Comparative Side Effects Between Distinct Integrase Inhibitors and Integrase Inhibitors Containing Regimens

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Comparative side effects between distinct integrase inhibitors and integrase inhibitors containing regimens

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Disclosures & disclaimers

- I am paid by ViiV, Gilead, Janssen, MSD, Cipla & Mylan to talk at meetings and/or rant at Advisory Boards

- I am an investigator on clinical trials sponsored by Janssen & Gilead

Content (AE= adverse event)

1. The challenges of capturing & interpreting AE
   - Some end points e.g. liver transaminase levels are objective, others less so (e.g. nausea)
   - Statistically significant may not be clinically important e.g. renal biomarkers, non-progressive BMD changes
2. Are INSTI better-tolerated as a class?
3. A comparison of individual INSTI & whole regimens

1. Clinical trials can be hard to interpret

- Differing baseline demographics
- Placebo effect
- Clumsy AE reporting
- Subjective interpretation

Baseline characteristics: lipids

- Change in lipids from baseline is a common safety endpoint in clinical trials

- Lipids at baseline will vary by population
  - Higher VL associated with lower LDL[1]
  - Older age associated with higher total-cholesterol[1]

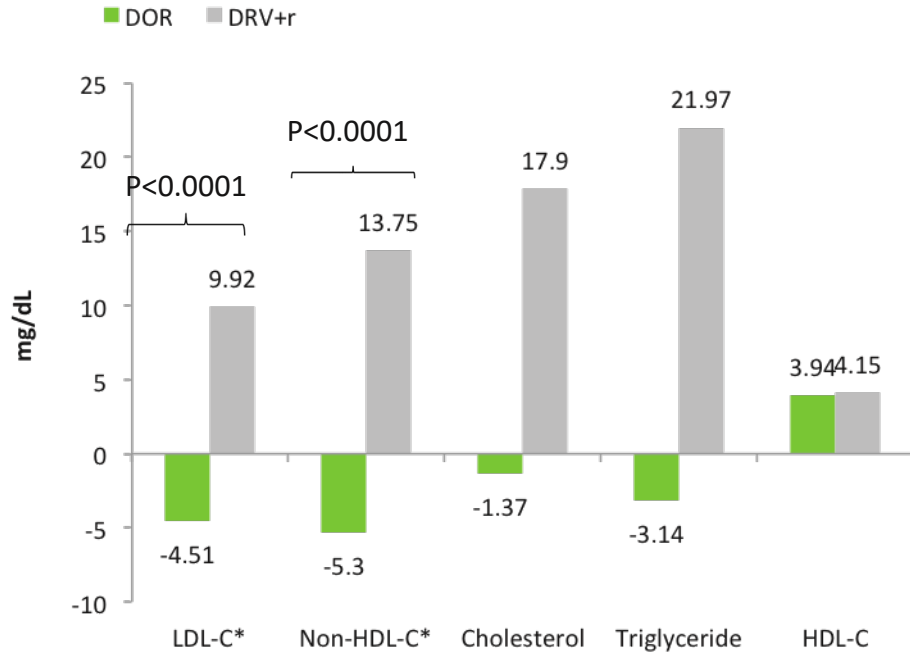1. El Sadr WM et al HIV Med 2005 Mar;6(2):114-21.

STARTMRK: lipid changes at W48
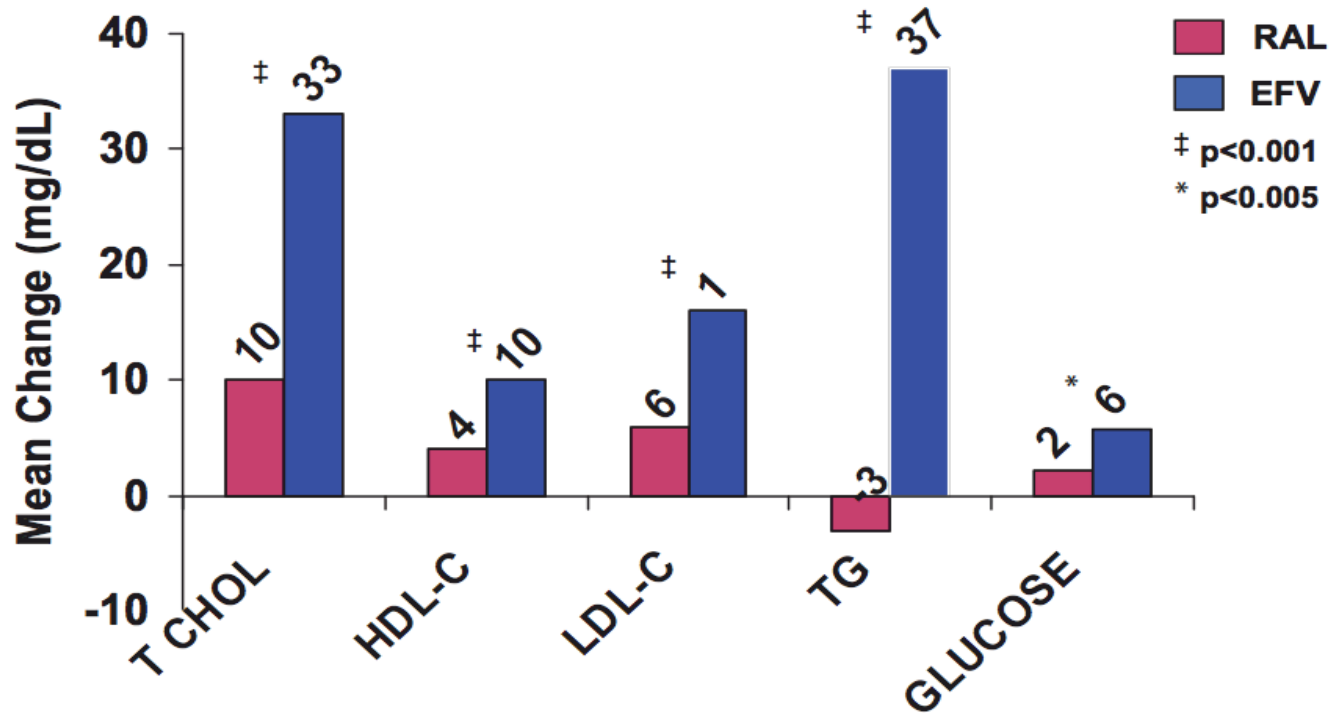
- The change from baseline in the T CHOL:HDL-C ratio was -0.3 for the RAL group and -0.1 for EFV group (p=0.292).

