The best of the rest: bNAbs, ART & weight

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Disclosures

Speaker/advisory fees

- ViiV, MSD, Janssen, Pfizer

Investigator on trials sponsored by

- Gilead, ViiV, & Janssen sponsored trials

Content

1 **BNABs**

2 **NOVEL ART**

3 **WEIGHT**

4 **CONCLUSIONS**

1 BROADLY NEUTRALISING ANTIBODIES

5 trials of note

1. BANNER (ViiV): ph1 monotherapy study of N6LS in ART-untreated people

- No baseline susceptibility testing, ART started if <0.5log decline at D11, rebound D11-D84 or D84 reached
- Lower exposure with SC vs IV dosing; up to 2log decline (3log in 1 person) & response correlated with retrospective baseline susceptibility

2. ACTG A5357: VRC07-523S + CAB LA maintenance in people with VS (n=71)

- Baseline susceptibility testing (25% not susceptible)
- 16 G3 events (n=11), 14/16 possibly related to VRC07-523S. No G4 events
- 5 cases of VF despite good PK, 2/5 resuppressed on same treatment
- 1 case emergent R263K INSTI mutation (high baseline VRC07-523S IC_{50})

5 trials of note

3. A5377 study: phase I of SAR441236 (trispecific bNAb) IV & SC

- n=44 VS people, n=7 people with viraemia (on & off ART)
- No AE, modest antiviral effect, transient drug-induced Abs, no impact on PK

4. LEN + TAB + ZAB* (with ZAB dosed at 2 different doses)

- Previous Ph1b study : a single dose of LEN + TAB + ZAB maintained VS for 6M in 18/20 people with high susceptiblity to TAB
- N=11 VS people susceptible to TAB or ZAB given single dose
- 2 people with low level VR in lower dose ZAB group, no resistance

5. PGDM1400 + PGT121 + VRC07-523 in 12 VS people

- Each bNAb given IV at DO, D28, D56, D84, D112 & D140, ART stopped at D1
- N=2 with early VR (<D100) both with baseline resistance to 2 of the 3 bNAbs; n=5 with late VR (>D200), emergent resistance to 1 bNAb in 1/3 tested; n=4 VS at W44

*TAB = teropavimab; ZAB = zinlirvimab

Scientifically fascinating
Clearly can achieve good short-term off ART virological outcomes for SOME

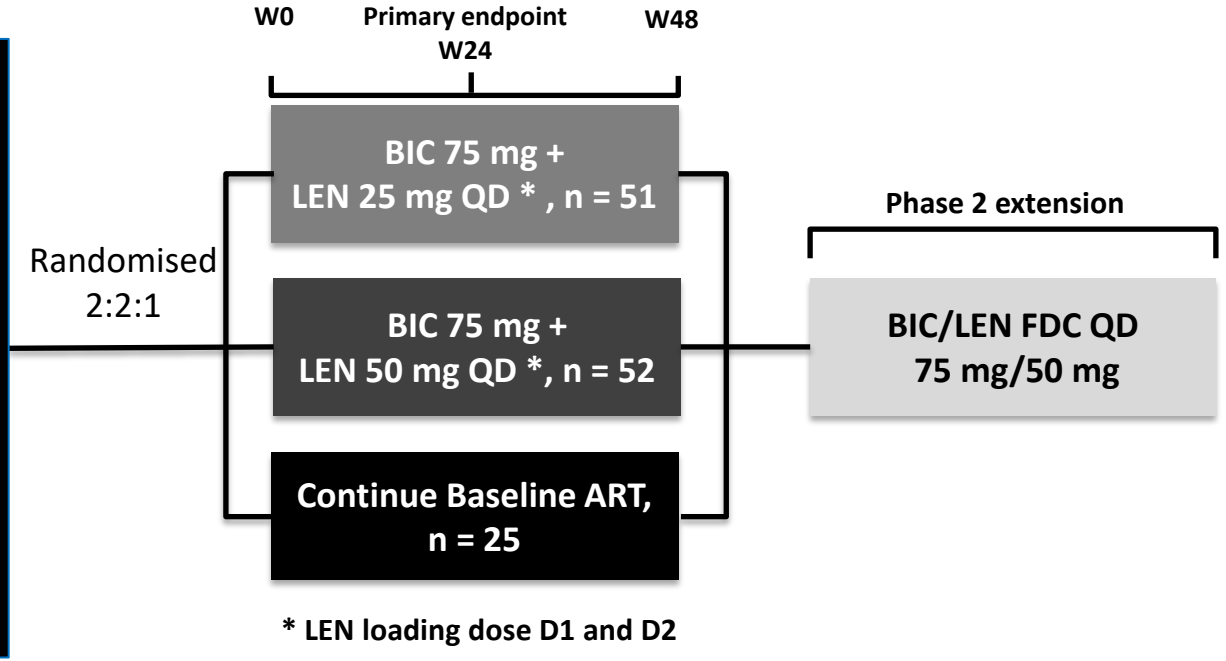
Over to Sarah Fidler:
“bNAbs are immune modulatory therapies, NOT antiretrovirals & should not be considered as such wrt resistance (no assay accurately predicts sensitivity yet); IC50 or 90 data is also unclear”
“Disappointing studies (including BANNER) but some far more positive primate & human immunological studies”

