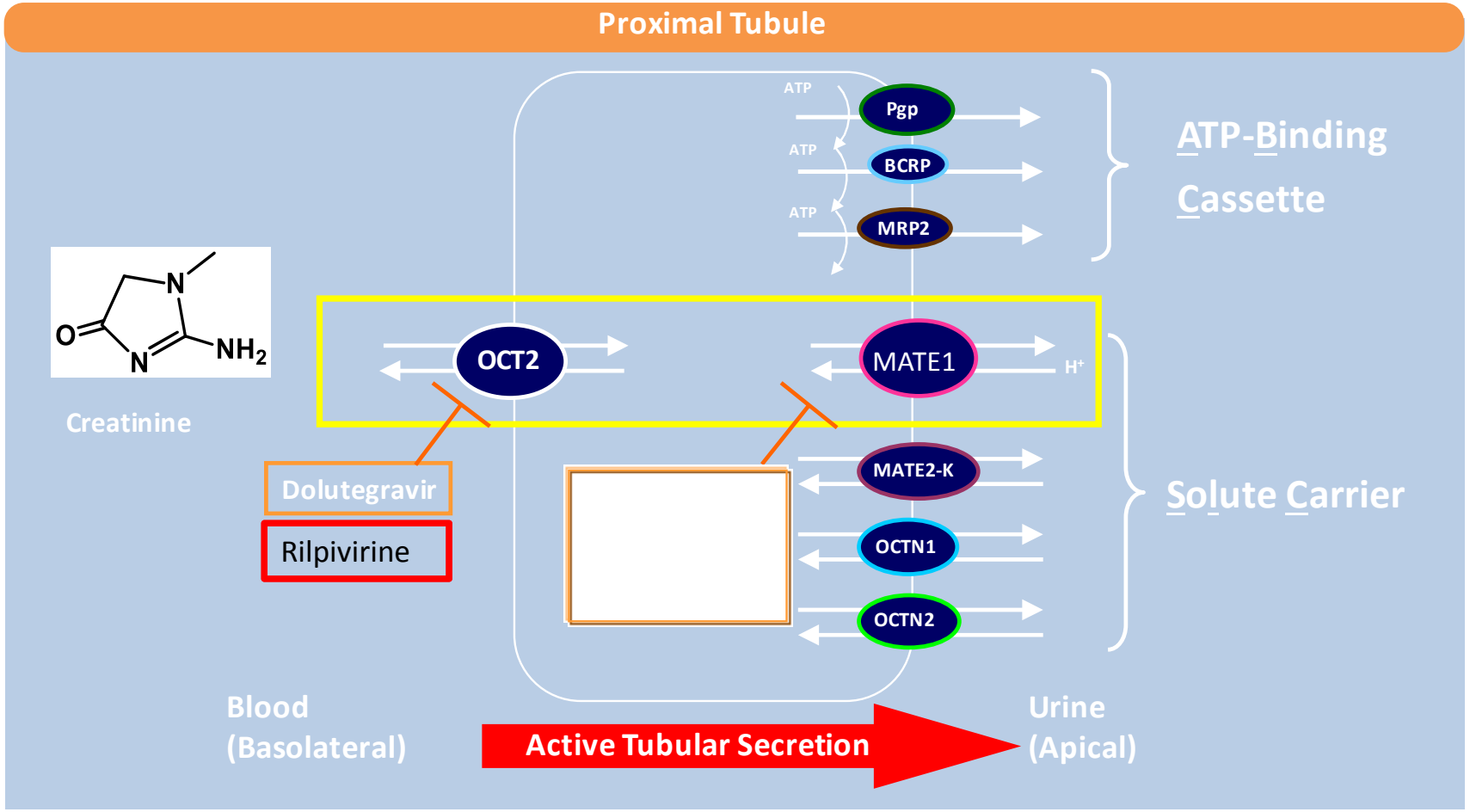
NNRTIs: Drug Characteristics

Preferred regimens	**RPV**/TAF/FTC[a] **RPV**/TDF/FTC[a]	**EFV**/TDF/3TC[b] **EFV**/TDF/FTC[b]
Toxicity	• No signature toxicity • Decreased eGFR	• Increased risk of CNS AEs • Possible increased risk of suicidality • Increased lipids
Drug interactions	• Do not co-administer with omeprazole or rifampicin • Take with food	• Potent CYP3A4 inducer • Multiple interactions
Resistance	• Low genetic barrier	• Low genetic barrier

[a] EACS guidelines.[1] [b] WHO guidelines.[2]

Source: 1. EACS. http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Published January 2017. Accessed April 13, 2017.
2. WHO. http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf. Published June 2016. Accessed April 13, 2017.

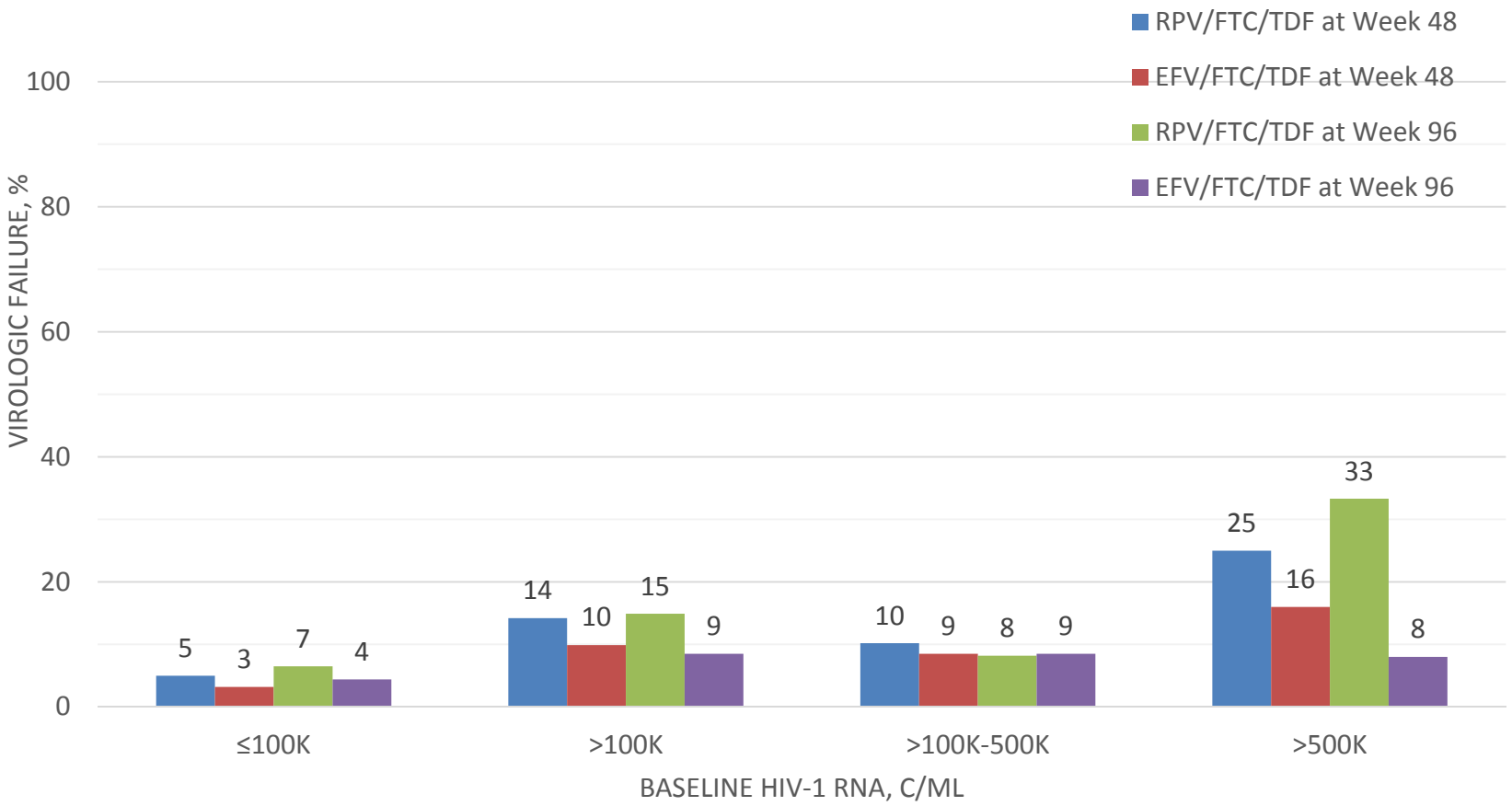
Model for Inhibition of the Active Tubular Secretion of Creatinine



Source: Lepist, XX et al. ICAAC 2011; Chicago.

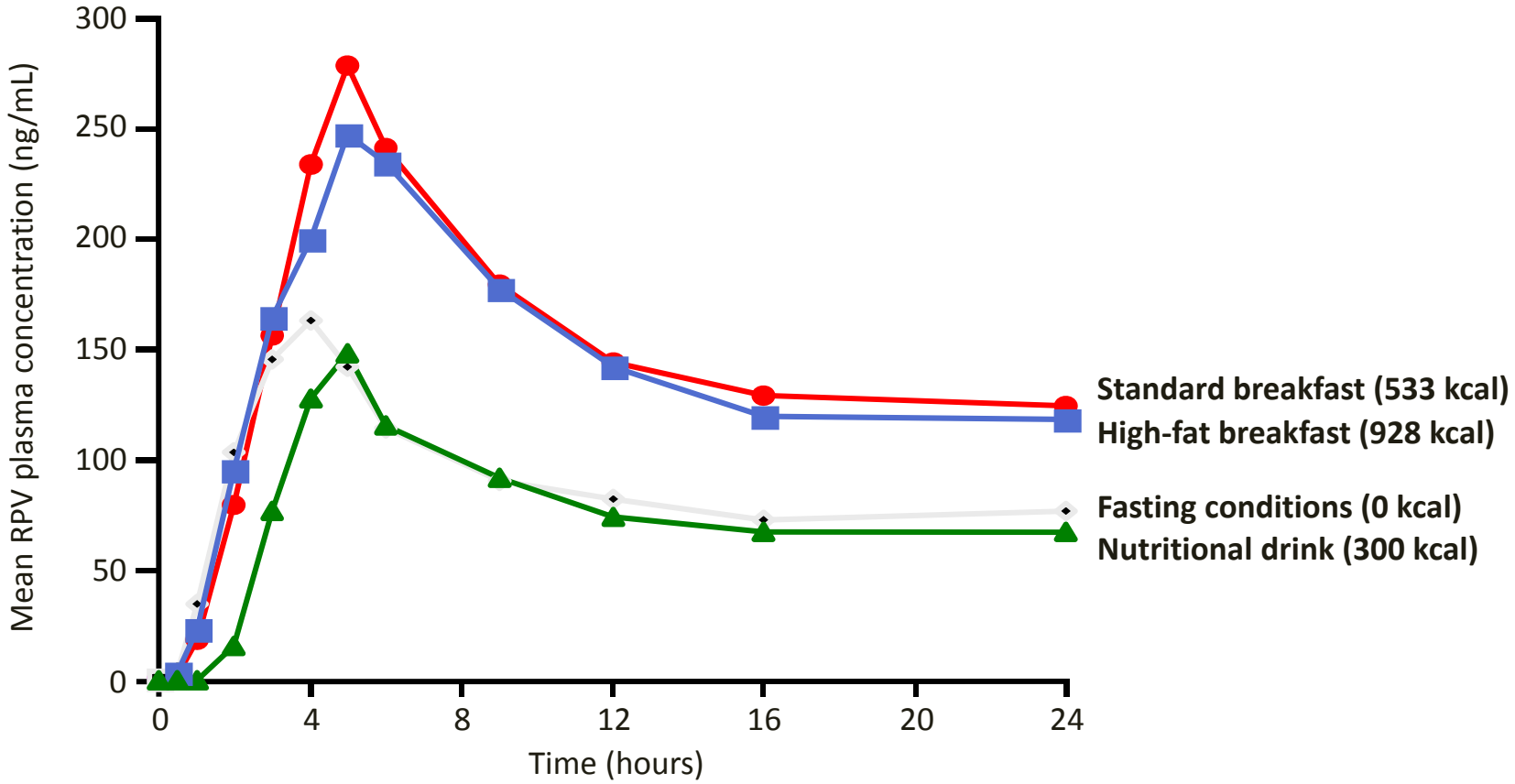
STaR: Virologic Failure at Weeks 48 & 96 Stratified by Baseline HIV-1 RNA - Snapshot Analysis

Virologic failure definition: Week 48 or 96 HIV-1 RNA > 50 c/mL, or discontinued study drug due to lack of efficacy or other reasons and last available HIV-1 RNA >50 c/mL



* Post hoc analyses; analyses for non-inferiority only pre-specified for ≤100,000 c/mL and >100,000 c/mL

Effect of Food Type on Mean RPV PK Profile



Taking RPV with food increases RPV exposure by 57% compared to fasting.
RPV AUC was similar when administered after a high-fat or standard breakfast.