De Jesus et al. ICAAC 2009

Fasting lipids: baseline to W48

DRIVE-FORWARD
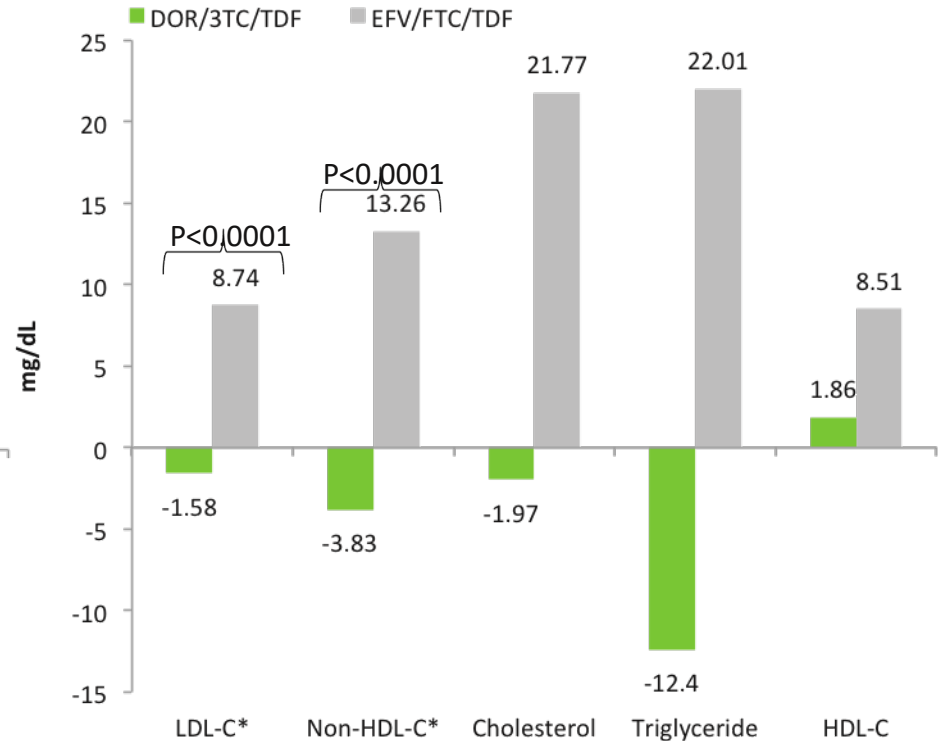**Superior LDL & non-HDL-C for DOR vs DRV/r**

DRIVE-AHEAD
Superior LDL & non-HDL-C for DOR vs. EFV

* **Statistical testing prespecified for these parameters .**

Molina et al. CROI 2017; Squires et al IAS 2017

But.....baseline characteristics

	DRIVE-AHEAD	STARTMRCK
CD4 <200	12%	47%
VL >100,000	21%	51-55%
Age (median)	32 years	37 years

Placebo: Stribild in GS-102 & GS-103
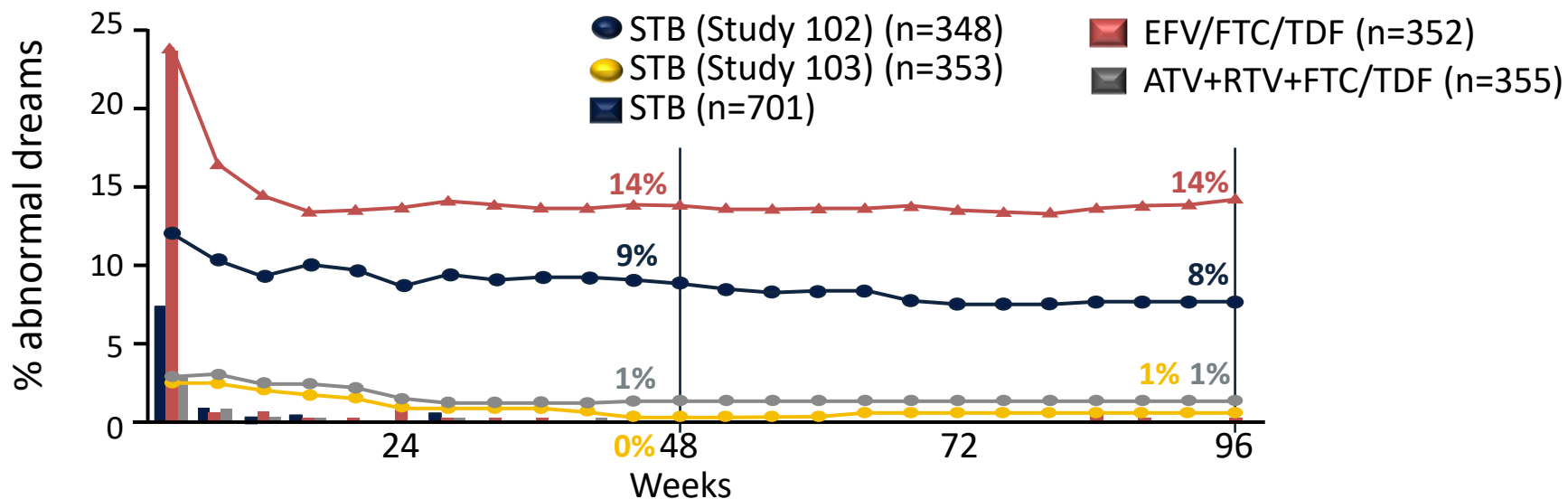
Most were Grade 1 (STB 94% vs. EFV/FTC/TDF 86% vs. ATV+RTV+FTC/TDF 93%)

Bar (incidence): Patients with new onset or worsening AEs at each 4-week window
Line (prevalence): Patients with ongoing events in the window

Clumsy reporting: 48W AE prevalence

- **Drug A:** 50% chance of diarrhoea
- **Drug B:** 5% chance of diarrhoea

B

Less clumsy reporting: 48W AE prevalence & duration

- **Drug A:** 50% chance of diarrhoea lasting 2 days
- **Drug B:** 5% chance of diarrhoea lasting 12 months

Subjective causality

- Drug-relatedness is determined by the investigator
- Can be hampered by binary categories
  - Related/non-related vs probable/possible etc
- The bias of familiarity
  - We are likely to attribute causality when an AE is already known to be associated with a drug

Optimal AE reporting?

- Incidence + point prevalence + grading

- Reporting of all AND 'drug-related' AE

  - More nuanced causality assignment

- Clustering

  - E.g. if 90% of people with insomnia are also those with low mood that impacts patient counselling

- Impact on ADLs & QoL via PROMs

ADLs = activities of daily living; QoL = quality of life; PROMs = patient reported outcomes

2. Are INSTI safer & better tolerated *as a class*?

- Against PI? Undoubtedly….

ACTG 5257: toxicity discontinuation

				DRV/r (N=601)
Any toxicity discon...				32 (5%)
Gastrointestinal to...				14
Jaundice/hyperbili...				0
Other hepatic toxic...				5
Skin toxicity				5
Metabolic toxicity				2
Renal toxicity (all n...				0
Abnormal chem/haeme (excl. LFTs)		0		2
Other toxicity		2		4

Boosted agents have the added issue of INDIRECT TOXICITY due to drug-drug interactions e.g. steroids (iatrogenic Cushing's) and statins (myotoxicity)

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

Against NNRTI?

