State of the ART of ARV Therapy

Dr Nicky Mackie

Imperial College Healthcare Trust

nicola.mackie@nhs.net

Disclosures

- Honoraria for advisory board contributions: Gilead Sciences, Janssen, MSD, ViiV Healthcare
- Executive trustee of British HIV Association (BHIVA) and member of the BHIVA Guidelines Writing group

Overview

- Current Treatment Guidelines
  - When to start
  - What to start
- Factors to consider when choosing a regimen
- The future
  - Decreasing ART exposure
  - Different ART formulations
  - Pipeline

International ART Guidelines

International Antiviral Society-USA Panel

- *https://jamanetwork.com/journals/jama/fullarticle/2688574*
- Last update: July 2018

European AIDS Clinical Society Guidelines (EACS)

- http://www.eacsociety.org/files/guidelinesv9.0-english.pdf
- Last update: October 2017

DHHS Panel Guidelines (USA)

- https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0
- Last update: May 2018

World Health Organization (WHO)

- http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf
- Last update: July 2018

WHEN TO START

When to start

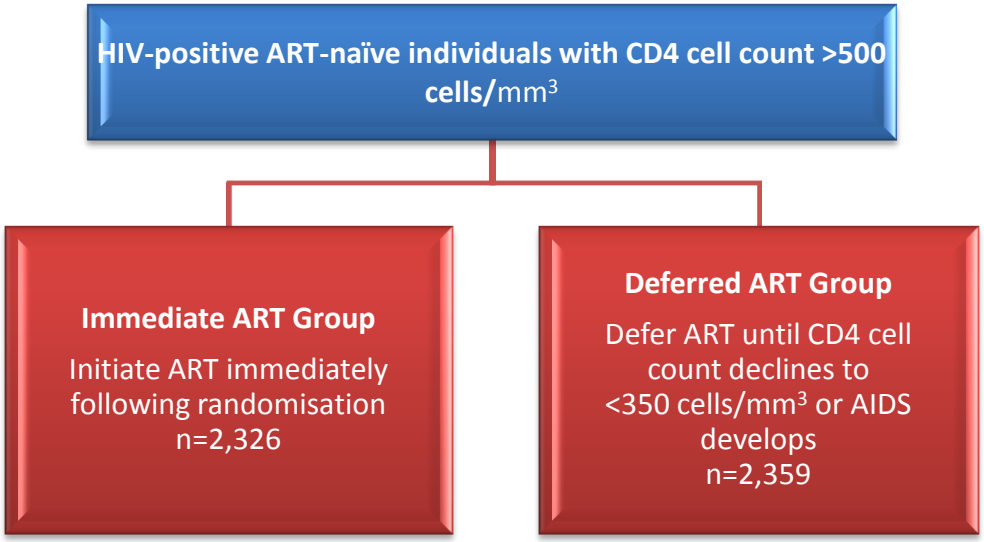
IAS-USA[1]	Initiate ART as soon as possible after HIV diagnosis. Rapid start (including same day) unless patient not ready to commit.
DHHS[2]	ART recommended for all regardless of CD4 T lymphocyte count. Therapy should be initiated as soon as possible.
WHO[3]	Start ART in all regardless of WHO clinical stage or CD4. Prioritise severe/advance clinical disease (WHO stage 3 or 4) and adults with CD4 ≤350
EACS[4]	ART should always be recommended irrespective of the CD4 count. Immediate (same day ART) should be considered in certain situations.

1. Saag M et al, JAMA, 2018;
2. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/10/initiation-of-antiretroviral-therapy ;
3. http://apps.who.int/iris/bitstream/10665/186275/1/9789241509565_eng.pdf 09/05/2016;
4. http://www.eacsociety.org/files/guidelines_9.0-english.pdf

Strategic Timing of Antiretroviral Treatment (START) Trial

START

- International RCT of immediate vs deferred ART
- The primary composite endpoint = a serious AIDS event, serious non-AIDS event, or death from any cause



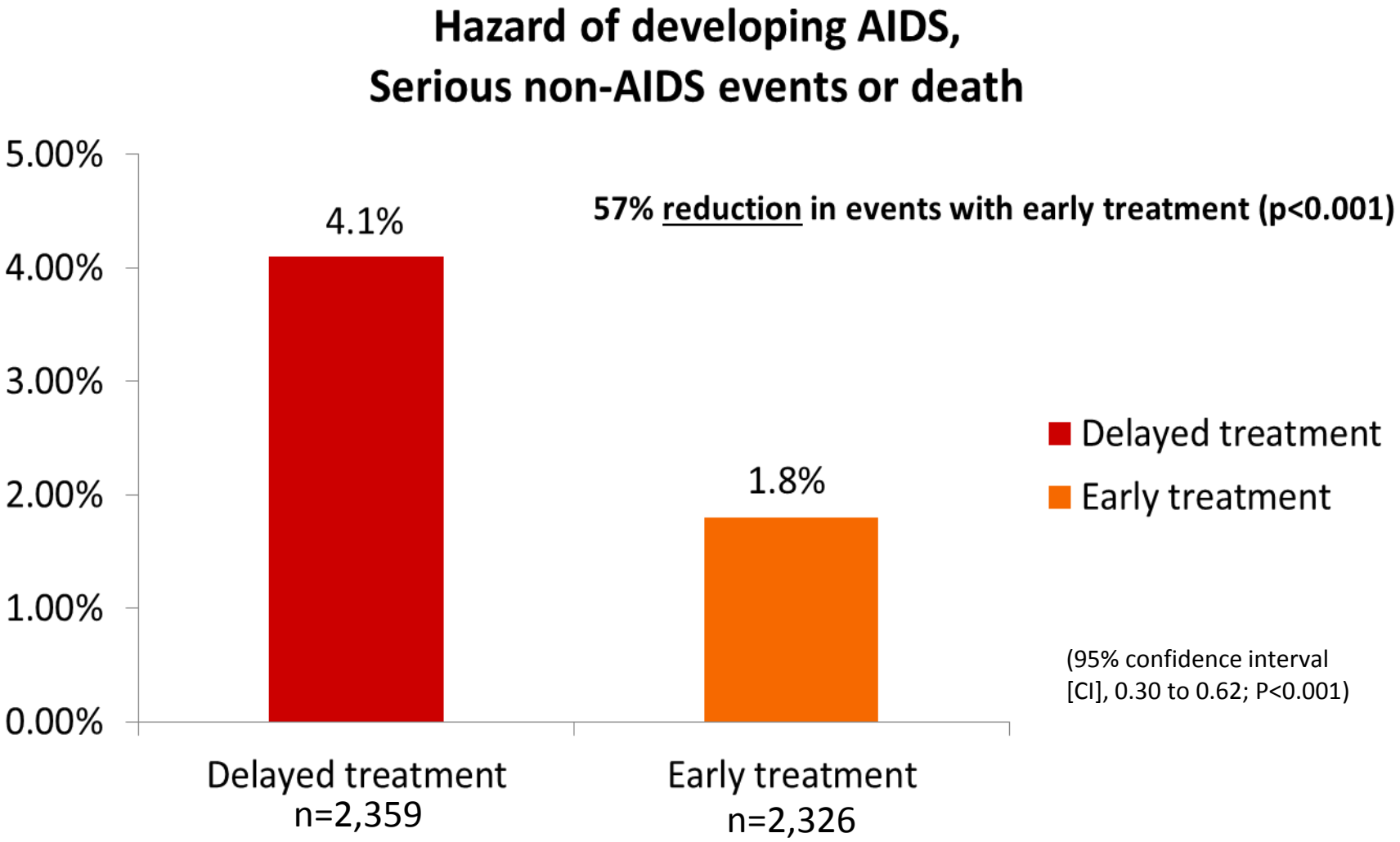
Characteristic	N=4,685
Age (year)*	36 (29, 44)
Female, n (%)	1257 (27)
Race, n (%)	
White	2086 (45)
Black	1,410 (30)
Time since HIV diagnosis (year)*	1.0 (0.4, 3.1)
CD4 cell count (cells/mm^3)*	651 (584–765)
Baseline HIV-RNA (copies/mL)*	12,759 (3,019–43,391)
TDF usage	89% in both groups

* Median (IQR)

- On 15 May 2015, at a planned interim review, DSMB recommended participants in the deferred arm not already on ART should be offered ART and follow-up should continue with all subjects on therapy. LFU (last contact >10/12) 4% immediate & 5% deferred

Lundgren D, et al. NEJM 2015 Published Epub ahead of print July 20, 2015 DOI: 10.1056/NEJMoa1506816

START: Primary results



Lundgren D, et al. NEJM 2015 Published Epub ahead of print July 20, 2015 DOI: 10.1056/NEJMoa1506816

Treatment as prevention:
serodifferent couples

PARTNER

HPTN 052

96% reduced transmissions initially

93% reduction in final analysis:

- 8 transmissions in ART arm
  - 4 virological failures
  - 4 prior to suppression

PARTNER 2

> 75,000 CLSI in 758 MSM serodifferent couples where HIV+ partner on suppressive ART (VL<200) = **ZERO transmissions**

1. Cohen MS *et al*. N Engl J Med. 2011; 2.Cohen MS *et al.* IAS 2015 MOAC0106LB; 3. Eshleman SH *et al*. IAS 2015 MOAC0106LB; 4. Rodger A et al. *Risk of HIV transmission through condomless sex in gay couples with suppressive ART: the PARTNER2 study expanded results in gay men.* 22nd International AIDS Conference, Amsterdam, abstract WEAX0104LB, 2018.

Rapid ART?

New recommendations

Rapid ART initiation should be offered to all people living with HIV following a confirmed HIV diagnosis and clinical assessment. *(Strong recommendation: high quality evidence for adults and adolescents; low-quality evidence for children)*

Rapid initiation is defined as within seven days from the day of HIV diagnosis; people with advanced HIV disease should be given priority for assessment and initiation.

ART initiation should be offered on the same day to people who are ready to start. *(Strong recommendation: high-quality evidence for adults and adolescents; low-quality evidence for children)*

World Health Organization

POLICY BRIEF

GUIDELINES FOR
MANAGING ADVANCED HIV DISEASE AND RAPID INITIATION OF ANTIRETROVIRAL THERAPY
JULY 2017

Rapid ART (same day or within 48 hrs)

CASCADE Trial

- Does it improve:
  - Engagement with care?
  - Virologic outcomes?
- Resistance
- Safety
  - Older patients
  - Co-morbidities
- Assess readiness
- Infrastructure

WHAT TO START

Recommended and preferred regimens

GUIDELINES	NRTI BACKBONE	NNRTI	INSTI	PI
EACS (2017)[1]	TAF/FTC TDF/FTC ABC/3TC*	RPV*	DTG RAL EVG	DRV/c or /r
DHHS (2018)[2]	TAF/FTC TDF/FTC ABC/3TC*	–	DTG **BIC** RAL EVG/c	–
IAS USA (2018)[3]	TAF/FTC ABC/3TC*	–	DTG **BIC**	–
WHO (2018)[5]	TDF/XTC		**DTG****	–

*Use recommended only if baseline viral load <100,000 copies/mL. (unless with DTG) and HLA B5701 negative

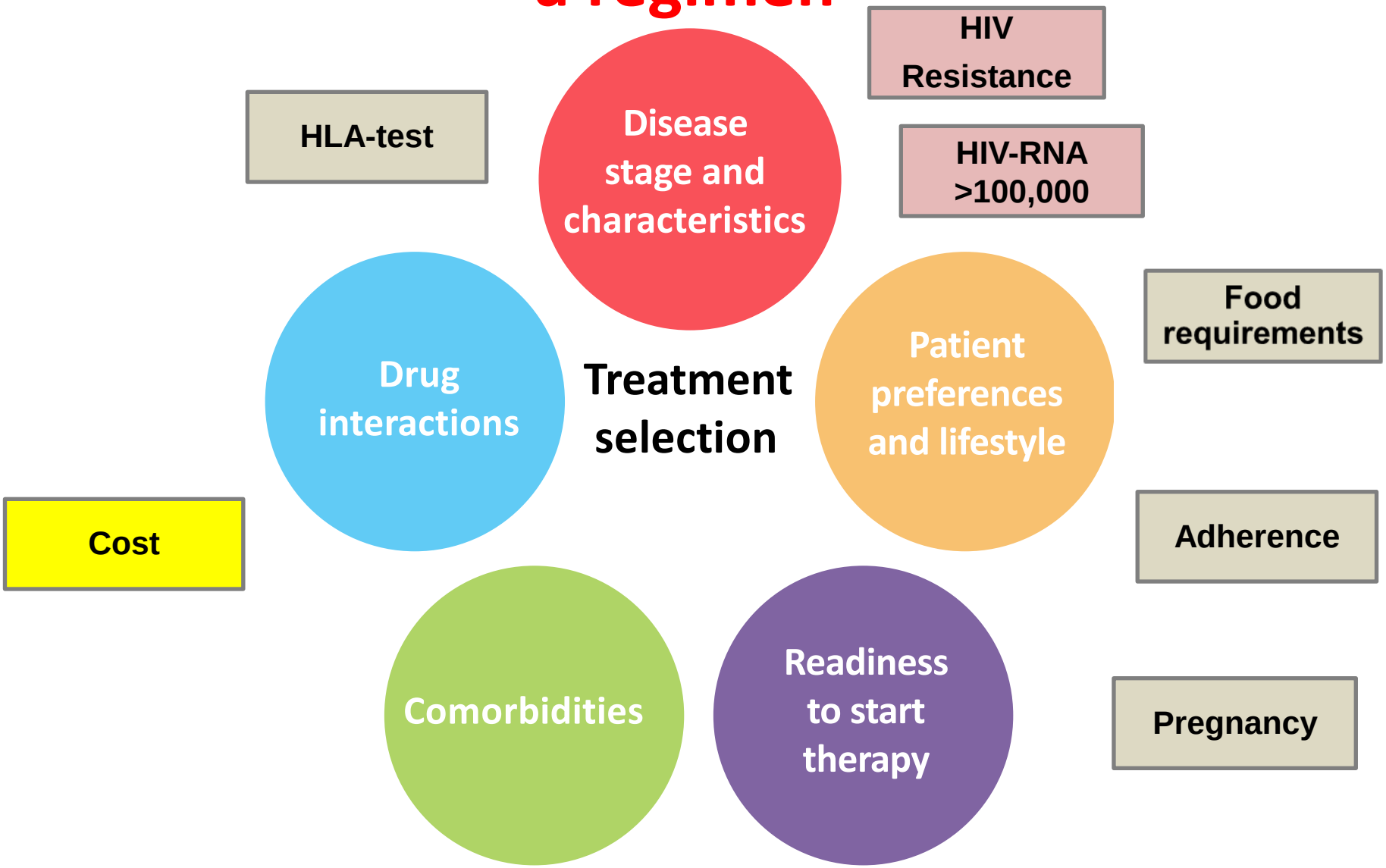
****Note of caution on using DTG during the periconception period and for women and adolescent girls of childbearing potential**

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; BIC, bictarvy; c, cobicistat; DHHS, Department of Health and Human Services; DRV, darunavir; DTG, dolutegravir; EACS, European AIDS Clinical Society; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; IAS USA, International Antiviral Society–USA; LPV, lopinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization; XTC, FTC or 3TC.