Baseline susceptibility critical (& many people have non-susceptible virus)
IV administration for now at least

OTHER NOVEL AGENTS

ARTISTRY-1: simplification to BIC/LEN OD

128 adults on complex ART
- bPI or NNRTI + ≥ 1 3rd agent other than NRTI
- Or ≥ 2 pills or ≥ 2 doses/day
- Or parenteral ART (excluding CAB/RPV) + oral agents
- HIV-1 RNA < 50 for ≥ 6M
- No prior LEN, no BIC RAMs, no HBV, eGFR ≥ 15



ARTISTRY-1: results

Participants

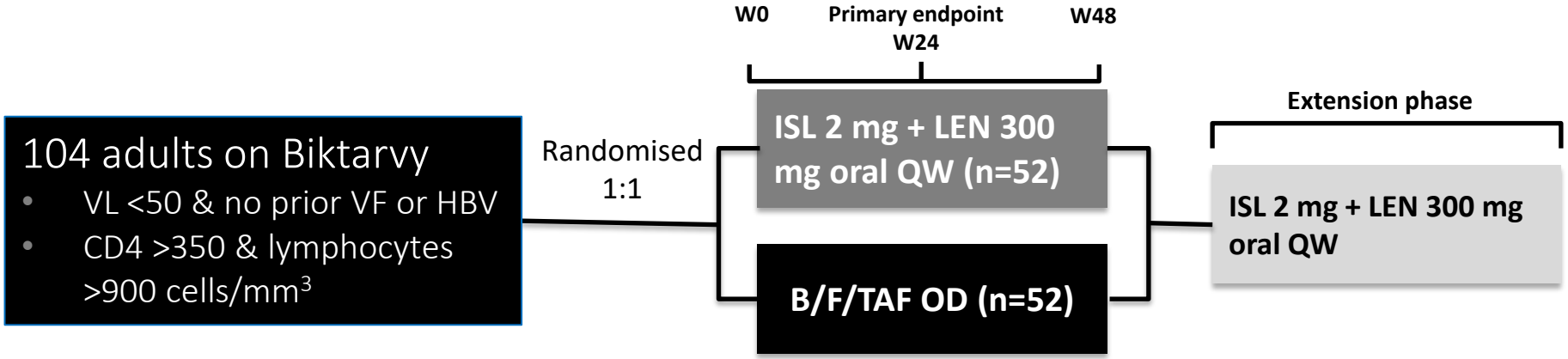
- Median age 60 years, living with HIV 27 years
- 81% on a complex ART due to resistance (RAMs not reported)
- Median pill number = 3 (63% on DRV/b + DTG ± TAF/FTC or NNRTI)

Viral suppression at W24

- BIC 75 + LEN 25 = 96.1%
- BIC 75 + LEN 25 = 96.2%
- Continued ART = 100%
- No CVFs

	BIC 75 mg + LEN 25 mg N = 51	BIV 75 mg + LEN 50 mg N = 52	SBR N = 25
ART-related AE	9 (18 %)	3 (6 %)	0
Serious AE	2 (3.9 %)	1 (1.9 %)	2 (8 %)
AE leading to discont^{n}	1 (2 %) Nausea	1 (1.9 %) Vomiting	0