Neuropsychiatric AEs associated with EFV

- NPS AEs usually begin during the first one or two days of therapy and generally resolve after 2–4 weeks[1]
- Effects have been shown to be dose-dependent[2,3]
- Polymorphisms in CYP2B6 affect steady-state plasma concentrations of efavirenz[4]

Most frequently reported NPS[1]

- Dizziness (8.5%)*
- Headache (5.7%)*
- Fatigue (5.5%)*
- Abnormal dreaming
- Impaired concentration
- Insomnia
- Drowsiness

Uncommon NPS[1]

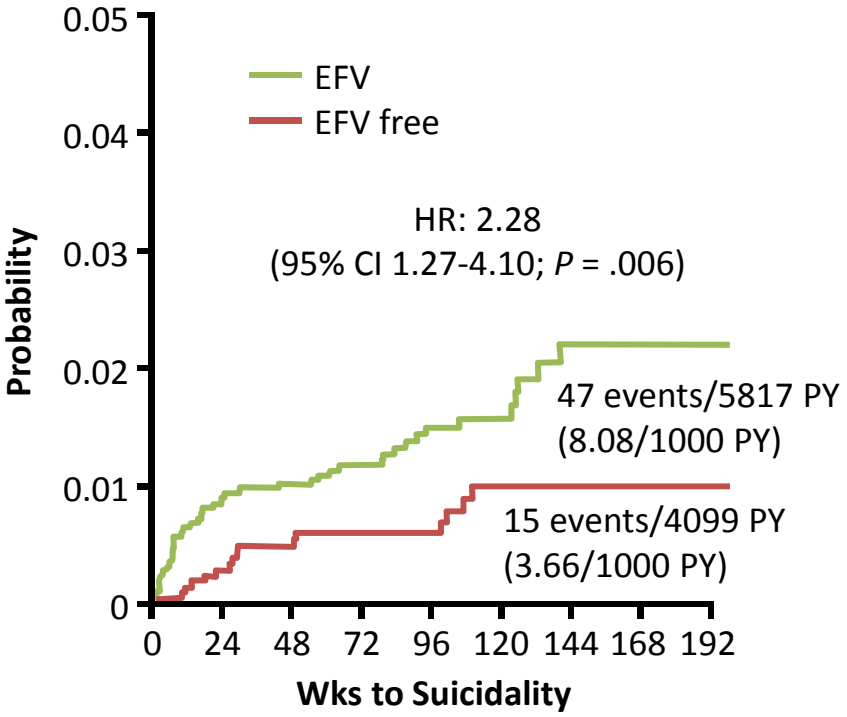
- Seizures
- Abnormal thinking
- Disturbances of coordination and balance

*Percentages refer to treatment-related undesirable effects of at least moderate severity reported in at least 5% of patients in a subset of 1,800 patients

Source: 1. Sustiva SmPC October 2008. http://emc.medicines.org.uk; last accessed 16 March 2009;
2. Gutierrez F, et al., CID 2005;41:1648–53; 3. Gutierrez-Valencia ?, et al. Ann Intern Med 2009;151:149–156;
4. Rotger M, www.HIVpharmacogenomics.org

Risk of Suicidality in Pts Treated With EFV-Containing Regimens in ACTG Trials

- Treatment with EFV associated with increased risk of suicidality
  - Absolute risk is small



- Trend toward higher incidence of attempted or completed suicide with EFV use (HR: 2.58; 95% CI: 0.94-7.06; *P* = .065)
- EFV also associated with increased risk of death from substance abuse, homicide, or accident

Multivariable Analysis of Factors Associated With Suicidality in ACTG Clinical Trials

Variable	HR (95% CI)	P Value
Randomly assigned EFV	2.08 (1.16-3.75)	.014
Weight category, kg ▪< 60 vs ≥ 80 ▪60-79 vs ≥ 80	 2.69 (1.25-5.79) 1.21 (0.64-2.29)	.022
Hx IDU	2.26 (1.15-4.46)	.019
Psychiatric Hx or psychoactive Rx	4.07 (2.32-7.13)	< .001

Source: Mollan K, et al. Ann Intern Med. 2014;161:1-10

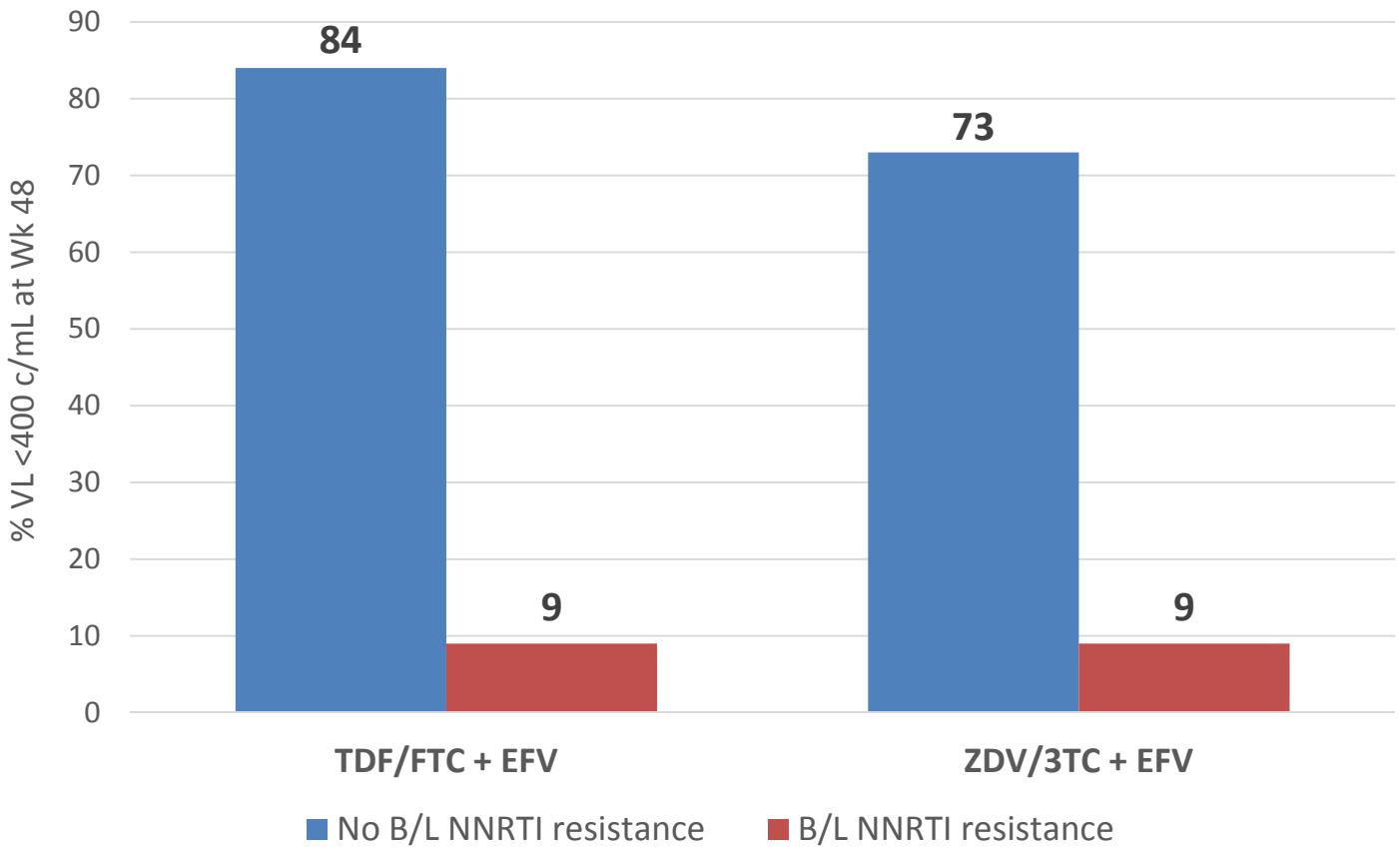
SINGLE: Common Adverse Events at Wk 144

AE in > 5% of Pts in Either Arm, %	DTG + ABC/3TC QD (n = 414)		EFV/TDF/FTC QD (n = 419)	
	Wk 96	Δ Wk 144	Wk 96	Δ Wk144
Any	44	+1	67	+1.2
Dizziness	7	+0	33	+0.2
Abnormal dreams	7	+0	16	+0.2
Nausea	11	+0.2	12	+0
Insomnia	10	+0	6	+0.7
Diarrhea	6	+0	8	+0
Fatigue	7	+0	7	+0
Headache	6	+0	7	+0
Rash	< 1	+0	8	+0

- Overall low rate of elevated liver chemistries in both treatment groups
- AEs leading to d/c occurred in 4% (DTG) vs 14% (EFV)

Source: Pappa K, et al. ICAAC 2014. Abstract H-647a.

