IAS 2021
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IAS 2021 Updates: Pregnancy/Pediatric HIV, ART-associated Weight Gain, and Opportunistic Infections

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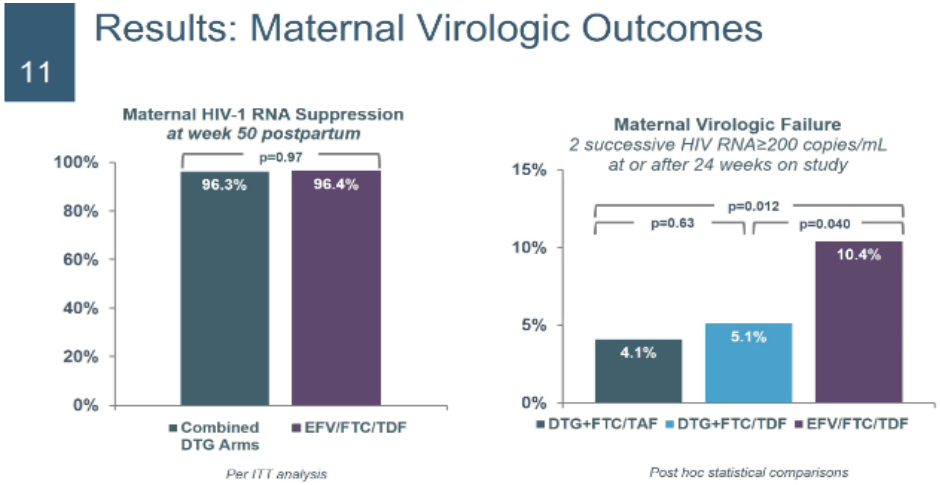
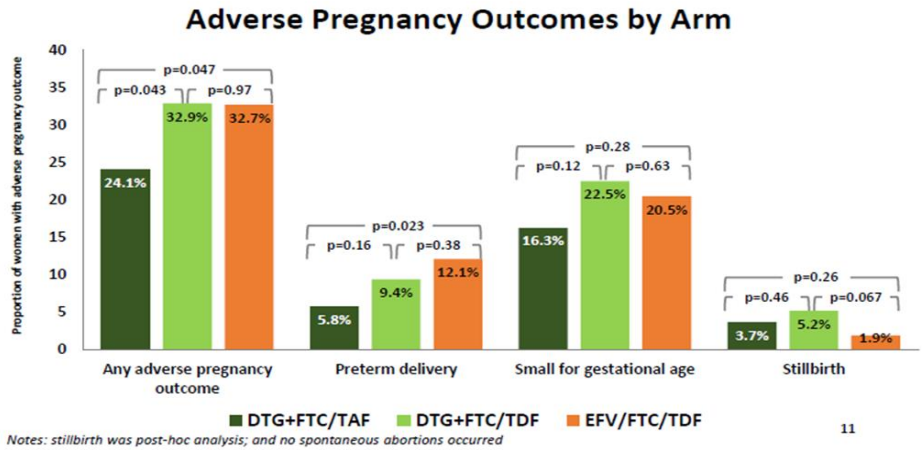
HIV and Pregnancy

Prior Data (IMPAACT 2010) suggests TAF/FTC/DTG may be best regimen started during pregnancy

VESTED (N=653): Three-arm, randomized, open-label study of pregnant women with HIV-1 initiating DTG/FTC/TDF vs. DTG/FTC/TAF vs. EFV/FTC/TDF at 14-28 weeks gestation. (Chinula et al. CROI 2021, Lockman Lancet 2021)



1. Better Viral Suppression



2. Fewer Adverse Birth Outcomes

Prior Data (IMPAACT 2010, 'VESTED') suggests TAF/FTC/DTG may be best regimen in pregnancy

DHHS Perinatal Guidelines Update

→2021: *upgraded TAF* from alternate to preferred NRTI (with TDF and ABC)

→*DTG already preferred* for pregnancy and people trying to conceive (with RAL, ATZ/r and DRV/r)

WHO ART Treatment Guidelines

→ Since 2019: TDF + XTC + DTG is preferred first-line

→ TAF in selected situations (renal failure, osteoporosis)

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1. Better Viral Suppression

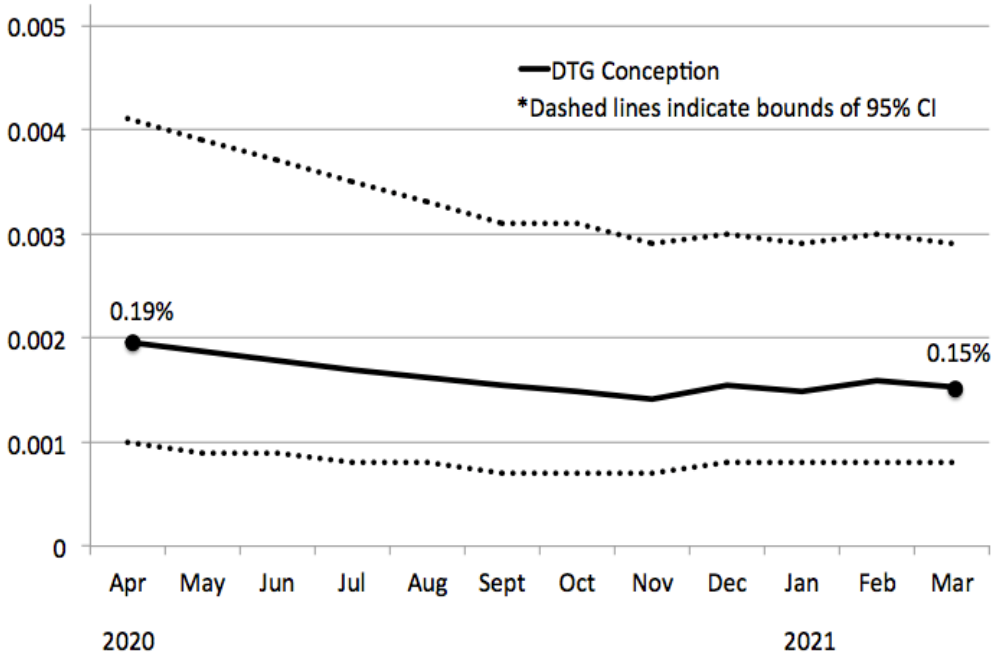
2. Fewer Adverse Birth Outcomes

What about Neural Tube Defects?