Ph2: ISL + LEN QW maintenance ART

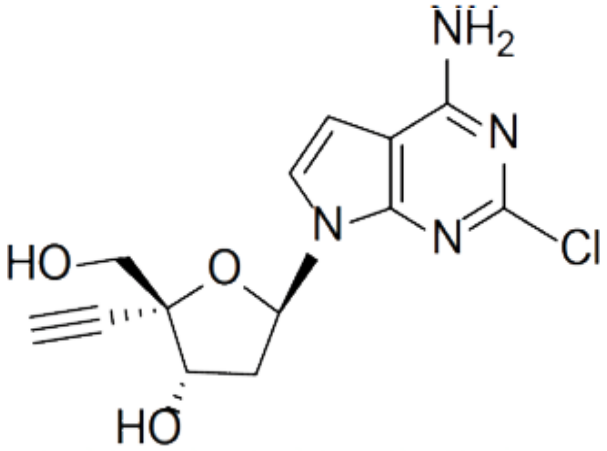


Viral suppression at W24

- ISL + LEN = 94.2%
- Biktarvy = 94.2%
- n=1 blip at W24 on ISL + LEN, adequate levels of both drugs

	ISL + LEN (n = 52)	B/F/TAF (n = 52)
Treatment-related AEs (G1/2)	9 (17.3 %) Dry mouth 3.8 %, nausea 3.8 %	3 (5.8%)
G3-4 lab abnormalities	6 (11.5 %)	4 (7.8 %)
Mean change lymphocytes	- 0.04	- 0.01
Mean change CD4	- 4	- 57

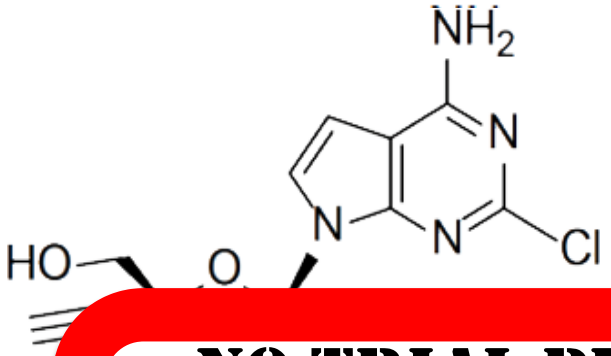
Carstens RP et al. abstract 115



I. **ISLATRAVIR**
II. **MK-8527**

NRTTIs: nucleoside reverse transcriptase translocation inhibitors
ISL development paused 2021, trials resumed at lower dose OD/OW
MK-8527 is v2 (presumably for OM oral PrEP??)
Confusing phase 1 monotherapy studies but promising (up to -1.8log)
No in vitro activity data & only on questioning was it revealed to be an adenosine analogue; good PK & safety in HIV-negative volunteers

Carstens RP et al. abstract 115



I. ISLATRAVIR
II. MK-8527

NO TRIAL PLANNED FOR ISL IMPLANT. THE 1 RECRUITING TRIAL ON CLINICALTRIALS.GOV WAS STOPPED "FOR BUSINESS REASONS"

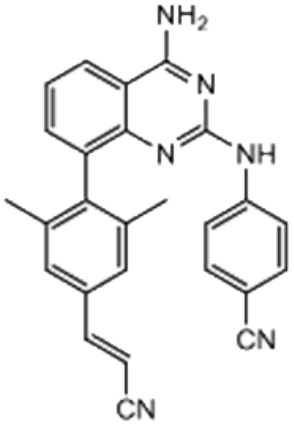
NRT
ISL d W
MK-8

Confusing phase 1 monotherapy studies but promising (up to -1.8log)
No in vitro activity data & only on questioning was it revealed to be an adenosine analogue; good PK & safety in HIV-negative volunteers

GS-1720

It's another INSTI! Potential for OW oral

Single dose in people without HIV = good PK ($t_{1/2}$ 9.4 days)
Phase 1b in people with HIV dosed D1 + 2 = -1.7 to -2.4 log VL D11
No INSTI RAMs on 150 or 450mg, pending for 30 & 900mg
Graph of good VL decline in all participants for 450 & 900mg
"Well-tolerated with favourable safety" in the 28 people studied



GS-5894

Welcome to the NNRTI party Gilead!!

In vitro activity against isolates with high-level resistance to EFV/RPV
Slow selection of resistant variants
Predicted to achieve good exposure with OW oral dosing

What about PIs….??

But PIs are BOOSTED?!
Why develop new PIs?

Welcome to the PI party Gilead!
GS-9770 is a new UNBOOSTED PI.
In vitro data only
400mg OD has predicted efficacy
Promising activity against DRV & ATV resistant variants….

