Initial ART- must we always use INSTI's?

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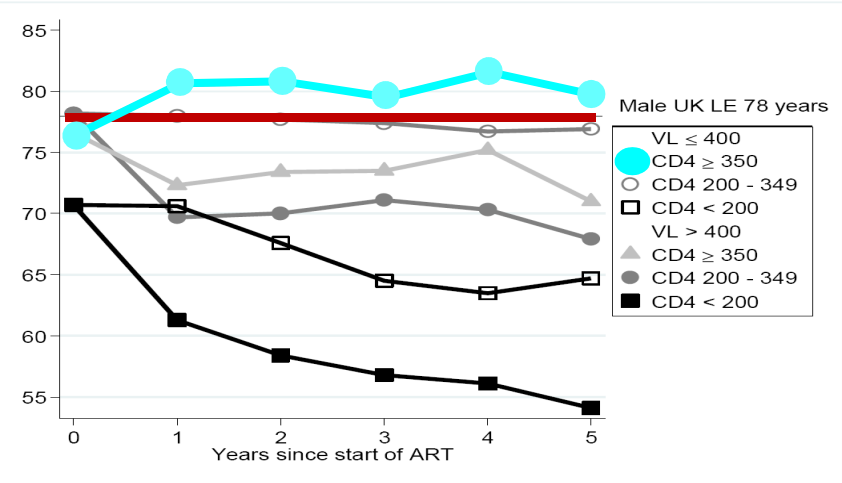
Disclosures

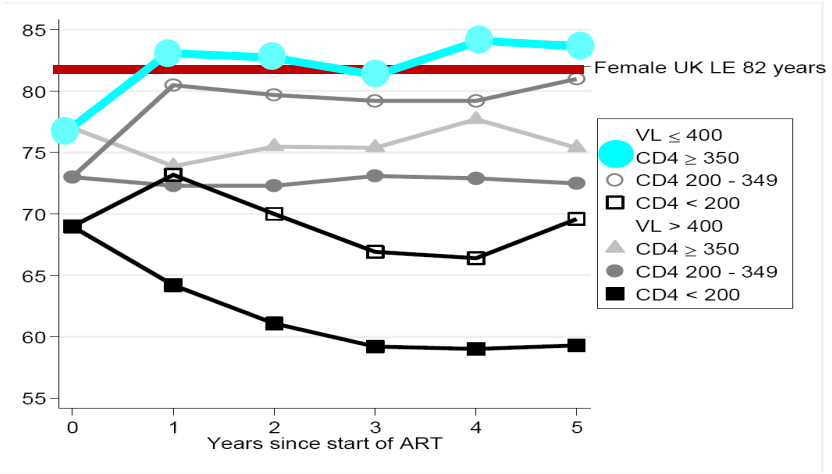
- Educational grants (HIV Unit): Merck Sharp & Dohme, Gilead Sciences, Janssen, ViiV Healthcare and Barts Charity
- Honoraria and travel sponsorship for lectures and advisory board contributions
- Member of the BHIVA Guidelines Subcommittee (2008–2017)
- Chair and executive trustee of BHIVA
- Not a patent holder or a shareholder
- No disclosures for spouse or family members

Life Expectancy = near normal, UK CHIC Cohort

Expected age at death* - men



Expected age at death* - women



* Expected age at death for a person aged 35 years with different durations of antiretroviral therapy according to current CD4 count and viral load suppression

Adapted from May M et al. AIDS (2014); 28: 1193-202.

London

FAST-TRACK CITIES

90%

Diagnosed

97%

On treatment

97%

Undetectable*

*VL <200 c/mL.
Public Health England, 2016.

But….we are in Europe...still (thank goodness!)

- What do the European guidelines recommend in first line ART

Guidelines: Recommended and preferred regimens

First-line ART

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*	–	BIC DTG RAL EVG/c	–
IAS USA (2016)[3]	TAF/FTC ABC/3TC*	–	DTG RAL EVG/c	–
BHIVA (2016)[4]	TAF/FTC TDF/FTC	RPV*	DTG RAL EVG/c	DRV/r ATV/r
WHO (2016)[5]	TDF/XTC	EFV	–	–

*Use recommended only if baseline viral load <100,000 copies/mL.
3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; BHIVA, British HIV Association; 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 January 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 April 2018;
3. Günthard HF, *et al. JAMA* 2016;316:191–210;
4. BHIVA Guidelines. Available from: http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf. Accessed January 2018;
5. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1. Accessed January 2018.

Recommended, preferred regimens + ALTERNATIVE

GUIDELINES	NRTI BACKBONE		NNRTI		INSTI		PI		NRTI-REDUCING
EACS (2017)[1]	TAF/FTC TDF/FTC ABC/3TC*	–	RPV*	EFV	DTG RAL EVG	–	DRV/c or /r	ATV/c or /r	DRV/c or /r + RAL LPV/r + XTC
DHHS (2018)[2]	TAF/FTC TDF/FTC ABC/3TC*	–	–	EFV RPV*	BIC DTG RAL EVG/c	–	–	ATV/c or /r DRV/c or /r	DRV/c or /r + RAL
IAS USA (2016)[3]	TAF/FTC ABC/3TC*	–	–	EFV RPV	DTG RAL EVG/c	–	–	DRV /c or /r	DRV/c or /r + RAL DRV/c or /r + DTG DRV/c or /r + XTC
BHIVA (2016)[4]	TAF/FTC TDF/FTC	ABC/3TC*	RPV*	EFV	DTG RAL EVG/c	–	DRV/r ATV/r	–	DRV/c or /r + RAL
WHO (2016)[5]	TDF/XTC	AZT/XTC	EFV	EFV 400 NVP	–	DTG	–	–	–

*Use recommended only if baseline viral load <100,000 copies/mL.
3TC, lamivudine; ABC, abacavir; ATV, atazanavir; AZT, zidovudine; BHIVA, British HIV Association; 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.

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3. Günthard HF, et al. JAMA 2016;316:191–210;
4. BHIVA Guidelines. Available from: http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf. Accessed January 2018;
5. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Available from: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1. Accessed January 2018.

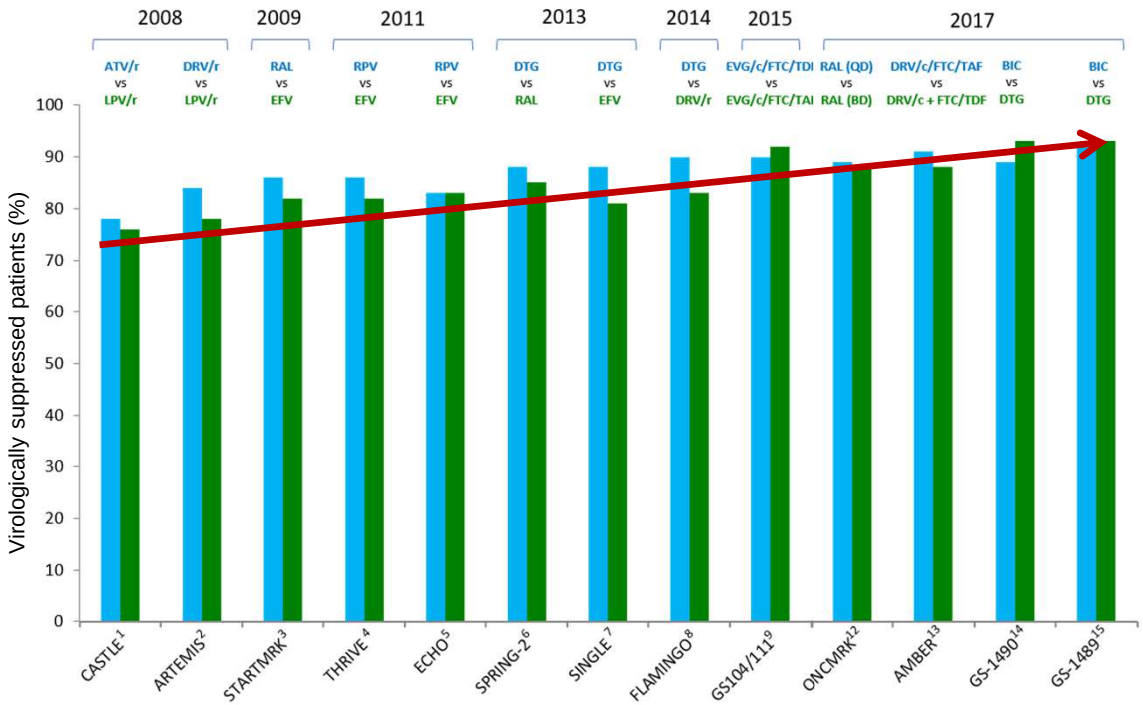
Note:

- In Europe and EU these guidelines do not yet take into account the most recently approved drugs:
  - BIC/FTC/TAF
  - D/C/F/TAF
- What do the efficacy trials show?

Efficacy outcomes excellent, improving year on year

First-line ART

Efficacy outcomes at week 48



Women-only studies

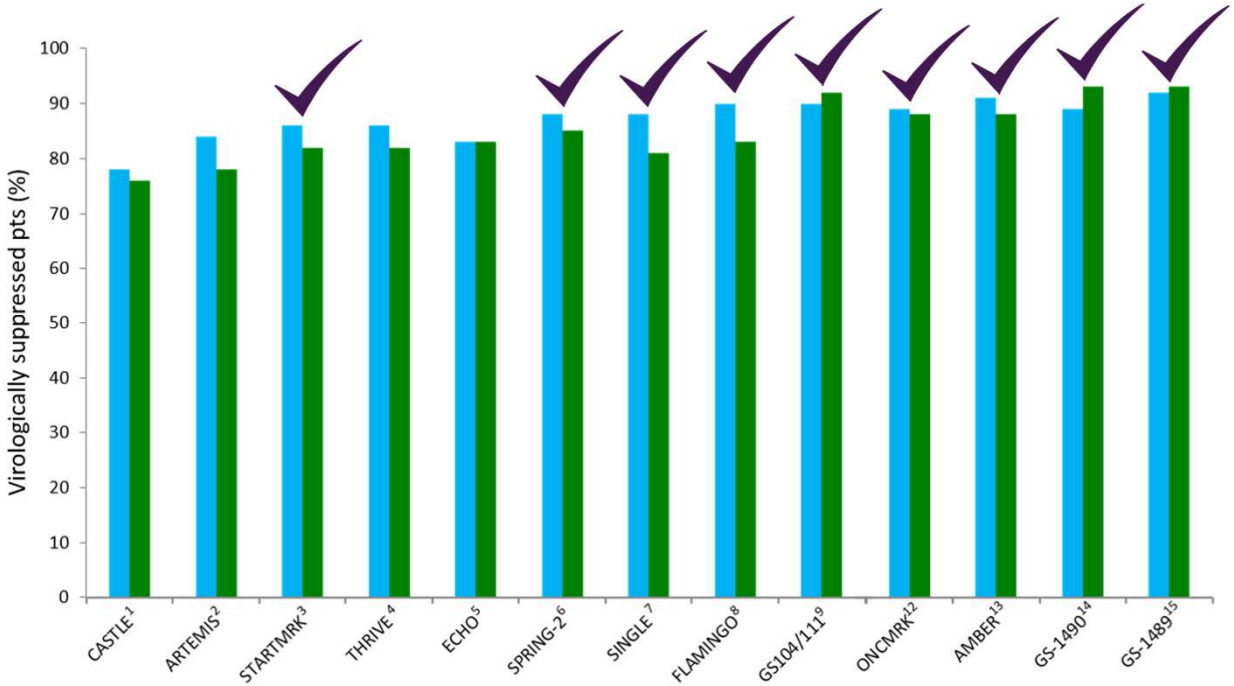
ATV, atazanavir; BD, twice daily; BIC, bictegravir; c, cobicistat; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FTC, emtricitabine; LPV, lopinavir; QD, once daily; r, ritonavir; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil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

Who is represented in these studies?