1. EACS Guidelines Version 9.0. Available from: http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html. Accessed August 2018;
2. DHHS Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Available from: https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0. Accessed August 2018;
3. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2018;320(4):1-18.[In press]
4. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available from: http://apps.who.int/iris/bitstream/handle/10665/273632/WHO-CDS-HIV-18.18-eng.pdf?ua=1. Accessed August 2018.

FACTORS TO CONSIDER WHEN CHOOSING A REGIMEN

Factors to consider when choosing a regimen



NRTI BACKBONE

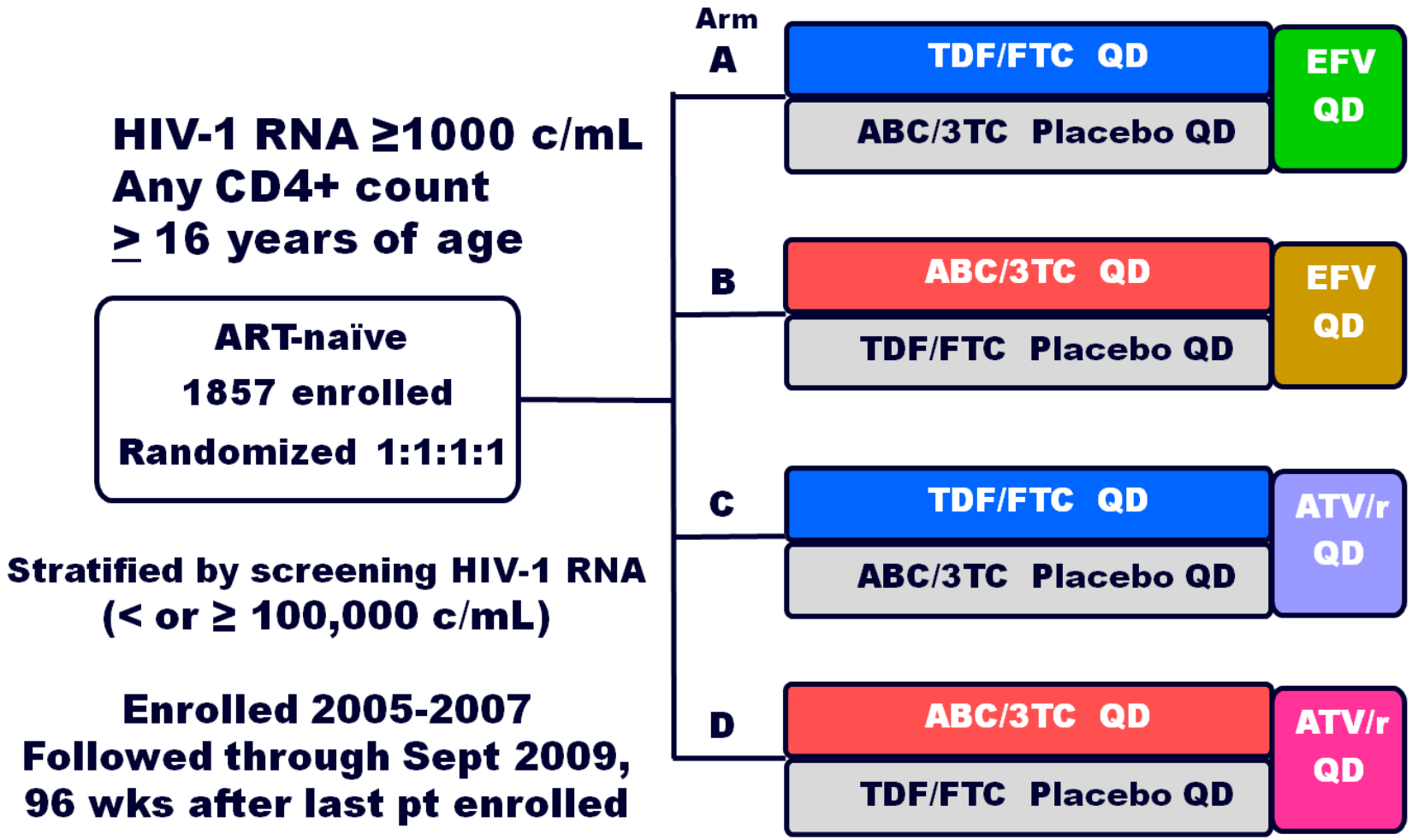
How to choose between NRTI backbones

Consideration	Potential Choice		
	ABC/3TC	FTC/TAF	FTC/TDF
Pt might benefit from STR (adherence or preference)	✓	✓	✓
Pt has high CVD risk		✓	✓
Confidence in high VL	Only with DTG	✓	✓
Pt is *HLA-B*5701* positive		✓	✓
Pt has osteopenia or osteoporosis	✓	✓	
Pt has renal impairment	✓*	✓	
Pt has hepatitis B co-infection		✓	✓

*DTG/ABC/3TC not recommended for pts with CrCl < 50 mL/min as 3TC dose adjustment required.

DTG/ABC/3TC [package insert]. September 2015.
FTC/TAF [package insert]. April 2016.
FTC/TDF [package insert]. April 2016.

ACTG 5202: Study Design



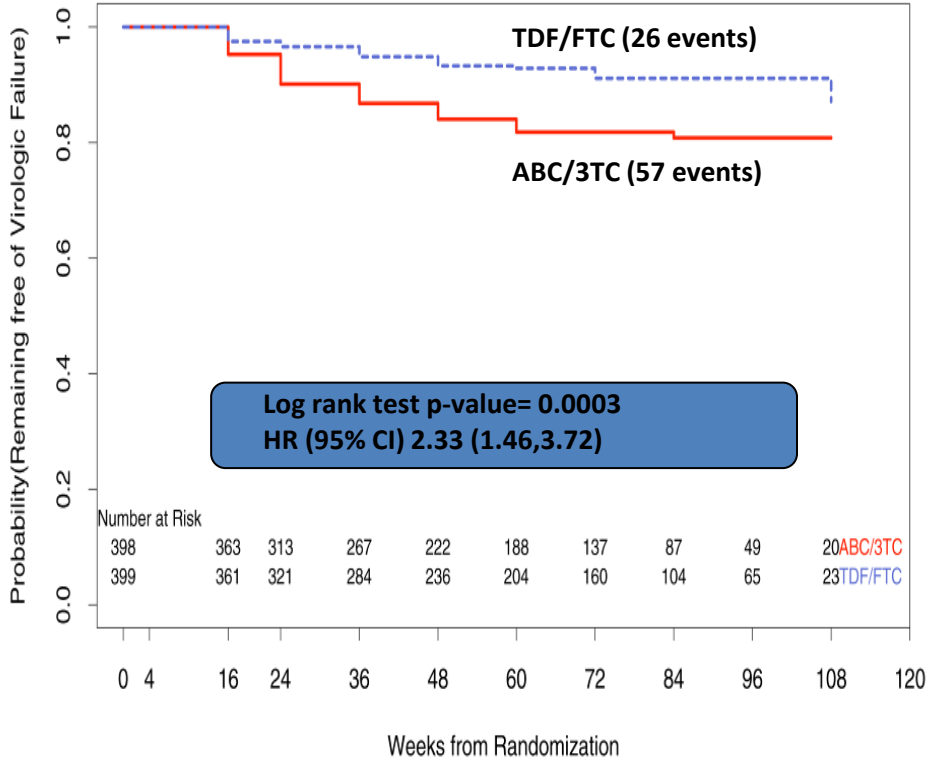
Routine HLA-B*5701 screening not used in this study

Sax PE, et al. NEJM 2009; 361:2230-2240

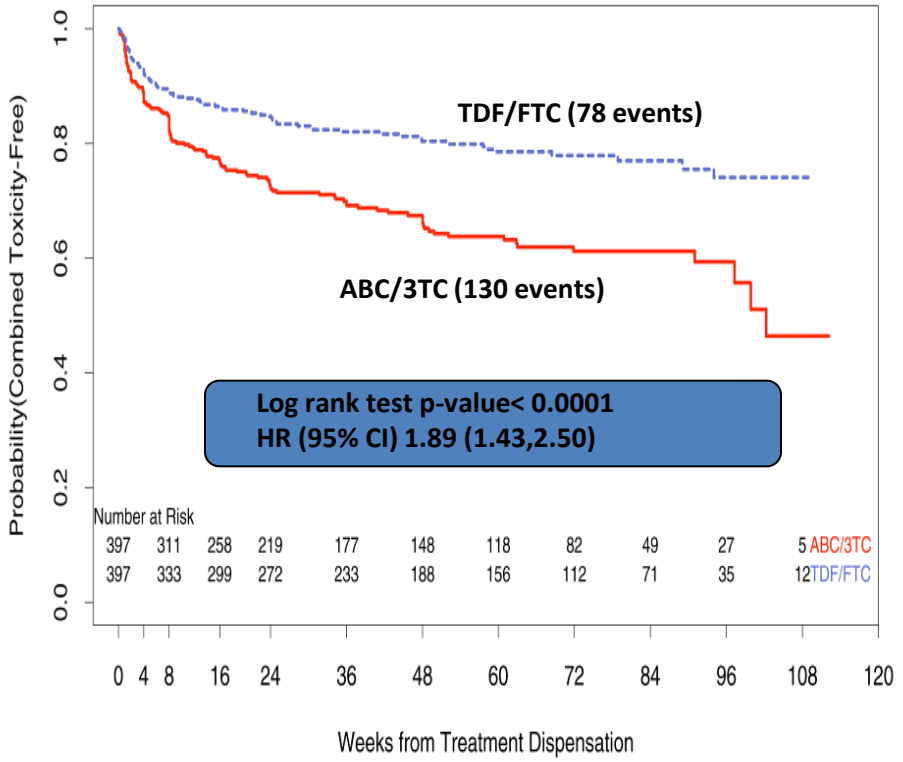
ACTG 5202: Primary Virologic and Safety Endpoints (High Viral Load Stratum)

N=797; median (25th, 75th) follow-up = 60 weeks (28, 84)

Time to Virologic Failure



Time to Safety Endpoint



Sax PE, et al. NEJM 2009; 361:2230-2240

CROI 2008 D:A:D Study

Recent Use of ABC and ddI Associated with Increased Risk of MI

Rates of MI	
NRTIs	Cum., recent[1] + past[2] use Rel. rate [95% CI]; p-value
Abacavir	
Cumulative use (per year)	1.00 [0.92, 1.08]; p = 0.91
Any recent[1] use	1.94 [1.48, 2.55]; p = 0.0001
Any past[2] use	1.29 [0.94, 1.77]; p = 0.12
Didanosine	
Cumulative use (per year)	1.00 [0.93, 1.07]; p = 0.91
Any recent[1] use	1.53 [1.10, 2.13]; p = 0.01
Any past[2] use	1.08 [0.84, 1.39]; p = 0.54

[1]Recent = still using or stopped within last 6 months; [2]Past = last used more than 6 months ago