Baseline resistance and response



Source: Gallant JE, et al. N Engl J Med. 2006;354:251-260

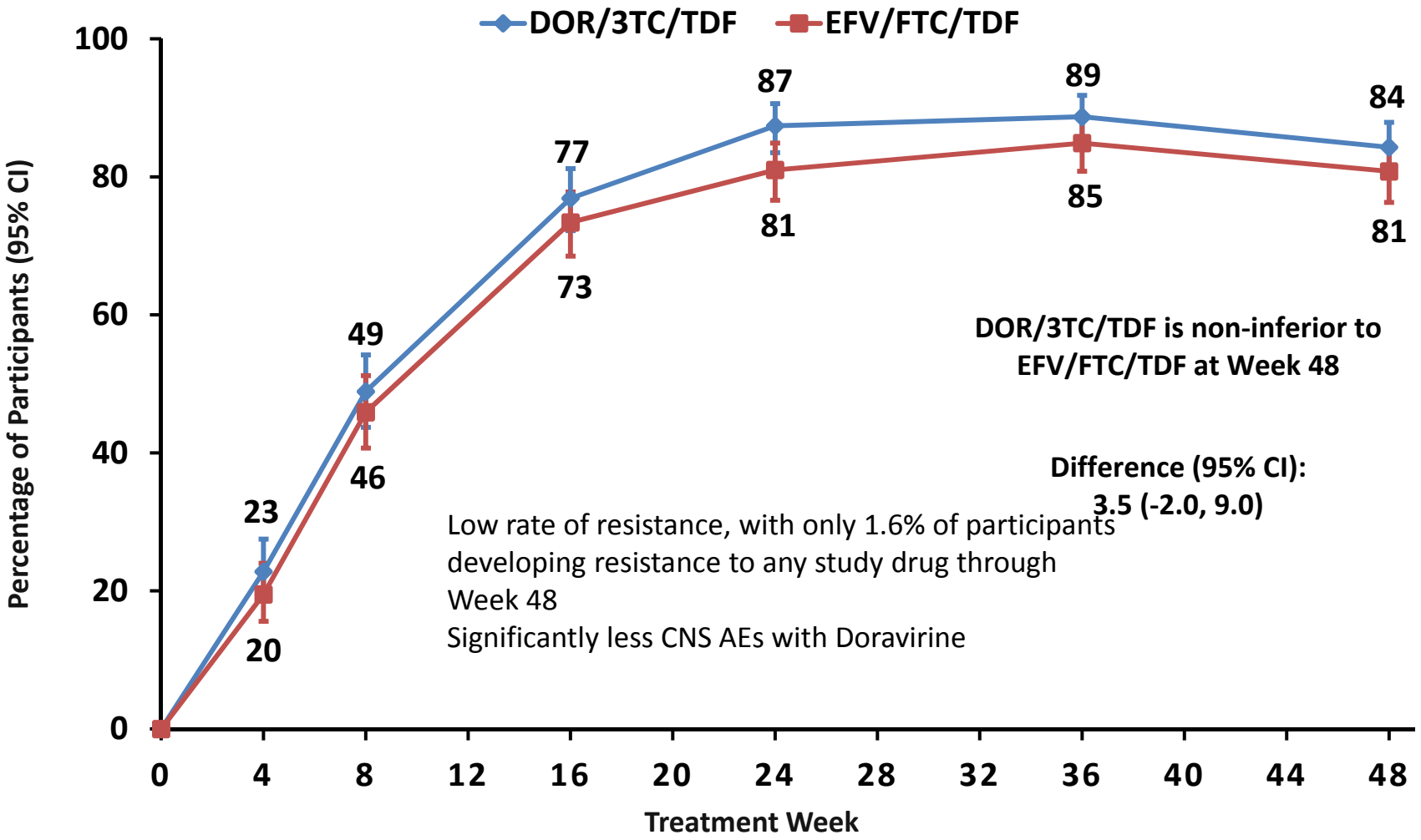
NNRTI-Based Regimens: Patient Factors to Consider[1-3]

	RPV	EFV
High viral loads and/or low CD4+ cell counts	✗[a]	✓
Preference for a single pill and/or once-daily dosing	✓	✓
Polypharmacy	✗	✗
Co-administration with omeprazole	✗	✓
High risk for CNS AEs	✓	✗
Co-administration with rifampicin (for TB)	✗	✓

[a] Only if CD4+ count >200 cells/µL and viral load <100,000 copies/mL.

Source: 1. JR Arribas, oral communication, April 2017.
2. EACS. http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Published January 2017. Accessed April 13, 2017.
3. WHO. http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf. Published June 2016. Accessed April 13, 2017.

DORAVIRINE. DRIVE-AHEAD STUDY



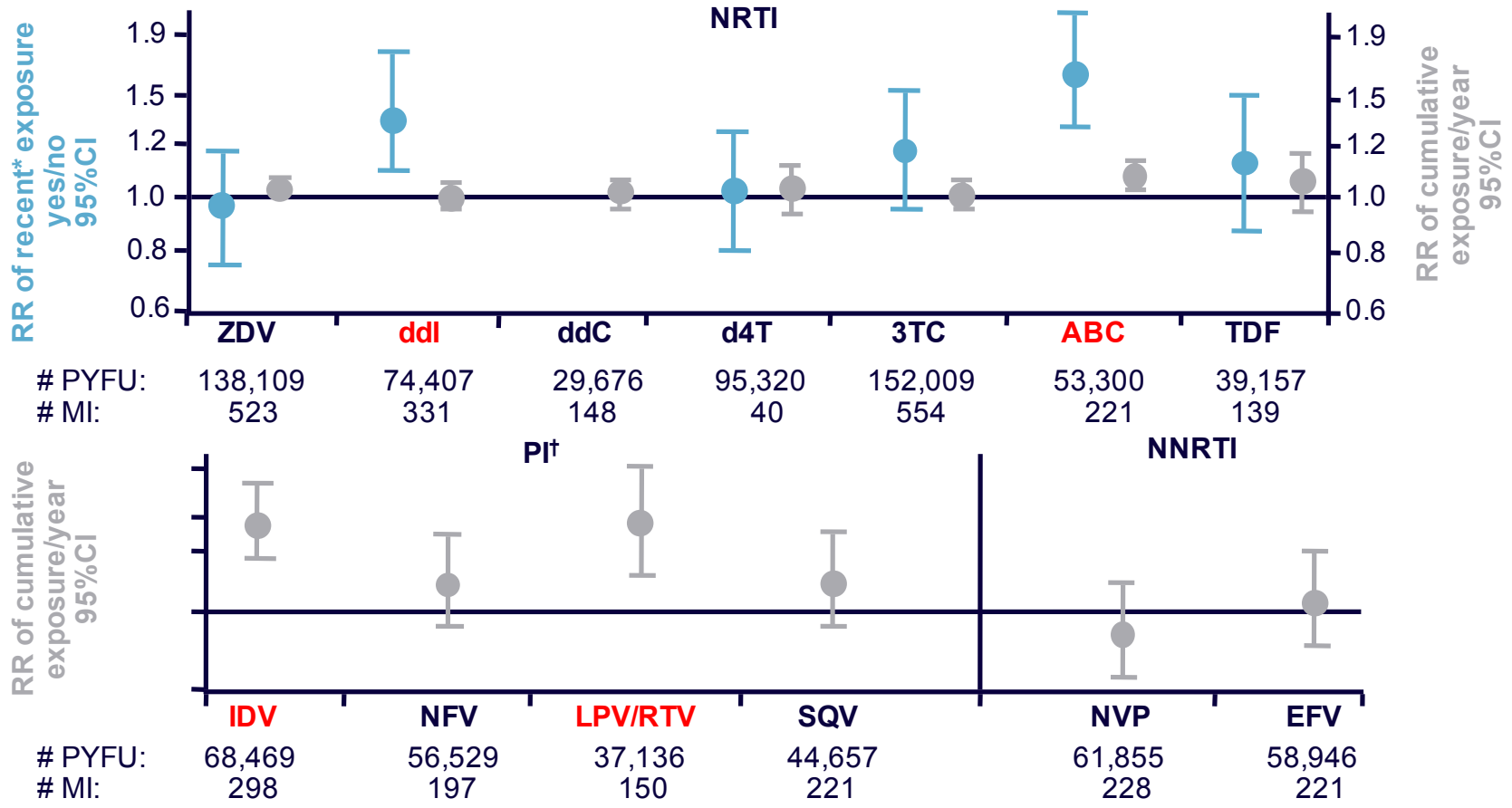
Source: Squires K, et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. TUAB0104LB.

PIs: Drug Characteristics

Preferred regimens	**DRV**/r + TAF/FTC[a,b] **DRV**/c + TAF/FTC[a] **DRV**/r + TDF/FTC[a,b] **DRV**/c + TDF/FTC[a]
Toxicity	**Increased risk of CV events?[1]**
Drug interactions	**CYP3A4 and tubular tranporters interactions with ritonavir/cobicistat**
Resistance	**High genetic barrier**

[a] EACS guidelines.[2] [b] US DHHS guidelines.[3]

D:A:D: Recent and/or Cumulative Antiretroviral Exposure and Risk of MI

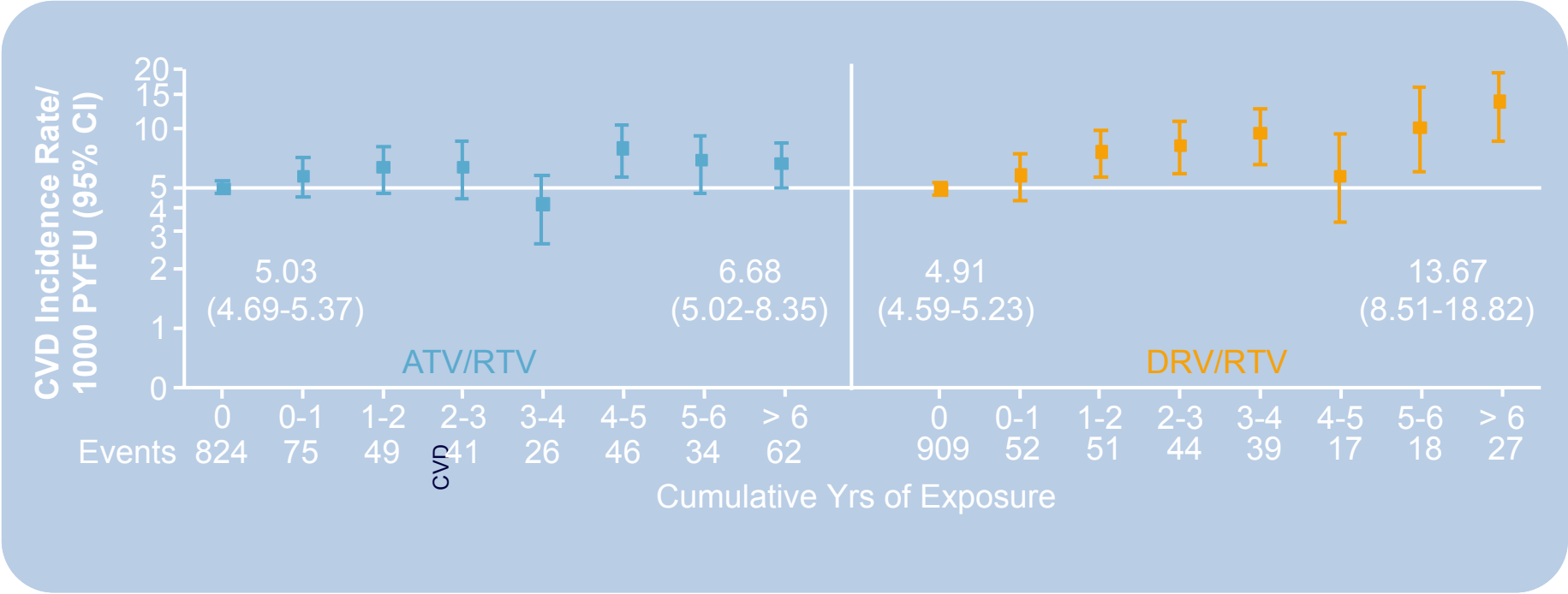


*Current or within last 6 months. †Approximate test for heterogeneity: *P* = 0.02

Source: Lundgren JD, et al. CROI 2009. Abstract 44LB.

D:A:D: Cumulative Exposure to DRV/RTV Increases CVD Risk

- Prospective analysis of pts followed from 2009 to earliest CVD, last visit + 6 mos, or February 2016 (N = 35,711)



- Cumulative exposure to DRV/RTV, but not ATV/RTV, associated with increased CVD risk in multivariate analysis: 59% risk increase per 5-yrs' DRV/RTV

Source: Ryom L, et al. CROI 2017. Abstract 128LB.