- **No data on TAF at conception**
  - TDF without any concern for birth defect with conception exposure
- **As data have accrued in Tsepamo, updates have been increasingly reassuring:**
  - Prevalence of NTDs with Periconception DTG Exposure
    - AIDS 2018: 0.94% (4/426)
    - IAS 2019: 0.30% (5/1693)
    - AIDS 2020: 0.19% (7/3591)

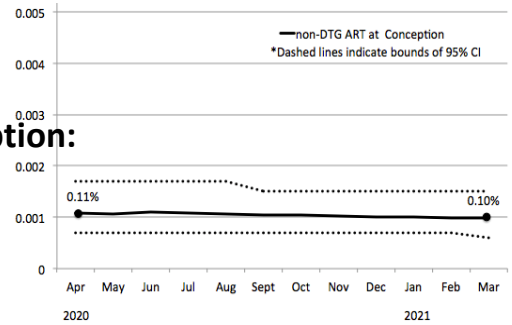
Tsepamo Results March 2021 (IAS 2021)

IAS2021 Abstract: Zash et al,

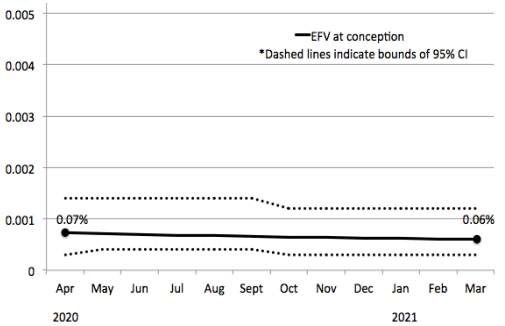


Total Prevalence of NTDs with conception DTG (entire study): 9 NTDs/5860 exposures

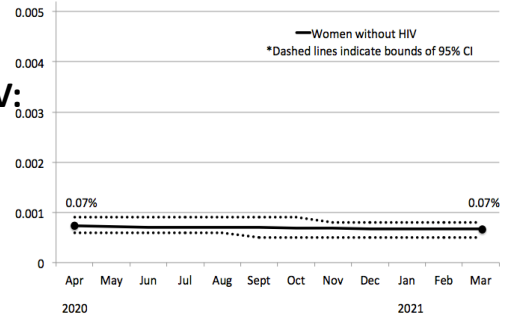
Non-DTG at conception: 0.10% (N= 22,475)



EFV at conception: 0.06% (N= 13,217)



Women without HIV: 0.07% (N= 144,967)



Tsepamo Results March 2021 (IAS 2021)

IAS2021 Abstract: Zash et al,

Prevalence Difference of NTDs by Antiretroviral and HIV Exposure Categories, 2014-2021

Exposure group vs. Comparison group	Prevalence Difference (%) (95% CI)
DTG at conception vs. Non-DTG at conception	0.06% (-0.03, 0.20)
DTG at conception vs. EFV at conception	0.09% (-0.00, 0.23)
DTG at conception vs. DTG started in pregnancy	0.10% (-0.03, 0.24)
DTG at conception vs. Women without HIV	0.09% (0.01, 0.23)

- **These data support WHO and DHHS guidelines for use of DTG as first-line among pregnant people, people of reproductive potential and people trying to conceive**

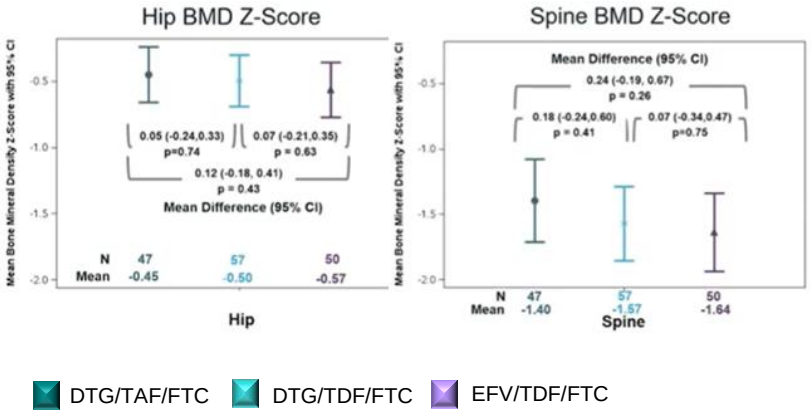
Bone Mineral Density in post-partum women and their infants Data from IMPAACT 2010

Mbengeranwa T et al. International Pediatric HIV Workshop Abs 12

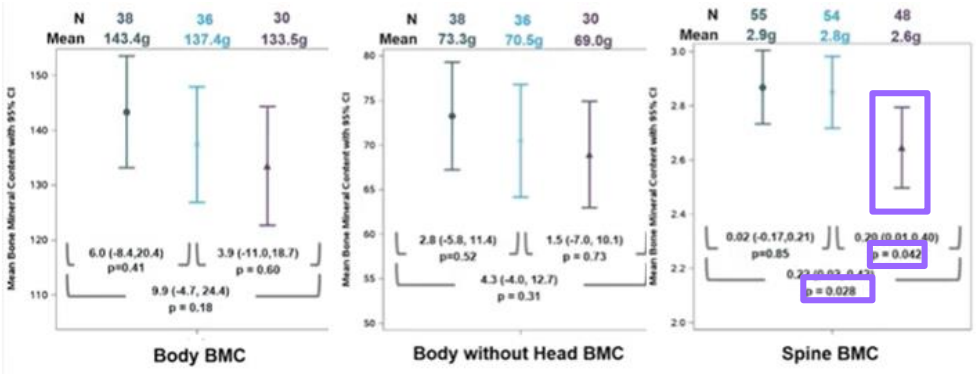
Pregnant women randomized to DTG/TDF/FTC vs. DTG/TAF/FTC vs. EFV/TDF/EFV at 14-28 weeks GA

- DXA evaluation at week 50 postpartum in 154 **participants** (median duration ART 66 wk, median duration BF 44 wk) and 165 **infants** (median age 5.8 mo) at 26 wks

Post-Partum Women: No significant difference BMD z scores between treatment arms; lowest in **EFV/TDF/3TC** arm



Infant: No significant difference BMD z-scores between treatment arms for whole body; but significantly lower **spine** BMC in **EFV/TDF/3TC** arm



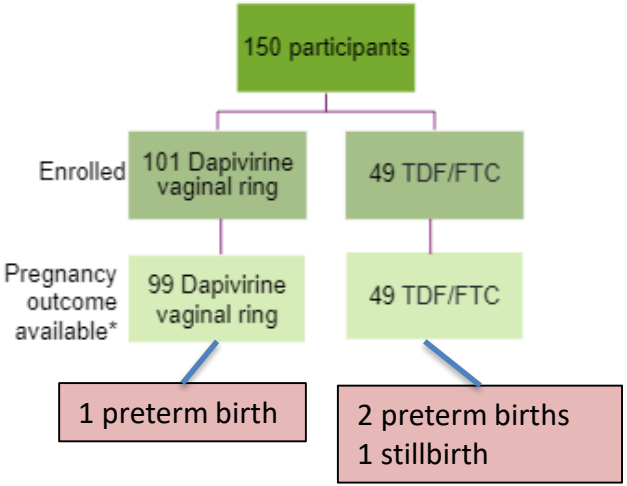
Prevention of HIV in pregnancy

- Is PrEP safe in pregnancy?
  - lots of data on safety of TDF/FTC from pregnant women living with HIV
  - but some see higher bar for PrEP because it is not required for maternal treatment

DELIVER/MTN-042 Cohort 1
Safety of Dapivirine Ring in Late Pregnancy

IAS 2021 Makanani B et al. Abs PECLB26

STUDY DESIGN: Pregnant women randomized 2:1 to monthly dapivirine ring or daily oral TDF/FTC starting at 36-37 weeks gestation (Cohort 1)



	Dapivirine n=99 n (%)	TDF/FTC n=49 n (%)
Any hypertensive disorder of pregnancy[3]	3 (3)	4 (8)
Gestational hypertension	3 (3)	2 (4)
Pre-eclampsia without severe features	0 (0)	1 (2)
Pre-eclampsia with severe features	0 (0)	1 (2)
Eclampsia	0 (0)	0 (0)
Hemorrhage		
Peripartum/Antepartum hemorrhage	0 (0)	1 (2)
Postpartum hemorrhage	2 (2)	1 (2)