Han X; abstract 637

What about PIs….??

But PIs are BOOSTED?!

Wh

Fold change in EC_{50}	GS-9770	DRV	ARV
Mean (SD)	3.8 (3.8)	52.8 (154.9)	16.4 (23.2)
Range	0.4 - 2.1	0.3 – 615	0.6 - > 132
Viruses with > 10-fold change in EC_{50}, n/N (%)	3/49 (6)	17/49 (35)	23/49 (47)

!

PI.

cy

Promising activity against DRV & ATV resistant variants….

WEIGHT

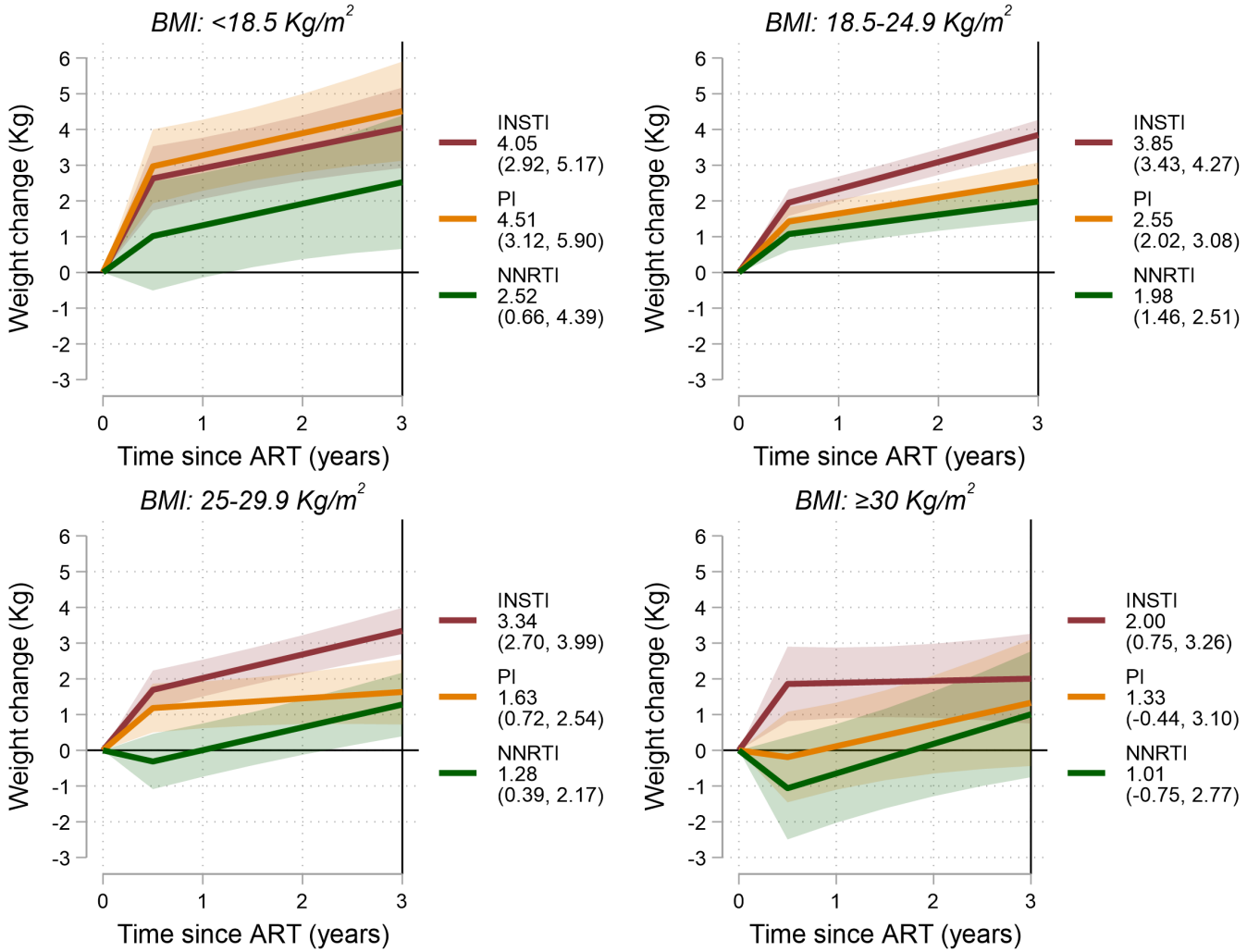
Weight gain on first-line ART is often attributed to “return to health”