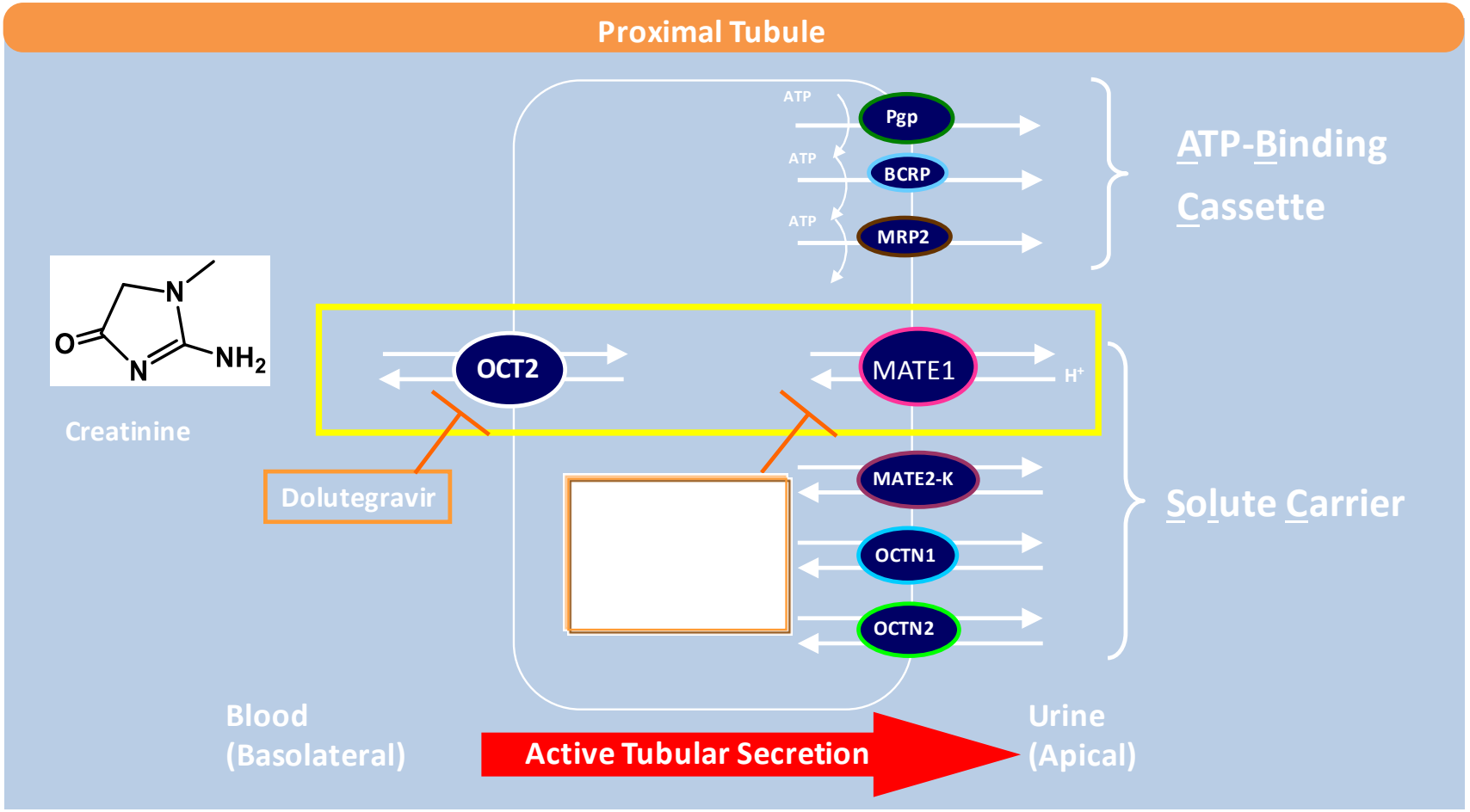
Potential Interactions With COBI and RTV

Both inhibit CYP3A and P-gp; RTV also an inducer of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or UGT1A1

Agents That Have Interactions With RTV and/or COBI	
▪ Analgesics	▪ Contraceptives
▪ Antiarrhythmics	▪ Digoxin
▪ Anticancer agents	▪ Glucocorticoids
▪ Anticoagulants	▪ Methamphetamine
▪ Anticonvulsants	▪ PDE5 inhibitors
▪ Antidepressants	▪ Rifabutin
▪ Beta-blockers	▪ Sedatives/hypnotics
▪ Clarithromycin	▪ Statins

Source: Marzolini C, et al. J Antimicrob Chemother. 2016;71:1755-1758.
COBI [package insert]. RTV [package insert].

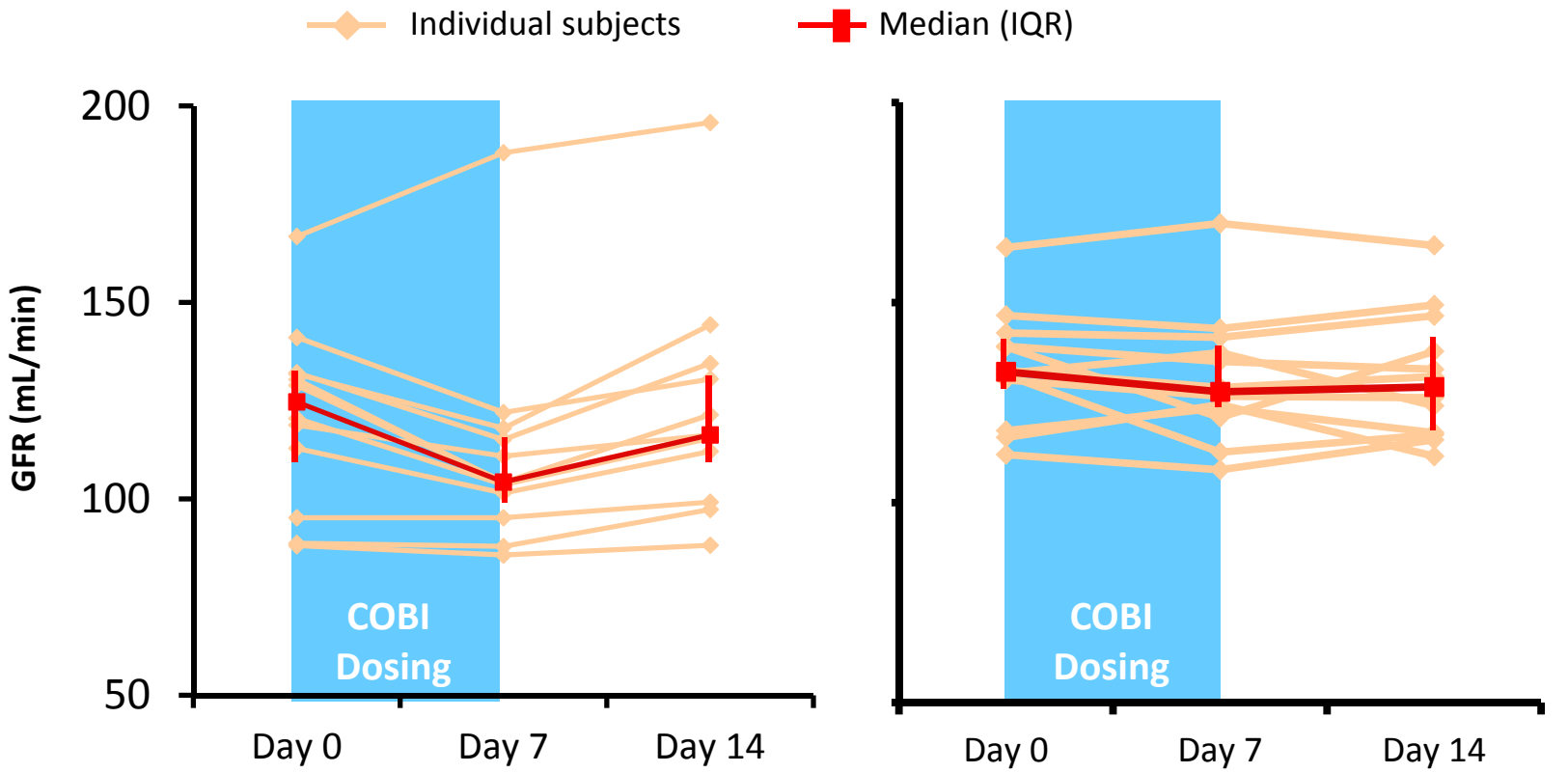
Model for Inhibition of the Active Tubular Secretion of Creatinine



Source: Lepist, XX et al. ICAAC 2011; Chicago.

Cobicistat: GFR Changes in Normal Renal Function

COBI Affected Estimated GFR_{CG} But Not Actual GFR



Estimated GFR (eGFR) (Cockcroft-Gault)

Actual GFR (aGFR) (iohexol)

COBI affects eGFR but not aGFR

Source: Adapted from German P, et al. JAIDS 2012.

Emergent PI Resistance Rare: Rationale for PI Use in Pts at Risk for Poor Adherence

Trial Name	F/U, Wks	Treatment Arm	Virologic Failure, n (%)	Treatment-Emergent Primary Mutations, n
CASTLE[1]	96	ATV/RTV + TDF/FTC (n = 440)	28 (6)	**1 (PI)**, 7 (NRTI)
		LPV/RTV + TDF/FTC (n = 443)	29 (7)	10 (NRTI)
ACTG A5202[2]	96	ATV/RTV + NRTIs (n = 928)	140 (15)	1 (NNRTI), **1 (PI)**, 16 (NRTI)
		EFV + NRTIs (n = 929)	129 (14)	68 (NNRTI), 36 (NRTI)
GS-103[3]	144	ATV/RTV + TDF/FTC (n = 355)	NR (7)	2 (NRTI)
		EVG/COBI/TDF/FTC (n = 353)	NR (8)	8 (INSTI), 8 (NRTI)
ARTEMIS[4]	96	DRV/RTV + TDF/FTC (n = 343)	NR (12)	2 (NRTI)
		LPV/RTV + TDF/FTC (n = 346)	NR (17)	5 (NRTI)
FLAMINGO[5]	96	DRV/RTV + NRTIs (n = 242)	4 (2)	0
		DTG + NRTIs (n = 242)	2 (< 1)	0
ACTG A5257[6]	96	ATV/RTV + TDF/FTC (n = 605)	95 (16)	1 (INSTI), 8 (NRTI)
		DRV/RTV + TDF/FTC (n = 601)	115 (19)	1 (INSTI), 3 (NRTI)
		RAL + TDF/FTC (n = 603)	85 (14)	1 (INSTI), 7 (NRTI), 10 (INSTI + NRTI)

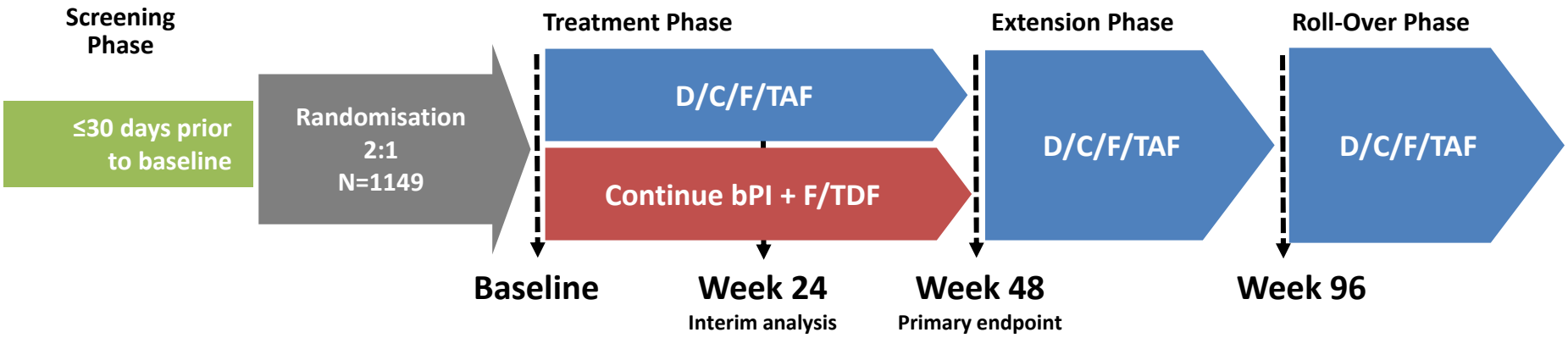
Source: 1. Molina JM, et al. J Acquir Immune Defic Syndr. 2010;53:323-332.
2. Daar ES, et al. Ann Intern Med. 2011;154:445-456.
3. Clumeck N, et al. J Acquir Immune Defic Syndr. 2014;65:e121-e124.
4. Mills AM, et al. AIDS. 2009;23:1679-1688.
5. Molina JM, et al. Lancet HIV. 2015;2:e127-e136
6. Lennox JL, et al. Ann Intern Med. 2014;161:461-471.