- Adverse pregnancy outcomes and complications were uncommon in small sample
- Study will move on to Cohort 2 (randomize at 30-35 weeks gestation)

PrIMA Study: Prenatal PrEP Exposure and Growth Outcomes in Kenyan Infants

IAS 2021Gomez L et al. Abs PEC353

Study Design: Cluster randomized trial of PrEP (with TDF/FTC) counseling strategies for women attending antenatal care in 20 facilities in Western Kenya

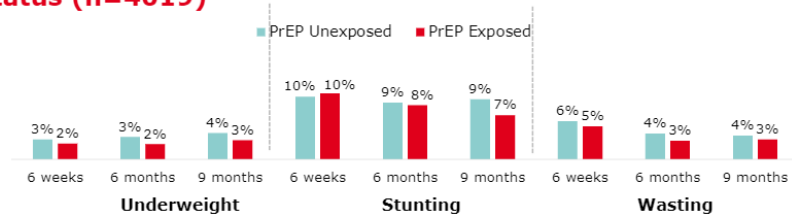
Table 2: Infant growth at 6-weeks, 6-months and 9-months by prenatal PrEP exposure (n=4019)

	Median (IQR)		Adjusted Coeff (95% CI)*	P-value
	PrEP Unexposed (n=3471)	PrEP Exposed (n=548)		
Weight (kg) 6-week	5.0 (4.5, 5.4)	5.0 (4.5, 5.4)	0.03 (-0.06, 0.11)	0.52
6-month	7.7 (7.0, 8.5)	7.8 (7.2, 8.7)	0.22 (0.08, 0.36)	0.004
9-month	8.6 (7.9, 9.6)	8.6 (8.0, 9.5)	0.09 (-0.04, 0.21)	0.16
Length (cm) 6-week	55.0 (54.0, 57.0)	55.3 (54.0, 57.2)	-0.60 (-2.01, 0.81)	0.39
6-month	66.0 (64.0, 68.0)	66.0 (64.0, 69.0)	0.31 (-0.51, 1.13)	0.44
9-month	70.0 (68, 72)	70.5 (68.6, 72.0)	-0.02 (-1.32, 1.28)	0.97

*Adjusted for gestational age at birth, maternal syphilis, maternal age and partner HIV status

No differences in median weight, length or adverse infant growth outcomes among infants exposed vs. unexposed to PrEP in-utero

Figure 1: Infant growth outcomes by prenatal PrEP exposure status (n=4019)*



Adj RR (95% CI)*	0.8 (0.4-1.5)	0.6 (0.4-1.4)	0.8 (0.4-1.9)	1.2 (0.8-1.7)	1.0 (0.7-1.4)	0.7 (0.4-1.5)	0.8 (0.5-1.4)	0.9 (0.4-1.7)	0.7 (0.3-1.5)
P-value	0.45	0.16	0.33	0.20	0.81	0.10	0.45	0.68	0.36

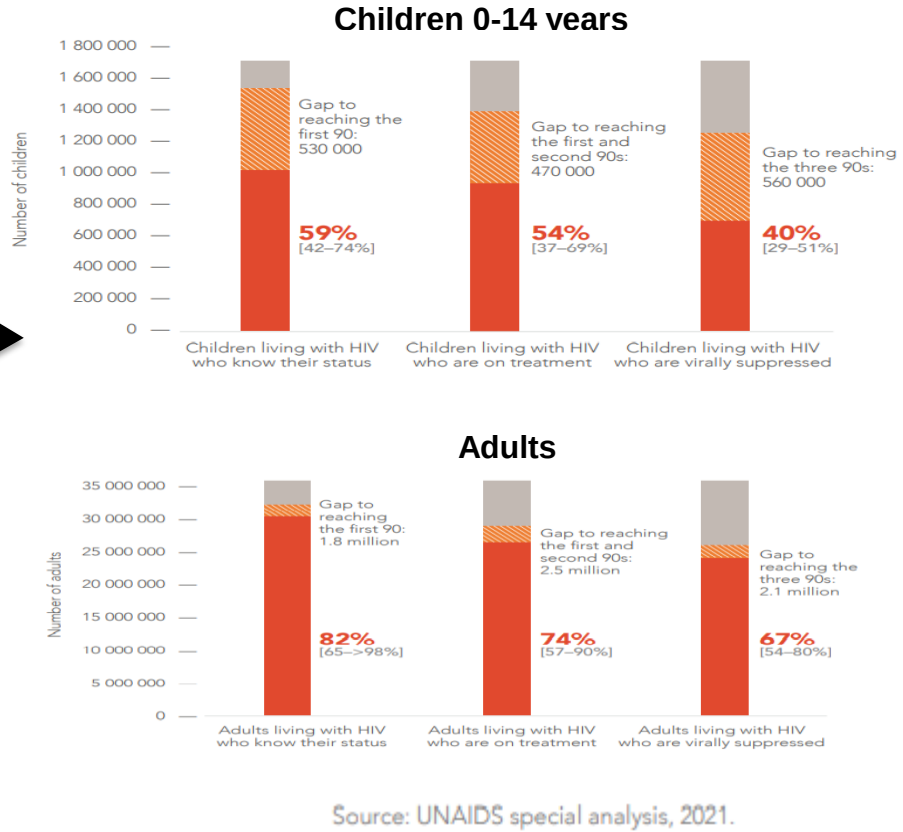
*Adjusted for gestational age at birth, maternal syphilis, maternal age and partner status

Results were similar when analyzed separately by trimester of PrEP initiation

Pediatric HIV

Poor Viral Suppression in Pediatric Populations

- **Generating data on newer ARVs has been frustratingly slow in pediatric populations**
  - Use of older, less well tolerated ART with more side effects in children
- Odyssey Trial (Turkova et al. CROI 2021 abs. 174) found that DTG-based ART was superior to standard of care (SOC) for children >14kg (older children, median age 12)



The ODYSSEY Trial: Evaluation of DTG-Based ART vs SOC in Young Children <14 Kg

IAS 2021 Amuge P et al. PEBLB18

85 children enrolled

- n= 23 <6kg; n=40, 6-<10kg; n=22, 10-<14 kg)
- Median baseline age (IQR): 1.4 years (0.6, 2.0)
- SOC ART was LPV/r in 74%

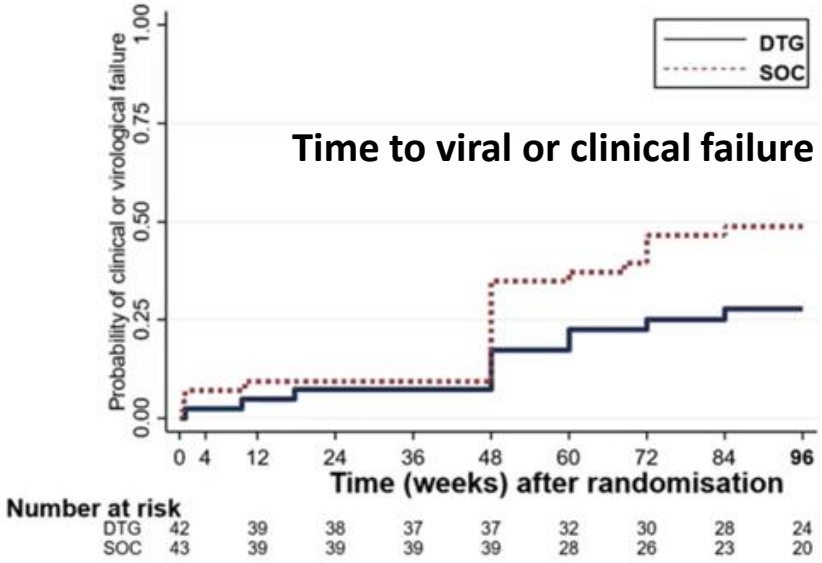
Follow-up:

- Median FU (IQR): 120 weeks (97, 132)
- Only 5 (6%) LTFU

The ODYSSEY Trial: Evaluation of DTG-Based ART vs SOC in Young Children <14 Kg

IAS 2021 Amuge P et al. PEBLB18

	DTG N=42	SOC N=43	Total N=85
Primary endpoint (viral or clinical failure)	**11 (26%)**	**21 (49%)**	32 (38%)
Confirmed VL >400 c/mL >36 weeks	**8 (19%)**	**16 (37%)**	24 (28%)
WHO stage 4 event	1 (2%)	1 (2%)	2 (2%)
Death	2 (5%)	4 (9%)	6 (7%)



Differences emerge after 1 yr

log-rank p=0.05

***No difference in AEs (higher cholesterol with SOC)**

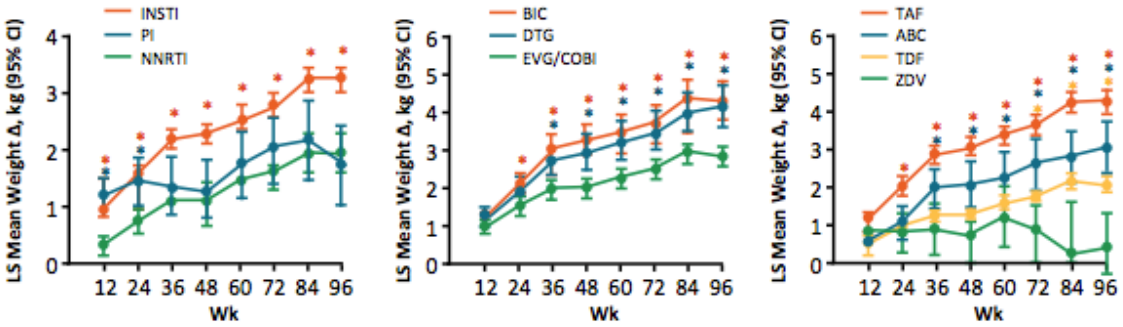
Evaluation of DTG-Based ART for children (real world data)

IAS 2021 Abstract Bacha et al. OALB0504

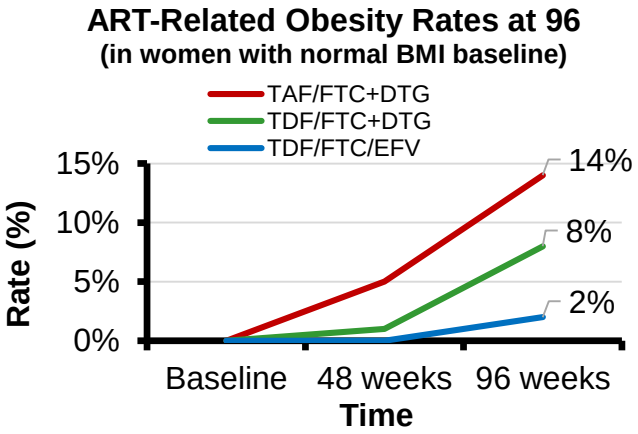
- **Retrospective review of data (Jan 2017-Dec 2020) from Baylor sites in 6 countries (Uganda, Tanzania, Malawi, Botswana, Eswatini, and Lesotho) (N=9419)**
  - Children 0-19 y.o. enrolled in HIV care who were switched to DTG ART (93% were virally suppressed pre-switch)
- **Previously suppressed who remained suppressed w/DTG:**
  - 6645/7026 (95%)
- **Previously unsuppressed who became suppressed w/DTG:**
  - 426/534 (80%) overall
  - including 73/88 (83%) who remained on the same NRTI backbone

Weight Gain and ART

- Accumulating evidence that while weight gain common with all ART:
  - **Weight gain is most highly associated with newer INSTIs (DTG and BIC) and TAF**
  - TDF may suppress weight gain



Sax P et al. Clin Infect Dis. 2020;71:1379



ADVANCE Study (S. Africa)

AIDS 2020 Sokhela et al. OAXLB0104

Cisgender women at particularly high risk of excess weight gain

Weight Gain in TANGO vs. SALSA: More data for TAF and INSTI

IAS 2021 abstract van Wyk et al. PEB164 and Llibre et al OALB0303

TANGO Study Design: Randomized, open label, non-inferiority study (multiple countries) among virally suppressed (>6m) adults on TAF-based ART to switch to DTG/3TC vs. continue TAF-based ART

SALSA Study Design: Randomized, open label, non-inferiority study (multiple countries) among virally suppressed (>6m) adults on any ART* to switch to DTG/3TC vs. continue TAF-based ART

***44% on TDF-based ART and 60% on NNRTI or PI**

Mean weight changes (144wks):
+2.2kg with switch to DTG/3TC
+1.7 kg with continued TAF-based ART

Mean weight changes (48wks):
+2.1kg with switch to DTG/3TC
+0.6 kg with continued ART

TANGO: Week 144 Weight Gain Metabolic Outcomes

IAS 2021 abstract van Wyk et al. PEB164

Study Design: Randomized, open label, non-inferiority study (multiple countries) among virally suppressed (>6m) adults on TAF-based ART to switch to DTG/3TC vs. continue TAF-based ART

Mean weight changes:
+2.2kg with DTG/3TC
+1.7 kg with TAF-based ART

No difference between groups in:
-change in glucose
-insulin resistance
-proportion with metabolic syndrome

Outcome: Adjusted Δ From Baseline*, %	Switch to DTG/3TC (n = 243)	Continue TAF-Based ART (n = 230)
TC, mmol/L	-3.3	+4.2
HDL, mmol/L	-2.4	+3.9
LDL, mmol/L	-3.0	+4.6
TG, mmol/L	-9.7	+2.2
TC: HDL ratio	-0.9	+0.3

TANGO: Week 144 Weight Gain Metabolic Outcomes

IAS 2021 abstract van Wyk et al. PEB164

Study Design: Randomized, open label, non-inferiority study (multiple countries) among virally suppressed (>6m) adults on TAF-based ART to switch to DTG/3TC vs. continue TAF-based ART

Mean weight changes:
+2.2kg wi
+1.7 kg w

No differe
groups in
-change in glucose
-insulin resistance
-proportion with metabolic syndrome

Outcome; Adjusted Δ	Switch to	Continue ased ART = 230)
		4.2
		3.9
LDL, mmol/L	-3.0	+4.6
TG, mmol/L	-9.7	+2.2
TC: HDL ratio	-0.9	+0.3

DISCOVER TRIAL: TDF/FTC vs. TAF/FTC PrEP also found more elevation in lipids with TAF.