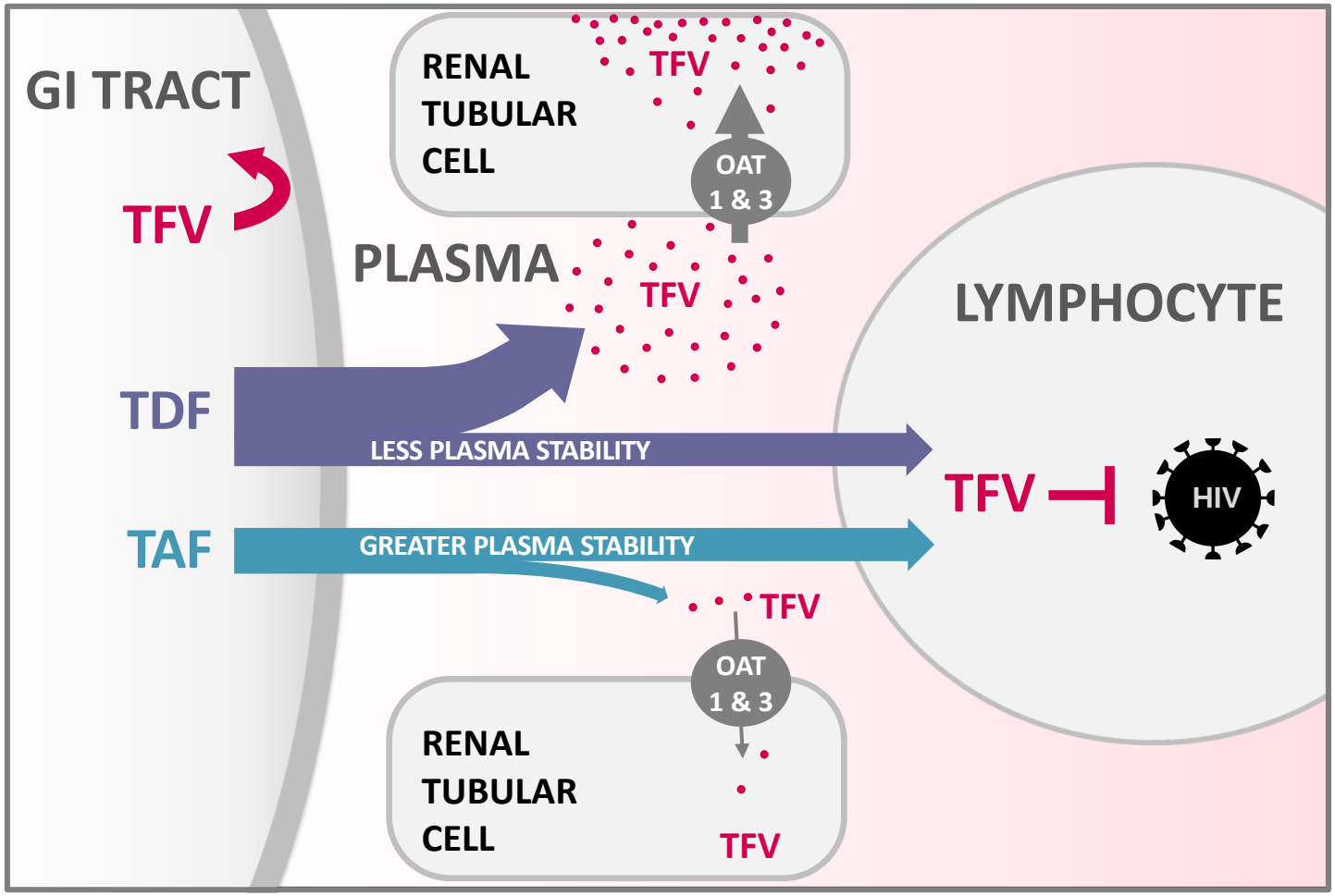
Sabin C et al., CROI 2008

Summary of studies 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.

Tenofovir Disoproxil Fumarate and Tenofovir Alafenamide



TAF 25 mg results in 80-90% lower TFV plasma levels

OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

1. Sax P, et al. Lancet 2014 2. Ruane P, et al. J Acquir Immune Defic Syndr 2013; 63:449-5. 3. Data on file

Clinical Trials Supporting FTC/TAF Use

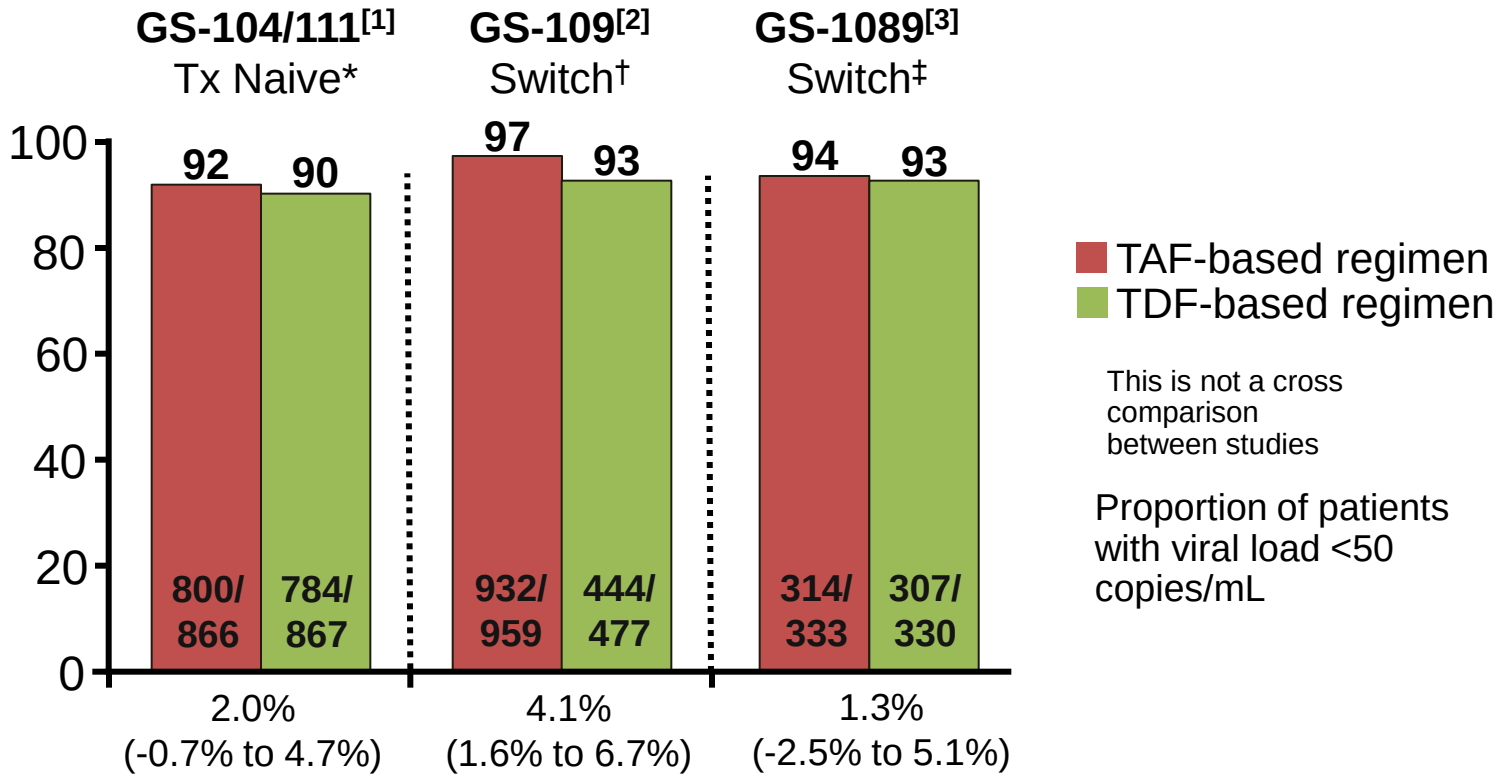
Study	Pt Population	Treatment
GS-104/111[1]	Treatment naive (N = 1733)	Pts randomized to EVG/COBI/FTC/TAF* *or* EVG/COBI/FTC/TDF
GS-109[2]	Virologically suppressed on TDF-based regimen (N = 1436)	Pts switched to EVG/COBI/FTC/TAF* *or* remained on TDF-based regimen
GS-1089[3]	Virologically suppressed on FTC/TDF + third ARV (N = 663)	Pts switched to FTC/TAF† + continued third ARV *or* remained on FTC/TDF + third ARV
GS-112[4]	Virologically suppressed on varied regimens; stable $eGFR_{CG}$ 30-69 mL/min (N = 242)	Pts switched to EVG/COBI/FTC/TAF*

* EVG/cobi/FTC/TAF dosing: 150/150//200/10 mg.
†FTC/TAF dosing: 200/10 mg with boosted PIs; 200/25 mg with unboosted third drug as per SmPC

1. Sax PE, et al. Lancet. 2015;385:2606-2615. 2. Mills A, et al. Lancet Infect Dis. 2016;16:43-52. 3. Gallant JE, et al. Lancet HIV. 2016;3:e158-e165. 4. Pozniak A, et al. J Acquir Immune Defic Syndr. 2016;71:530-537.

Slide credit: clinicaloptions.com

Primary End Points
Wk 48 Efficacy: TAF-Based Treatment Non-inferior to TDF-Based Treatment

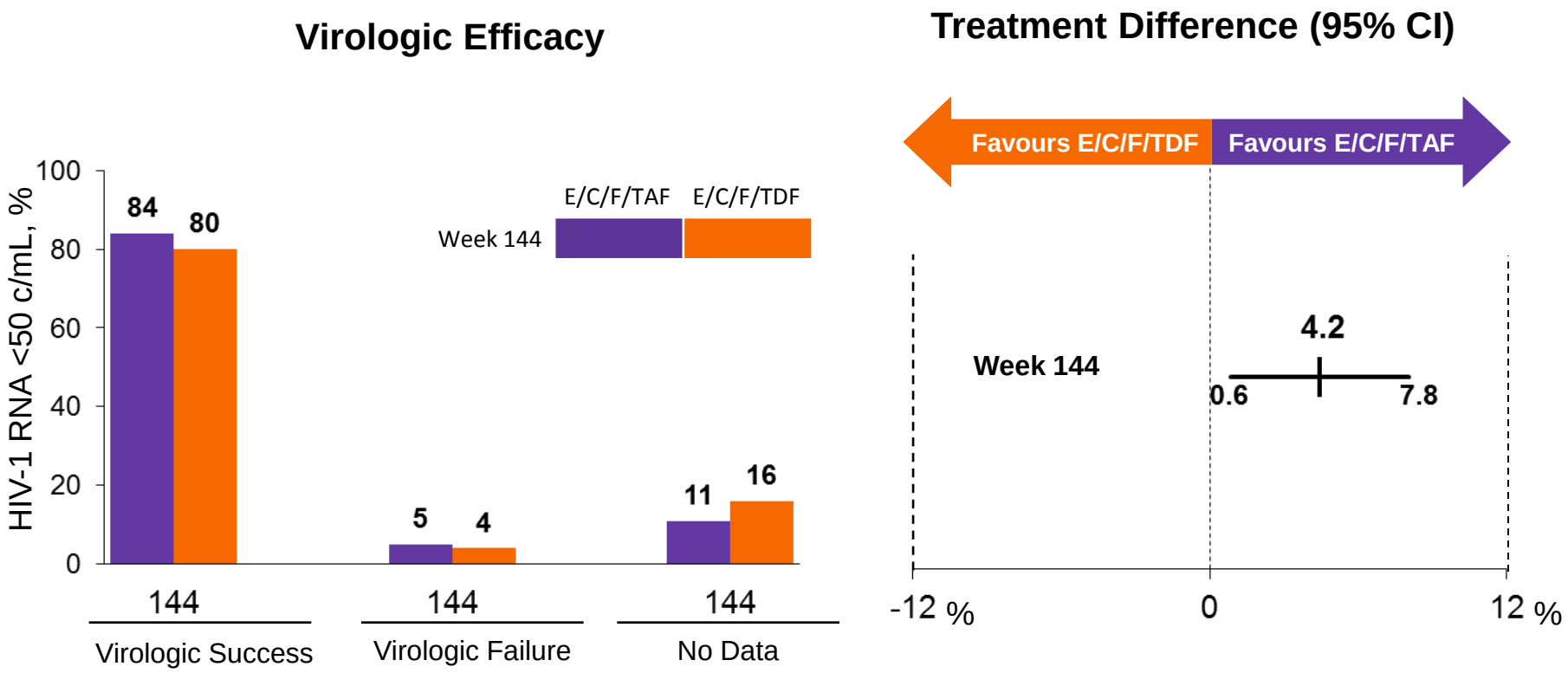


*GS-104/111: EVG/COBI/FTC/TAF vs EVG/COBI/FTC/TDF. †GS-109: Switched to EVG/COBI/FTC/TAF or remained on TDF-based ART. ‡GS-1089: Switched to FTC/TAF + third ARV or remained on FTC/TDF + third ARV.

1. Sax PE, et al. Lancet. 2015;385:2606-2615. 2. Mills A, et al. Lancet Infect Dis. 2016;16:43-52. 3. Gallant JE, et al. Lancet HIV. 2016;3:e158-e165.

Slide credit: clinicaloptions.com

Overall Virologic Efficacy at Week 144



- **For patients ≥ 50 , treatment difference: 11.8% (95% CI: 1.3-22.2)**
- **At Week 144, E/C/F/TAF was superior in efficacy to E/C/F/TDF**

Ward, D. et al. HIV and Aging 2016. Washington, DC. #33

Overall Week 144: Renal Events Leading to Discontinuation

Reason for Treatment Discontinuation	E/C/F/TAF n	E/C/F/TDF n
Total Renal Event Discontinuations	**0**	**12**
Creatinine increased and GFR decreased	0	1
Reduced GFR	0	1
Fanconi syndrome + glycosuria	0	1
Nephropathy	0	1
Proteinuria	0	1
Renal failure	0	2
Renal tubular disorder	0	3
Creatinine increased + bone density decreased	0	1
Bladder spasm	0	1

- On the E/C/F/TAF arm through 144 weeks there were
  - No cases of renal tubulopathy (including Fanconi Syndrome) vs. 2 for E/C/F/TDF
  - No discontinuations due to renal AE vs. 12 for E/C/F/TDF ($p<0.001$)

TDF vs TAF

- Renal
  - TAF has greatest safety benefits in patients at high risk of renal disease (older, with co-morbidities) or with established renal disease
  - Patients with low risk of renal disease show less marked improvement in tubular function
- Bone
  - Individuals with low bone mineral density or high fracture risk are most likely to benefit from TAF over TDF

INTEGRASE INHIBITORS

Why are INIs* first line?