PI-Based Regimens: Patient Factors to Consider[1-3]

	DRV/r	DRV/c	ATV/b
High viral loads and/or low CD4+ cell counts	✓	✓	✓
Suboptimal adherence	✓	✓	✓
Preference for a single pill and/or once-daily dosing	✗	✓	✓
Rrisk of renal impairment[a]	✓	✓	✗
Co-administration with omeprazole[b]	✓	✓	✗
Increased CV risk	✗	?	✓

Source: 1. JR Arribas, oral communication, April 2017.
2. EACS. http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Published January 2017. Accessed April 13, 2017.
3. US DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Updated July 2016. Accessed April 13, 2017.

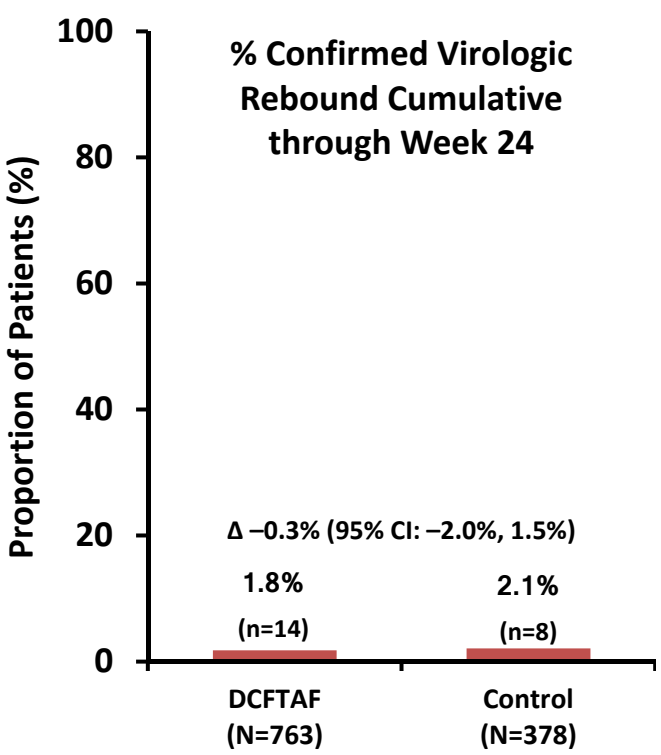
D/C/F/TAF. EMERALD: Study Design

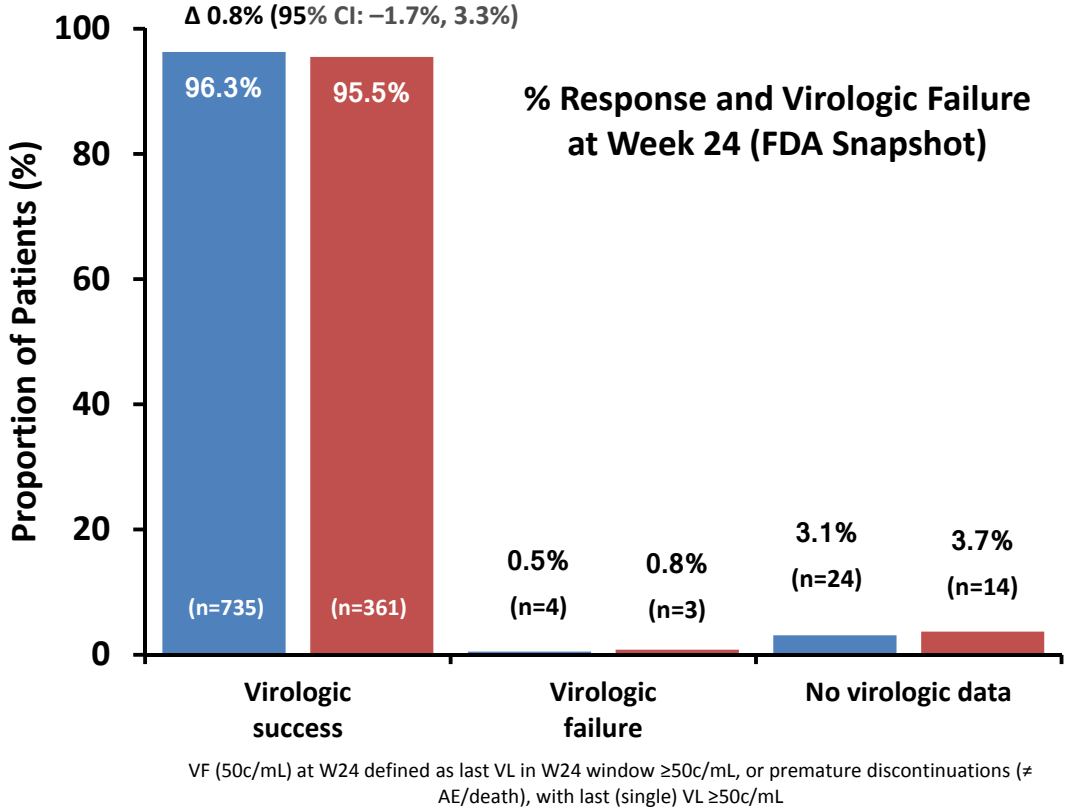


- Previous ART VF allowed
- Absence of history of VF on DRV, and if historical genotype available, absence of DRV RAMs
- Viral load (VL) <50 c/mL for ≥2 months before screening; one VL ≥50 and <200 c/mL within 12 months prior to screening allowed
- Creatinine clearance (by Cockcroft-Gault) ≥50 mL/min

Source: Molina JM, et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. TUAB0101.

EMERALD Study: Efficacy





VF (50c/mL) at W24 defined as last VL in W24 window ≥50c/mL, or premature discontinuations (≠ AE/death), with last (single) VL ≥50c/mL

- Most rebounders (10/14 D/C/F/TAF and 5/8 control) resuppressed (<50c/mL) by Week 24
- No confirmed rebounds ≥200 c/mL
- No discontinuations for VF
- No DRV/primary PI or NRTI RAMs were observed (2 patients genotyped in each group

Source: Molina JM, et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. TUAB0101.

ISTIs: Drug Characteristics

Preferred regimens	**DTG**/ABC/3TC[a,b,c] **DTG** + TAF/FTC[a,b,c] **DTG** + TDF/FTC[a,b]	**EVG**/c/TAF/FTC[a,b,c] **EVG**/c/TDF/FTC[a,b]	**RAL** + TAF/FTC[a,b,c] **RAL** + TDF/FTC[a,b]
Toxicity	Possible increased CNS AE	Nausea at initiation	No signature toxicity
Drug interactions	Compounds containing calcium, aluminium, or iron (eg, antacids/laxatives)		
	Metformin	CYP3A4/tubular transporters interactions	-
Resistance	High genetic barrier	•Low genetic barrier •Cross resistance with RAL	•Low genetic barrier •Cross resistance with EVG

Source: 1. EACS. http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Published January 2017. Accessed April 13, 2017.
2. US DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Updated July 2016. Accessed April 13, 2017.
3. Günthard HF et al. JAMA. 2016;316:191-210.

Genetic Barrier to Resistance: Recommended INSTI-Based Regimens

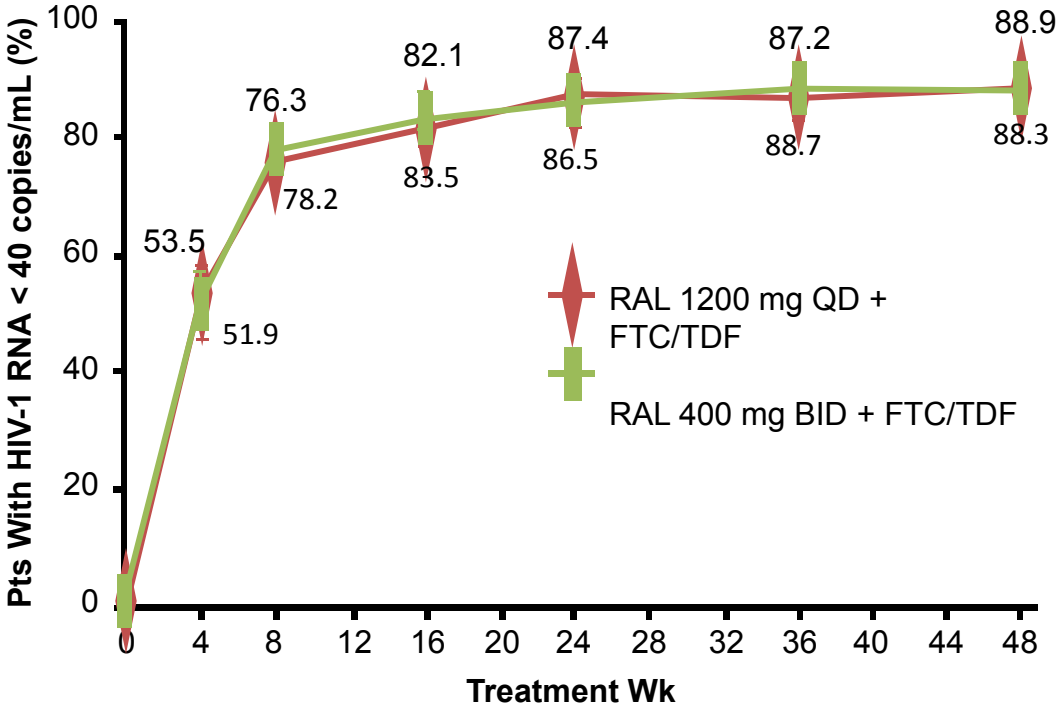
Regimen	Barrier to Resistance	Comments	Mutations Highly Reducing Susceptibility*[2]
DTG/3TC/ABC DTG + FTC/TDF or FTC/TAF	High	▪ Resistance to DTG emerges slowly; multiple mutations required for resistance[1,2] ▪ DTG + FTC/TDF or FTC/TAF recommended by DHHS if must treat before resistance results available[1]	--
EVG/COBI/FTC/TDF EVG/COBI/FTC/TAF	Low/Moderate	▪ Few EVG mutations required for resistance[2]	T66I/A/K E92Q S147G Q148H/R/K N155H
RAL + FTC/TDF or FTC/TAF	Low/Moderate	▪ Few RAL mutations required for resistance[2]	Y143C/R/H Q148H/R/K N155H

*NRTI backbone mutations not shown in column: **FTC/TDF**, M184V/I, K65R, T69ins; **ABC/3TC**, M184V/I, K65R, L74V/I, T69ins, Y115F, Q151M.

Source: 1. DHHS Guidelines. July 2016.
2. Clutter DS, et al. Infect Genet Evol. 2016;[Epub ahead of print].