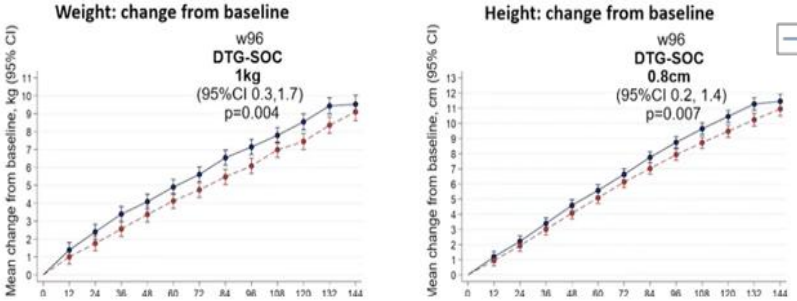
Lipid Abnormalities may be most closely associated with TAF???

Weight Gain and Change in BMI *in Children*
DTG vs SOC in the ODYSSEY Trial

IAS 2021 Mujuru H et al., PEB202

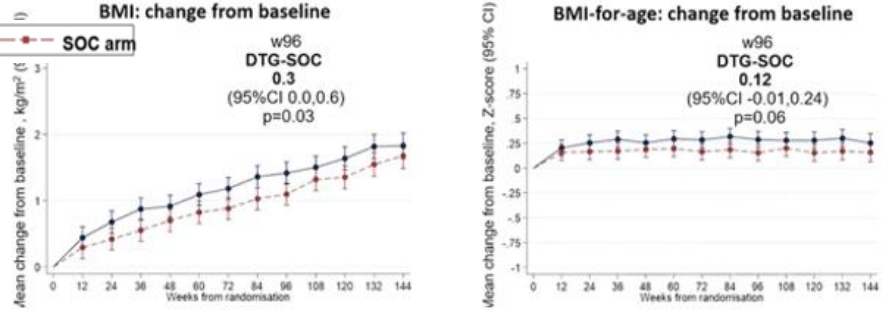
At baseline only 5% overweight, 1% obese → 25 (4%) were newly overweight/obese at 96 weeks: **14 (4%) DTG, 11 (3%) SOC, p=0.55.**

Change from Baseline in Weight and Height DTG vs SOC



- Small additional gains from baseline in height and weight in DTG vs SOC
- At 96 weeks, mean added gain in DTG vs SOC in weight was 1 kg and height 0.8 cm
- The differences occurred early and stabilized

Change from Baseline in BMI and BMI-for-Age DTG vs SOC



Small additional gains from baseline in BMI and BMI-for-age in DTG vs SOC

At 96 weeks, mean additional gain in BMI in DTG vs SOC was 0.3

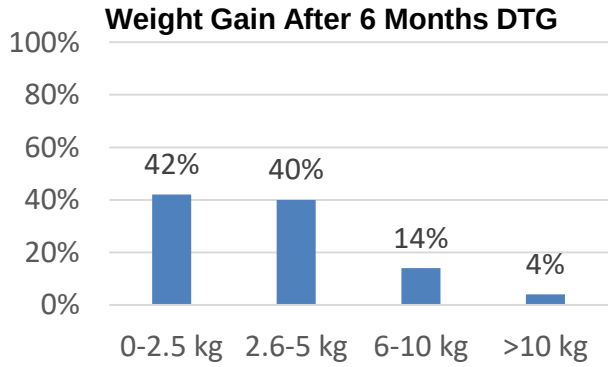
The differences occurred early and gap between arms did not increase with time

Children grew better after switching tp DTG vs SOC; differences between arms in weight, height and BMI were small …**DTG-based ART was not associated with excessive weight gain in children.**

Impact of DTG on Weight Gain *in Adolescents*

International Pediatric HIV Workshop 2021. Masunga E et al Abs 8

Study Design: Retrospective study of 229 adolescents in routine care (aged 10-19 years) on DTG ART for >6 months (91% switched from other ART regimen) and compared weight before (DTG switch visit) and after (visit after six months DTG).



The percent of adolescents who were overweight increased

- From 1.7% (4/229) before DTG to 8.7% (20/229) after being on DTG for 6 months
- 16 overweight, 4 obese

- **Somewhat difficult to interpret because they were lacking a comparator group**
- **Unknown if there was a positive impact on underweight**

Opportunistic Infections

Cryptococcal Meningitis

- **Cryptococcal Meningitis is the second-leading cause of AIDS-associated mortality**
- In resource limited settings, WHO recommended treatment with amphoteracin B (7-14 days) is associated with high rate of adverse effects and high costs for inpatient admission and laboratory monitoring
  - The alternative recommended treatment, with high dose fluconazole, has ~60% mortality
- The liposomal formulation of amphoteracin (LAmB) has fewer side effects, and a long half life
  - LAmB is not widely available in sub Saharan Africa where the burden of crypto is the highest

Cryptococcal Meningitis: AMBITION-CM Trial

IAS2021 Abstract: Lawrence et al OALB01LB03

Study Design: Randomized, open label, non-inferiority study (multiple African countries)

≥18 years old w/HIV infection with first episode of HIV-associated cryptococcal meningitis

Liposomal AmB 10 mg/kg single dose **+**
5FC 100 mg/kg QD for 14 days **+**
FLU 1200 mg QD for 14 days
(n = 421)

AmB 1 mg/kg for 7 days **+**
5FC 100 mg/kg QD for 7 days followed by
FLU 1200 mg QD for 7 days
(n = 423)

WHO recommended treatment in resource limited settings

FLU 800 mg QD for 8 wk;
ART initiated 4-6 wk after start of antifungal therapy

Cryptococcal Meningitis: AMBITION-CM Trial

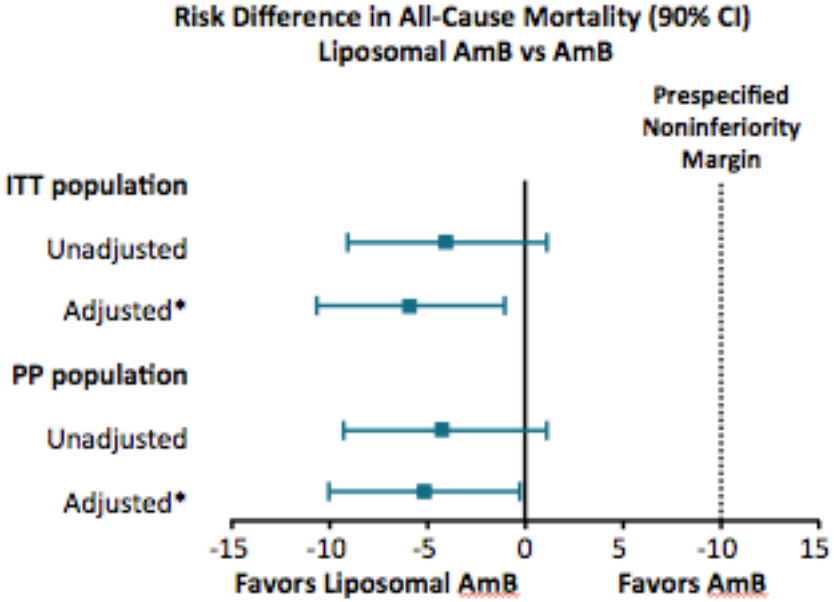
IAS2021 Abstract: Lawrence et al OALB01LB03

Primary outcome: all-cause mortality at 10 wk with noninferiority margin of 10%

Overall Mortality at 10 weeks:

- Liposomal AmB: 101/407 (24.8%)
- Amphoteracin B:117/407 (28.75)