Trials where participants are:

- ✓ 50% white
- ✓ >70% male
- ✓ 100% CD4 >300
- ✓ >75% VL <100,000



1. Molina JM, *et al*. *Lancet* 2008;372:646–55;
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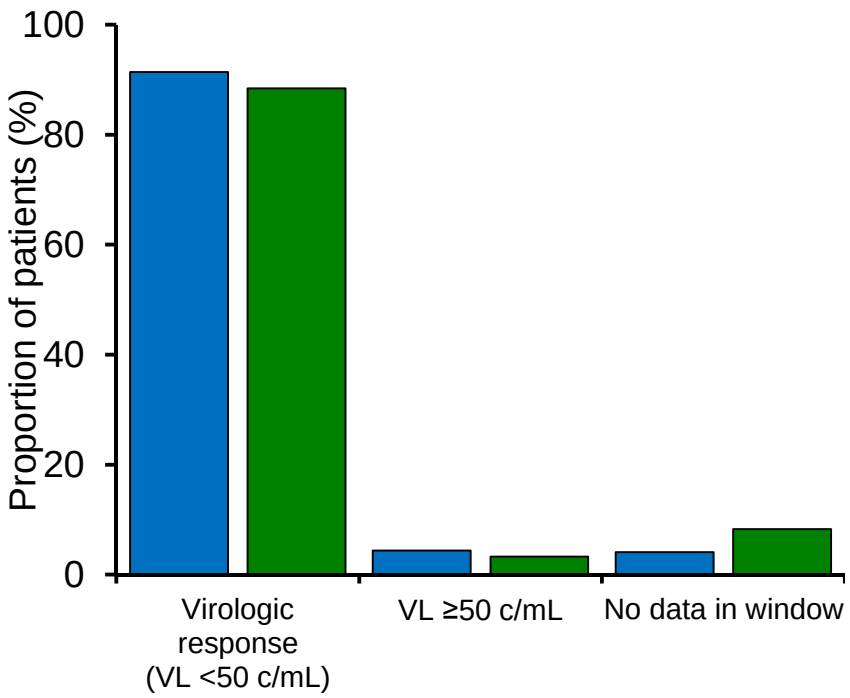
We need longer term data AND…

Trials enrolling:

- ✓ Older adults
- ✓ Women
- ✓ Trans and non-binary
- ✓ Ethnically diverse
- ✓ Adolescents
- ✓ Injecting drug users
- ✓ HCV and HBV co-infected
- ✓ CDC C diagnoses
- ✓ Comorbidities allowed

Describing efficacy outcomes (FDA snapshot)



3 categories:

VL < 50 c/mL

VL >50 c/mL driven by:

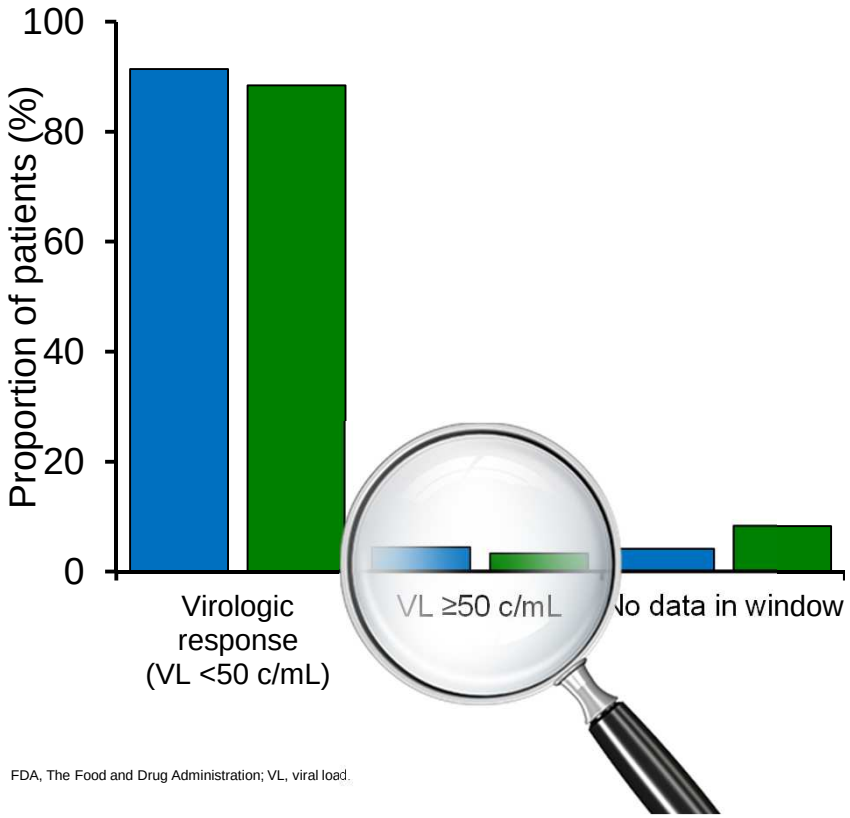
- Baseline VL
- Barrier to resistance

No data in window = did not get to end:

- Disengagement from trial / care
- Tolerability (discontinuations)
- Safety (withdrawals)

FDA, The Food and Drug Administration; VL, viral load.

Describing efficacy (FDA snapshot)

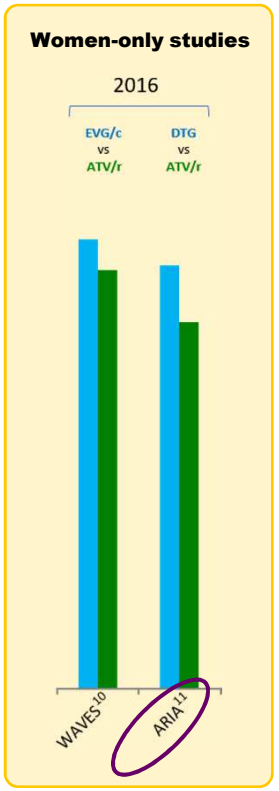


FDA, The Food and Drug Administration; VL, viral load.

VL >50 c/mL driven by:

- **Baseline VL**
- **Barrier to resistance**

Not all regimens work well if baseline VL >100,000 c/mL



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15. Gallant J, *et al*. *Lancet* 2017;390:2063–72.

Last 5 years: Moving toward zero resistance 48 weeks

STUDY	104/111[7] (TAF vs TDF)		FLAMINGO[1]		ARIA[2]		SINGLE[3]		GS1489 (ABC)[4]		GS 1490 (TDF)[5]		AMBER (TAF* vs TDF~)	
3rd agent	EVG/c	EVG/c	DTG	DRV/r	DTG	ATV/r	DTG	EFV	BIC	DTG	BIC	DTG	DRV/c*	DRV/c~
NRTI	7	5	0	0	0	1	0	1	0	0	0	0	1	0
PI	-	-	0	0	0	0	0	-	-	-	-	-	0	0
INSTI	5	3	0	0	0	0	-	-	0	0	0	0	-	-
NNRTI	-	-	-	-		-	-	4	-	-	-	-	-	-

1.Clotet B, *et al. Lancet* 2014;383:2222-31;
2.Orrell C, AIDS 2016, Durban;
3.Walmsley SL, *et al. N Engl J Med* 2013;369:1807-18;
4.Gallant J, *et al. Lancet* 2017;[epub ahead of print];
5.Sax PE, *et al. Lancet* 2017;[epub ahead of print].
6.Eron J. EACS 2017 Milan
7. . Wohl D,. CROI 2015; Seattle, Abstract 113LB.

No RPV data on the last slide: why ?

- Studies done prior 2013
- Prior to START data, and enrolled much lower CD4 counts, more with VL> 100,000c/ml
- No TAF so we cant compare them
- That is why EACS and BHIVA have included Odefesey as preferred option in 1st line

We now have convenient NNRTI, PI, INSTI TAF combinations

TRIPLE

DRUG	ATRIPLA[1]	EVIPLERA[2]	STRIBILD[3]	TRIUMEQ[4]	GENVOYA[5]	ODEFSEY[6]	SYMTUZA[7]	BIKTARVY[8]
COMPONENTS	Generic FDC TDF/XTC/EFV	TDF/FTC/RPV	TDF/FTC/EVG/c	ABC/3TC/DTG	TAF/FTC/EVG/c	**TAF/FTC/RPV**	**TAF/F/DRV/c**	TAF/BIC/FTC
CONSIDERATIONS	Premorbid Psychiatric	VL <100,000	Drug–drug interactions	HLAB*5701 co-infection	Drug–drug interactions	**VL <100,000**	**Drug–drug interactions**	UGT1A1 and CYP3A4 metabolism

Licensed once-daily fixed-dose combinations. Pill sizes are not to scale.

Filed for licensing: TDF/3TC/DOR (1439A)

1. Atripla SmPC. Available from: https://www.medicines.org.uk/emc/medicine/20505. Updated May 2017. Accessed October 2017;
2. Eviplera SmPC. Available from: https://www.medicines.org.uk/emc/medicine/25518. Updated June 2017. Accessed October 2017;
3. Stribild SmPC. Available from: https://www.medicines.org.uk/emc/medicine/27810. Updated June 2017. Accessed October 2017;
4. Triumeq SmPC. Available from: https://www.medicines.org.uk/emc/medicine/29178. Updated January 2017. Accessed October 2017;
5. Genvoya SmPC. Available from: https://www.medicines.org.uk/emc/medicine/31225. Updated September 2017. Accessed October 2017;
6. Odefsey SmPC. Available from: https://www.medicines.org.uk/emc/medicine/32117. Updated September 2017. Accessed October 2017;
7. Symtuza SmPC. Available from: http://www.medicines.org.uk/emc/medicine/34148. Updated September 2017. Accessed October 2017;
8. Biktarvy PI. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210251s000lbl.pdf. Accessed February 2018;
9. Juluca SmPC. Available from: https://www.viivhealthcare.com/our-medicines/juluca.aspx. Updated November 2017. Accessed December 2017.

Toxicity and tolerability: ACTG 5257

Equivalent in terms of virologic failure endpoint but…

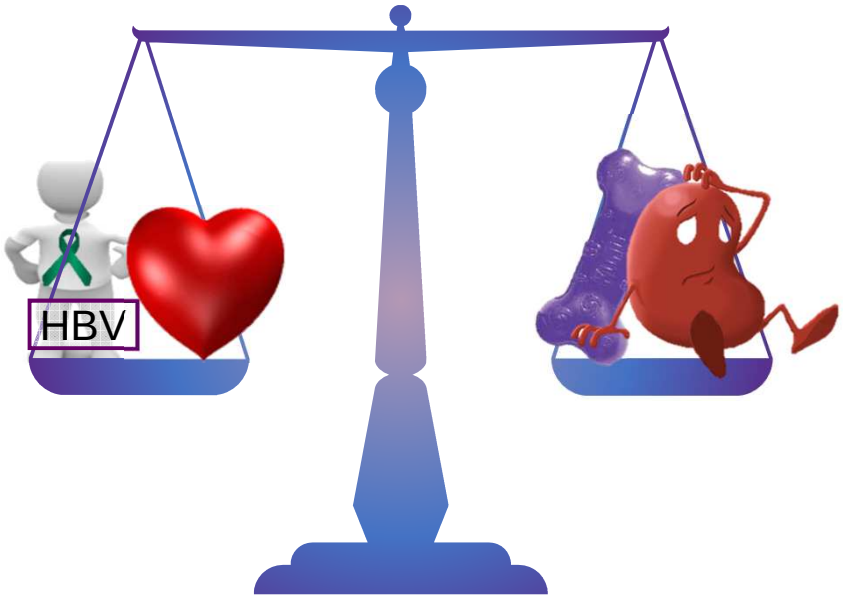
	RAL (N=603)	ATV/r (N=605)	DRV/r (N=601)
Any toxicity discontinuation	8 (1%)	95 (16%)	32 (5%)

Cumulative failure*		
ATV/r vs RAL	RAL superior	15% (10%, 20%)
DRV/r vs RAL	RAL superior	7.5% (3.2%, 12%)
ATV/r vs DRV/r	DRV/r superior	7.5% (2.3%, 13%)

*Difference in 96-week cumulative incidence (97.5% CI)

ACTG, AIDS Clinical Trials Group; ATV, atazanavir; CI, confidence interval; DRV, darunavir; r, ritonavir; RAL, raltegravir.
Landovitz RJ, *et al.* CROI 2014, Boston, MA, United States; abstract #85.