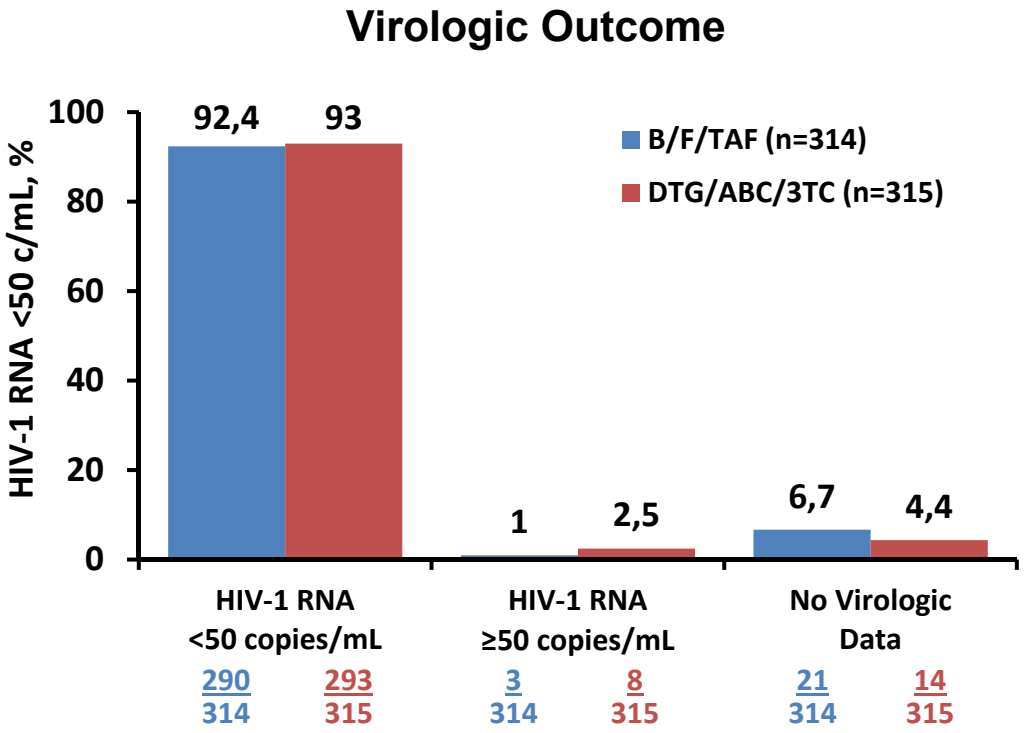
ONCEMRK: RAL 1200 mg QD Noninferior to 400 mg BID at Wk 48 in ART-Naive Pts

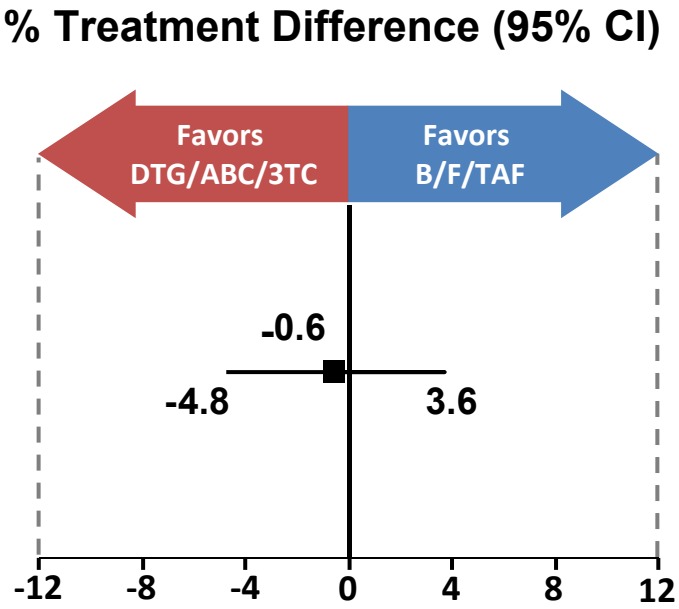
- Multinational, double-blind phase III trial in ART-naive pts with HIV-1 RNA ≥ 1000 c/mL
  - Pts randomized to RAL 1200 mg QD vs RAL 400 mg BID + FTC/TDF (N = 802)
- Noninferior Wk 48 HIV-1 RNA < 40 copies/mL in pts with BL HIV-1 RNA > 100,000 copies/mL
  - RAL QD: 86.7%; RAL BID: 83.8% (Δ 2.9; 95% CI: -6.5 to 14.1)
- RAL QD associated with overall safety profile similar to RAL BID



Source: Cahn P, et al. AIDS 2016. Abstract FRAB0103LB.

GS-1489 STUDY (BICTEGRAVIR): Results





- BF-TAF non-inferior to DTG/ABC/3TC
  - No resistance in either study arm
- Lipids not significantly different
- No drug-related renal events
- Significantly less nausea and minor adverse events with BF-TAF

Source: Gallant J, et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. MOAB0105LB.

INSTI-Based Regimens: Patient Factors to Consider[1-4]

	DTG/BIC?	EVG/c	RAL
High viral loads	✓	✓	✓
Previous failure on EVG/c or RAL	✓ ?	✗	✗
Without baseline genotyping and/or suboptimal adherence	✓	✗	✗
Polypharmacy	✓	✗[a]	✓
Preference for a single pill and/or once-daily dosing	✓	✓	✗

[a] Potential drug interactions with EVG/c should be reviewed.

Source: 1. JR Arribas, oral communication, April 2017.
2. EACS. http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Published January 2017. Accessed April 13, 2017.
3. US DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Updated July 2016. Accessed April 13, 2017.
4. Günthard HF et al. JAMA. 2016;316:191-210.

Impact of Medical Comorbidities on Treatment Selection[1-3]

	Options	Consider Avoiding	Avoid
CKD[a]	ABC, TAF, NRTI-sparing regimens (DRV/r + RAL, LPV/r + 3TC)	TDF (especially in combination with boosted PIs)	TDF/FTC/c/EVG
Osteoporosis	ABC, TAF	TDF	-
Psychiatric disease[b]	-	EFV	-
High cardiac risk	-	ABC, DRV/r, LPV/r	-
Hyperlipidaemia	ABC, EFV, and boosted PIs increase lipid levels		
Hepatitis	**HBV**: TDF/FTC or 3TC or TAF/FTC	**HCV**: Careful review of interactions with DAAs	
Tuberculosis	If rifampicin is used then EFV, RAL, or DTG preferred; others contraindicated		

[a] eGFR <60 mL/min. [b] Also including HIV-associated dementia and methadone programmes.

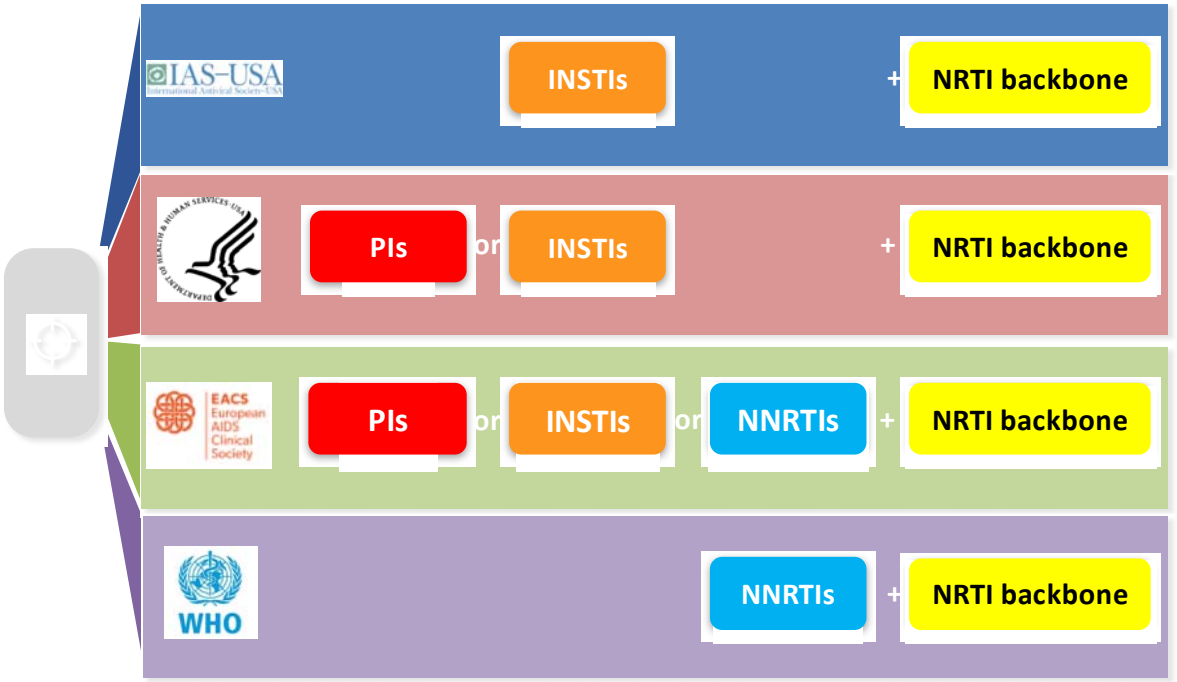
Source: 1. EACS. http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Published January 2017. Accessed April 13, 2017.
2. US DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Updated July 2016. Accessed April 13, 2017.
3. Günthard HF et al. JAMA. 2016;316:191-210.

Individual Patient Characteristics to Consider When Choosing Treatment[1-3]

Other medications	**Regimens without PK interactions, or with manageable PK interactions**
Daily routine / patient preferences	**Regimens that account for patient lifestyle and preferences**
Low adherence (perceived or actual)	**Drugs with high genetic barrier preferred (PIs, DTG); regimens that facilitate adherence**
Lack of baseline genotype testing	**Boosted PIs or DTG**