The CASCADE cohort is a longitudinal study of people starting ART within 12M of seroconversion

Of 5698 individuals (4519 MSM), approx 50%/30%/20% started an INSTI/PI/NNRTI

INSTIs (especially BIC & EVG) + TAF associated with fastest weight gain ART initiated very close to seroconversion, so likely to reflect direct ART effect

Baseline BMI (kg/m^2) Category	Estimated weight change (kg)	INSTI	PI	NNRTI	TAF	TAF+INSTI
<18.5	At 6 months	2.50 (1.63, 3.37)	3.03 (2.02, 4.04)	0.88 (-0.64, 2.39)	3.26 (1.75, 4.77)	3.28 (1.69, 4.88)
	At 3 years	4.22 (3.14, 5.30)	5.02 (3.67, 6.38)	2.74 (0.89, 4.60)	4.94 (2.31, 7.56)	4.78 (2.09, 7.47)
18.5-24.9	At 6 months	1.89 (1.60, 2.19)	1.55 (1.20, 1.90)	0.90 (0.48, 1.31)	2.23 (1.79, 2.68)	2.39 (1.91, 2.87)
	At 3 years	3.95 (3.65, 4.25)	2.87 (2.44, 3.31)	1.98 (1.54, 2.41)	4.61 (3.96, 5.27)	4.76 (4.05, 5.46)
25-29.9	At 6 months	1.78 (1.30, 2.26)	1.63 (1.00, 2.27)	-0.18 (-0.92, 0.55)	3.50 (2.67, 4.33)	3.75 (2.84, 4.66)
	At 3 years	3.43 (2.87, 3.99)	2.18 (1.33, 3.03)	1.46 (0.63, 2.29)	5.10 (3.78, 6.42)	4.98 (3.49, 6.47)
≥30	At 6 months	2.02 (1.01, 3.04)	0.36 (-0.88, 1.60)	-0.97 (-2.39, 0.44)	4.66 (2.73, 6.58)	4.56 (2.39, 6.73)
	At 3 years	2.25 (1.04, 3.46)	2.32 (0.58, 4.06)	1.04 (-0.70, 2.77)	3.99 (1.13, 6.85)	2.17 (-1.07, 5.41)


BMI: <18.5 Kg/m2
Weight change (Kg)
Time since ART (years)
INSTI
4.05
(2.92, 5.17)
PI
4.51
(3.12, 5.90)
NNRTI
2.52
(0.66, 4.39)
BMI: 18.5-24.9 Kg/m2
Weight change (Kg)
Time since ART (years)
INSTI
3.85
(3.43, 4.27)
PI
2.55
(2.02, 3.08)
NNRTI
1.98
(1.46, 2.51)
BMI: 25-29.9 Kg/m2
Weight change (Kg)
Time since ART (years)
INSTI
3.34
(2.70, 3.99)
PI
1.63
(0.72, 2.54)
NNRTI
1.28
(0.39, 2.17)
BMI: ≥30 Kg/m2
Weight change (Kg)
Time since ART (years)
INSTI
2.00
(0.75, 3.26)
PI
1.33
(-0.44, 3.10)
NNRTI
1.01
(-0.75, 2.77)

Dreschler H; abstract 812

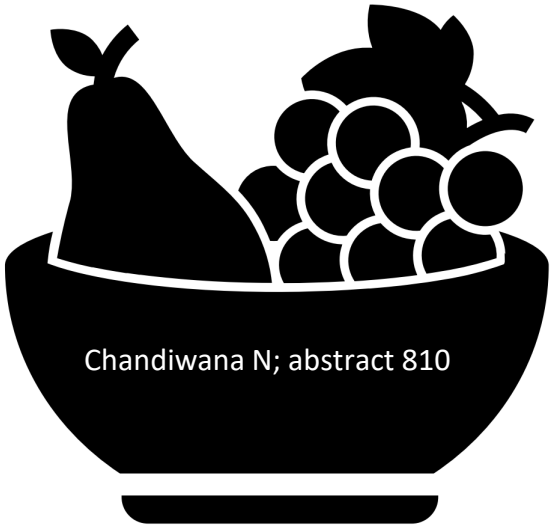
There was a LOT that wasn't very novel, & a fair bit that wasn't very good….
….but this one took the prize!

TDF and Efavirenz but Not INSTI or TAF Use Are Associated With Weight Gain After cART Initiation.