Challenge is reducing toxicity, lets start with NRTI toxicity



- TAF backbone in triple ART
- Two-drug regimens (2DR)- not yet enough data

2DR, two-drug regimen; ART, antiretroviral therapy; HBV, hepatitis B; NRTI, nucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide fumarate.

TAF Bone and Renal outcomes naïve studies

EVG/r GS-104/111[1,2]

- EVG/c + TAF/FTC vs TDF/FTC
- TAF: favorable renal biomarkers & BMD
- No renal or bone discontinuations TAF

BIC GS-1489[3]

- TAF/FTC/BIC vs ABC/3TC/DTG
- No differences in renal / bone biomarkers at Week 48
- No renal/bone discontinuations

BIC GS-1490[3]

- TAF/FTC/BIC vs ABC/3TC/DTG
- TAF favourable renal / bone biomarkers at Week 48
- No renal/bone discontinuations

DRV/c AMBER

- F/TAF/DRV c vs F/TAF + DRV/c
- TAF: favorable renal biomarkers & BMD
- No renal or bone discontinuations on F/TAF
- One discontinuation due to bone marrow oedema on TDF

3TC, lamivudine; ABC, abacavir; BIC, bictegravir; BMD, bone mineral density; c, cobicistat; DTG, dolutegravir; EVG, elvitegravir; FTC, emtricitabine; TAF, tenofovir alafenamide fumarate; TDF tenofovir disoproxil fumarate.

1.Sax PE, *et al*. *Lancet* 2015;385:2606–15; 2.
2.Sax PE IAS Paris 2017
3. Gallant J, *et al*. *Lancet* 2017;390:2063–72.
3.Eron J EACS 2017 Milan

TAF Lipid outcomes Wk 48

EVG/r GS-104/111[1,2]

- EVG/c + TAF/FTC vs TDF/FTC
- TC ratio similar
- No statistical differences in % started lipid lowering agents

BIC GS-1489[3]

- TAF/FTC/BIC vs ABC/3TC/DTG
- TC ratio similar
- No statistical differences in % started lipid lowering agents

BIC GS-1489[3]

- TAF/FTC/BIC vs ABC/3TC/DTG
- TC ratio similar

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DRV/c AMBER

- F/TAF/DRV c vs F/TAF + DRV/c
- TC ratio similar
- No statistical differences in % started lipid lowering agents

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3. Gallant J, *et al*. *Lancet* 2017;390:2063–72.
3.Eron J EACS 2017 Milan

Current challenges of the INSTI as third agent

CNS AEs

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 events 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

Resistance

First-generation INSTI

- RAL and EVG more resistance than PI

Second-generation INSTI

- Genetic barrier closer to PI/r

DDIs

INSTI drug–drug interactions

- RAL/DTG chelation
- EVG/c booster, so DDIs
- BIC: UGT1A1 and Cyp3 A4 metabolism

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.

Current challenges of the NNRTI as third agent

CNS AEs[1,2]

EFV

- Especially insomnia
- Cognitive function
- Mood
- Suicidality

RPV:

- Better than EFV on this

Virological[3,4]

Resistance: EFV and RPV

Failures with both NRTI and NNRTI mutations

High viral load:

- EFV : ok
- RPV : worse outcomes VL > 100,000c/ml

Drug –Drug/Food Interactions[5]

Drug–food issues

- Rilpivirine: 375KPa meal
- Efavirenz:-

Drug–drug interactions

- Rilpivirine: Acid lowering drugs
- Efavirenz: strong inducer

1.Arenas-Pinta START Abstract: THAB0202
3 Cohen CJ, *et al*. *Lancet* 2011;378:229–37;
4 Molina JM, *et al*. *Lancet* 2011;378:238–46;
5. www.hivdruginteractions.org.uk

Current challenges of the b/PI as third agent

Renal adverse events[1,2]

ATV/r and Lop/r and CKD

- Cumulative risk
- Use more than doubles the risk of CKD
- ATV worse with TDF

CVS signal[3]

Darunavir/r

- Cohort suggests worse outcomes than ATV/r

Atazanavir /r

- Possible link to bilirubin association with cardio-protection

Drug-Drug Interactions

Ritonavir driven drug–drug interactions

- CYP 3A4

Cobicistat driven drug–drug interactions

- CYP 3A4 and CYP 2D6

. 1. Ryom L et al. CROI 2012. Seattle, WA. #865;
2. Nishijima T et al. AIDS 2014;28:1903–191.
3. Ryom L, et al. CROI, 2017, #128LB.

Key Drug–Drug Interactions With RTV

Exposures Increase With RTV

- Maraviroc
- Antiarrythmics
- Anticancer agents
- Anticonvulsants (some)
- Antidepressants (some)
- Beta-blockers
- Calcium channel blockers
- Colchicine
- Digoxin
- Erectile dysfunction drugs
- Glucocorticoids
- Methamphetamine
- Rifabutin
- Sedatives/hypnotics
- Statins (some)

Exposures Decrease With RTV

- Anticonvulsants (some)
- Antidepressants (some)
- Bupropion
- Ethinyl estradiol
- Methadone
- Theophylline
- Rifampin

Key Drug–Drug Interactions With COBI

Exposure Increased With COBI

- Antacids
- Antiarrythmics
- Benzodiazepines
- Beta-blockers
- Calcium channel blockers
- Erectile dysfunction drugs
- Inhaled/injectable corticosteroids
- OCPs (norgestimate)
- Statins

Increase COBI Exposure

- Azole antifungals
- Clarithromycin

Decrease COBI Exposure

- Rifabutin
- Carbamazepine
- Phenytoin

No interaction between COBI and methadone

Drug interactions cobicistat ≠ ritonavir

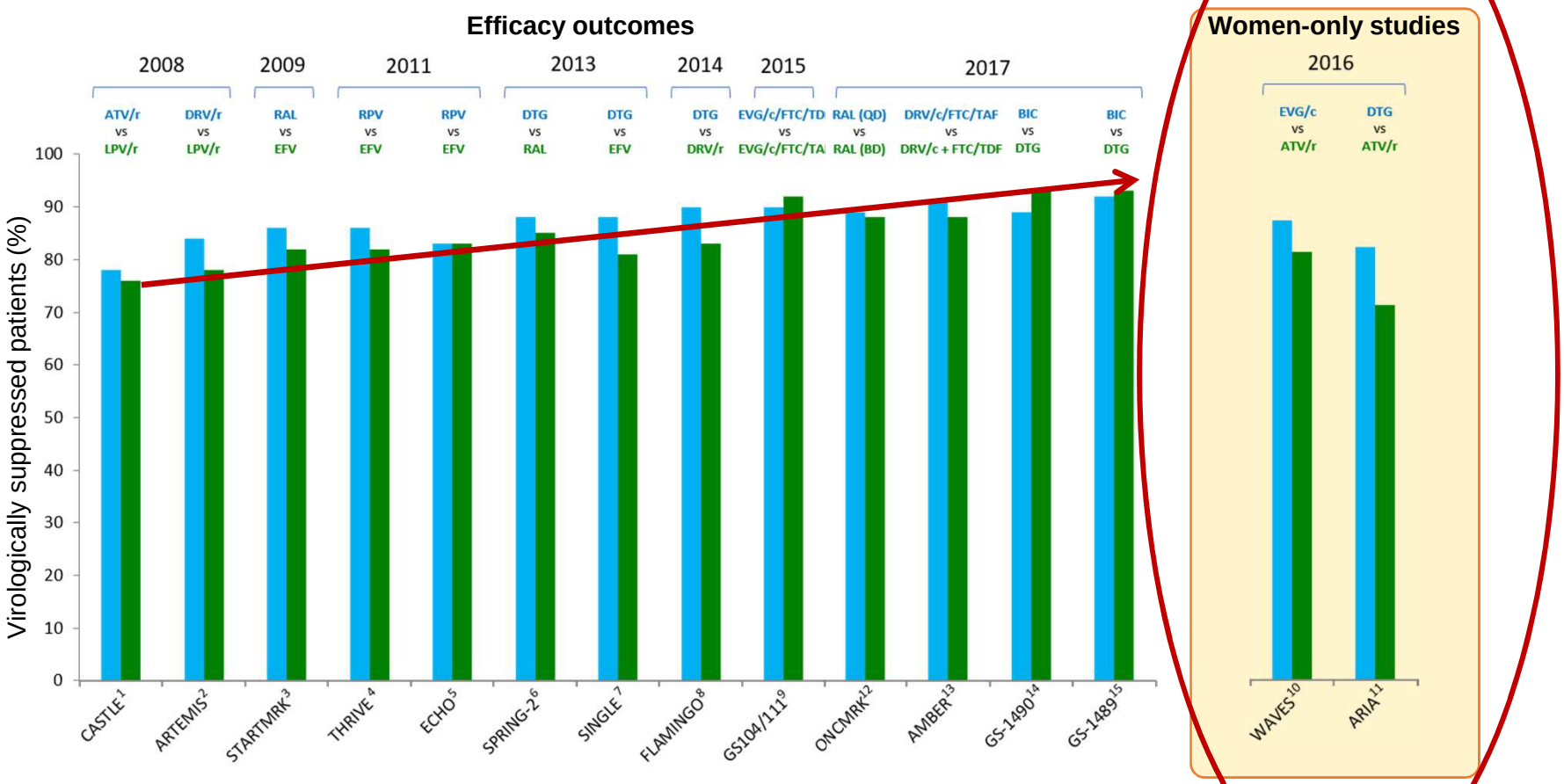
Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected | No Clear Data

Do Not Coadminister | Potential Interaction | Potential Weak Interaction | No Interaction Expected | No Clear Data

Results Key

	Cobicistat (with ATV or DRV)	Elvitegravir/Cobi/FTC/TAF	Ritonavir
Carbamazepine	Do Not Coadminister	Do Not Coadminister	Potential Interaction
Citalopram	Potential Weak Interaction	Potential Weak Interaction	Potential Weak Interaction
Fluoxetine	Potential Weak Interaction	Potential Weak Interaction	Potential Interaction
Haloperidol	Potential Weak Interaction	Potential Weak Interaction	Potential Weak Interaction
Lamotrigine	No Interaction Expected	No Interaction Expected	Potential Interaction
Mirtazapine	Potential Interaction	Potential Interaction	Potential Interaction
Olanzapine	No Interaction Expected	No Interaction Expected	Potential Interaction
Quetiapine	Do Not Coadminister	Do Not Coadminister	Do Not Coadminister
Sertraline	Potential Weak Interaction	No Interaction Expected	Potential Interaction

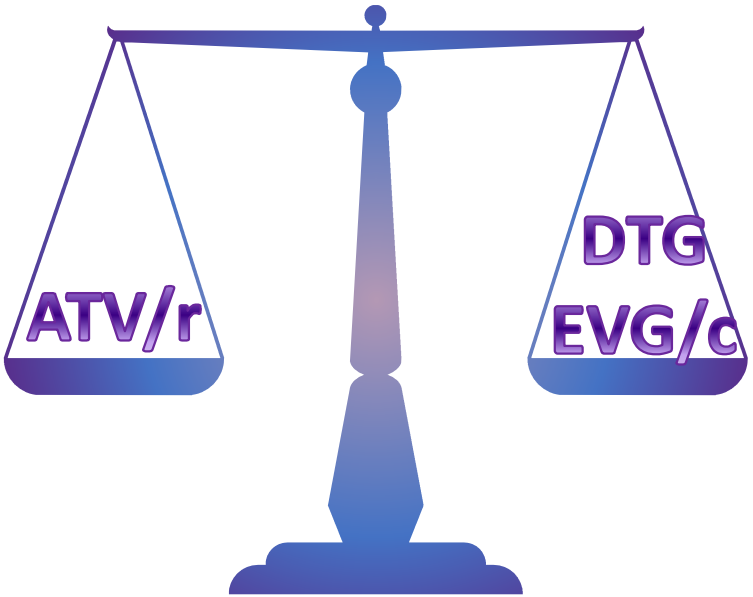
What about efficacy in women?