- ALL core agents compare favourably against efavirenz in terms of neuropsychatric AE
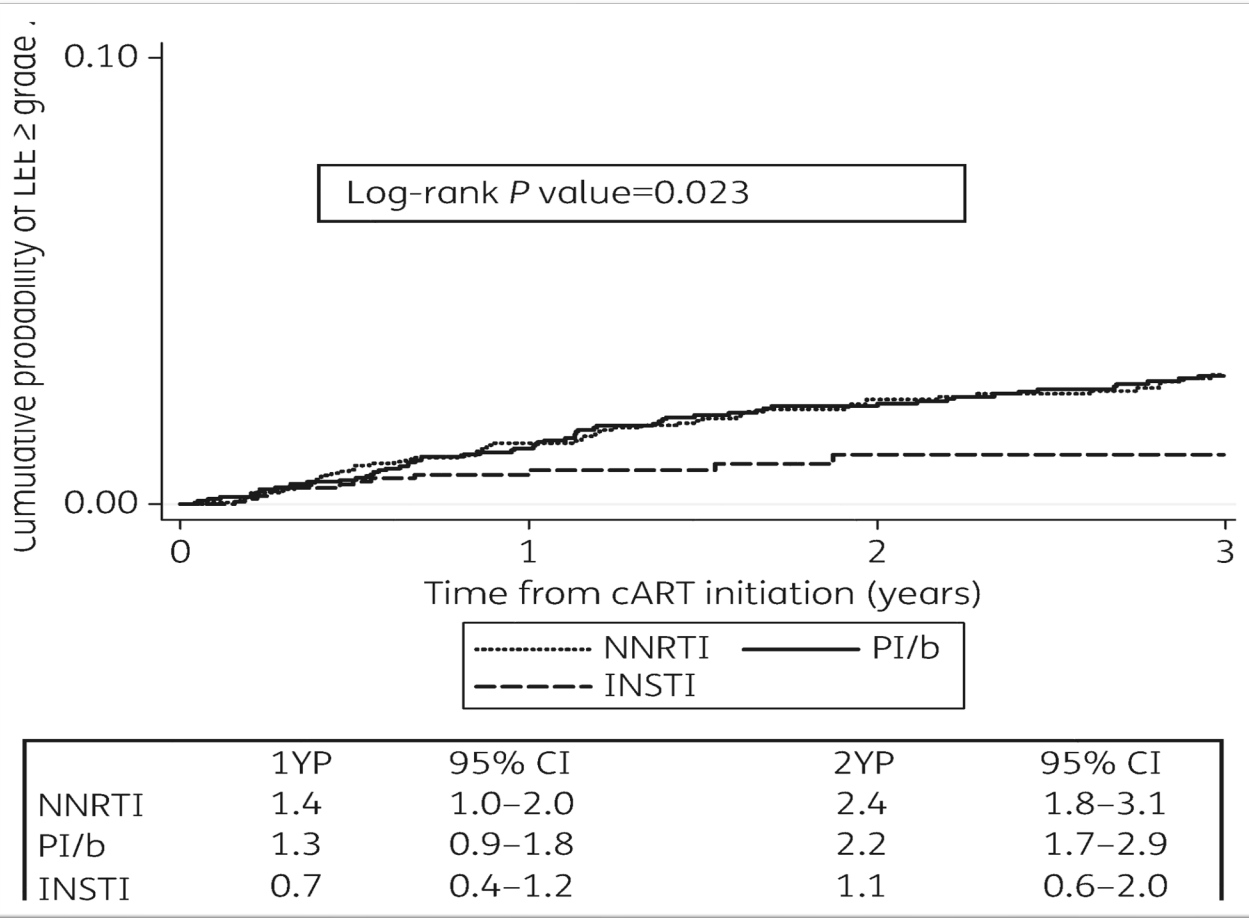
- Less hepatoxicity…..?

Liver   NA

- 6,575
  - 2N
  - HB
  - LE
- 183 L   nt
  - LE   36),
    pa
  - HR   olled HIV
    inf

Log-rank P value=0.023

	1YP	95% CI	2YP	95% CI
NNRTI	1.4	1.0–2.0	2.4	1.8–3.1
PI/b	1.3	0.9–1.8	2.2	1.7–2.9
INSTI	0.7	0.4–1.2	1.1	0.6–2.0

Figure axes: Cumulative probability of LEE ≥ grade (0.00–0.10) vs Time from cART initiation (years) 0–3. Curves: NNRTI, PI/b, INSTI.

Taramasso L et al. J Antimicrob Chemother. 2019 Nov 1;74(11):3295-3304.

On the topic of liver enzyme elevations

- Data used to be presented by HBV/HCV status

- Are steatosis/fibrosis a better 'modern' stratifier?

- IAS Conference 2019: German cohort (n=486)
  - Adults starting DTG, EVG or RAL, median baseline ALT 26-28
  - Significant W4 ALT rise (median 10): DTG only, >60s only
  - No association with co-morbidities or concomitant meds although **1% vs 6%** of <60s and >60s had **liver fibrosis**

de Leuw P, Wiedmann K, Filmann N, et al. Elderly patients on antiretroviral therapy with dolutegravir are at increased risk for ALT elevation. AIDS 2018: 22nd International AIDS Conference, Amsterdam, Netherlands, July 23-27, 2018. Abstract TUPEB131.

EACS guidelines v10.1: October 2020
Recommended regimens

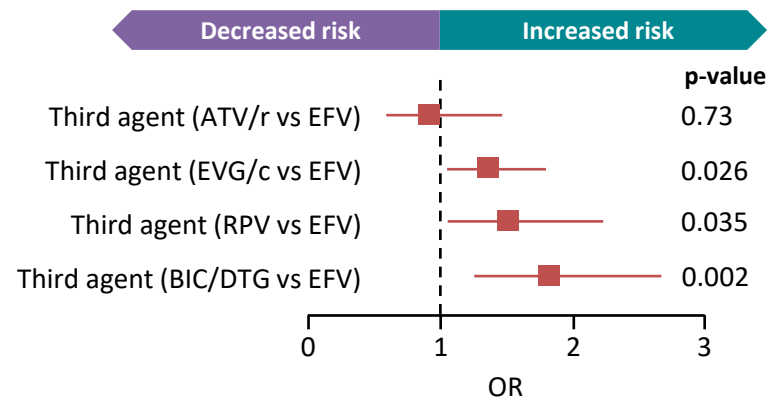| INSTI + 1 or 2 NRTI	Notes & restrictions
ABC/3TC/DTG or ABC/3TC + DTG	ABC: HLA, CV risk DTG: weight gain
TAF/FTC or TDF/FTC or TDF/3TC + DTG	DTG, TAF: weight increase TDF: prodrug types. Renal and bone toxicity TAF dosing
TAF/FTC/BIC	BIC: weight gain
TAF/FTC or TDF/FTC or TDF/3TC + RAL	TDF: prodrug types. Renal and bone toxicity. TAF: dosing RAL: dosing
3TC/DTG or 3TC + DTG	HBVsAg negative VL <500,000