VA

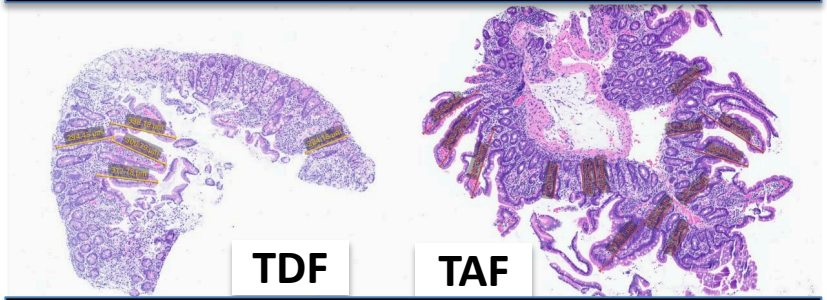
Marginal Means for predicted BMI gain		Model1	
		Baseline covariates	
		BMI gain (95% CI)	p-value
Anchor Drug	*Dolutegravir*	2.12 (1.91-2.33)	REF
	Bictegravir	2.36 (2.09-2.63)	0.13
	Elvitegravir	1.79 (1.50-2.08)	**0.05**
	Raltegravir	1.60 (1.21-1.99)	**0.01**
	Darunavir	1.75 (1.49-2.01)	**0.02**
	Atazanavir	1.68 (1.40-1.96)	**0.01**
	Rilpivirine	1.66 (1.35-1.96)	**0.009**
	Efavirenz	1.16 (0.97-1.35)	**<0.0001**

South African cohort (DISCO) 66 people **with** ≥10% weight gain on DTG ate more fruit but same amount fast food & sugary drinks as 301 **without**