*INI=integrase inhibitors

	Dolutegravir	Raltegravir	Elvitegravir/c	Bictegravir
Efficacy[1, 2, 3, 4]	✓✓	✓	✓	✓
Once daily dosing	✓	✓	✓	✓
Available as a STR	✓		✓	✓
High genetic barrier[1, 2, 3, 4]	✓			✓
Few drug interactions	✓	✓		✓
Tolerability		✓	✓	
Studies in women[5, 6]	✓		✓	

1. SINGLE study: Walmsley S et al. *NEJM* 2013; 2. SPRING-2 study: Raffi F et al. *Lancet* 2013. 3. FLAMINGO study. Molina JM et al. *Lancet HIV* 2015; 4. GS-1490. Sax PE et al. *Lancet* 2017; 5. ARIA study: Orrell C et al. *Lancet HIV* 2017; 6. WAVES study: Squires K et al. *Lancet HIV* 2016

Current challenges of INIs as third agent

CNS AEs	Resistance	DDIs
Phase III FDA trials DTG[1] ▪Only SINGLE reported >5% events (especially insomnia) **Six cohorts[3–8]: CNS discontinuations** ▪More DTG discontinuations than other INSTIs **Opera cohort[6]** ▪ Similar CNS incident eve for third agents **Wohl series[9]** ▪ Depression and sleep disturbances were significantly higher in DTG vs EVG, and DRV/r, but not RAL ▪ Suicidal ideation rates similar among INIs	**First-generation INI** ▪RAL and EVG more resistance than PI **Second-generation INI** ▪Genetic barrier closer to PI/r	**INI drug–drug interactions** ▪RAL/DTG chelation ▪EVG/c booster, so DDIs ▪BIC: UGT1A1 and Cyp3 A4 metabolism (cannot be used with rifampicin)

Concerns regarding neural tube defects in 4 infants born to women who conceived whilst taking DTG (?class effect)

1. Viswanathan P, *et al.* CROI 2017, Seattle, WA, United States; poster #372; 2. Quercia R, *et al.* HIV Glasgow 2016, Glasgow, United Kingdom; poster #210; 3. Hoffmann C, et al. *HIV Med* 2017;18:56–63; 4. Padilla M, *et al.* International Workshop on Comorbidities and ADRs in HIV 2016, New York, NY, United States; 5. Lepik KJ, *et al.* IAS 2015, Vancouver, Canada; abstract #TUPEB256; 6. Hsu R, *et al.* CROI 2017, Seattle, WA, United States; poster #664; 7. Llibre JM, *et al.* CROI 2017, Seattle, WA, United States; poster #651; 8. Baldin G, *et al.* HIV Glasgow 2016, Glasgow, United Kingdom; poster #P106; 9. Wohl D, *et al.* ID Week 2017; San Diego, CA, United States; abstract #664.

NNRTIS

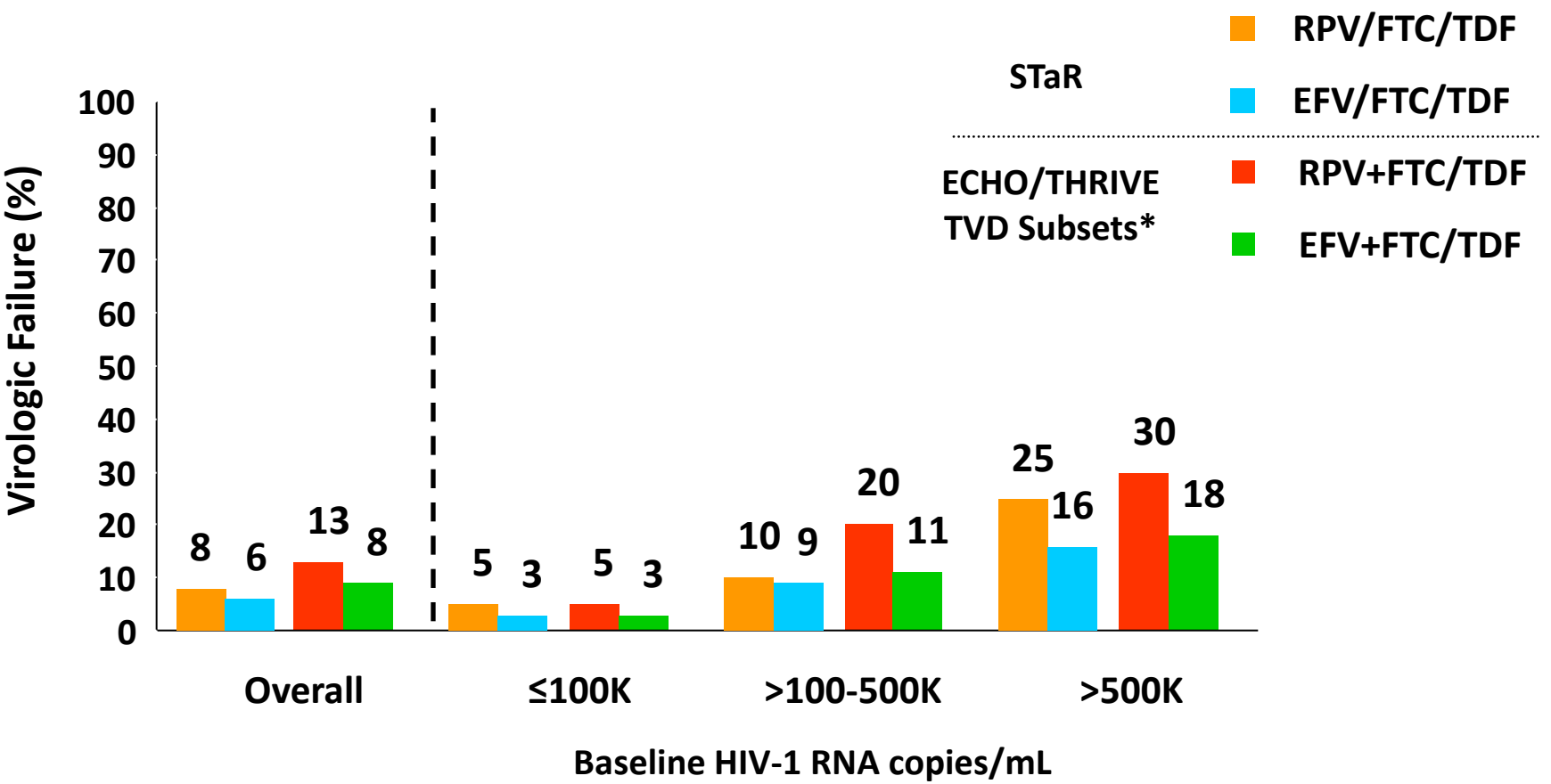
NNRTIs

GUIDELINES	NRTI BACKBONE	NNRTI	INSTI	PI
EACS (2017)[1]	TAF/FTC TDF/FTC ABC/3TC*	RPV*	DTG RAL EVG	DRV/c or /r
DHHS (2018)[2]	TAF/FTC TDF/FTC ABC/3TC*	–	DTG **BIC** RAL EVG/c	–
IAS USA (2018)[3]	TAF/FTC ABC/3TC*	–	DTG **BIC**	–
WHO (2018)[5]	TDF/XTC		**DTG****	–

- Well tolerated, exists as a STR
- Less effective at high viral load (>100K) and low baseline CD4 count (<200)
- Restricted use with PPIs and H2 blockers

STaR & ECHO/THRIVE: RPV non inferior to EFV for VL<100000

Virologic Failure at Week 48 by baseline HIV-1 RNA



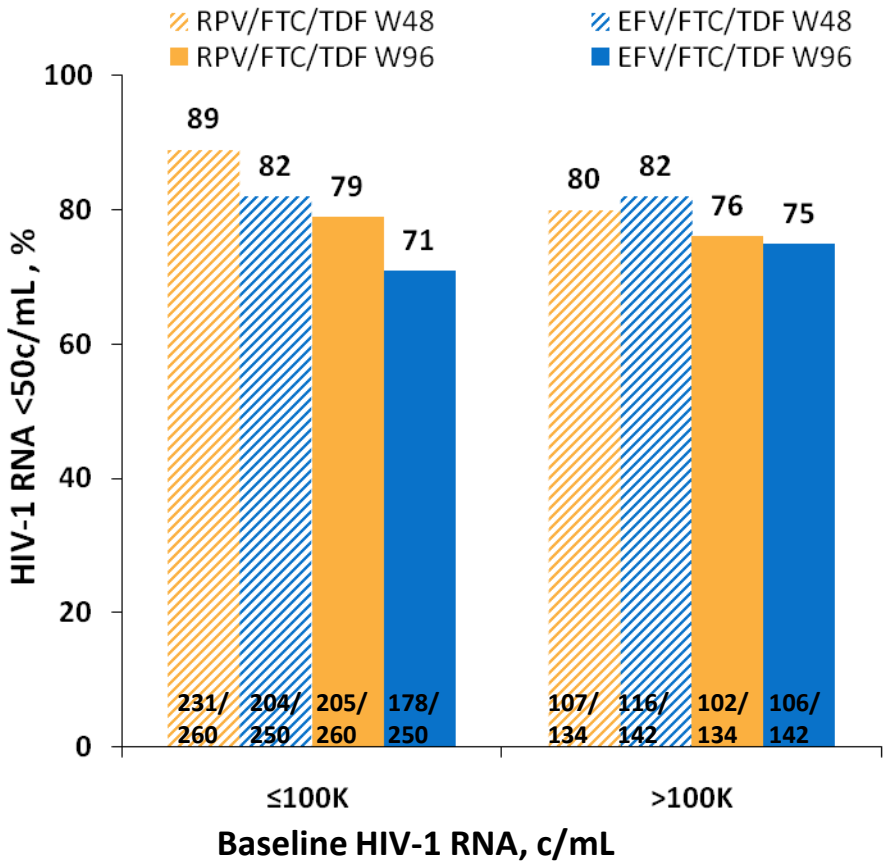
ECHO/THRIVE: Two Phase III double-blinded, double dummy, mulitcenter 96 week studies in treatment-naïve HIV-1 infected subjects randomized to receive either RPV (25mg) or EFV (600mg) in combination with 2 NRTIs (ECHO, FTC/TDF; THRIVE, Investigator's choice [FTC/TDF, n=406; 3TC/AZT, n=204; 3TC/ABC, n=68]). In the pooled TVD subset analysis (N=1096), RPV+TVD was non-inferior to EFV+TVD (HIV-1 RNA <50 c/mL [83%, 81%])

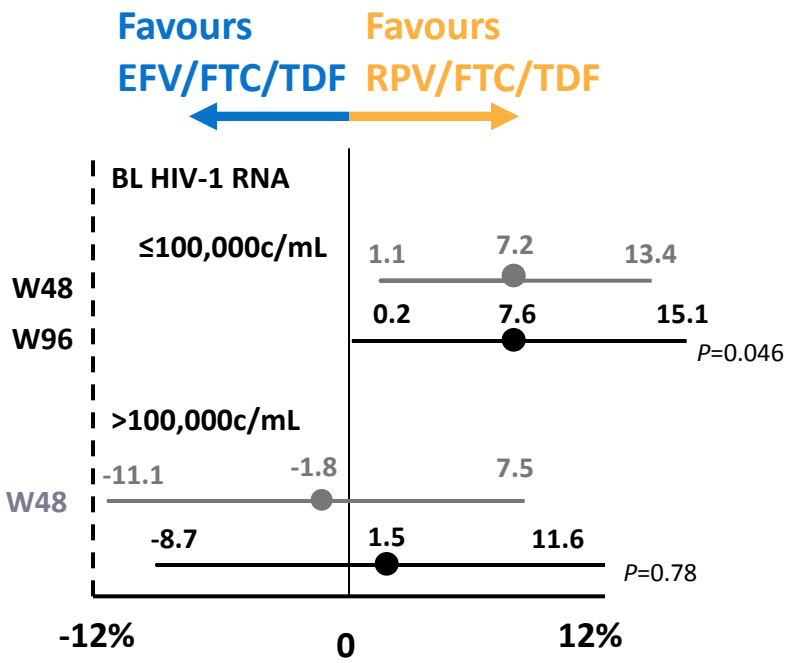
***COMPLERA Prescribing Information. Gilead Sciences Inc. 2011.**

STaR: week 96

Virologic suppression by baseline VL

RPV/FTC/TDF statistically significant difference better in efficacy at Week 96 compared to EFV/FTC/TDF in patients with low baseline viral load (≤ 100k copies/mL)