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.

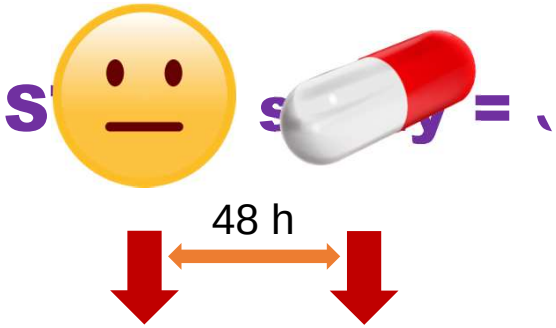
Women only studies: ARIA and WAVE compared against ATV/r



- Atazanavir levels are higher in women
- Failures were driven by safety outcomes
- We don't have a head to head DRV/r to 2nd gen INSTI comparator in women

2DR, two-drug regimen; ART, antiretroviral therapy; HBV, hepatitis B; NRTI, nucleoside reverse transcriptase inhibitor; TAF, tenofovir alafenamide fumarate.

When to start



- Engagement with care
- Infrastructure
- Resistance
- Virologic outcomes
- Safety

Chelsea and Westminster Hospital NHS
NHS Foundation Trust

INSIGHT START Study Group, *et al. N Engl J Med* 2015;373:795–807.

Caution 2DR studies : First line

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]

Adapted from clinicaloptions.com

2DR, two-drug regimen; 3TC, lamivudine; ACTG, AIDS Clinical Trials Group; CAB, cabotegravir; DRV, darunavir; DTG, dolutegravir; PDVF, protocol-defined virologic failure; r, ritonavir; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.

1. Sued O, *et al.* IAS 2017, Paris, France; abstract #MOAB0106LB;
2. Taiwo BO, *et al.* IAS 2017, Paris, France; abstract #MOAB0107LB.

First line ART - summary

Thank you

?

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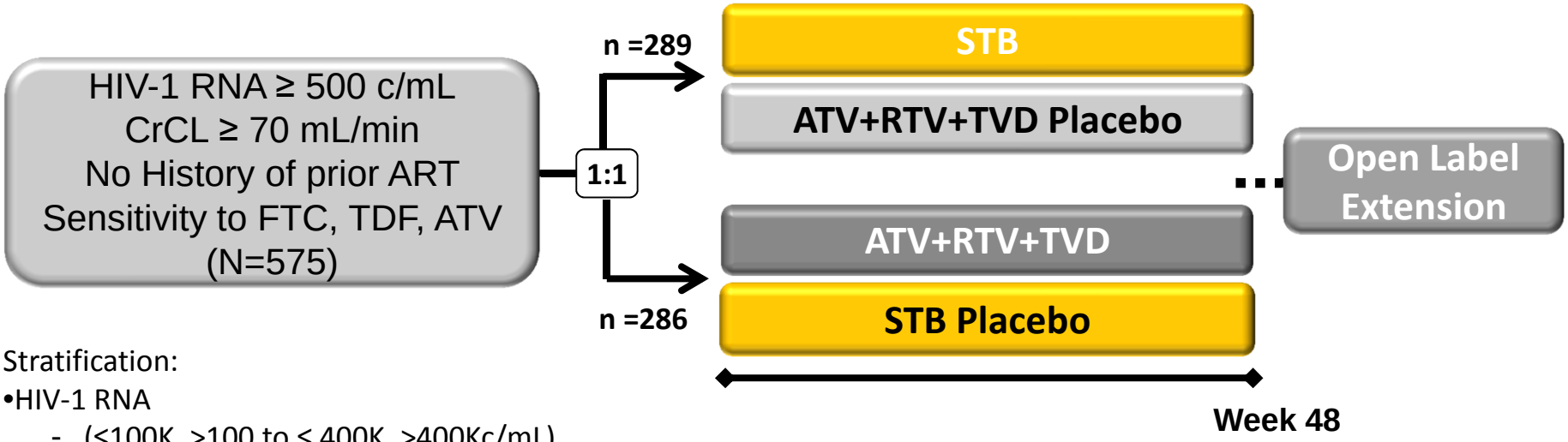
@profchloe_orkin

WAVES: Women AntiretroViral Efficacy and Safety Study

Study Design

First all-women, international, randomized, double-blind, phase 3 trial



Stratification:
- HIV-1 RNA
  - (≤100K, >100 to ≤ 400K, >400Kc/mL)
- Race (Black or non-Black)

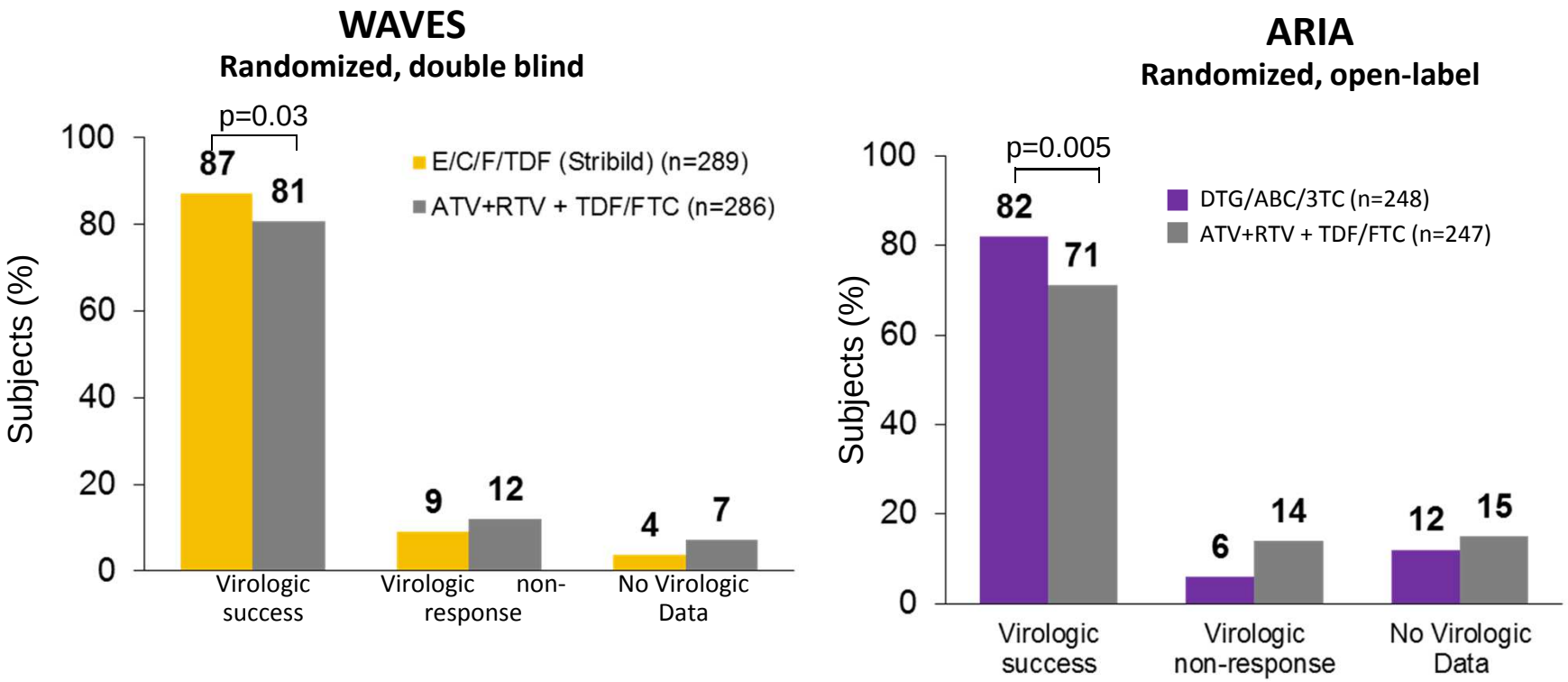
Primary endpoint: HIV-1 RNA < 50 c/mL at Week 48 by FDA Snapshot (non-inferiority margin of 12%). If non-inferiority is established, then superiority will be tested

Squires K, et al .IAS 2015. Vancouver, Canada. # MOLBPE08
Hodder S, et al. ICAAC 2015; San Diego. Oral
Kityo C, et al. EACS 2015; Barcelona, Spain. Poster Discussion #BPD1/4

(EVG/COBI/FTC/TDF): elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
ATV + RTV + TVD: atazanavir + ritonavir + emtricitabine/tenofovir disoproxil fumarate

WAVES & ARIA
Virology Outcomes and Resistance Emergence in HIV-infected Women on INSTI-based ART at Week 48

These regimens have not been compared in a head-to-head trial.

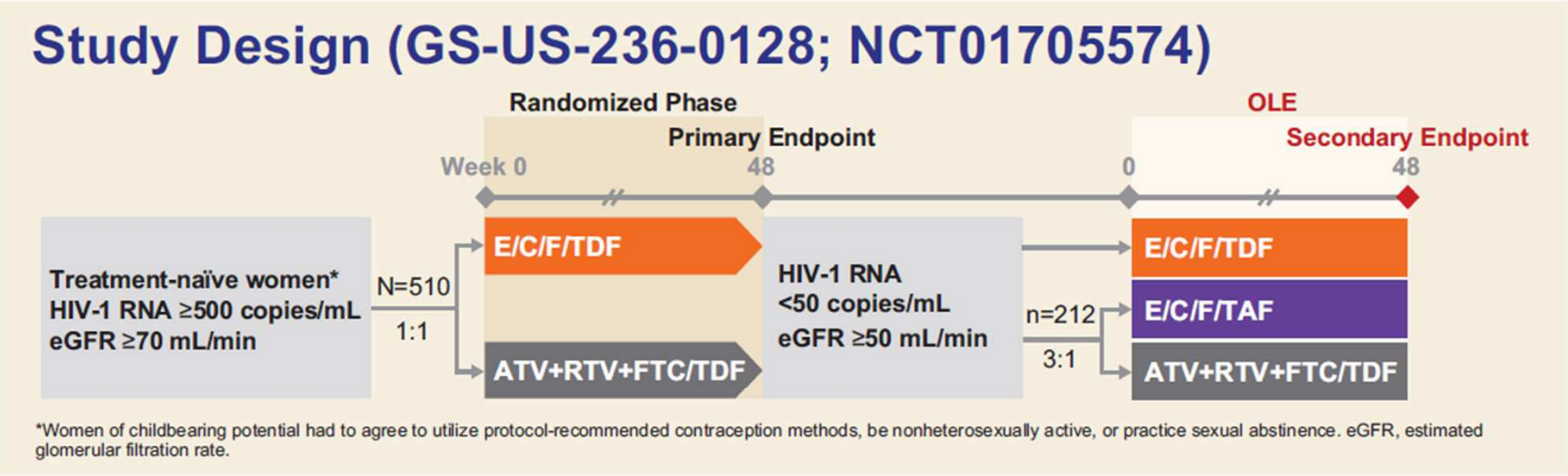


Superior virologic efficacy for INSTI-based regimens in women compared to ATV+RTV regimens

There was no emergent resistance to the regimen components in the INSTI arms

Hagins D, et al. ID Week 2016 New Orleans. #949
Kulkarni R, et al. ID Week 2016. New Orleans. #1509