DHHS guidelines: December 2019
Recommended for most people with HIV

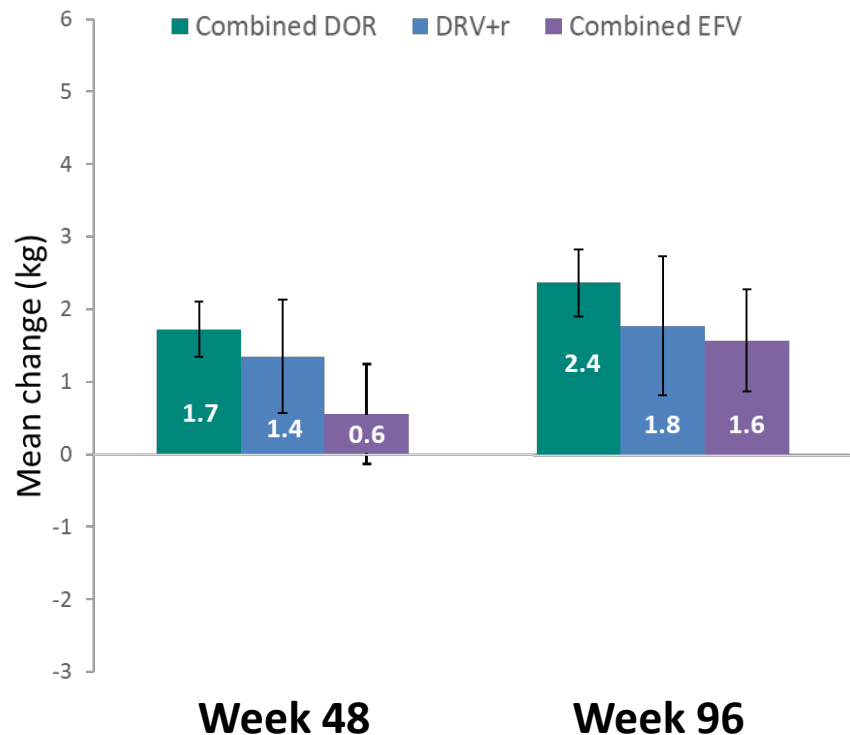| INSTI + 2 NRTI	Key requirements
TAF/FTC/BIC	
ABC/3TC/DTG	HLA B*5701 negative, known HBV status, no HBV co-infection
DTG + (TAF or TDF) + (3TC or FTC)	
RAL + (TAF or TDF) + (3TC or FTC)	
INSTI + 1 NRTI	
DTG + 3TC	VL <500,000, HBV negative, HBV & resistance status known

Pooled analysis of 8 1st line trials (n=5,680)

LS mean weight change over time in patients on INI-based regimens
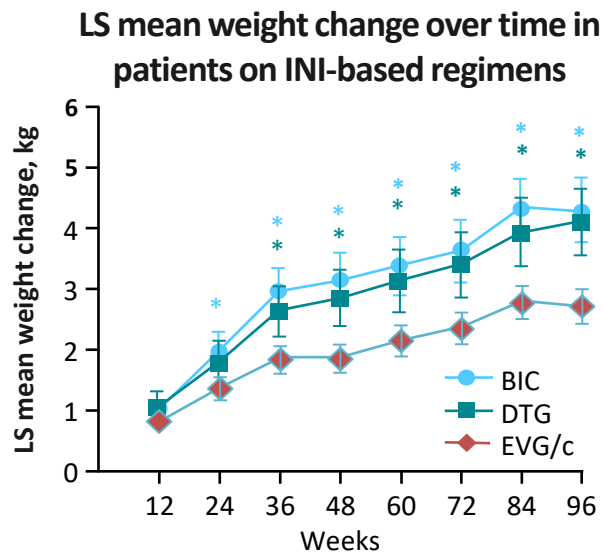
Risk factors for significant (≥10%) weight gain in individuals initiating ART[†]

Chart created from original data from Sax P, et al. Clin Infect Dis 2019. doi: 10.1093/cid/ciz999

DRIVE 1st line studies: weight change

CI, confidence interval; IQR, interquartile ratio.
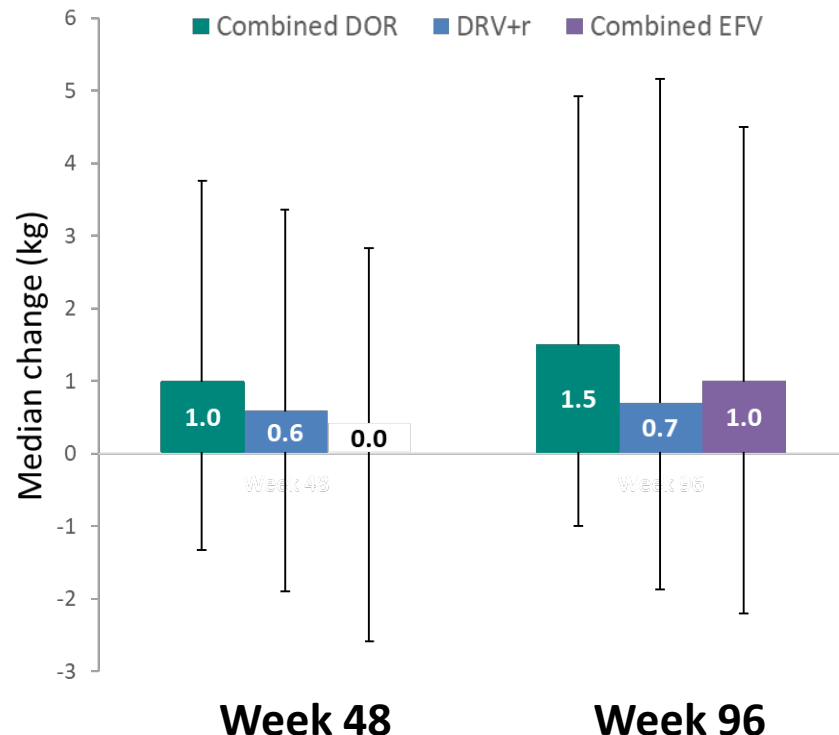
Good vs bad fat?

- DEXA & CT undertaken in people switching to INSTI (INSTI-s) & matched controls on non-INSTI (INSTI-n)

- Greater BMI increase in INSTI-s, mainly driven by SAT

- Differences in VAT density associated with INSTI-s does not suggest a metabolically abnormal fat gain
  - Significantly bigger reduction in VAT-density vs INSTI-n