Cohen C et al. EACS 2013; Brussels, Belgium. #LBPE7/17

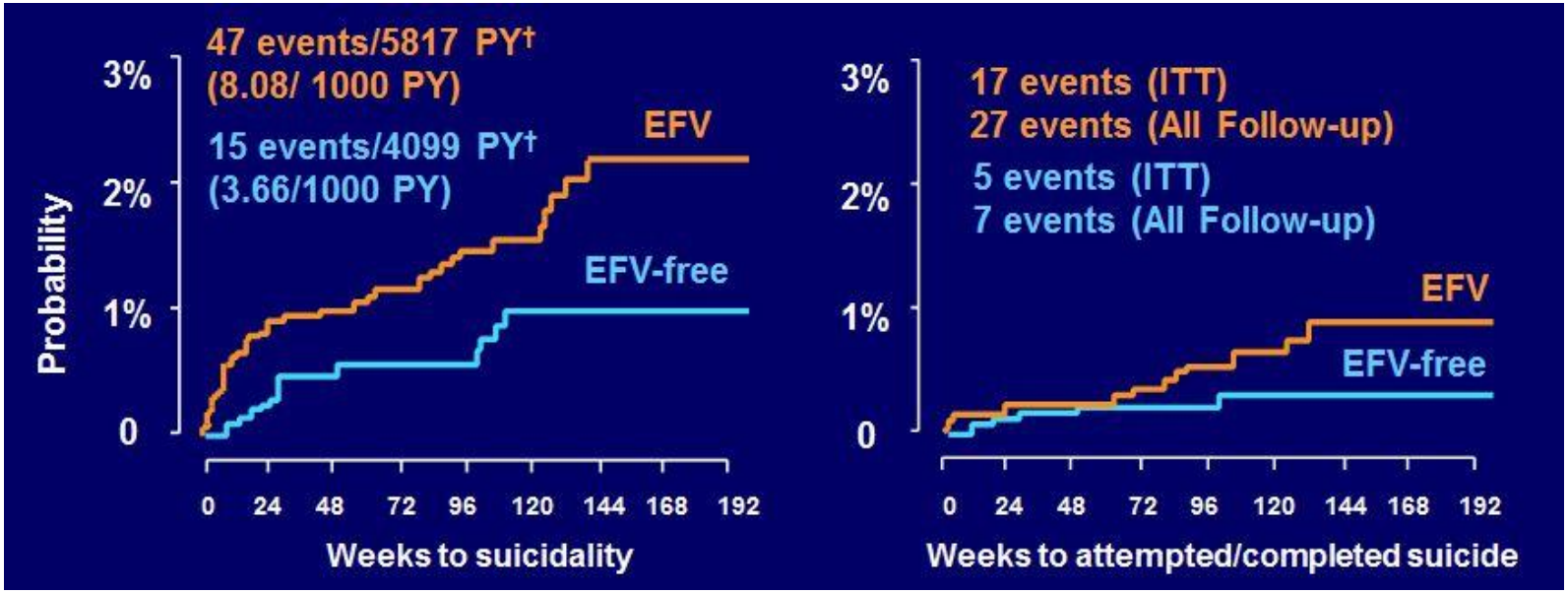
Why the change? EFV

- EFV moved from preferred to alternative
- Newer drugs superior:
  - DTG at primary endpoint in SINGLE
  - RAL after long enough follow-up in STARTMRK
  - RPV in subgroup analysis of StAR
- ACTG suicidality analysis
- Lipids

ACTG suicidality analysis

ACTG (5095, 5142, 5175, 5202) ARV-naïve studies evaluating associations between patient baseline characteristics and suicide in HIV infected adults from 2001-2007, N=5,332

	HR (95%CI)	P-value
Suicidality – ITT	2.28 (1.27 – 4.10)	0.006
Attempted/Completed Suicide **– ITT** **– All Follow-up***	 2.58 (0.94 – 7.06) 2.6 (1.1 – 5.9)	 0.06 0.03



† Person-years, sum of at-risk follow-up

Mollan K, et al. ID Week 2013. San Francisco, CA. Oral #670

* Includes follow-up beyond DSMB decisions for A5095 and A5175

START: EFV & risk of suicidal behaviour

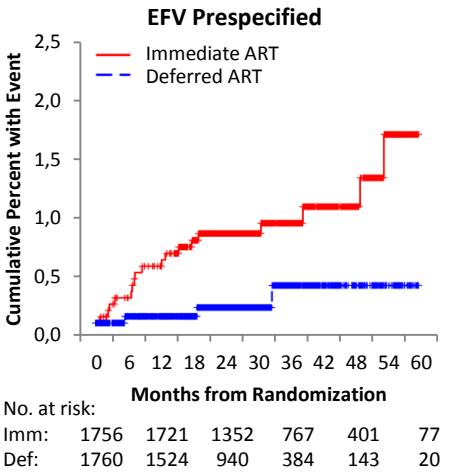
To Assess Effects of EFV on "Suicidal Behavior*" by Comparing the Immediate (IMM) versus Deferred (DEF) ART Groups

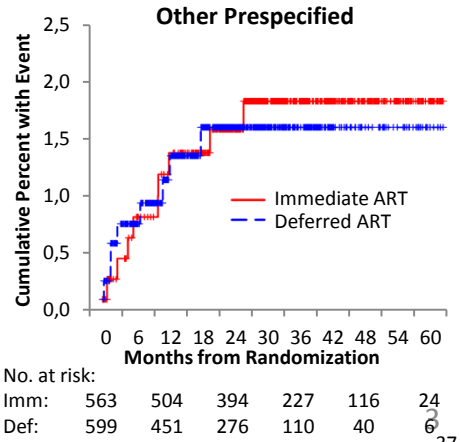
Suicidal/Self Harming Events by Randomisation Arm

		IMM ART	DEF† ART	HR (95%CI)	P-value
	N	Events/Rate	Events/Rate		
EFV use Pre-specified#	3516	17/0.35	3/0.08	**4.16 (1.2, 14.4)**	0.02
Other ART use Pre-specified#	1137	9/0.59	8/0.69	1.04 (0.4, 2.7)	0.93
Predictors of Suicidal Behavior for IMM ART (EFV re-specified)					
Prior psychiatric diagnosis¥				**12.8 (4.7, 34.9)**	<0.001

†Follow-up was censored at the start of ART in the Deferred arm
#In the START study, combination ART was pre-specified before randomization
¥Major depression, bipolar disorder, psychotic disorder incl. schizophrenia

Time to suicidal/self harming behavior



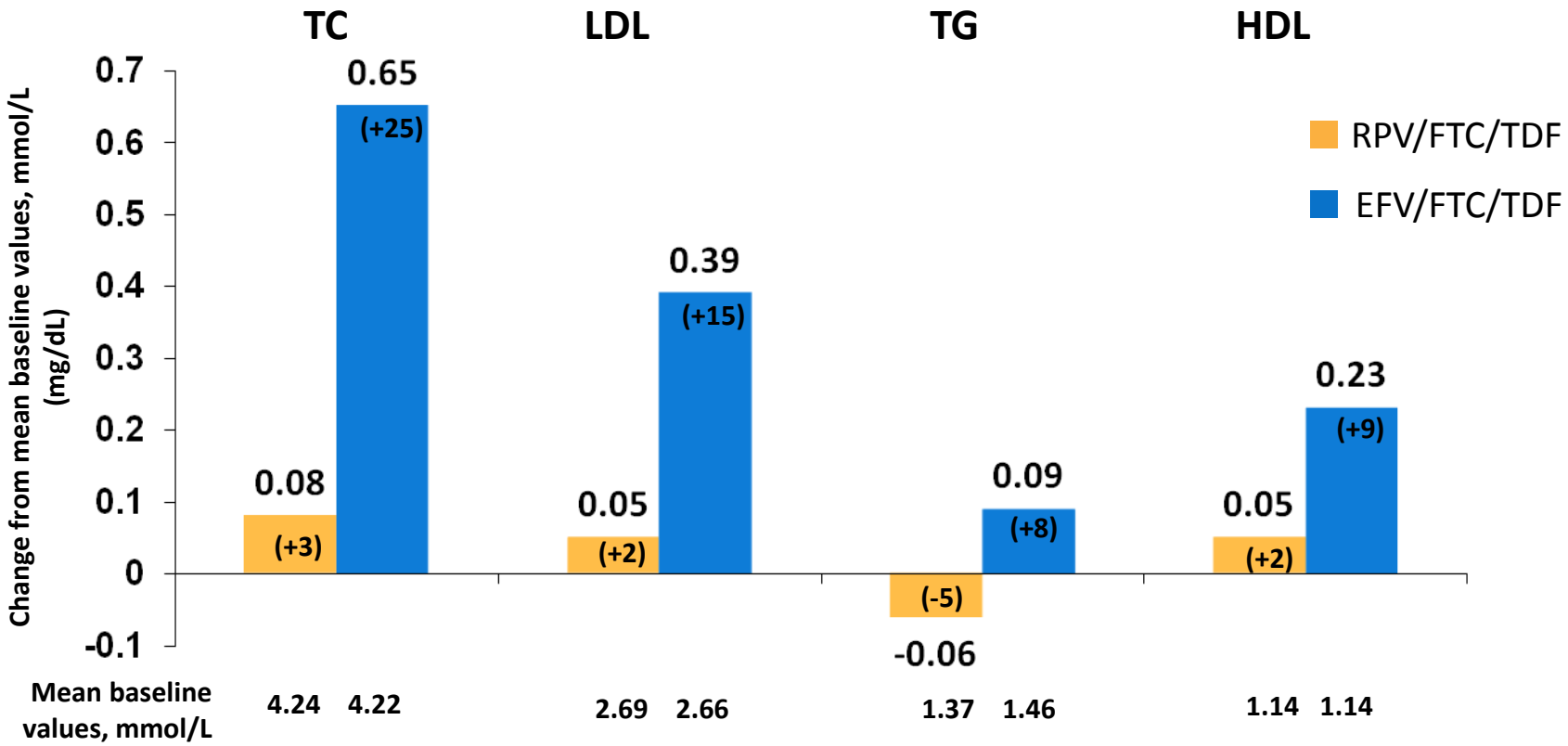


- **Use of EFV in the IMM arm was associated with an increased risk of suicidal behavior* compared to their ART-naïve controls in the DEF arm**

*Suicidal behavior composed of: Suicidal ideation, Suicidal attempt, Completed suicide, Self-injurious ideation and Intentional self-injury.

Arenas-Pinto A, et al. AIDS 2016. Durban, South Africa. Oral #THAB0202

STaR: Changes from baseline to week 96 in fasting lipids

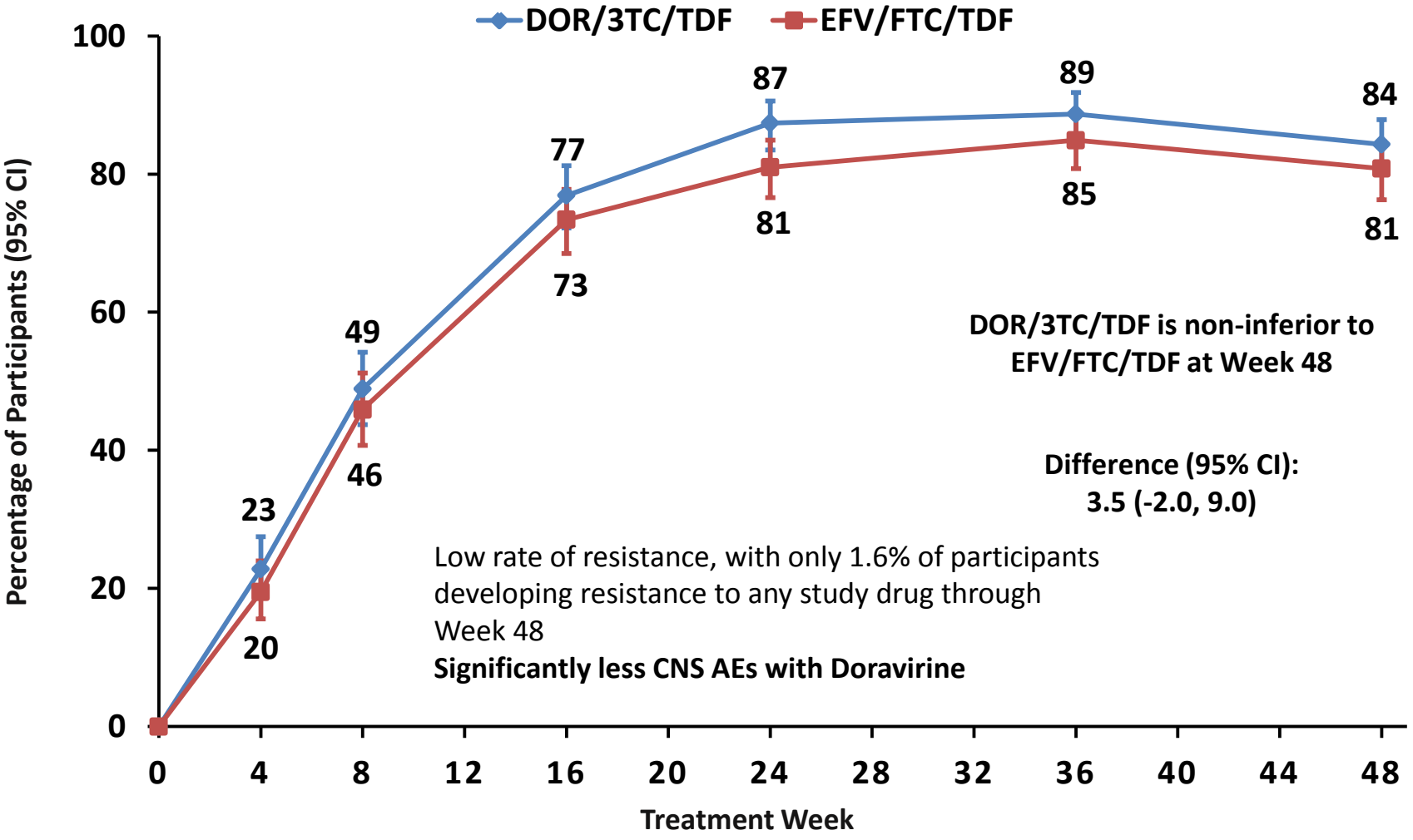


- **Change in TC: HDL at Week 96 was –0.2 in both arms**
- **Changes to lipid lowering therapy from baseline:**
  - RPV/FTC/TDF 2.3% vs EFV/FTC/TDF 4.1%

P<0.001 for TC, LDL, HDL and *P*=0.09 for TG, using ANOVA analysis

TC = total cholesterol
LDL = low-density lipoprotein
TG = triglycerides
HDL = high-density lipoprotein