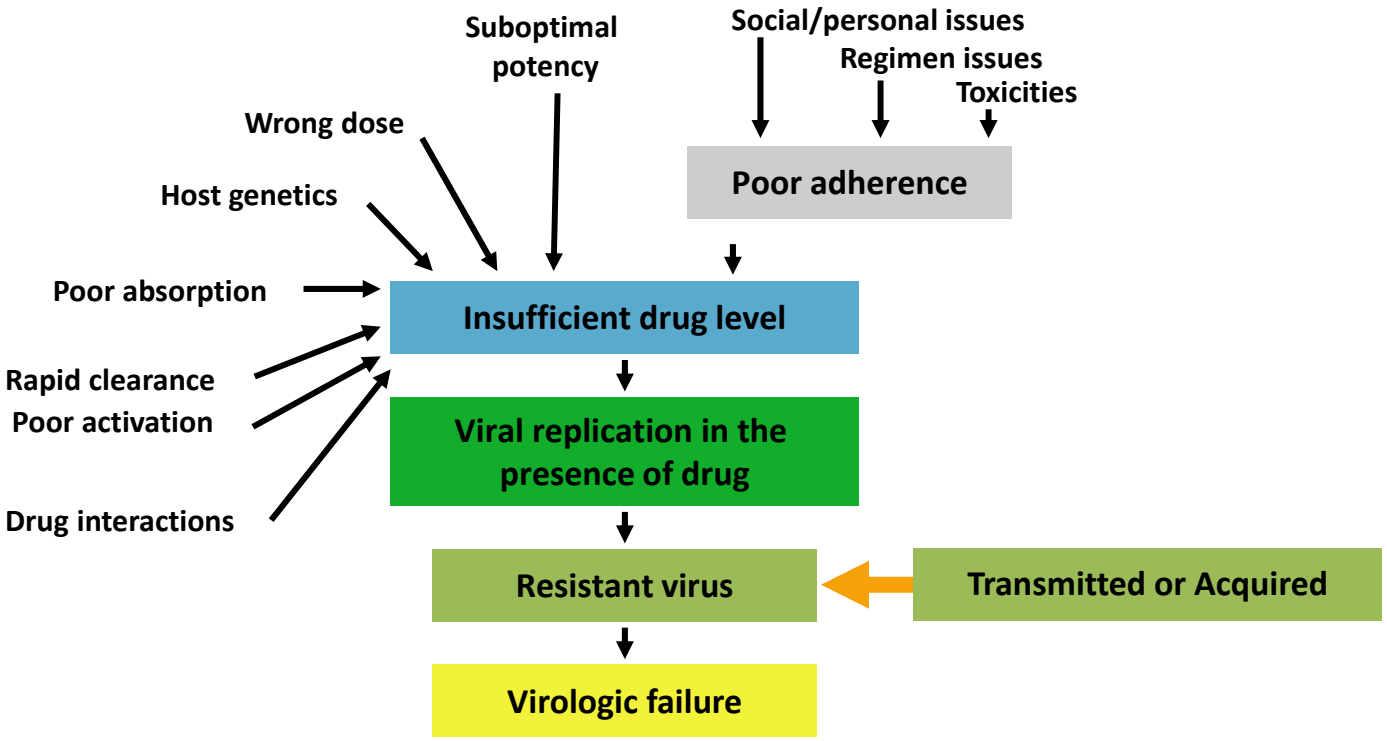
Source: 1. EACS. http://www.eacsociety.org/files/guidelines_8.2-english.pdf. Published January 2017. Accessed April 13, 2017.
2. US DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Updated July 2016. Accessed April 13, 2017.
3. Günthard HF et al. JAMA. 2016;316:191-210.

Summary: Optimising ART for Treatment-Naïve Patients With HIV



Factors to Consider for Treatment Selection
Comorbidities
Drug interactions
Disease stage/characteristics
Patient preferences/lifestyle
Readiness to start therapy
Benefit/risk profile of regimen

Causes of Treatment Failure



DHHS Guidelines.

DHHS: Management of First-line Failure

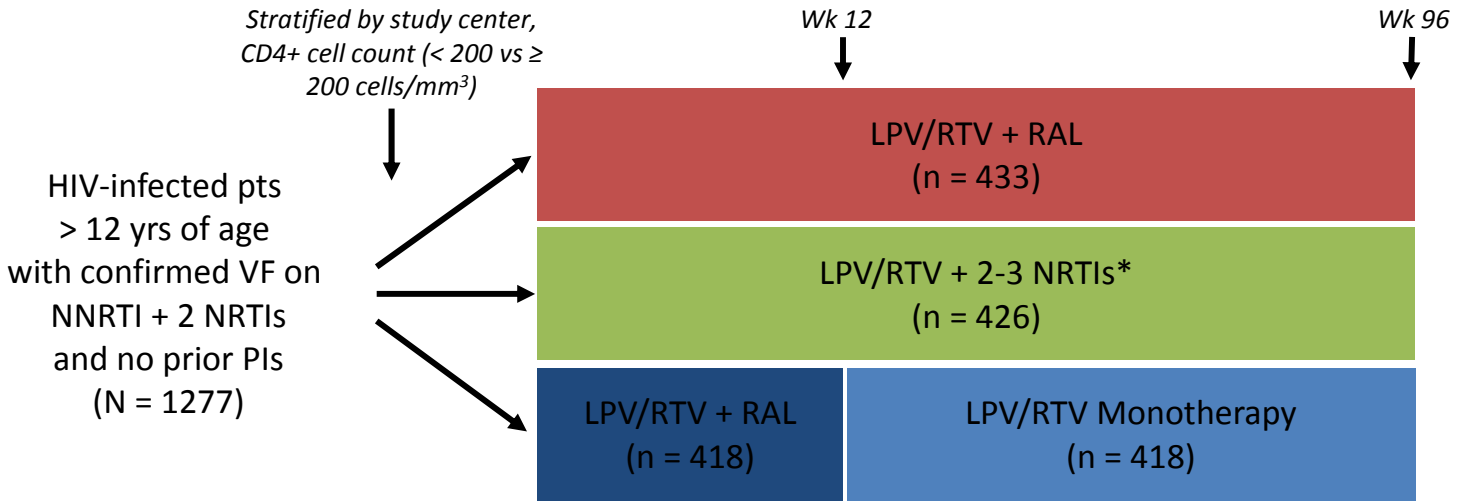
Failing Regimen (+ NRTIs)	
▪ Boosted PI:	Enforce adherence Modify for convenience or toxicity
▪ NNRTI:	Boosted PI + NRTIs Boosted PI + INSTI
▪ INSTI:	Boosted PI + NRTIs Boosted PI + active INSTI*

*If RAL or EVG resistance detected, DTG + boosted PI can be used if DTG susceptible.

DHHS Guidelines.

EARNEST: Second-line LPV/RTV ± RAL or 2-3 NRTIs in PI-Naive Pts

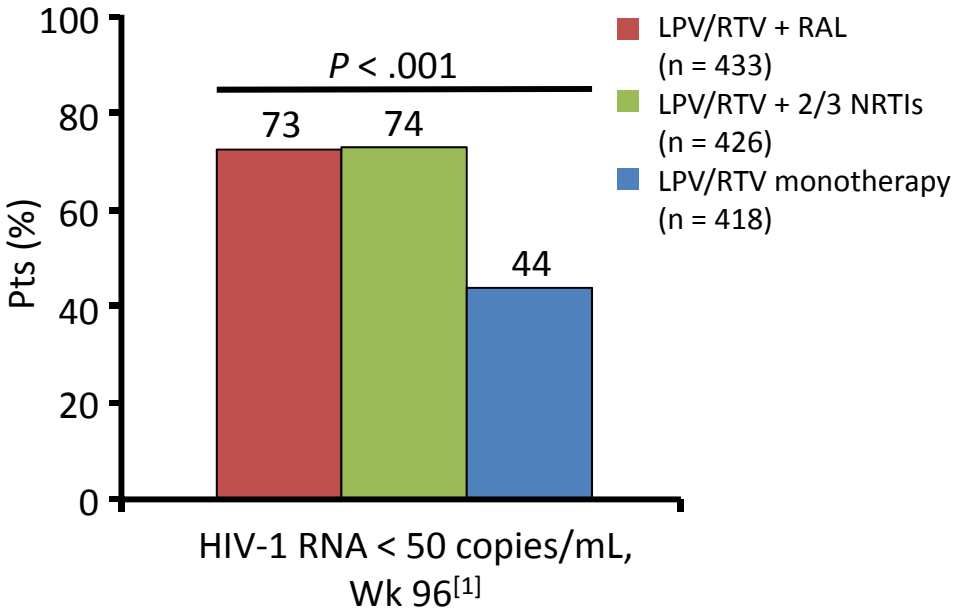
- Randomized, open-label, multicenter phase III trial in sub-Saharan Africa

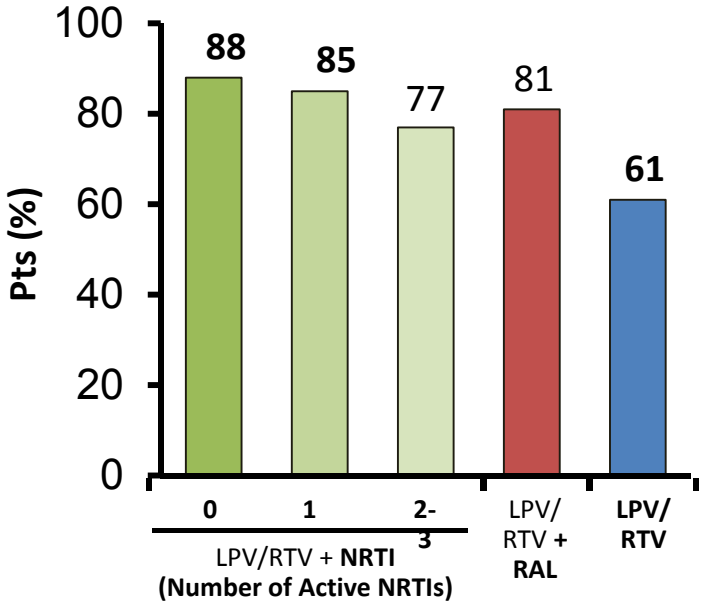


LPV/RTV 400/100 mg and RAL 400 mg dosed BID.
*New or recycled NRTIs chosen WITHOUT genotype by clinician.

Paton NI, et al. N Engl J Med. 2014;371:234-247.

EARNEST: Boosted PI + RAL Comparable to Boosted PI + NRTIs



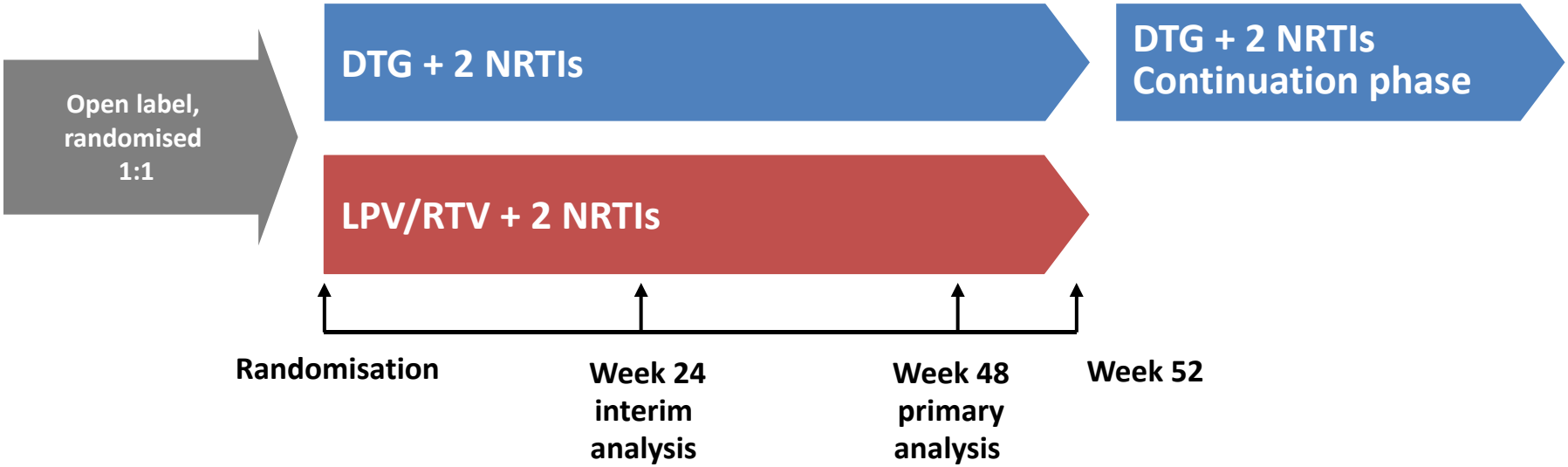


- SECOND-LINE[3] and ACTG 5273[4,5] showed similar results

Source:
1. Paton NI, et al. N Engl J Med. 2014;371:234-247.
2. Paton, NI, et al. ACHA 2015.
3. Amin J, et al. PLoS One. 2015;10:e0118228.
4. La Rosa AM, et al. CROI 2016. Abstract 30.
5. La Rosa AM, et al. Lancet HIV. 2016;3:e247-e258.