3. A comparison of INSTIs

- Focus on two key issues for INSTI:
  - CNS toxicity
  - Metabolic profile
- The importance of
  - Other regimen components
  - Baseline regimen in switch studies
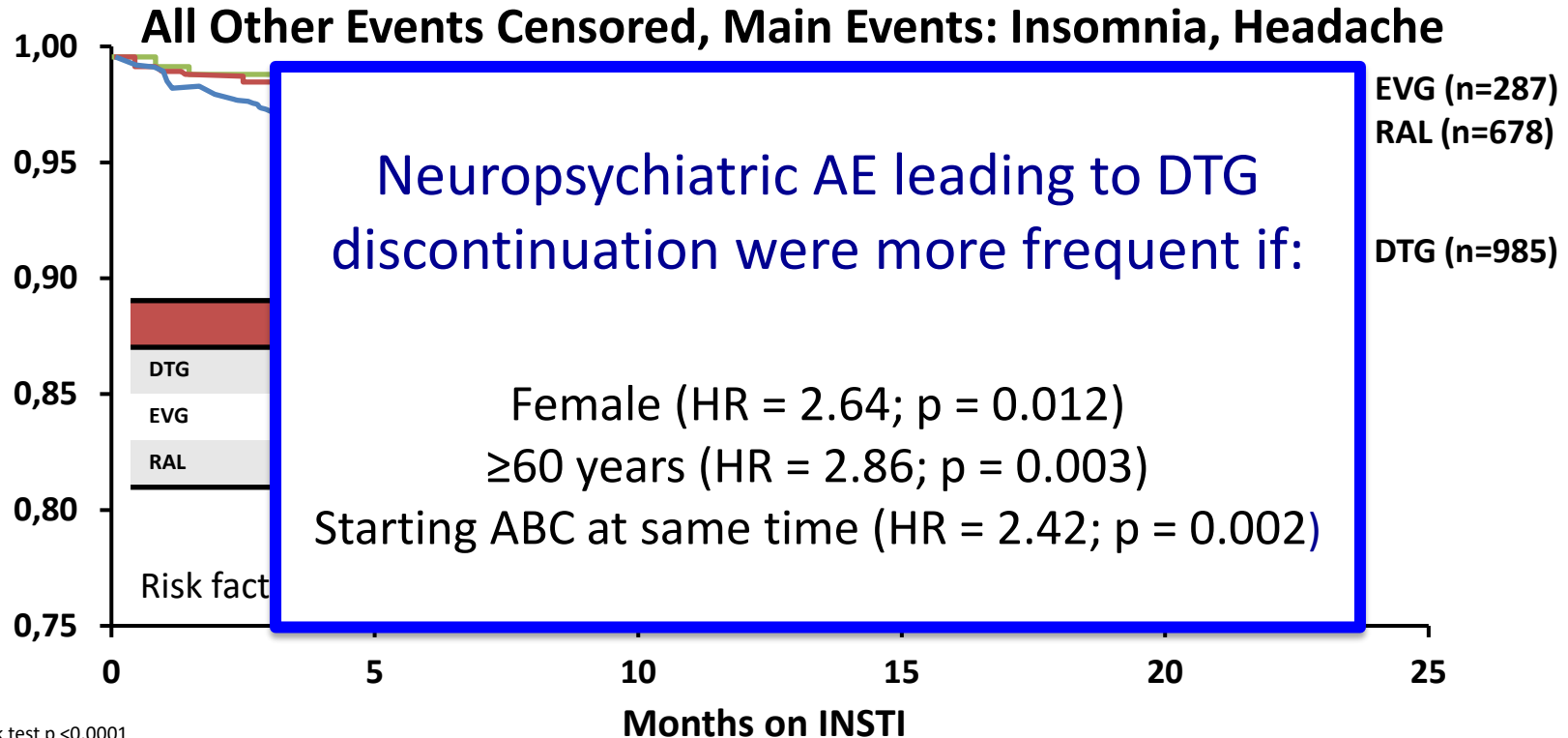
Summaries of Product Characteristics

Drug	Abnormal dreams	Suicidality
Triumeq	**Common**	Suicidal ideation or suicide attempt* **uncommon**
Biktarvy	**Common**	
Genvoya	**Common**	Suicid... ...non
Delstrigo	**Common**	Suicidal idea... **uncommon**
Eviplera	**Common**	Not men... ...ed in SPC
Isentress	**Common**	Suicide attempt, ideation, behaviour* **uncommon**

Caution should be used in patients with a pre-existing history of depression or psychiatric illness.

Common   ≥ 1/100 to < 1/10
Uncommon   ≥ 1/1000 to < 1/100
*in patients with a pre-existing history of depression or psychiatric illness

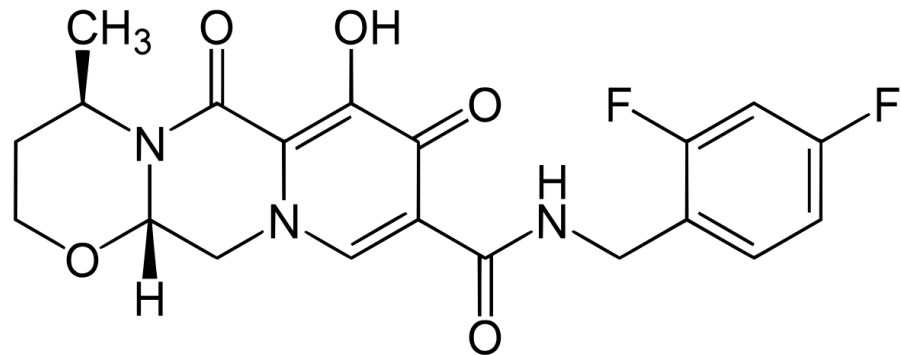# Hamburg/Cologne INI Cohort Discontinuation Due to Neuropsychiatric AES
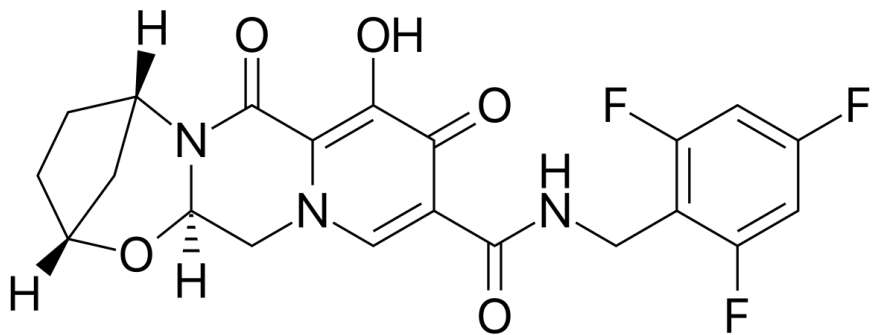
All Other Events Censored, Main Events: Insomnia, Headache

EVG (n=287)

RAL (n=678)

DTG (n=985)

Neuropsychiatric AE leading to DTG discontinuation were more frequent if:

Female (HR = 2.64; p = 0.012)
≥60 years (HR = 2.86; p = 0.003)
Starting ABC at same time (HR = 2.42; p = 0.002)

Months on INSTI

The importance of backbone

1489 AE ≥5%	BIC (n=314)	DTG (n=315)
Nausea	32 (10%)	72 (23%)
Insomnia	12 (4%)	25 (8%)

1490 AE ≥5%	BIC (n=320)	DTG (n=325)
Nausea	25 (8%)	29 (9%)
Insomnia	16 (5%)	14 (4%)

Zolopa A. Presented at CROI 2013, poster 553; GS-1489: Gallant J et al. Lancet 2017;390:2063-2072; GS-1490: Sax P et al. Lancet 2017;390:2073-20