DORAVIRINE: DRIVE AHEAD STUDY



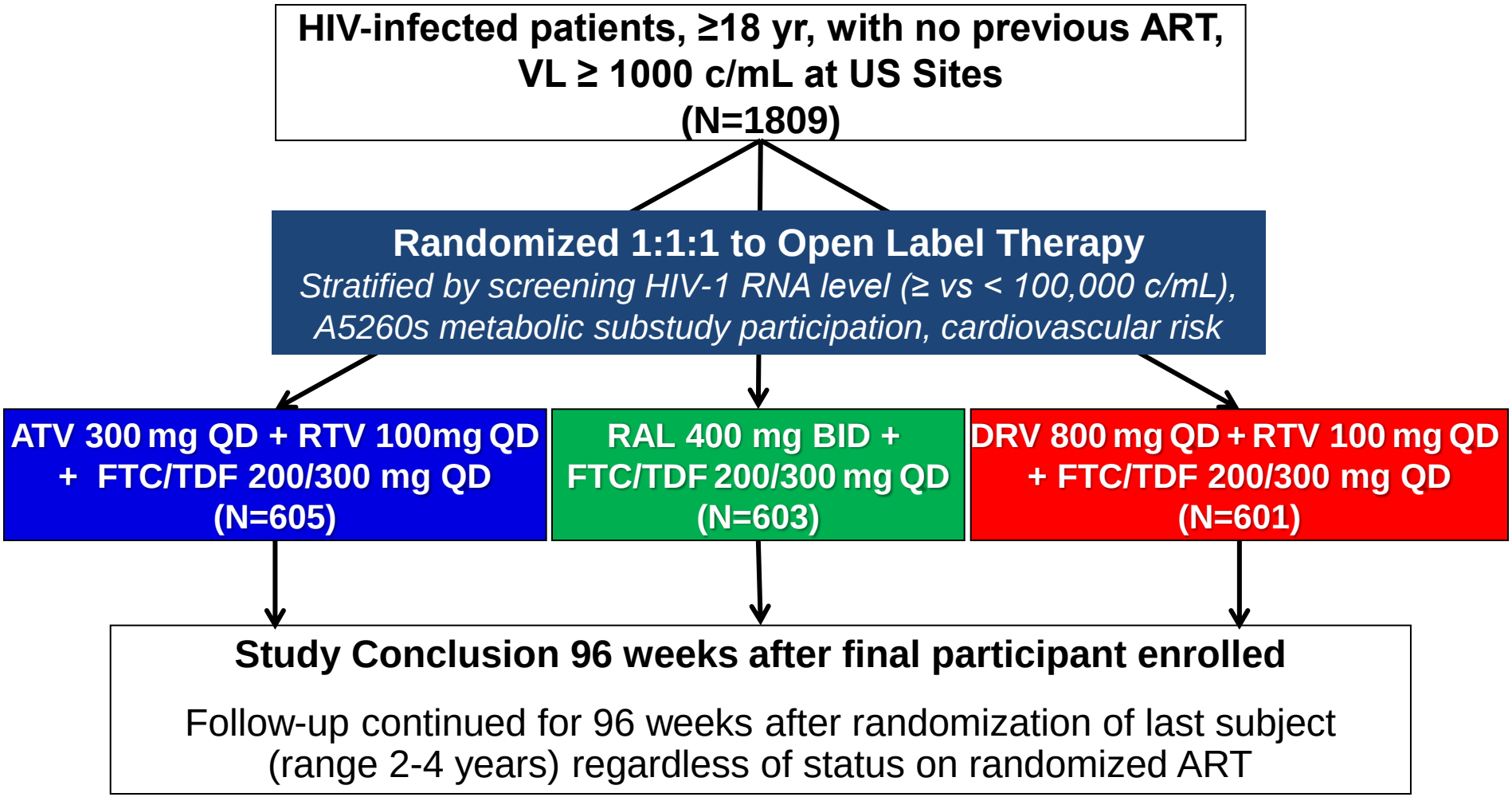
Squires K, et al; 9th IAS, Paris, France, July 23-26, 2017; Abst. TUAB0104LB.

BOOSTED PROTEASE INHIBITORS

Boosted Protease inhibitors

- Many guidelines have downgraded ATV/r
- Based mainly on ACTG 5257…..

A5257 Study Design*



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

ACTG 5257: failures

Virologic failure			
Arms	**Difference**	**97.5% CI**	**Favours**
ATV/r vs RAL	3.4%	-0.7%, 7.4%	Equivalent
DRV/r vs RAL	5.6%	1.3%, 9.9%	Equivalent
ATV/r vs DRV/r	-2.2%	-6.7%, 2.3%	Equivalent

Tolerability failure			
Arms	**Difference**	**97.5% CI**	**Favours**
ATV/r vs RAL	13%	9.4%, 16%	RAL superior
DRV/r vs RAL	3.6%	1.4%, 5.8%	Equivalent
ATV/r vs DRV/r	9.2%	5.5%, 13%	DRV/r superior

Cumulative failure			
Arms	**Difference**	**97.5% CI**	**Favours**
ATV/r vs RAL	15%	10%, 20%	RAL superior
DRV/r vs RAL	7.5%	3.2%, 12%	RAL superior
ATV/r vs DRV/r	7.5%	2.3%, 13%	DRV/r superior

ACTG 5257: toxicity discontinuation

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

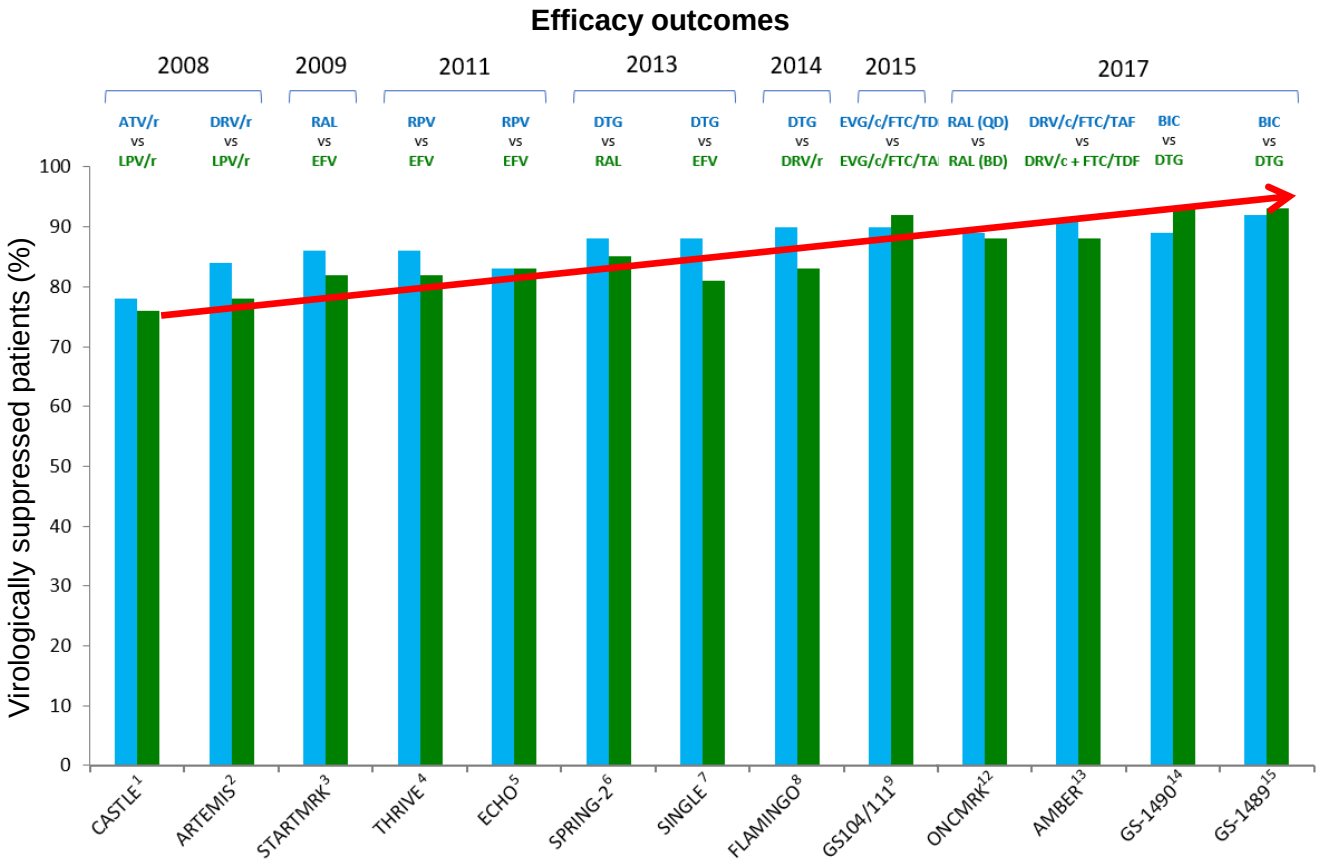
Landovitz L, et al. 21st CROI; Boston, MA; March 3-6, 2014. Abst. 85.

DRV/cobi/FTC/TAF: First PI-based STR

- Once daily single-tablet regimen approved by FDA in July 2018
  - For treatment-naïve patients
  - For patients with virological suppression for >6 months with no resistance to DRV or TDF
- Take with food
- Multiple potential drug-drug interactions

Symtuza SmPC. Available from: http://www.medicines.org.uk/emc/medicine/34148. Updated September 2017. Accessed October 2017

Overall efficacy outcomes at Week 48



The future: what next??

ATV, atazanavir; BD, twice daily; BIC, bictegravir; c, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; LPV, lopinavir; QD, once daily; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate.

1. Molina JM, *et al*. *Lancet* 2008;372:646–55; 2. Ortiz R, *et al*. *AIDS* 2008;22:1389–97; 3. Lennox JL, *et al*. *Lancet* 2009;374:796–806;
4. Cohen CJ, *et al*. *Lancet* 2011;378:229–37; 5. Molina JM, *et al*. *Lancet* 2011;378:238–46; 6. Raffi F, *et al*. *Lancet* 2013;381:735–43;
7. Walmsley SL, *et al*. *N Engl J Med* 2013;369:1807–18; 8. Clotet B, *et al*. *Lancet* 2014;383:2222–31; 9. Sax PE, *et al*. *Lancet* 2015;385:2606–15;
10. Squires K, *et al*. *Lancet HIV* 2016;3:e410–20; 11. Orrell C, *et al*. *Lancet HIV* 2017;4:e536–46; 12. Cahn P, *et al*. *Lancet HIV* 2017;4:e486–94; 13. TBA;
14. Sax PE, *et al*. *Lancet* 2017;390:2073–82; 15. Gallant J, *et al*. *Lancet* 2017;390:2063–72.

The future of ART

- **Decreasing ART exposure**
  - Decreasing drug dose
  - Decreasing dosing frequency
  - Decreasing numbers of drugs*
- **Different ART formulations**
  - Long-acting oral agents
  - Implantable agents
  - Long-acting injectables*
- **Pipeline***

The future of ART

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  - **Decreasing numbers of drugs***
- Different ART formulations
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- Pipeline*

2 drug regimen (2DR)-naïve studies

ANDES[1] (n=145)

- DRV/r + 3TC vs DRV/r + TDF/3TC
- One PDVF on DRV/r + TDF/3TC

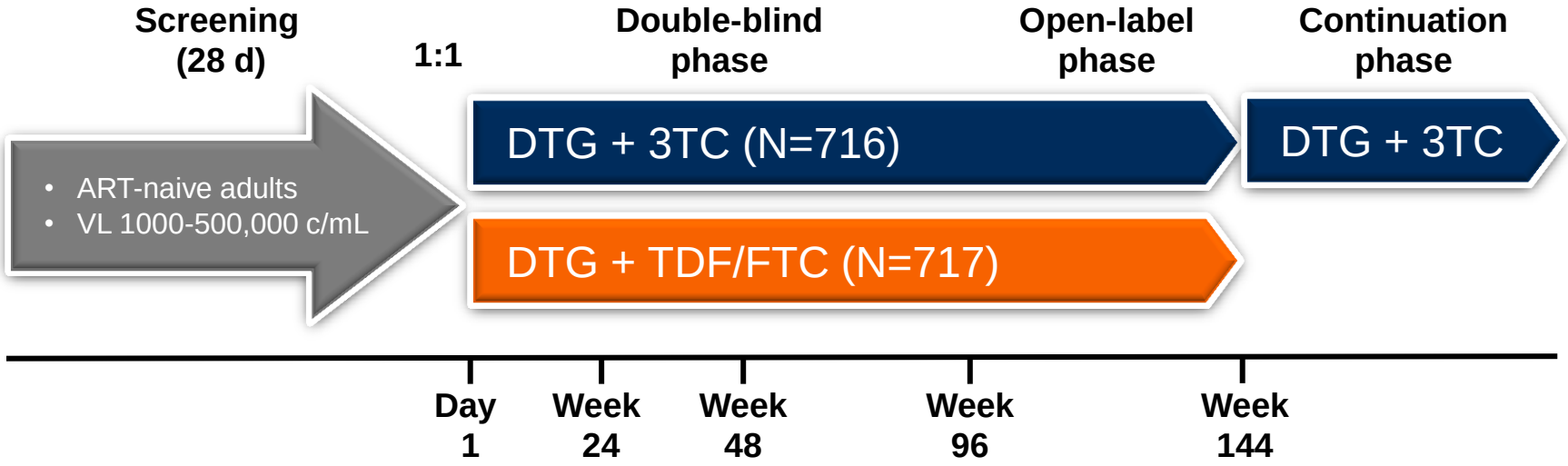
ACTG 5353[2] (n=120)

- Single-arm study DTG + 3TC
- >100,000 c/mL vs <100,000 c/mL randomization
- Three PDVFs
- n=1 [emergent M184V, R263R/K]

[1]Figueroa MI et al. CROI 2018. Boston, MA. Poster #489
[2]Taiwo BO et al. IAS 2017. Paris, France. Abstract MoAB0107LB

GEMINI-1 and -2 Phase III Study Design

Identically designed, randomized, double-blind, parallel-group, multicenter, noninferiority studies



Eligibility criteria
- ≤10 days of prior ART
- No evidence of pre-existing viral resistance based on presence of any major resistance-associated mutation
- No HBV infection or need for HCV therapy

Primary endpoint at Week 48: participants with HIV-1 RNA <50 c/mL (ITT-E snapshot)[a]

Countries

Argentina	Australia	Belgium
Canada	France	Germany
Italy	Republic of Korea	Mexico
Netherlands	Peru	Poland
Portugal	Romania	Russian Federation
South Africa	Spain	Switzerland
Taiwan	United Kingdom	United States

Baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL) CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3).