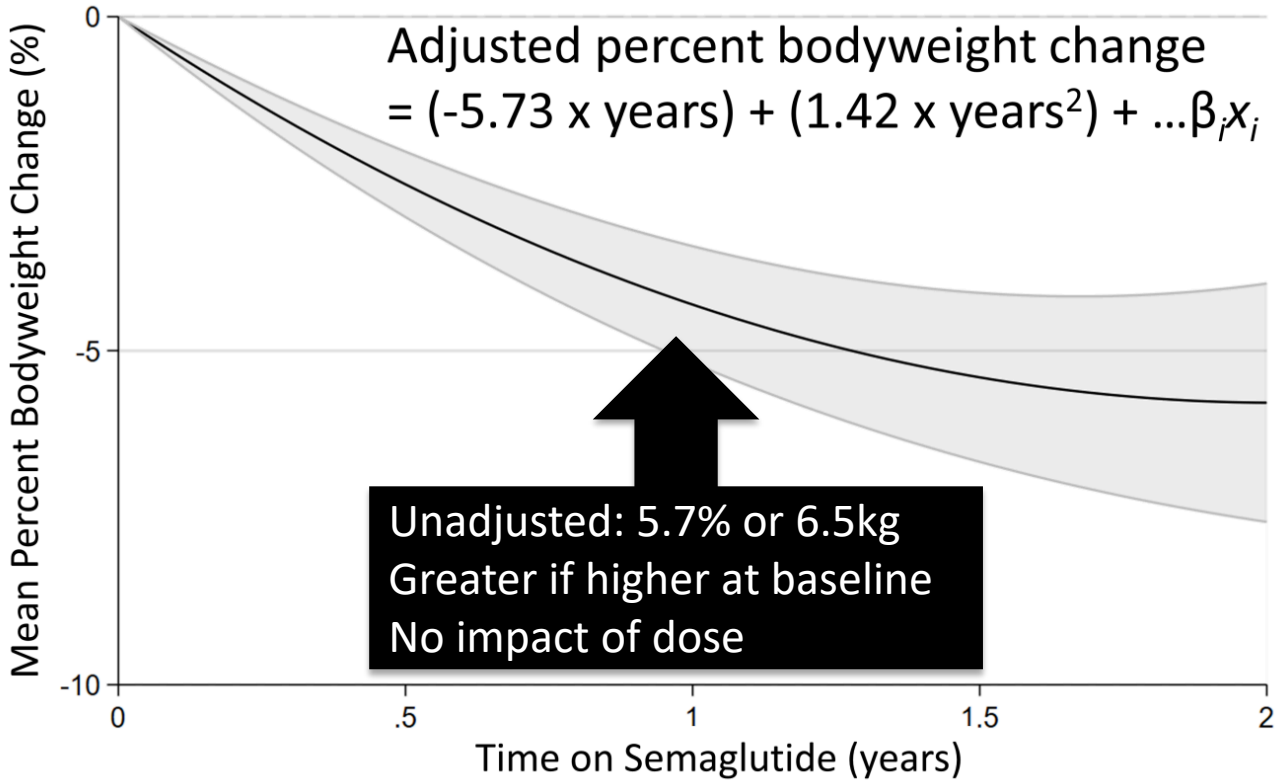
Chandiwana N; abstract 810

Lower **body weight** and **plasma lipids** in patients taking **TDF vs. TAF** may be caused by **damage to duodenal villi.** Kauppinen KJ; abstract 806



12 on TDF & 12 on TAF, "no GI Sx" but 5 on TDF & 2 on TAF had **GI pathology on biopsy** **Not adjusted** for duration of HIV or CD4 nadir

Semaglutide cohort (n=111)



More semaglutide (SG) headlines

ACTG A5371 n=49
Lake JE; abstract 159

'SLIM LIVER study'

Central adiposity, insulin resistance/pre-diabetes & MASLD on MRI

Low-dose SG (1mg OW 24W) significantly improved:
- liver fat (normal in 29%!)
- weight & WC
- fasting glucose & triglycerides

SLIM LIVER n=48
Ditzenberger GL; abstract 799

People with paired MRIs
Muscle loss may accompany weight loss & impact function

After 24W semaglutide:
- loss of psoas volume
- physical function maintained
- interventions that preserve muscle mass may help

RCT SG vs PBO
Eckard AR; abstract 798

N=108 with HIV-associated lipodystrophy, 32W SG/PBO VS on ART, no DM/CVD

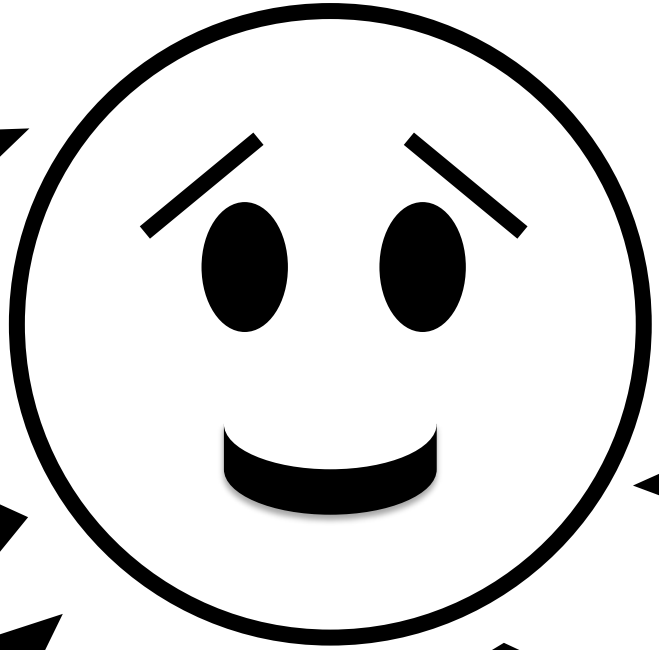
Previously showed reduced total body/central fat & VAT

This analysis showed significant decreases in hsCRP & sCD163 (& trends with IL-6) independent of changes in VAT

CLOSING THOUGHTS

More bNAbs studies than progress?

Looks like we'll see weekly oral before 6 monthly parenteral whole regimens



Still not clear IF some ART drives weight gain & if it does…HOW?

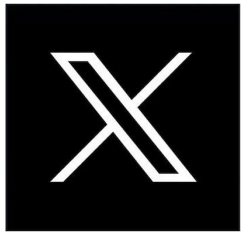
Welcome to the 2DR party Gilead!

Semaglutide works but how to get it?

THANK YOU! Anton Pozniak & Carolin Sabin for slides & to YOU for listening!

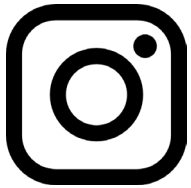
Thank you for listening: questions?

lwaters@nhs.net



@drlaurajwaters

peoplefirstcharter.org



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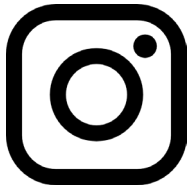

@flame_and_dame