BIC vs DTG

Real world data for DTG/3TC

GROWING REAL-WORLD DATA SUPPORT ViiV-SPONSORED DTG + 3TC PHASE III RESULTS

Real-world effectiveness studies*

10 STUDIES
in virologically suppressed patients[21,29-37]

~1,650
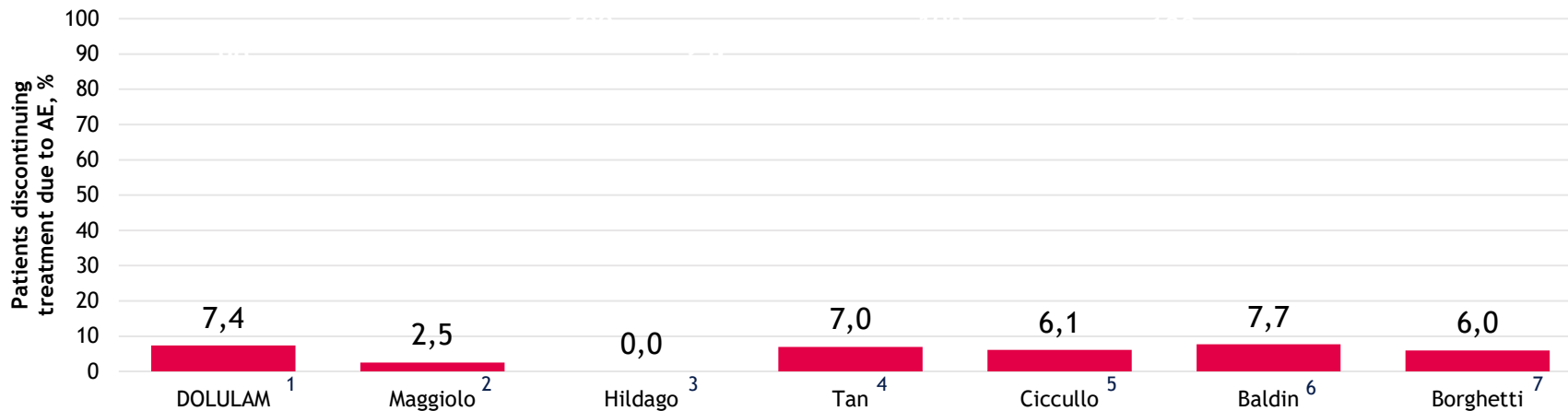
SUPPORT FINDINGS FROM PHASE III RANDOMISED CONTROLLED TRIALS:
- LOW RISK OF VIROLOGIC FAILURE
- HIGH BARRIER TO RESISTANCE
- LOW RATE OF TREATMENT DISCONTINUATIONS

21. Maggiolo F, et al. HIV Glasgow 2018. Poster P104; **29.** Borghetti A, et al. Clin Infect Dis 2020; ciaa313. **30.** Castelli A, et al. EACS 2019. Poster PE2/35. **31.** Diaco N, et al. EClinicalMedicine 2018;6:21–5. **32.** Digaetano M, et al. HIV Glasgow 2018. Poster P203. **33.** Gagliardini R, et al. CROI 2020. Poster 486. **34.** Hart J, et al. BHIVA 2019. Poster P9. **35.** Hidalgo-Tenorio C, et al. Medicine 2019;98:e16813. **36.** Lanzafame M, et al. New Microbiology 2018;41:262–7. **37.** Pereira Goulart S, et al. EACS 2019. Poster PE2/34

Real world DTG/3TC discontinuations

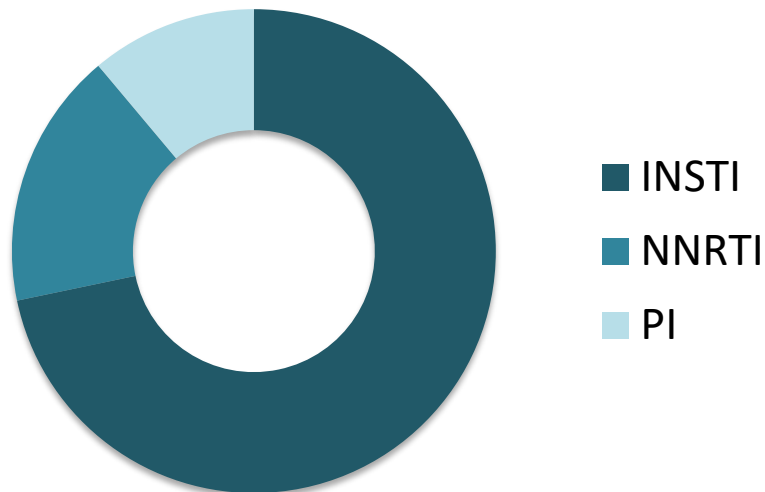|	DOLULAM [1]	Maggiolo [2]	Hildago [3]	Tan [4]	Ciccullo [5]	Baldin [6]	Borghetti [7]
N	27	203	177	56	229	556	183
Endpoint or time of follow-up	48 weeks	48 weeks	48 weeks	2.3 years (median)	22.3 months (median)	22.1 months (median)	96 weeks
Discontinuation due to AE, n	2	5	6	4	14	43	11
Study type	Prospective cohort	Prospective, multicentre cohort	Observational retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort

*Including intolerance/toxicity

Potential overlap between patient cohorts in real-world studies cannot be ruled out

References: 1. Reynes J, et al. HIV Glasgow 2016. Poster P080 2.Maggiolo F, et al. EACS 2017. Poster PE9/49 3.Hidalgo-Tenorio C, et al. Medicine 2019;98:1–7 4. Tan M, et al. HIV Med 2019;20:634–7 5.Ciccullo A, et al. Antivir Ther 2019;24:63–7 6. Baldin G, et al. Int J Antimicrob Agents 2019;54:728–34 7. Borghetti A, et al. BMC Infect Dis 2019;19:59
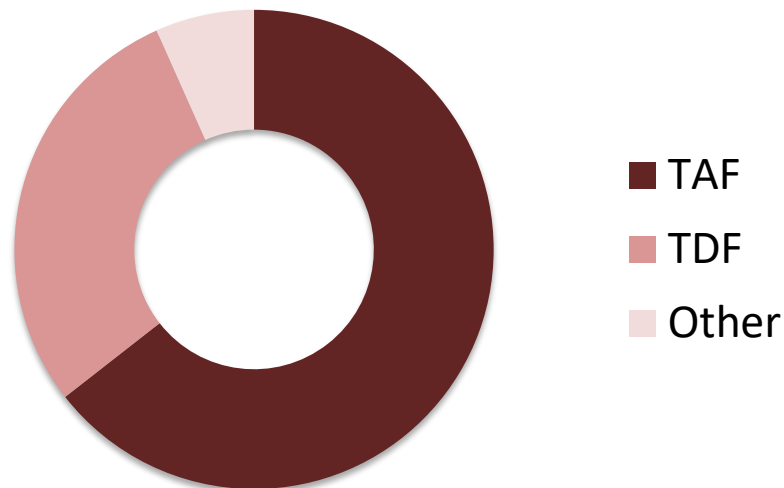
BICSTaR: 48W results; n=513 (n=429 TE)
Germany, Canada, France & Netherlands