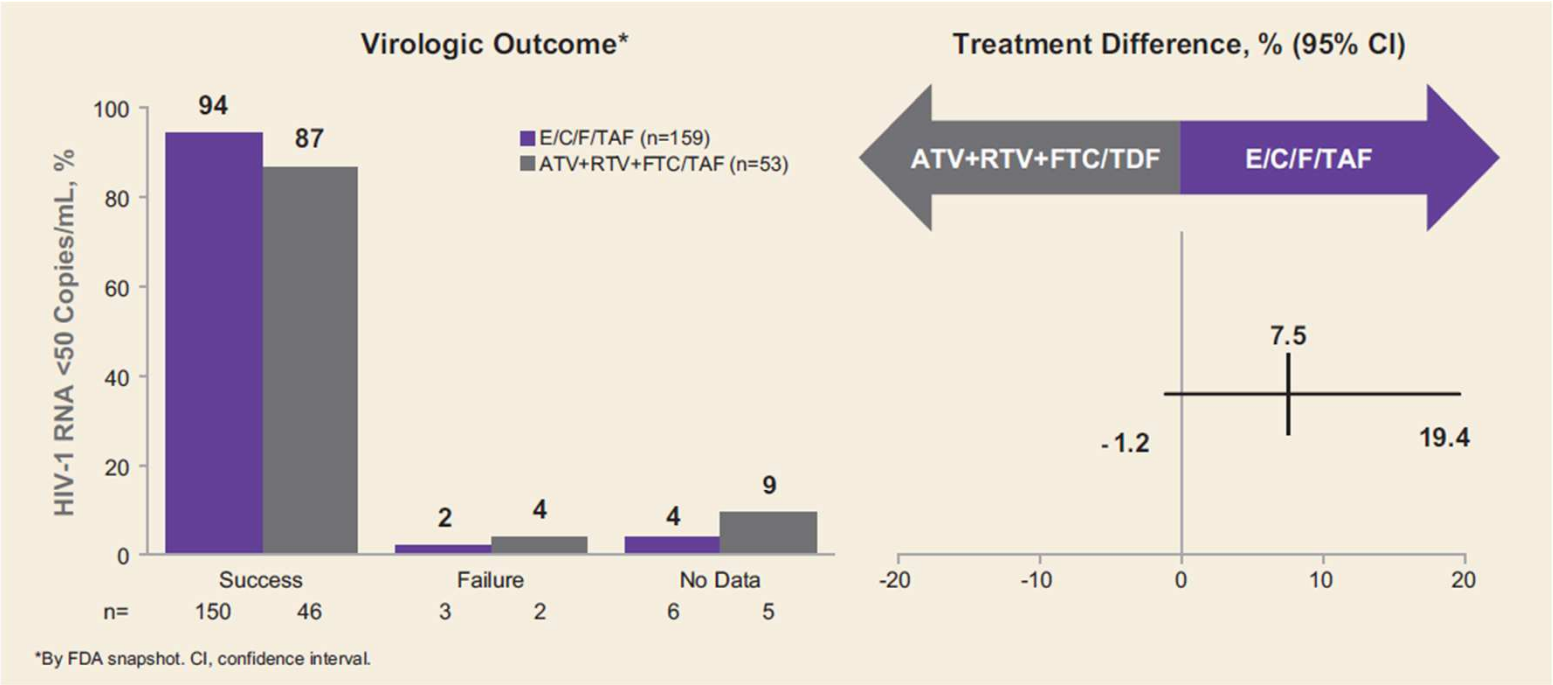
WAVES : E/C/F/TAF OLE Wk 48 results Design



- Phase 3b, randomized, double-blind, active-controlled phase with rerandomized, open-label, active-controlled, extension phase
- Primary efficacy endpoint in randomized phase met: proportion of participants with HIV-1 RNA <50 copies/mL based on Week 48 FDA snapshot analysis[1]
- Secondary endpoints: efficacy, safety, and tolerability at Week 48 in OLE

Hoddder S & al. CROI 2017. Poster 443

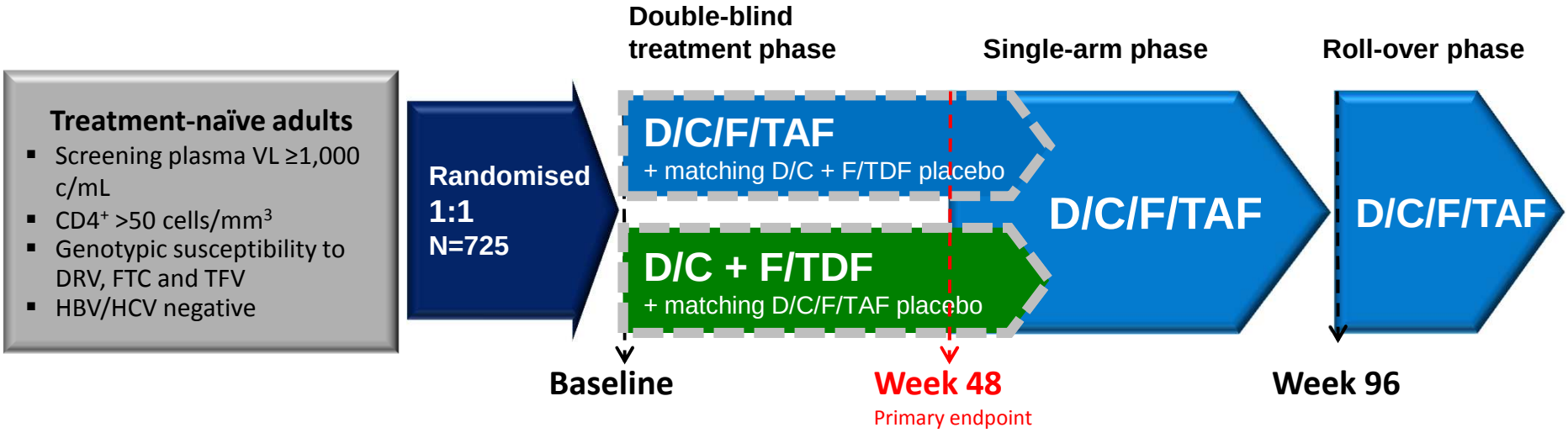
WAVES : E/C/F/TAF OLE Wk 48 results
Virological outcomes at Wk 48



- Greater proportion of participants maintained virologic suppression with E/C/F/TAF vs ATV+RTV+FTC/TDF
- 85% on E/C/F/TAF vs 72% on ATV+RTV+FTC/TDF had HIV-1 RNA <20 copies/mL (difference 13%; 95% CI 0%, 28%)
- No emergent resistance mutations were detected in either group

Hoddder S & al. CROI 2017. Poster 443

AMBER: Phase 3, Randomised, Double-blind, Multicenter* Trial



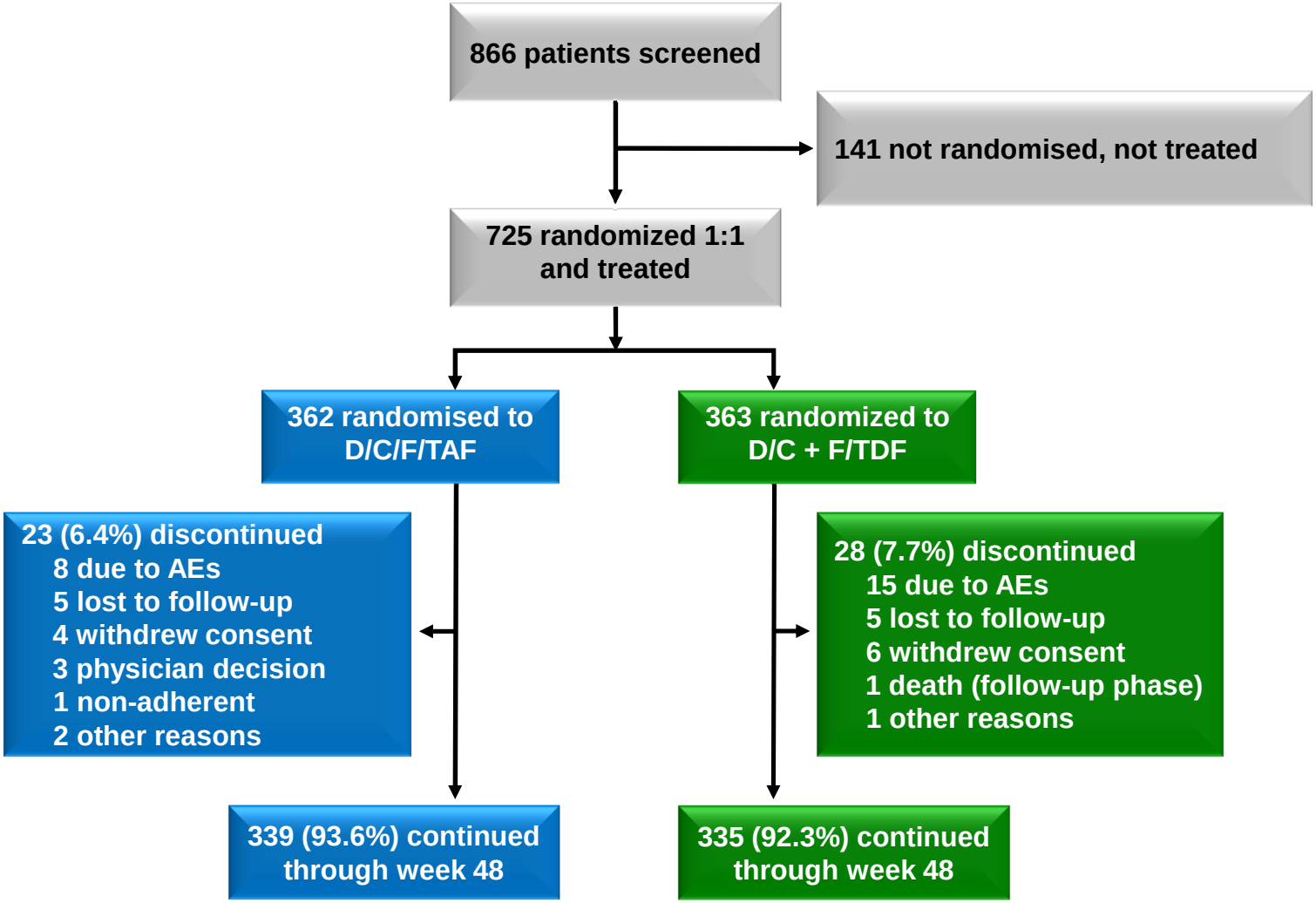
Primary objective: Assess non-inferiority of D/C/F/TAF vs D/C + F/TDF by proportion of patients with VL <50 c/mL at 48 weeks (NI margin 10%; FDA-Snapshot algorithm)†

Randomisation stratified by screening VL ≤/>100,000 c/mL and CD4+ </≥ 200 cells/mm3

*121 sites in USA, Canada, Belgium, France, Germany, Italy, Poland, Russia, Spain, UK
†Lower limit of 95% CI of stratified Mantel-Haenszel difference between D/C/F/TAF and control >–10%

AMBER (NCT02431247)

Patient Disposition



Baseline Characteristics

	D/C/F/TAF QD N=362	Control N=363	Total N=725
Median (IQR) age, years	34 (27–42)	34 (27–42)	34 (27–42)
Male, n (%)	318 (87.8)	322 (88.7)	640 (88.3)
Race, n (%)			
White	300 (82.9)	300 (82.6)	600 (82.8)
Black/African-American	40 (11.0)	40 (11.0)	80 (11.0)
Other races	22 (6.1)	23 (6.3)	45 (6.2)
Median (IQR) $\log_{10}$ VL, c/mL	4.4 (4.0–4.8)	4.6 (4.2–4.9)	4.5 (4.1–4.9)
Median (IQR) $CD4^+$ count, cells/mm^3	461.5 (342–617)	440.0 (325–594)	453.0 (333–601)
Median (IQR) $eGFR_{cr}$, mL/min (Cockcroft-Gault)	119 (105–135)	118 (103–138)	119 (104–136.5)
Hepatitis B or C co-infection	0	0	0
Genotype at screening	**N=361**	**N=362**	**N=723**
≥1 primary PI RAMs	7 (1.9)	8 (2.2)	15 (2.1)
≥1 NRTI RAMs	18 (5.0)	16 (4.4)	34 (4.7)
≥1 NNRTI RAMs	55 (15.2)	63 (17.4)	118 (16.3)