[a]–10% noninferiority margin for individual studies.

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

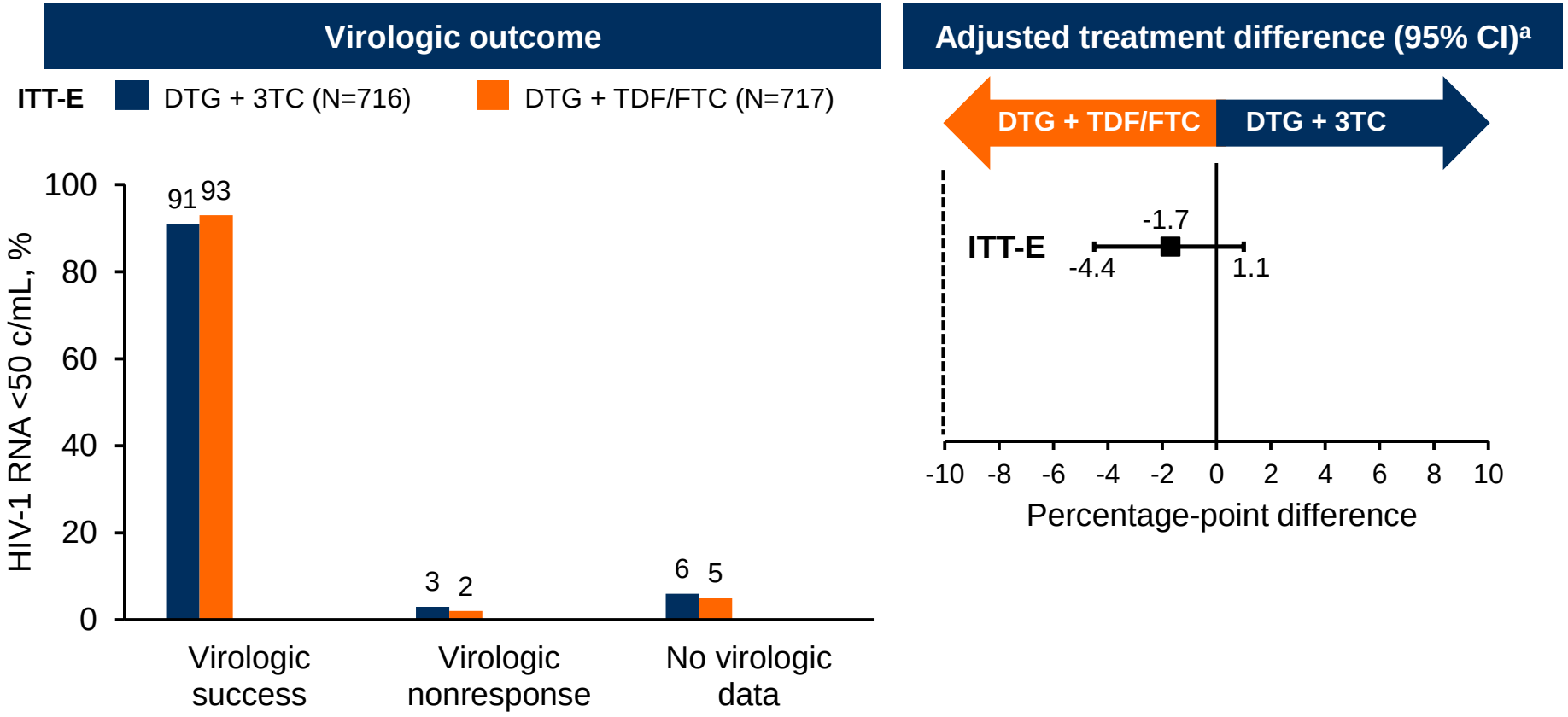
Demographic and Baseline Characteristics

Characteristic	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Age, median (range), y	32.0 (18-72)	33.0 (18-70)
≥50 y, n (%)	65 (9)	80 (11)
Female, n (%)	113 (16)	98 (14)
Race, n (%)		
African American/African heritage	99 (14)	76 (11)
Asian	71 (10)	72 (10)
White	480 (67)	497 (69)
Other	66 (9)	72 (10)
Ethnicity, n (%)		
Hispanic or Latino	215 (30)	232 (32)
Not Hispanic or Latino	501 (70)	485 (68)
HIV-1 RNA, median (range), log_{10} c/mL	4.43 (1.59-6.27)	4.46 (2.11-6.37)
≤100,000	576 (80)	564 (79)
>100,000[a]	140 (20)	153 (21)
CD4+ cell count, median (range), cells/mm^3	427.0 (19-1399)	438.0 (19-1497)
>200	653 (91)	662 (92)
≤200	63 (9)	55 (8)

[a]2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

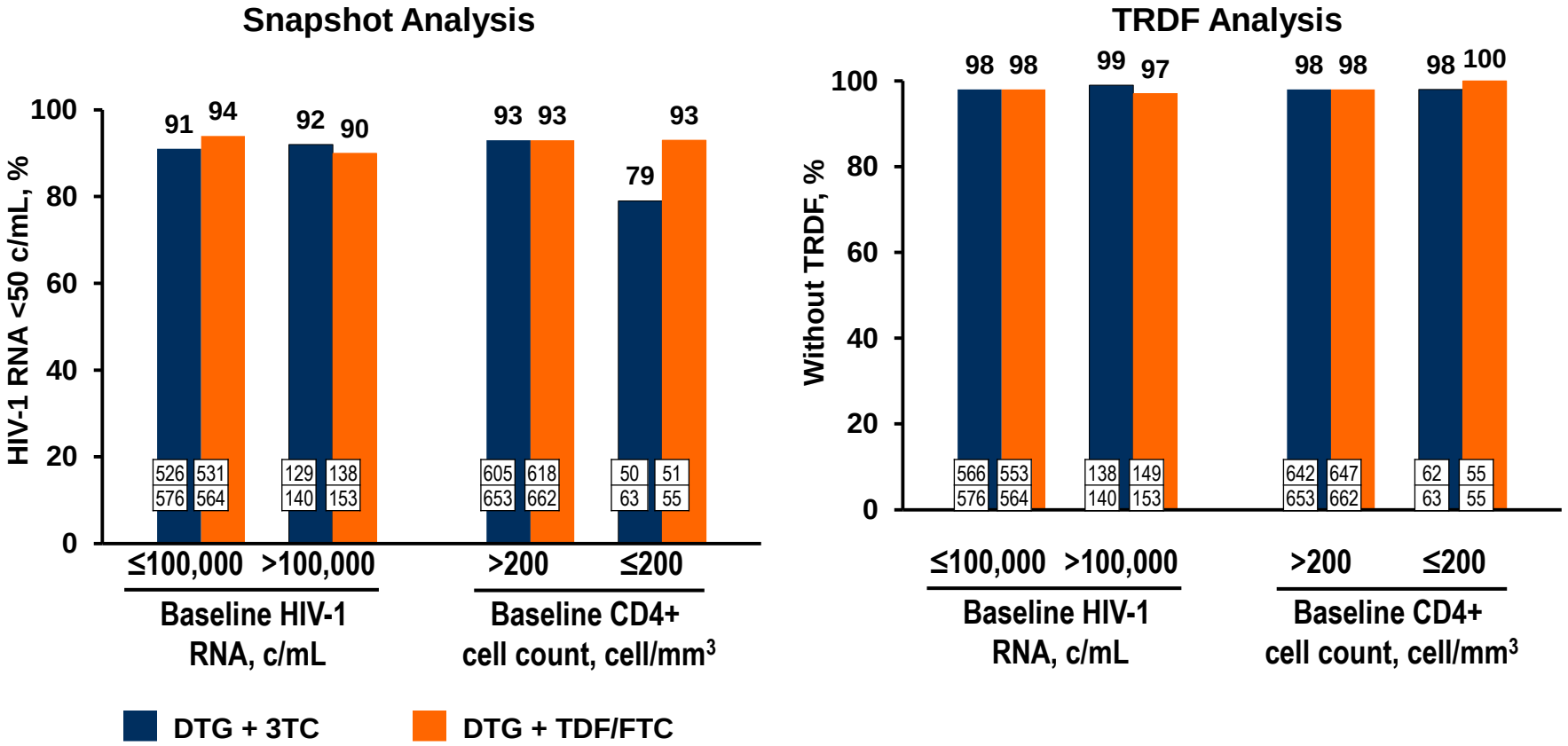
Pooled Snapshot Outcomes at Week 48: ITT-E Population



[a]Based on Cochran-Mantel-Haenszel stratified analysis adjusting for the following baseline stratification factors: plasma HIV-1 RNA (≤100,000 c/mL vs >100,000 c/mL), CD4+ cell count (≤200 cells/mm^3 vs >200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2).

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Pooled Outcomes at Week 48 Stratified by Baseline HIV-1 RNA and CD4+ Cell Count: Snapshot and TRDF Analysis



- 2% of participants in each arm had baseline HIV-1 RNA >500,000 c/mL
- Treatment related discontinuation = failure (TRDF) population accounts for confirmed virologic withdrawal (CVW), withdrawal due to lack of efficacy, withdrawal due to treatment-related AE, and participants who met protocol-defined stopping criteria
- DTG + 3TC CD4 <200 Snapshot non-response (n=13): **1 CVW**, 3 with VL >50 in window **(2 of 3 re-suppressed),** 2 discontinued due to AE (TB, Chagas disease), 2 protocol violations, 2 lost to follow-up, 1 withdrew consent, 1 withdrew to start HCV treatment, 1 change in ART (incarcerated)
- DTG + TDF/FTC < 200 Snapshot non-response (n=4):1 investigator discretion, 1 withdrew consent, 1 lost to follow-up, 1 VL >50 (re-suppressed)

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Confirmed Virologic Withdrawals Through Week 48: ITT-E Population

- Low rates of virologic withdrawals were observed at Week 48

Variable, n (%)	GEMINI 1		GEMINI 2		Pooled	
	DTG + 3TC (N=356)	DTG + TDF/FTC (N=358)	DTG + 3TC (N=360)	DTG + TDF/FTC (N=359)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
CVW	4 (1)	2 (<1)	2 (<1)	2 (<1)	6 (<1)	4 (<1)
Treatment-emergent resistance	**0**	**0**	**0**	**0**	**0**	**0**

- No treatment-emergent INSTI mutations or NRTI mutations were observed among participants who met CVW (confirmed virologic failure) criteria

Confirmed virologic withdrawal criteria is defined as a second and consecutive HIV-1 RNA value meeting virologic non-response or rebound. Virologic non-response is defined as either a decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ c/mL by Week 12 with subsequent confirmation unless plasma HIV-1 RNA is <200 c/mL, or confirmed plasma HIV-1 RNA levels ≥200 c/mL on or after Week 24. Virologic rebound is defined as confirmed rebound in plasma HIV-1 RNA levels to ≥200 c/mL after prior confirmed suppression to <200 c/mL.

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

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Adverse Events: Pooled ITT-E Population

n (%)	DTG + 3TC (N=716)	DTG + TDF/FTC (N=717)
Any AE	543 (76)	579 (81)
AE occurring in ≥5% of participants in either group		
Headache	71 (10)	75 (10)
Diarrhea	68 (9)	77 (11)
Nasopharyngitis	55 (8)	78 (11)
Upper respiratory tract infection	56 (8)	44 (6)
Nausea	27 (4)	53 (7)
Insomnia	27 (4)	45 (6)
Pharyngitis	36 (5)	32 (4)
Back pain	35 (5)	31 (4)
Drug-related AE	126 (18)	169 (24)
Grade 2-4 AE occurring in ≥1% of participants	42 (6)	47 (7)
Headache	8 (1)	8 (1)
AE leading to withdrawal from the study	15 (2)	16 (2)
Neuropsychiatric AEs leading to withdrawal	6 (<1)	4 (<1)
Any serious AE[a]	50 (7)	55 (8)

[a]2 deaths (acute myocardial infarction, n=1; Burkitt's lymphoma, n=1) in the GEMINI-2 study; both were in the DTG + 3TC group and were considered unrelated to the study drug regimen.

Cahn et al. AIDS 2018; Amsterdam, the Netherlands. Slides TUAB0106LB.