- Cohort of treatment-naïve (TN) & -experienced (TE)
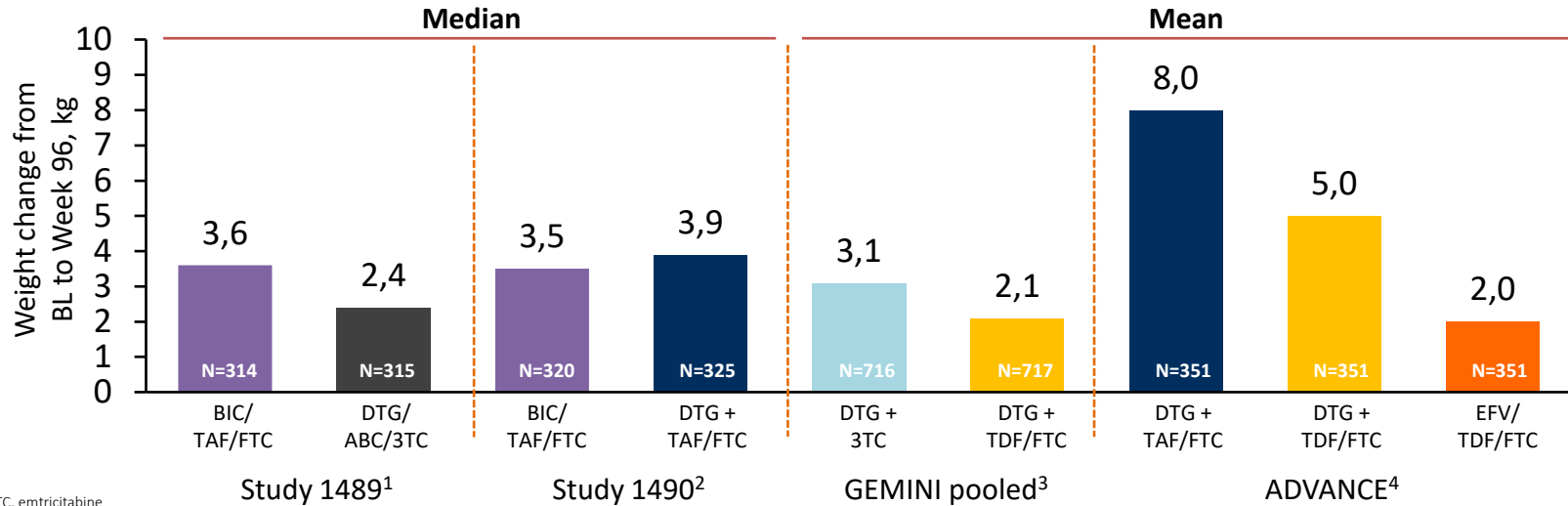- Pre-switch regimen in TE

INSTI, NNRTI, PI

TAF, TDF, Other

INSTI: DTG 34%, EVG 24%, RAL 14%

Spinner C et al. Poster 046, HIV Glasgow 2020.

BICSTAR Study: discontinuations to M12

N (%)	TN (n=84)	TE (n=429)
Any discontinuations	**4 (4.7%)**	**47 (11%)**
Pregnancy	0	1 (0.2%)
Participant decision	0	3 (0.7%)
Death	0	3 (0.7%)
Lack of efficacy	0	3 (0.7%)
Investigator decision	0	4 (0.9%)
Adverse event	4 (4.7%)	33 (7.7%)

Spinner C et al. HIV Glasgow 2020.

BICSTAR Study: adverse events

N (%)	All (n=513)	TN (n=84)	TE (n=429)
Any DRAE	**76 (15%)**	**12 (14%)**	**64 (15%)**
Nausea	1 (1.4%)	1 (1.2%)	6 (1.4%)
Diarrhoea	6 (1.2%)	0	6 (1.4%)
Depression	8 (1.6%)	1 (1.2%)	7 (1.6%)
Weight increased	14 (2.7%)	2 (2%)	12 (3%)
Fatigue	8 (1.6%)	1 (1.2%)	7 (1.6%)
DRAE discontinuations	**32 (6.2%)**	**3 (3.6%)**	**29 (6.8%)**

Spinner C et al. HIV Glasgow 2020.

1st line studies: weight change at 96W
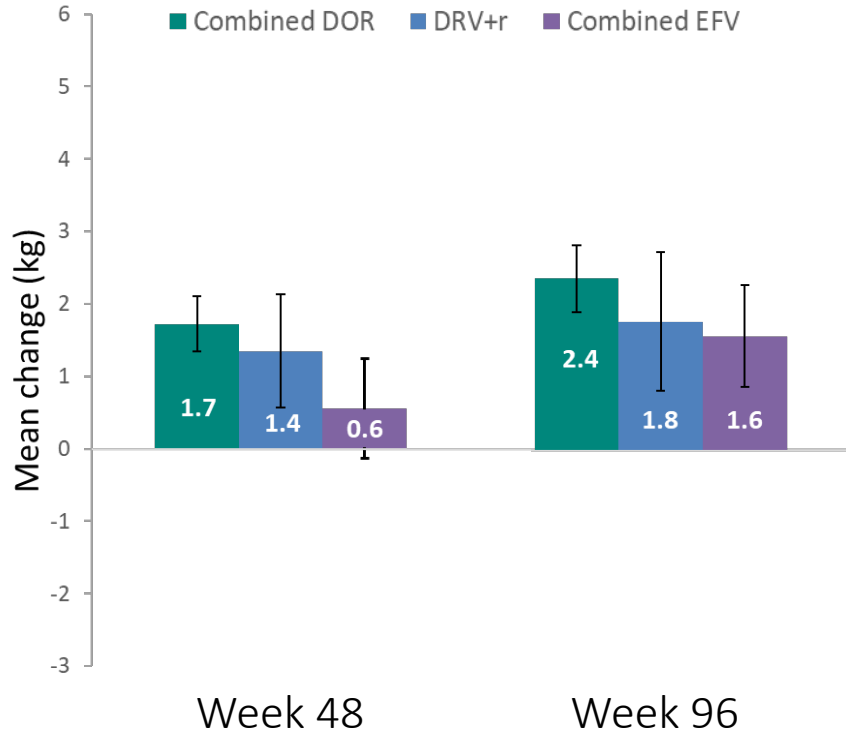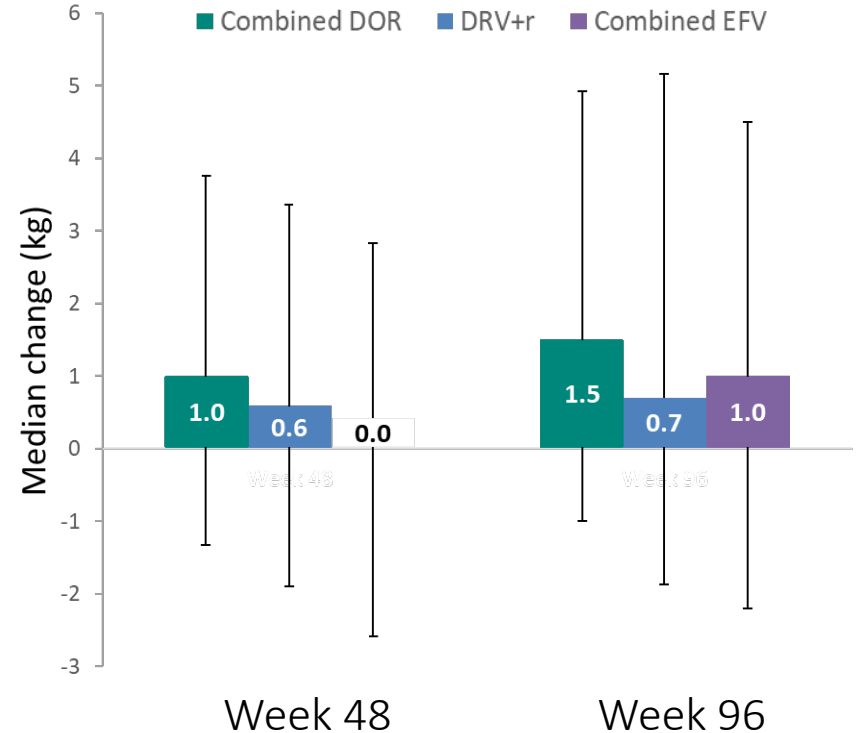

Variable levels of weight gain observed in different studies and variable reporting of mean and median weight gain
Differences in gender, race, age, weight and other BL demographics between clinical trial populations

3TC, lamivudine; FTC, emtricitabine

1. Wohl DA, et al. Lancet HIV 2019;6:e355–e363; 2. Stellbrink HJ, et al. Lancet HIV 2019;6;e364–e372
3. Cahn P, et al. IAS 2019. Oral WEAB0404LB; 4. Hill A, et al. IAS 2019. Oral MOAX0102LB

Change in Body Weight from Baseline

CI, confidence interval; IQR, interquartile ratio.