***0 LTFU*



Cryptococcal Meningitis: AMBITION-CM Study

IAS2021 Abstract: Lawrence et al OALB01LB03

	LAmB (n = 420)	AmB (n = 422)	P Value
Total # grade 3/4 events	382	579	<.001
Any AE, n (%) ▪ **Grade 3** ▪ **Grade 4**	173 (41) 91 (22)	225 (53) 127 (30)	<.001 .005
Anemia, n (%) ▪ **Grade 3** ▪ **Grade 4**	44 (10) 12 (3)	108 (26) 62 (15)	<.001 <.001
Rcvd transfusion, n (%)	32 (8)	76 (18)	<.001
Hypokalemia ▪ **Grade 3** ▪ **Grade 4**	6 (2) 0 (0)	27 (6) 3 (1)	<.001 .25
Mean % change in creatinine level to Day 7	20.2	49.7	<.001

Safety Outcomes: Liposomal formulation (LAmB) vs. Standard Amphoteracin B (AmB)

	LAmB (n = 420)	AmB (n = 422)	P Value
Creatinine increase, n (%) ▪ **Grade 3** ▪ **Grade 4**	17 (4) 5 (1)	22 (5) 3 (1)	.42 .505
Neutropenia ▪ **Grade 3** ▪ **Grade 4**	27 (6) 20 (5)	21 (5) 16 4)	.36 .49
Thrombocytopenia ▪ **Grade 3** ▪ **Grade 4**	9 (2) 4 (1)	17 (4) 6 (1)	.11 .75
Elevated ALT ▪ **Grade 3** ▪ **Grade 4**	6 (1) 1 (0.2)	4 (1) 1 (0.2)	.52 1.0

Drug Resistant Tuberculosis

WHO Classification of drug resistant TB	
Rifampin-resistant TB **(RR)**	Resistant to RIF
Multidrug resistant TB **(MDR)**	Resistant to at least INH and RIF
Pre-extensively drug resistant TB **(pre-XDR)**	MDR/RR TB also resistant to any fluoroquinolone
Extensively drug resistant TB **(XDR)**	MDR/RR TB TB that is also resistant to any fluoroquinolone AND any Group A drug (levo, moxi, bedaquiline and linezolid)

Approximately 500,000 people per year develop multi-drug resistant TB

- Cure rates are only ~50-60% for MDR-TB
- Regimens are complicated (up to 20 pills/day) with lengthy duration (9-24 months)

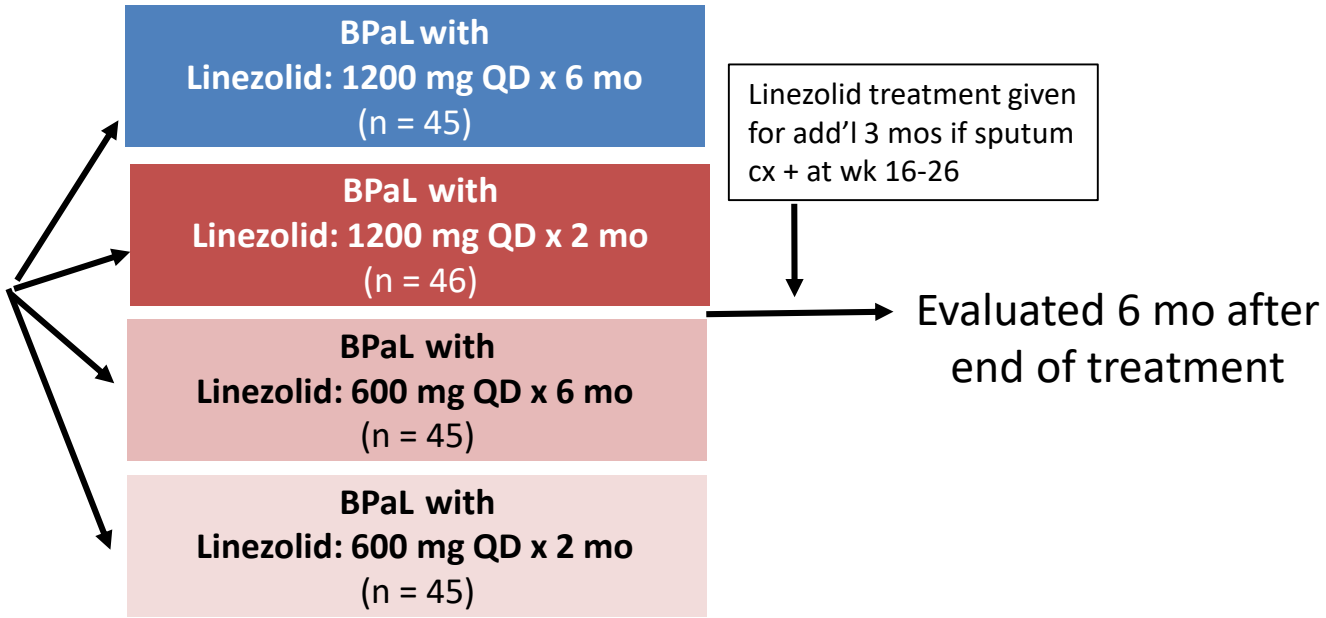
ZeNix: Pretomanid, Bedaquiline, and Linezolid (BPaL) in Treatment of *Highly Resistant TB*

IAS2021 Abstract: Conradie et al. OALB01LB02

Study Design: Randomized, partially-blind (to linezolid dose and duration) phase 3

≥14 yr olds with XDR, or pre-XDR drug-resistance, treatment-intolerant or non-responsive MDR TB

- 88% with pre/XDR-TB
  - 20% with HIV



ZeNix: Pretomanid, Bedaquiline, and Linezolid (BPaL) in Treatment of Highly Resistant TB

IAS2021 Abstract: Conradie et al. OALB01LB02

	BPaL With Linezolid 1200 mg x 6 mo (n = 45)	**BPaL With Linezolid 1200 mg x 2 mo (n = 46)**	**BPaL With Linezolid 600 mg x 6 mo (n = 45)**	**BPal With Linezolid 600 mg x 2 mo (n = 45)**
No. assessable	44	45	44	44
Favorable [95% CI]	41 (**93.2**) [81.3-98.6]	40 (**88.9**) [75.9-96.3]	40 (**90.9**) [78.3-97.5]	37 (**84.1**) [69.9-93.4]
Unfavorable	3 (6.8)	5 (11.1)	4 (9.1)	7 (15.9)
▪ Lost to follow-up	0	0	0	1
▪ Withdrawn – AE	1	1	0	2
▪ Withdrawn – investigator/sponsor	0	0	1	0
▪ Withdrawn – patient	0	2	1	1
▪ Withdrawn – treatment failure	0	0	0	**1**
▪ Confirmed relapse post-treatment	0	2	1	1
▪ Re-treatment post-treatment	2	0	1	1

Only 1 treatment failure

ZeNix: Pretomanid, Bedaquiline, and Linezolid (BPaL) in Treatment of Highly Resistant TB

IAS2021 Abstract: Conradie et al. OALB01LB02

Treatment Emergent Adverse Event	BPaL With Linezolid 1200 mg x 6 mo (n = 45)	BPaL With Linezolid 1200 mg x 2 mo (n = 46)	BPaL With Linezolid 600 mg x 6 mo (n = 45)	BPal With Linezolid 600 mg x 2 mo (n = 45)
Any TEAE Grade ≥3	14 (31.1)	11 (23.9)	9 (20.0)	11 (24.4)
Any serious TEAE	3 (6.7)	4 (8.7)	1 (2.2)	3 (6.7)
Peripheral neuropathy	17 (37.8)	11 (23.9)	11 (24.4)	6 (13.3)
Optic neuropathy	4 (8.8)	0 (0)	0 (0)	0 (0)
Worsening grade of anemia	10 (22.2)	8 (17.4)	1 (2.2)	3 (6.7)
Linezolid dose modification (reduction, interruption, or discontinuation)	23 (51)	13 (28)	6 (13)	6 (13)

Higher dose linezolid with more adverse effects

Thank you!