Implications for clinical practice

- Strategy may reduce potential toxicities and cost but who are the best candidates for dual therapy?
- ?applicability in resource limited settings (Hep B)
- How much adherence is enough?
- How often would you need to monitor (6/12 enough)?
- Role of dual therapy in more complex situations is unclear
  - High VL (?and CD4<200)
  - Comorbidities including TB
  - Pregnancy
  - Same day ART initiation (no VL/no resistance)

The future of ART

- **Decreasing ART exposure**
  - Decreasing drug dose
  - Decreasing dosing frequency
  - Decreasing numbers of drugs*
- **Different ART formulations**
  - Long-acting oral agents
  - Implantable agents
  - Long-acting injectables*
- **Pipeline***

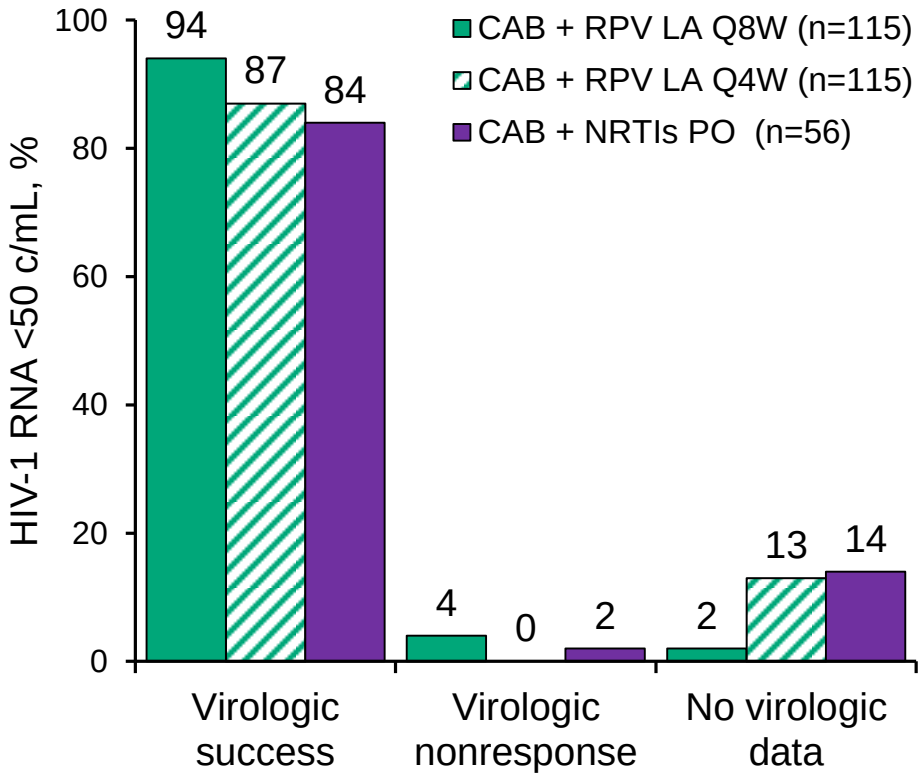
Long-acting injectables

- Cabotegravir (CAB) is an HIV-1 integrase inhibitor
  - Oral 30mg tablet ($t_{1/2}$ ~ 40 hours)
  - IM LA injection 200 mg/ml ($t_{1/2}$ ~20-40 days)
- Rilpivirine (RPV) is an HIV-1 NNRTI
  - Oral 25mg tablet ($t_{1/2}$ ~ 50 hours)
  - IM LA injection 300mg /ml ($t_{1/2}$ ~ 30-90 days)
- Oral 2DR CAB + RPV proof of efficacy through week 144 in LATTE[1]

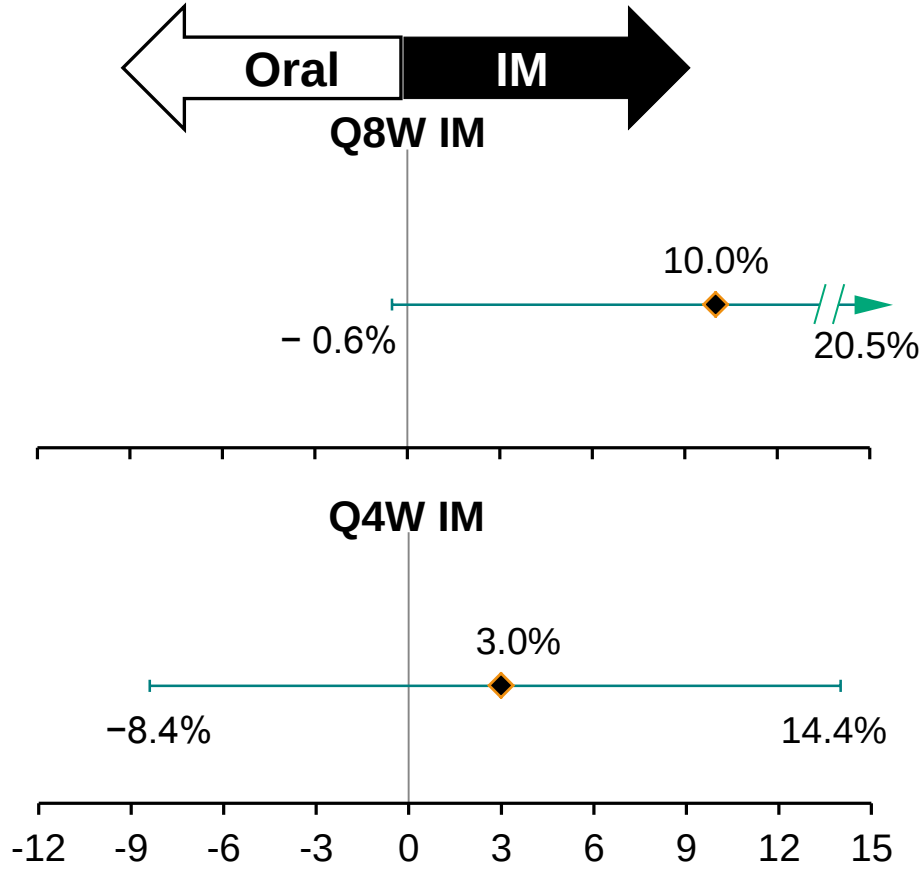
[1]Margolis D et al. Lancet ID 2015

LATTE-2: Induction with CAB + NRTIs followed by LA CAB + RPV Maintenance

Virologic outcomes



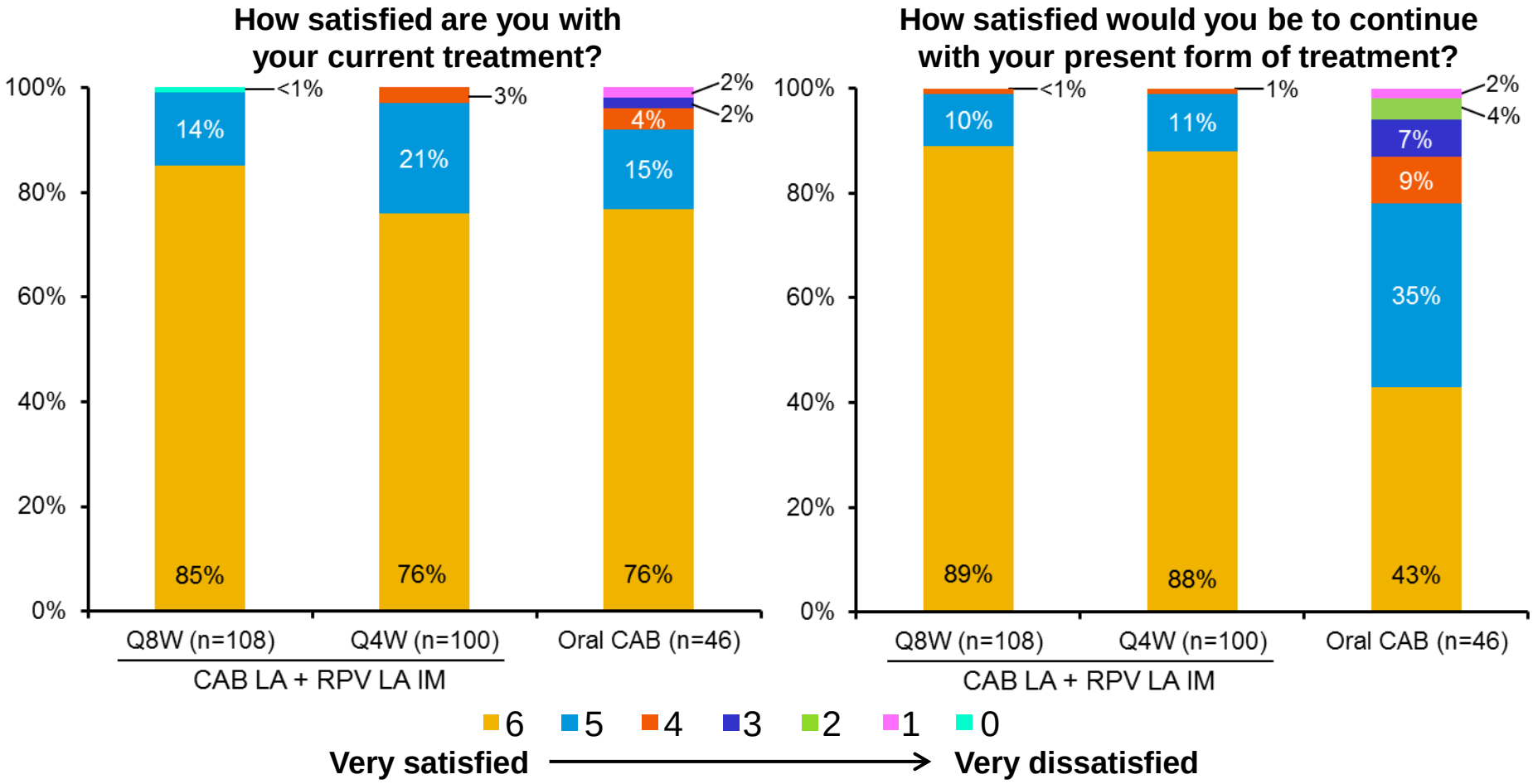
Treatment differences (95% CI)



CAB, cabotegravir; CI, confidence interval; IM, intramuscular; ITT-ME, intent-to-treat maintenance exposed; LA, long acting; NRTI, nucleoside reverse transcriptase inhibitor; PO, orally; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB; Margolis D et al. Lancet 2017.

Patient-Reported Outcomes at Week 96



CAB, cabotegravir; IM, intramuscular; LA, long acting; Q4W, every 4 weeks; Q8W, every 8 weeks; RPV, rilpivirine.

[a]Based on observed case data set of subjects who completed HIV Treatment Satisfaction Questionnaire status version at Week 96.

Eron et al. IAS 2017; Paris, France. Slides MOAX0205LB.

Long-acting injectables

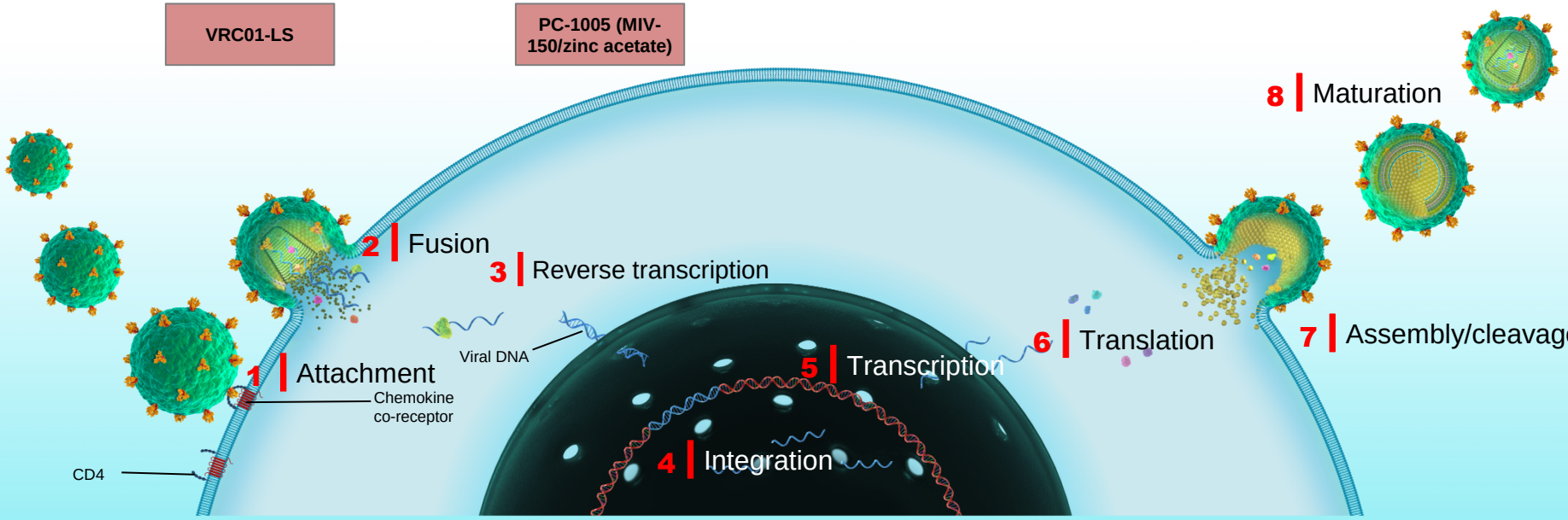
- Who would be the ideal candidate for injectable therapies?
- Implementation: is it feasible?
  - Where will people receive injections?
  - How to track injection schedules?

The future of ART

- **Decreasing ART exposure**
  - Decreasing drug dose
  - Decreasing dosing frequency
  - Decreasing numbers of drugs*
- **Different ART formulations**
  - Long-acting oral agents
  - Implantable agents
  - Long-acting injectables*
- **Pipeline***

HIV drug pipeline under clinical evaluation (Phase I–III)

Entry inhibitors	Monoclonal antibodies (mAb)	NRTIs/NtRTIs ('nukes')	NNRTIs ('non-nukes')	Integrase inhibitors	Protease inhibitors	Capsid inhibitors	Maturation inhibitors	Unique/ unknown MoA
Fostemsavir (GSK-934; FTR)	UB-421 (CD4 receptor)	EFdA (MK-8591)	Doravirine (MK-1439)	Bictegravir (GS-9883)	GS-PI1	GS-CA1	GSK2838232	MK-8507
Cenicriviroc (TBR-652; CVC)	PRO-140 (CCR5 receptor)	GS-9131	Elsulfavirine (VM1500)	Cabotegravir-LAI (GSK-744; CAB)				ABX464
Sifuvirtide (FS-0101)	Ibalizumab (TMB-355)		Rilpivirine-LAI (TMC278; RPV)	MK-2048				LEDGINs
Albuvirtide (FB006M; ABT)	VRC01		Dapivirine (TMC120; DPV)					
	VRC01-LS		PC-1005 (MIV-150/zinc acetate)					



HIV LIFE CYCLE

Thank you

- Chloe Orkin
- Laura Waters
- ViiV