Dawning: Study DESIGN

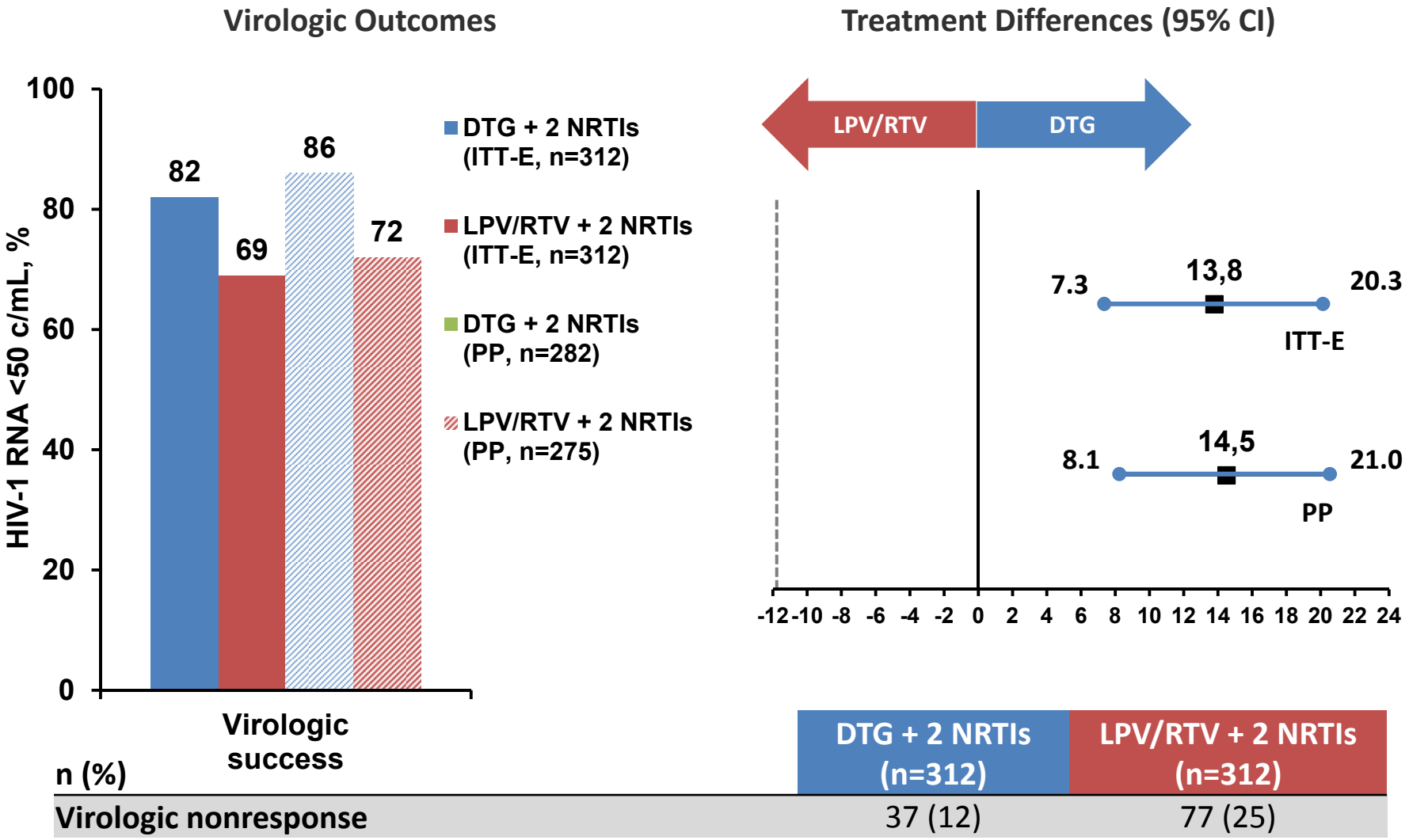
Open-Label Randomised Noninferiority Phase IIIb Study



- Key eligibility criteria: on first-line 2 NRTIs + NNRTI regimen for ≥6 months, failing virologically (HIV-1 RNA ≥400 c/mL on 2 occasions); no primary viral resistance to PIs or INSTIs
- Stratification: by HIV-1 RNA (≤ or >100,000 copies/mL), number of fully active NRTIs in the investigator-selected study background regimen (2 or <2)
- Primary endpoint: proportion with HIV-1 RNA <50 c/mL at Week 48 using the FDA snapshot algorithm (12% noninferiority margin)

Source:Aboud M , et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. TUAB0105LB.

Dawning Study: Efficacy at Week 24



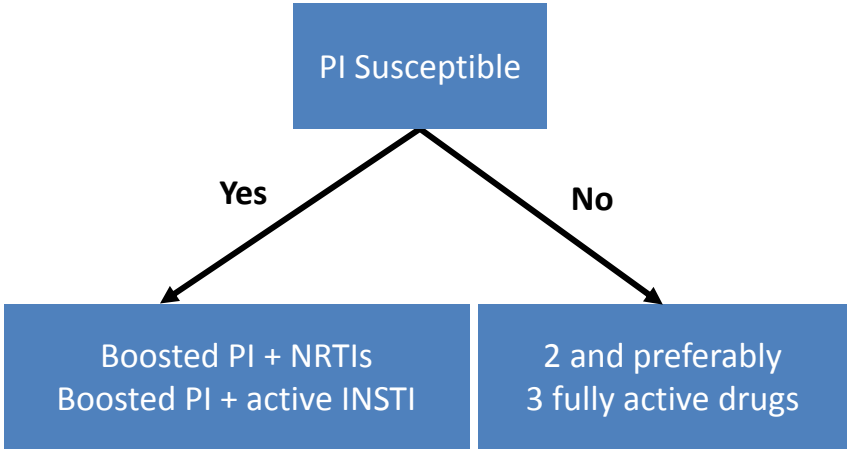
n (%)	DTG + 2 NRTIs (n=312)	LPV/RTV + 2 NRTIs (n=312)
Virologic nonresponse	37 (12)	77 (25)

CI, confidence interval; ITT-E, intent-to-treat exposed; PP, per protocol.

Source:Aboud M , et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. TUAB0105LB.

DHHS: Management of ART Failure Second-line ARV Failure

- Goal: fully suppressive ARV regimen
- If susceptible to boosted PI, regimen can be similar to those for first-line failure
- If not susceptible to boosted PI, new regimen should have a minimum of 2 (preferably 3) fully active drugs if possible
  - Susceptibility to drug predicted from pt treatment history, prior and current resistance and tropism testing, MoA of novel drug class
- Not recommended to add single agent to failing regimen due to risk of developing resistance to entire regimen



DHHS Guidelines.

Emerging Investigational Agents for Pts With MDR HIV

Investigational Agent	Phase	MoA
Fostemsavir[1-3]	III	Prodrug; when metabolized binds gp120 to prevent CD4+ cell attachment, entry
Ibalizumab[4,5]	III	Humanized anti-CD4 receptor mAb
PRO 140[6]	IIb/III	Humanized anti-CCR5 mAb

1. Lalezari JP, et al. Lancet HIV. 2015;2:e427-437.
2. Granados-Reyes ER, et al. HIV Glasgow 2016. Abstract O335A.
3. ClinicalTrials.gov. NCT02362503.
4. Lewis S, et al. CROI 2017. Abstract 449LB.
5. Lin H-H, et al. CROI 2017. Abstract 438.
6. Lalezari J, et al. CROI 2017. Abstract 437

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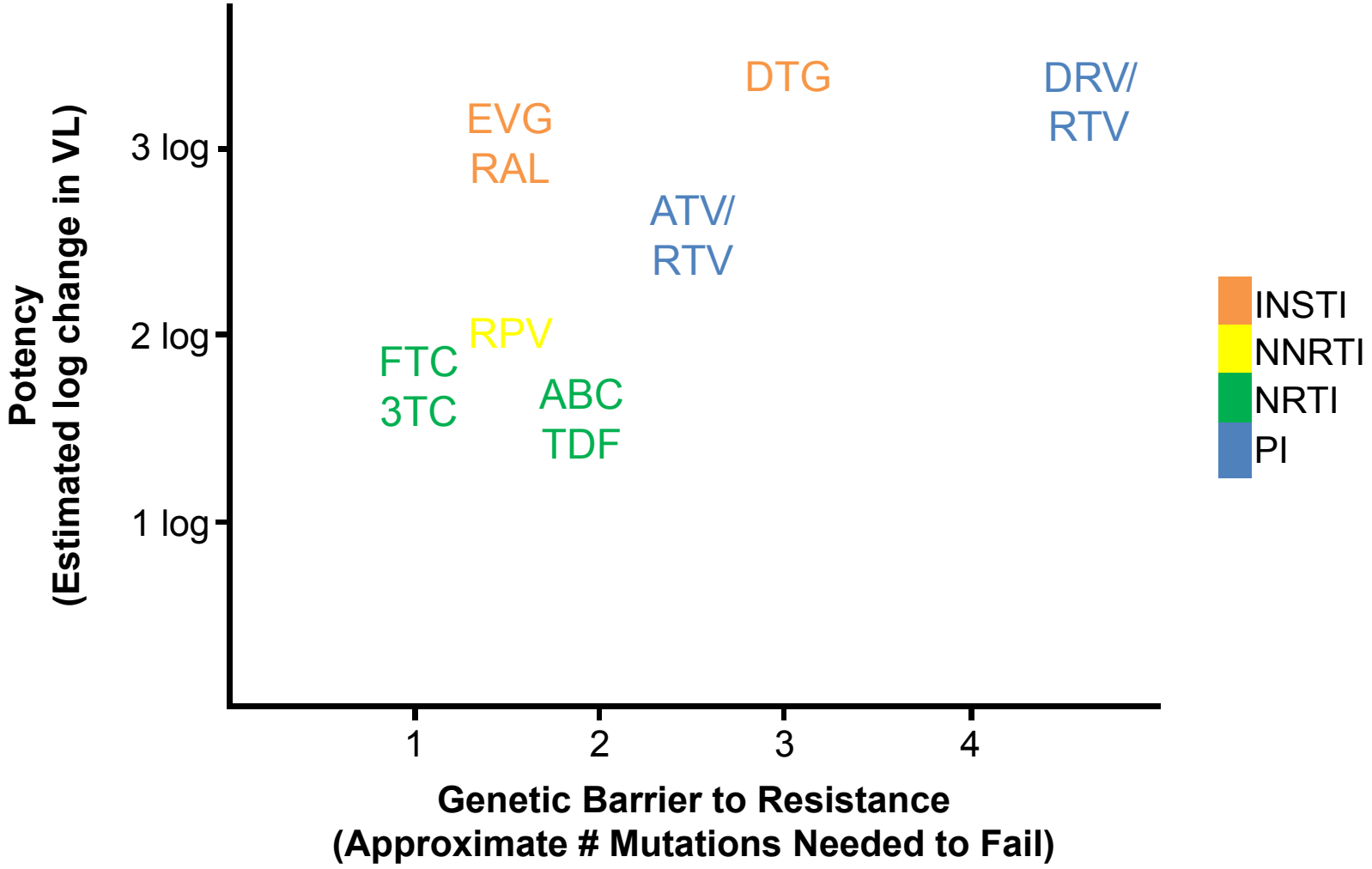
SaludMadrid Hospital Universitario La Paz
Hospital Carlos III
Hospital Cantoblanco
IdiPAZ Instituto de Investigación Hospital Universitario La Paz

Genetic Barrier to Resistance for Specific ARVs



Source: Clutter DS, et al. Infect Genet Evol. 2016;[Epub ahead of print].