- Questions…..

IAS 2021 Update

Raj Gandhi, MD
Massachusetts General Hospital
Harvard Medical School

Disclosures: None in the past year.
Thanks to Efe Airewele for assistance with slides

Outline

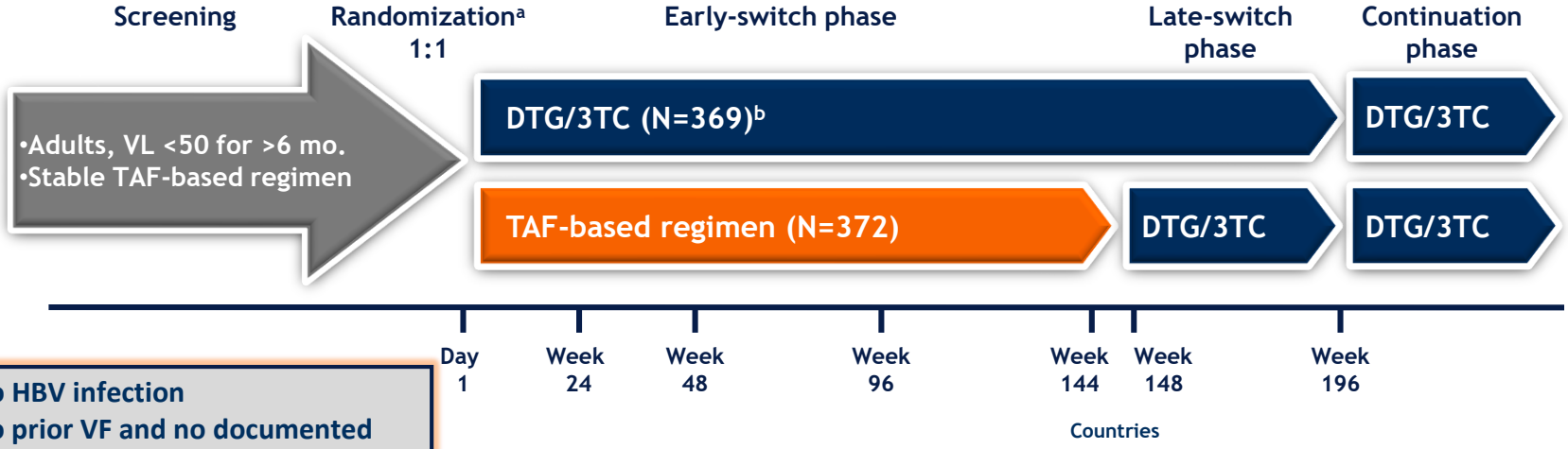
- ART Advances
- HIV Cure Updates
- COVID-19 and HIV

ART Advances

- 2 drug therapy with DTG/3TC
- Cabotegravir/rilpivirine
- New Drugs

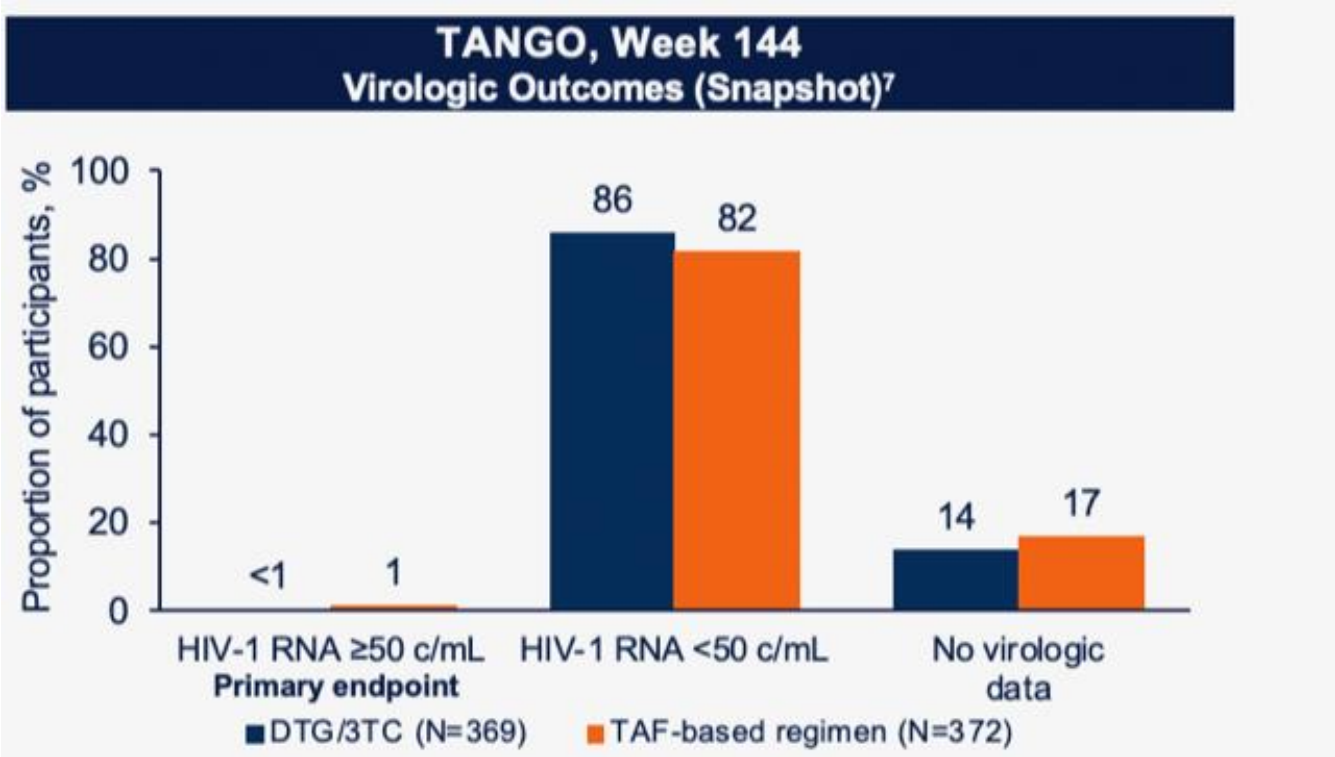
TANGO: Switching from TAF-based ART to DTG/3TC

Phase 3, non-inferiority open label study in people on stable TAF-based ART with VL<50



- No HBV infection
- No prior VF and no documented NRTI/INSTI resistance
- TAF/FTC + INSTI 79% (about 66% EVG/c), 12% RPV, 7% bDRV
- Median duration of ART before switch: almost 3 yr

TANGO: Switching from TAF-based ART to DTG/3TC



What about low-level viremia with DTG/3TC?