CO [4]2

Diapositiva 40

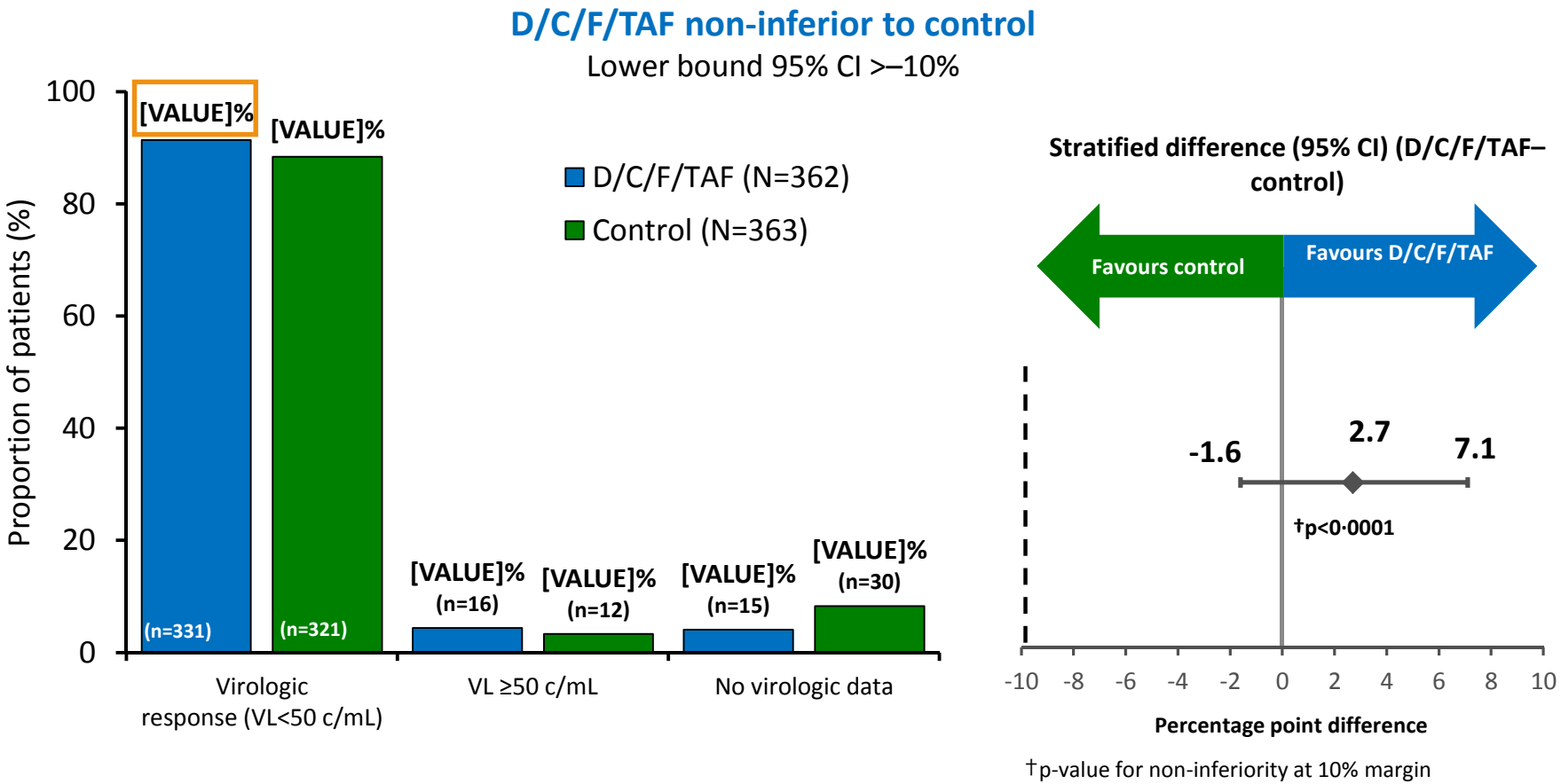
CO [3]2 question for Janssen: what percentage had more than one class baseline resistance i.e. NNRTI+NRTI ec (not for the slides but for questions)
Chloe Orkin; 18/10/2017

CO [4]2 i have realised we definitely need VL > 100,000 and CD4 <200 categories here
Chloe Orkin; 18/10/2017

VL ≥50 c/mL definition now in slide notes

Virologic Outcome at Week 48

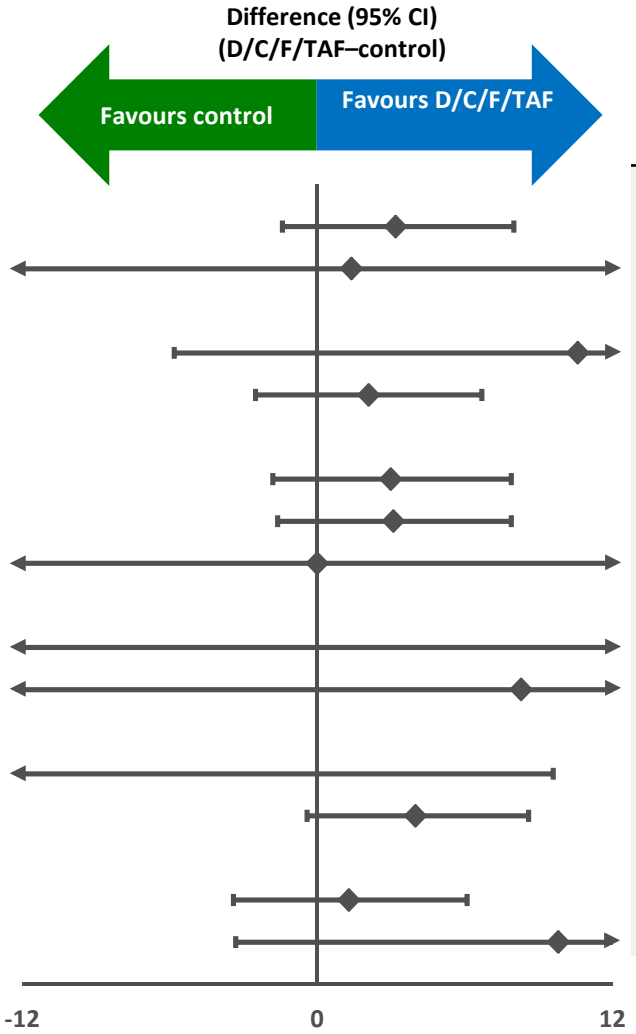
(FDA Snapshot; <50 c/mL) (ITT)



- Per Protocol analysis: 94.0% vs 92.2%; difference 1.5%; 95% CI –2.3%; +5.2%; p<0.0001

Virologic Response by Subgroups at Week 48
(FDA Snapshot; <50 c/mL) (ITT)

	Virologic response		Difference (95% CI)
	D/C/F/TAF n/N (%)	Control n/N (%)	Difference (95% CI)
Age (years)			
≤50	299/326 (91·7)	293/331 (88·5)	3·2 (-1·4; 8·0)
>50	32/36 (88·9)	28/32 (87·5)	1·4 (-15·5; 19·8)
Gender			
Female	39/44 (88·6)	32/41 (78·0)	10·6 (-5·8; 28·0)
Male	292/318 (91·8)	289/322 (89·8)	2·1 (-2·5; 6·7)
Race			
White	276/300 (92·0)	267/300 (89·0)	3 (-1·8; 7·9)
Non-Black or African American	281/305 (92·1)	275/309 (89·0)	3·1 (-1·6; 7·9)
Black or African American	34/40 (85·0)	34/40 (85·0)	0 (-16·9; 16·9)
Asian	4/4 (100·0)	7/7 (100·0)	
American Indian or Alaskan Native	1/1 (100·0)	1/2 (50·0)	50 (-77·0; 98·7)
Other	15/15 (100·0)	11/12 (91·7)	8·3 (-16·8; 38·5)
Baseline CD4$^+$ count, cells/mm^3			
<200	16/22 (72·7)	25/29 (86·2)	-13·5 (-37·8; 9·6)
≥200	315/340 (92·6)	296/334 (88·6)	4 (-0·4; 8·6)
Baseline viral load, copies/mL			
≤100 000	278/303 (91·7)	265/293 (90·4)	1·3 (-3·4; 6·1)
>100 000	53/59 (89·8)	56/70 (80·0)	9·8 (-3·3; 22·5)



← or → 95% CI limit beyond x-axis range

TBD if this should go in backup

Virologic Outcome Categories at Week 48 (FDA Snapshot; <50 c/mL) (ITT)

Outcomes, n (%)	D/C/F/TAF QD N=362	Control N=363
Virologic response (VL <50 c/mL)	**331 (91.4%)**	**321 (88.4%)**
VL ≥50 c/mL	**16 (4.4%)**	**12 (3.3%)**
Last VL in week 48 window ≥50 c/mL	9 (2.5%)	9 (2.5%)
Discontinued for efficacy reasons	1 (0.3%)*	0
Discontinued due to other reasons (≠efficacy/AE/death) and last available VL ≥50 c/mL†	6 (1.7%)	3 (0.8%)
No VL data in week 48 window	**15 (4.1%)**	**30 (8.3%)**
Discontinued due to AE	8 (2.2%)	16 (4.4%)
Deaths§	0	0
Discontinued due to other reasons and last available VL <50 c/mL (or missing)¶	4 (1.1%)	9 (2.5%)
Missing data during window but on study drug	3 (0.8%)	5 (1.4%)

*Patient reached a virologic endpoint (investigator's assessment: withdrawal decision at week 36 with VL 168 c/mL; last VL on-treatment 31 c/mL)
†Lost to follow-up (4 vs 2 patients), patient withdrew (1 vs 1), other reasons (1 vs 0)
¶Lost to follow-up (0 vs 3), physician decision (2 vs 0), patient withdrew (1 vs 5), other reasons (1 vs 1)
§One death occurred in the control group, but in follow-up (not considered related to study drug)

Resistance Analysis Through 48 Weeks

	D/C/F/TAF QD N=362	Control N=363
Virologic failures with paired screening and endpoint genotypes*, n	7	2
Patients developing mutations (IAS 2015) post-baseline, n		
DRV RAMs	0	0
Primary PI RAMs	0	0
NRTI RAMs	1 (M184I/V)†	0
NNRTI RAMs	0	0

*Post-baseline genotyping/phenotyping performed for patients who met the criteria for protocol-defined virologic failure (virologic non-response, virologic rebound, and/or viraemic at final timepoint) and who had VL ≥400 c/mL at failure (unconfirmed or confirmed failure) or at later time points