It's not just about weight: W48 TANGO lipids

Boosted subgroup

Unboosted subgroup

Boosted subgroup chart (Change from baseline, %[a]):
- Total cholesterol (mmol/L): DTG/3TC −5,7; TAF-based 2,2 **
- HDL cholesterol (mmol/L): DTG/3TC −0,8; TAF-based 1.02
- LDL cholesterol (mmol/L): DTG/3TC −6,6; TAF-based 2,9 **
- Triglycerides (mmol/L): DTG/3TC −14,1; TAF-based 4.0 **
- Total cholesterol/HDL cholesterol ratio: DTG/3TC −4,8; TAF-based 0,1 *

Unboosted subgroup chart (Change from baseline, %[a]):
- Total cholesterol (mmol/L): DTG/3TC −0,8; TAF-based 2.0
- HDL cholesterol (mmol/L): DTG/3TC −2,3; TAF-based 0.1
- LDL cholesterol (mmol/L): DTG/3TC −2.0; TAF-based −0,3
- Triglycerides (mmol/L): DTG/3TC −1,6; TAF-based 12,2
- Total cholesterol/HDL cholesterol ratio: DTG/3TC 1,4; TAF-based 1,8

Legend: ■ DTG/3TC (N=202)[b]   ■ TAF-based regimen (N=203)[b]   ■ DTG/3TC (N=97)[b]   ■ TAF-based regimen (N=94)[b]

[a]Percent change from baseline with 95% CIs based on adjusted geometric mean ratio (Week 48 to baseline) in each arm calculated from a repeated measures model applied to change from baseline in $\log_e$-transformed data adjusting for the following: treatment, visit, baseline boosting status, CD4+ cell count (continuous), $\log_e$-transformed baseline value (continuous), treatment-by-visit interaction, baseline value-by-visit interaction, treatment-by-baseline boosting status interaction, baseline boosting status-by-visit interaction, and baseline boosting status-by-treatment-by-visit interaction, with visit as the repeated factor. [b]Number of participants with non-missing fasting lipid data at baseline and Week 48, removing those with lipid-modifying agent administered at baseline.

*P=0.007. **P<0.001.

TANGO: insulin resistance at W48

- Change from baseline in adjusted geometric mean HOMA-IR was −9.7% in the DTG/3TC arm and 4.5% in the TAF-based regimen arm (P=0.001)

- Odds of insulin resistance (HOMA-IR ≥2; adjusted odds ratio) was significantly lower in the DTG/3TC arm vs the TAF-based regimen arm in the boosted subgroup
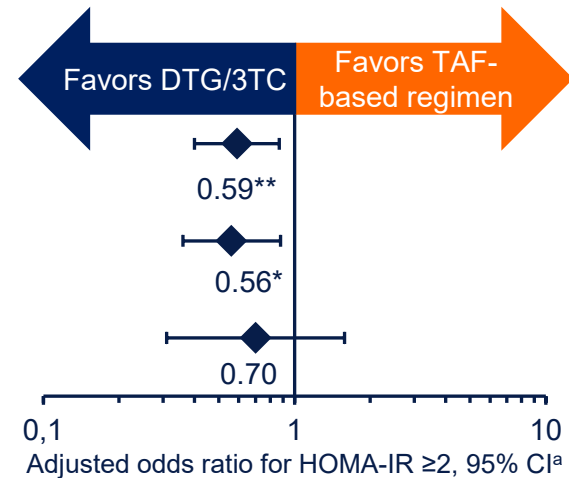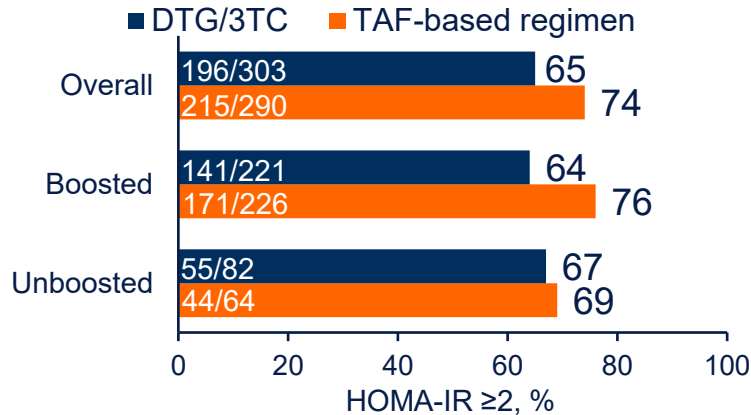
[a]Odds ratios and 95% CIs were calculated using a logistic regression model. Overall population adjusted for treatment, baseline third agent class, CD4+ cell count (continuous), age (continuous), sex, race, baseline BMI (continuous), baseline hypertension, baseline smoking status, log-transformed baseline HOMA-IR (continuous), and treatment-by-baseline third class agent interaction. Boosted and unboosted subgroups adjusted for treatment regimen (DTG/3TC vs TAF-based regimen), baseline boosting status (boosted vs unboosted), race (black, other vs white), sex (female vs male), baseline BMI (continuous), baseline CD4+ cell count (continuous), age (continuous), baseline hypertension (yes vs no), log-transformed baseline HOMA-IR (continuous), and treatment-by-baseline boosting status interaction.

*P=0.012 in boosted subgroup. **P=0.008 in overall population.

Challenges

- Associations vs causality
  - HIV ↔ inflammation ↔ MetS etc
- A lot of data is based on old antiretrovirals
- Untreated advanced HIV associated with greater lipid abnormalities than asymptomatic untreated HIV[1]
- How to explore ART impact in era of immediate ART immediately?
- Do drug-induced/-exacerbated hyperlipidaemia, obesity & insulin resistance have same consequences as 'endogenous'

Grunfeld C et al. Am J Med. 1989 Jan;86(1):27-31.

Conclusions

- The evolution of ART has led to marked improvement in toxicity and tolerability profiles

- Incidence and point prevalence should be standard

- As AE get less common, post-marketing surveillance, reporting and are all the more crucial

- As new toxicities emerge, understanding of mechanisms is key

Thank you

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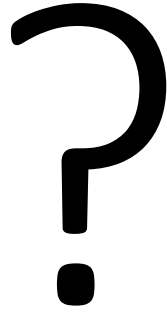
lwaters@nhs.net
@drlaurajwaters