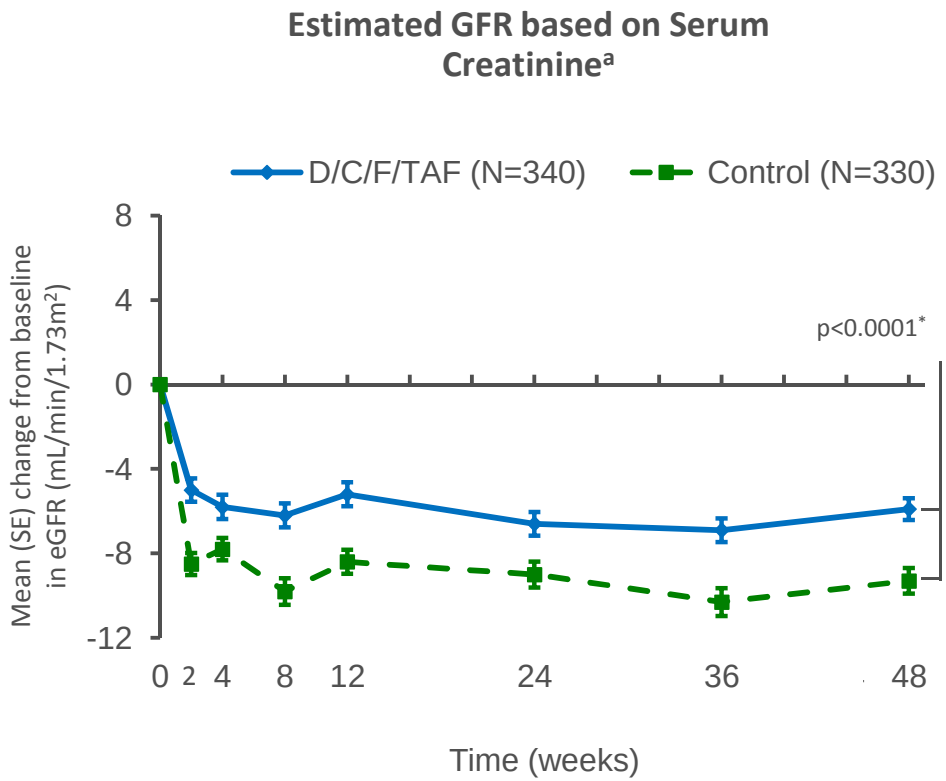
†M184I/V, conferring resistance to FTC and 3TC, was identified in one patient who also had K103N at screening, indicating transmitted NNRTI (efavirenz/nevirapine) resistance

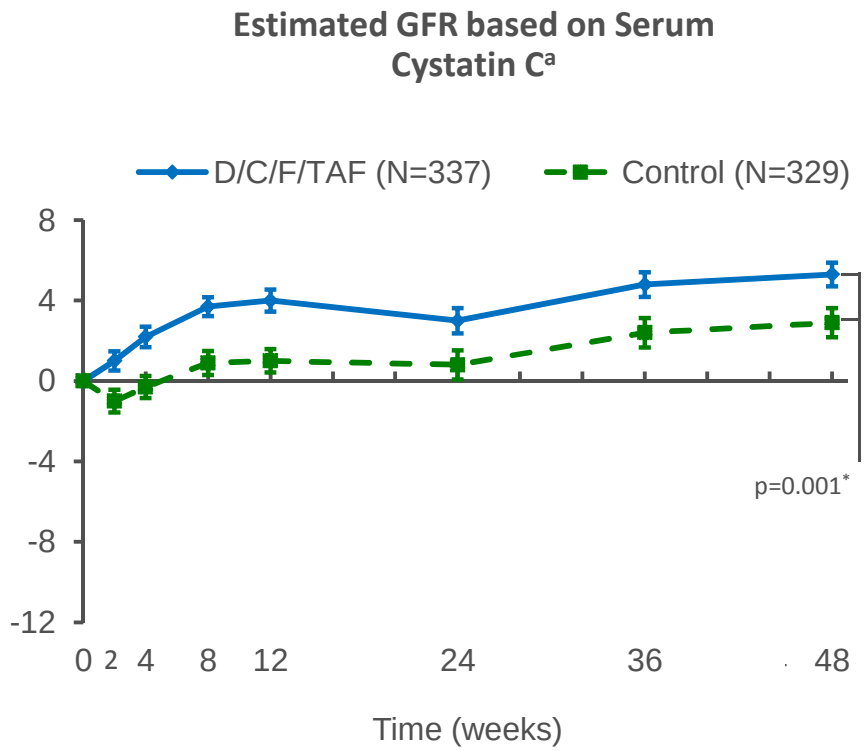
Adverse Events Through 48 Weeks

Incidence, n (%)	D/C/F/TAF QD N=362	Control N=363
≥1 AE, any grade	312 (86.2)	307 (84.6)
≥1 grade 3–4 AE	19 (5.2)	22 (6.1)
≥1 serious AE	17 (4.7)	21 (5.8)
Deaths	0	0
AEs leading to discontinuation		
≥1 AE	7 (1.9)	16 (4.4)
	Rash (n=6) Diarrhoea (n=1)	Rash/erythema (n=7) Diarrhoea (n=1) Toxic skin eruption (n=2) SJS (n=1) Bone marrow oedema (n=1) Increased Beta 2 macroglobulin (n=1) Arthralgia (n=1) Neoplasms (n=2)

- Incidences and types of laboratory abnormalities were similar in both treatment arms being mostly Grade 1 or 2

Mean Changes in eGFR Through 48 Weeks

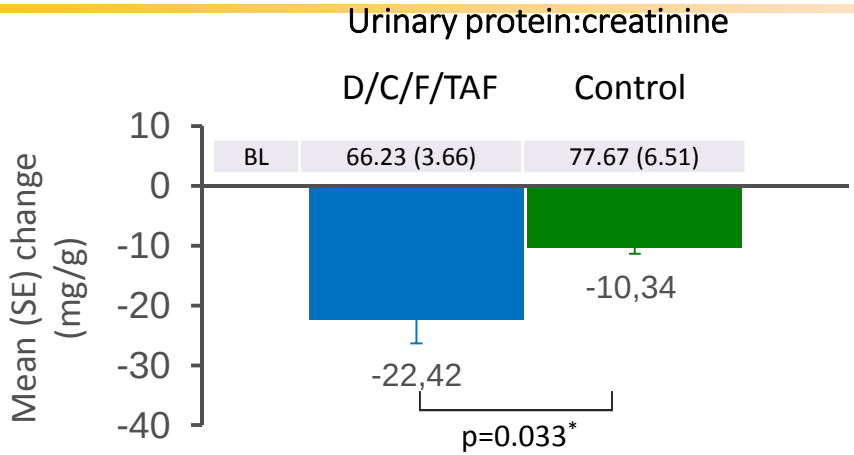


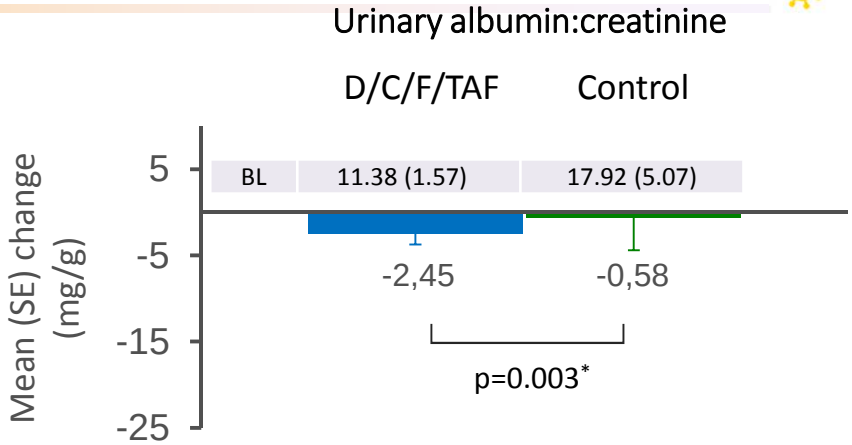


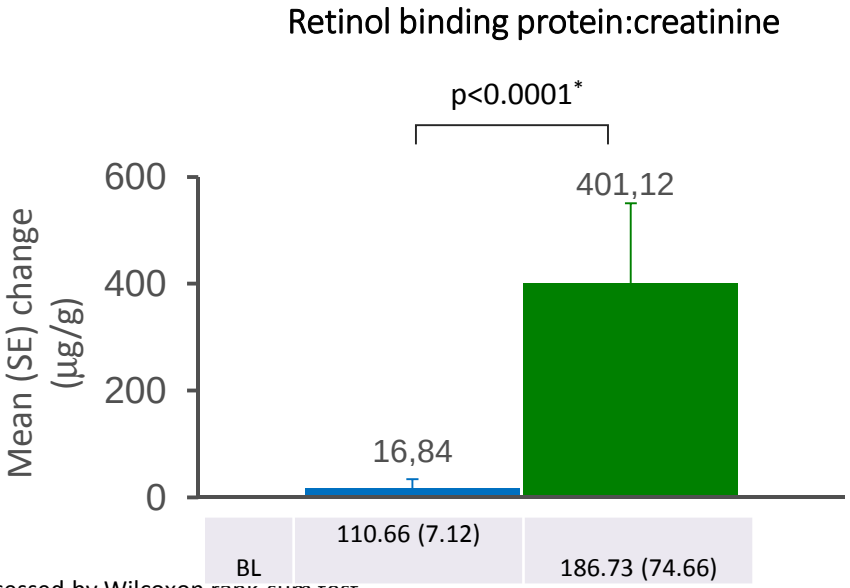
- Results are consistent with the known effect of cobicistat on inhibition of tubular secretion of creatinine

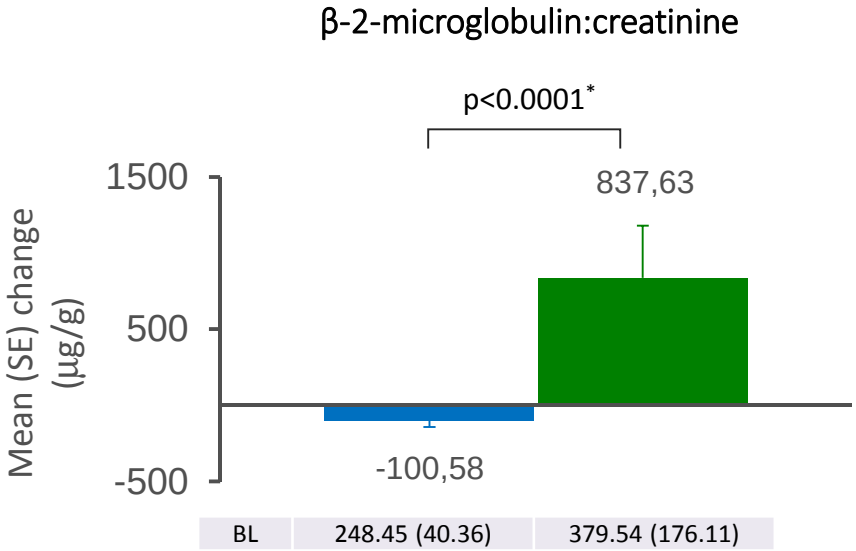
[a]Based on serum levels and CKD-EPI formula
*p value for difference estimated using ANCOVA, including treatment as a factor and baseline eGFR as a covariate

Mean changes in proteinuria through 48 Weeks



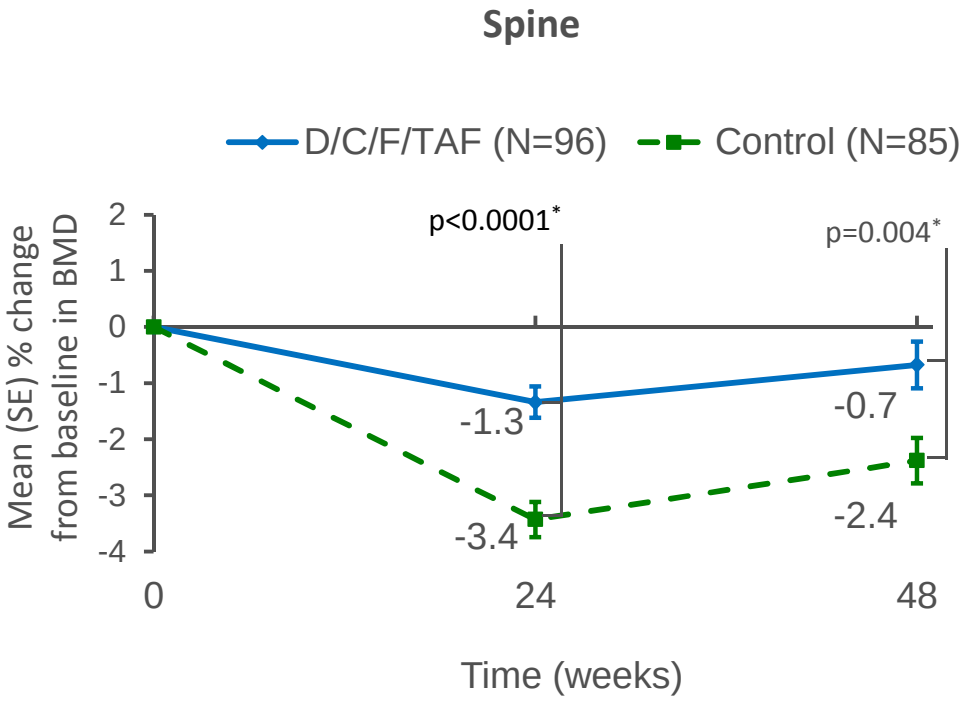


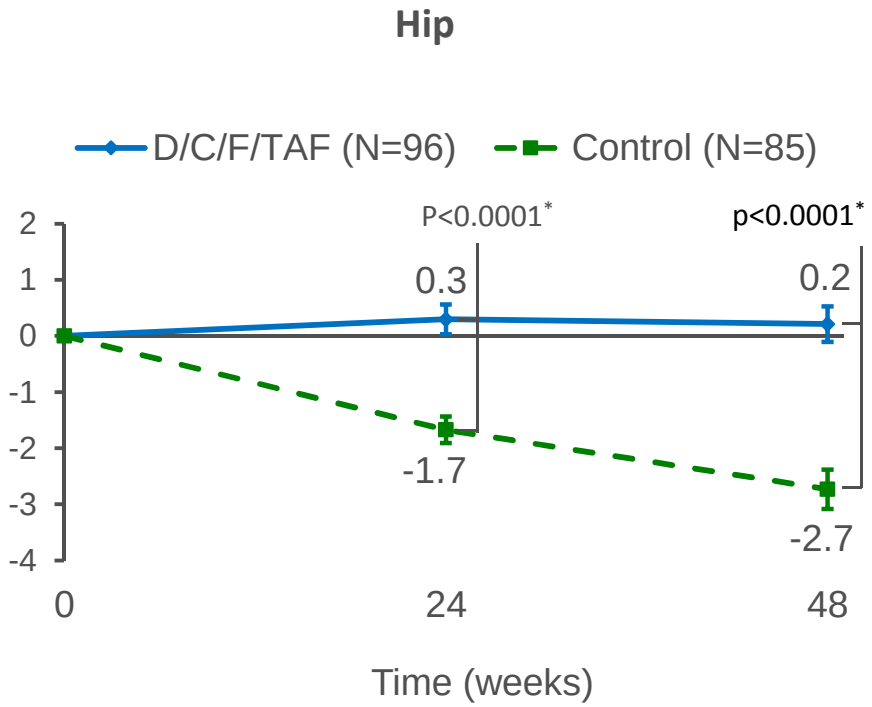




*Assessed by Wilcoxon rank-sum test

Mean % changes in BMD Through 48 Weeks



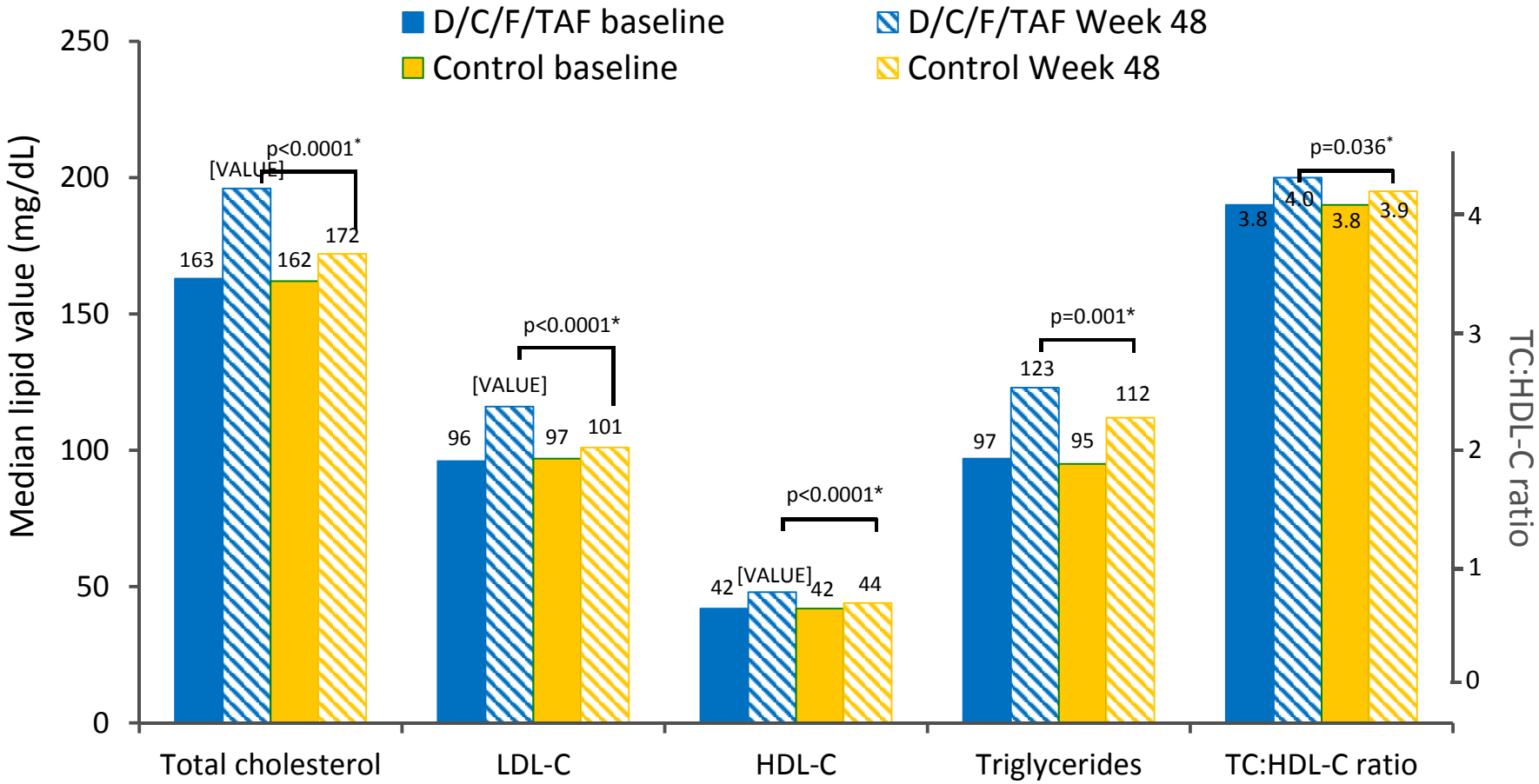


	D/C/F/TAF	Control
≥3% decrease	27.1%	41.2%
≥3% increase	12.5%	4.7%

D/C/F/TAF	Control
12.5%	44.7%
12.5%	2.4%

*p value for difference estimated using ANCOVA, including treatment as a factor and baseline BMD as a covariate

Fasting Lipid Levels at Baseline and Week 48



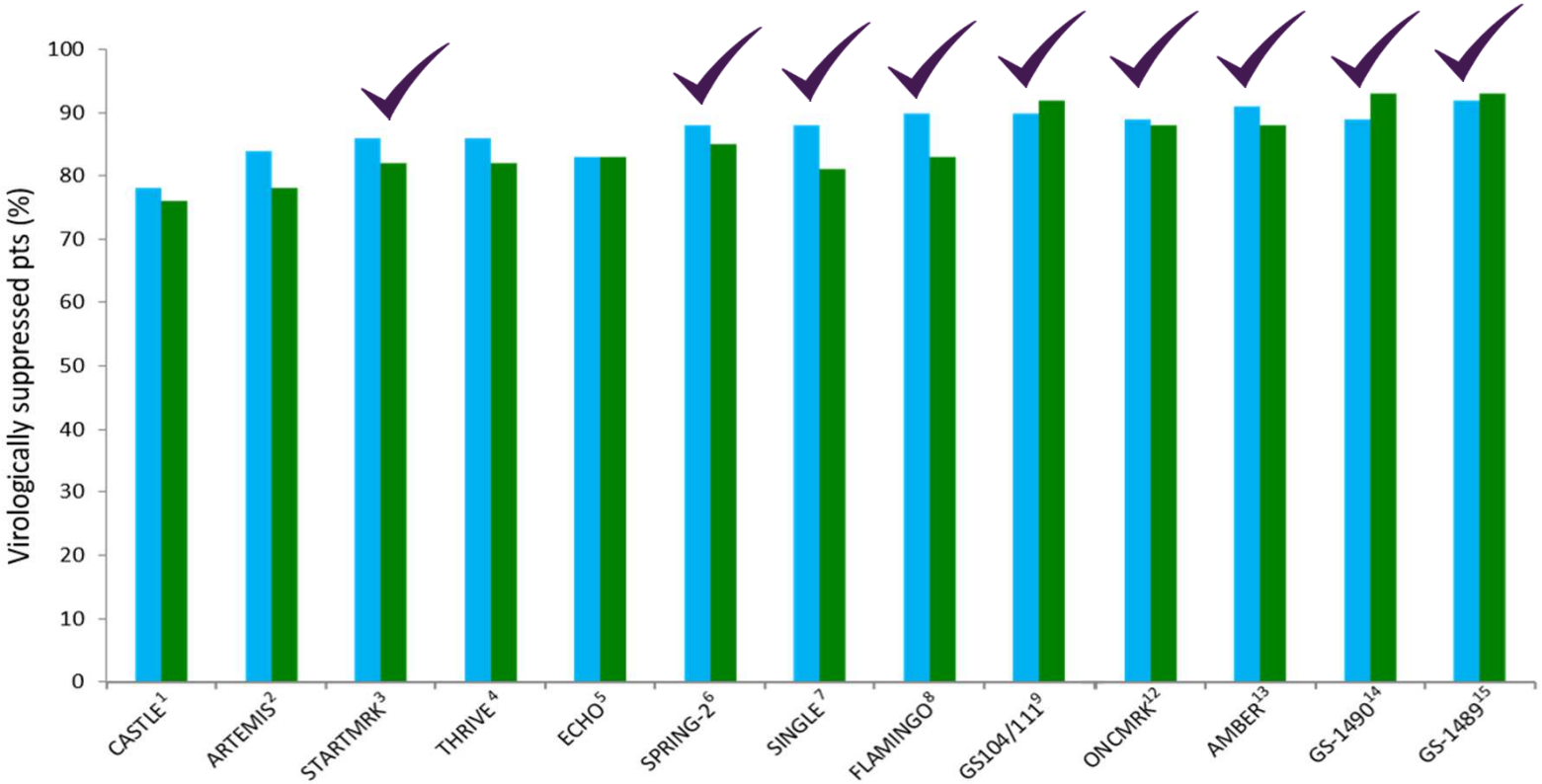
During treatment, lipid-lowering drugs started by 6 (1.7%) vs 2 (0.6%) patients (p=0.18)

*p values are for differences between arms in changes from baseline (assessed by the Wilcoxon rank-sum test)

Who is represented in these studies?

Trials where participants are:

- ✓ 50% white
- ✓ >70% male
- ✓ 100% CD4 >300
- ✓ >75% VL <100,000



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.

AMBER Week 48 Analysis: Conclusions

- Through Week 48, D/C/F/TAF resulted in:
  - High virologic suppression rate in treatment-naïve patients (91.4%; FDA Snapshot) and non-inferiority to DRV/COBI + F/TDF (88.4%)
  - No development of DRV, primary PI or TDF/TAF RAMs
    - One patient (D/C/F/TAF) developed M184I/V conferring resistance to FTC
  - Few serious and grade 3/4 AEs and AE-related discontinuations
  - Bone, renal and lipid safety consistent with known profiles of TAF and cobicistat

D/C/F/TAF STR combines the known efficacy and high genetic barrier to resistance of DRV with the safety advantages of TAF in ART-naïve, HIV-1 infected patients