		DTG/3TC (N=369)			TBR (N=372)		
		Baseline			Baseline		
	VL sub-categories	TND n[1]=302 (82%)	TD n[1]=51 (14%)	≥40 c/mL n[1]=11 (3%)	TND n[1]=303 (81%)	TD n[1]=59 (16%)	≥40 c/mL n[1]=9 (2%)
Post-baseline	At least one VL ≥50 c/mL[2]	14 (5%)	7 (14%)	2 (18%)	26 (9%)	9 (15%)	1 (11%)
	At least one 40≤ VL <50 c/mL[2]	5 (2%)	5 (10%)	1 (9%)	10 (3%)	3 (5%)	1 (11%)
	At least one VL <40 c/mL & TD[2]	152 (50%)	33 (65%)	8 (73%)	160 (53%)	41 (69%)	6 (67%)
	All VLs <40 c/mL & TND[2]	131 (43%)	6 (12%)	0 (0%)	107 (35%)	6 (10%)	1 (11%)

Low level viremia (VL <40, target not detected) not more frequent with DTG/3TC

Wang. IAS 2021. Abstr OAB0301

SALSA: DTG/3TC for Maintenance Therapy

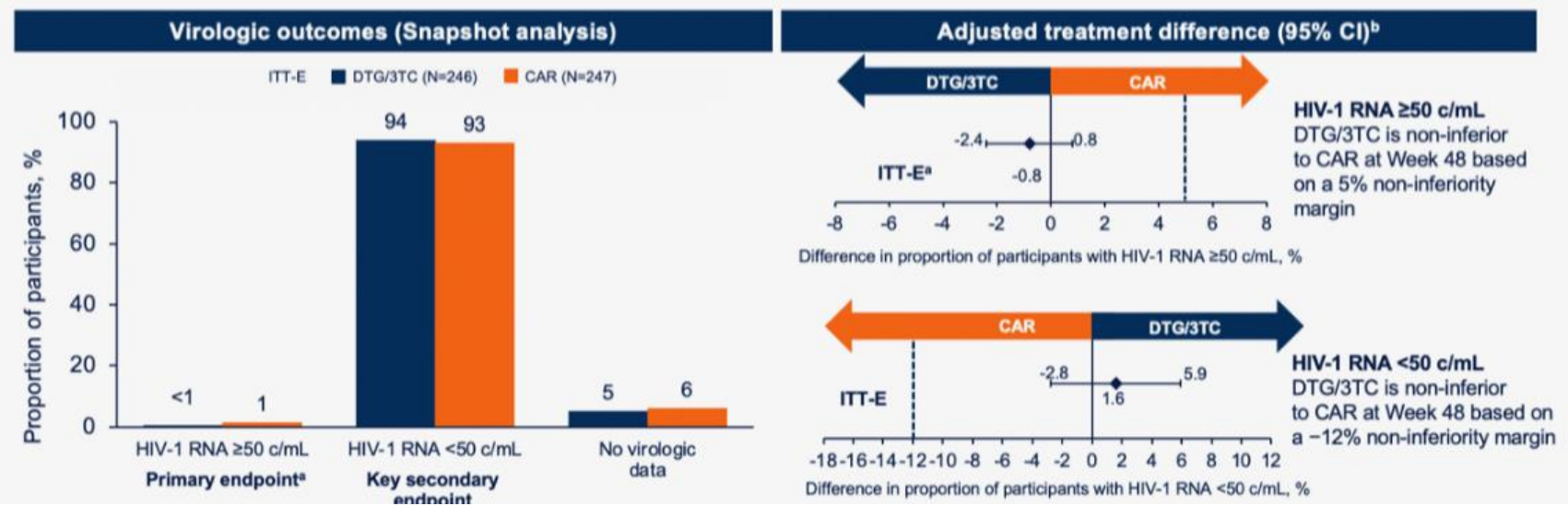
- SALSA: efficacy of switching to DTG/3TC compared with continuing any current 3- or 4-drug ART regimen

Who was in SALSA?

- Duration of ART: about 5-6 yr
- NRTI: TDF (44%)
- Baseline 3rd agent:
  - INSTI (40%)
  - NNRTI (50%)
  - PI (10%)

CAR: current antiretroviral therapy

SALSA: DTG/3TC Non-Inferior to Continuing 3- or 4-Drug Therapy

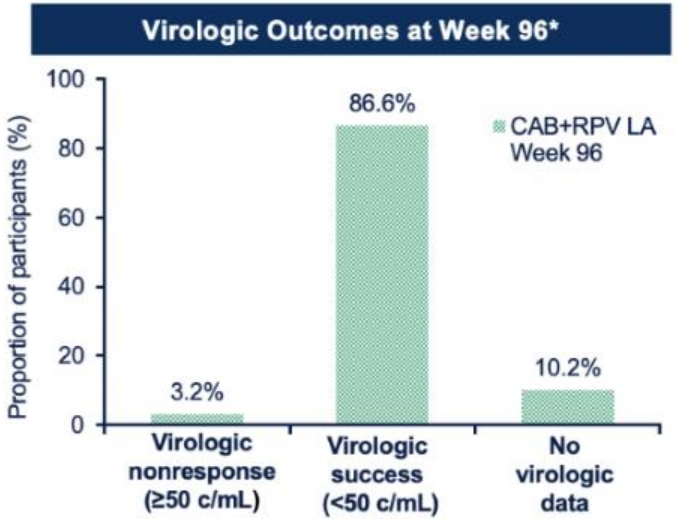


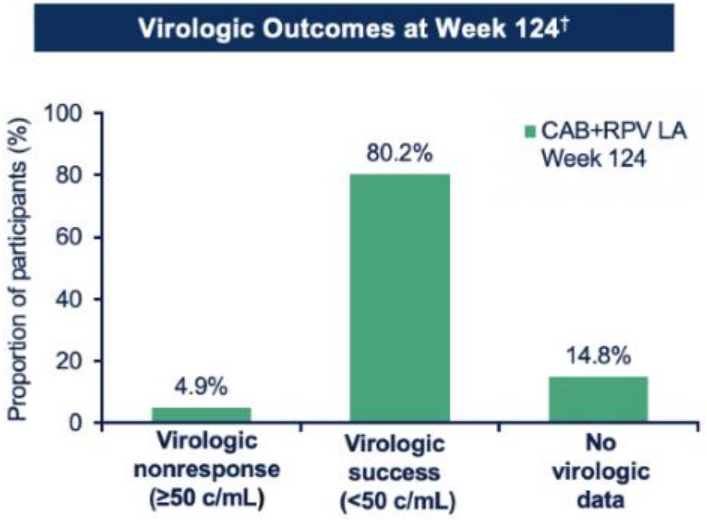
- No participant had confirmed virologic withdrawal; no participant had resistance
- Adjusted mean change in weight from baseline to wk 48: 2.1 kg in DTG/3TC group, 0.6 kg in CAR group

Llibre J et al, IAS 2021, Abstract OALB0303

LA Cabotegravir/Rilpivirine in PWH with Suppressed HIV RNA: FLAIR Week 124 Results

Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI, available in long-acting nanosuspension formulations that can be given by injection





One additional participant had confirmed virologic failure since week 96 analysis: developed NNRTI and INSTI resistance; total of 5 participants with confirmed virologic failure

CAB/RPV: Risk factors for Virologic Failure

- 13/1039 (1.25%) participants had confirmed virologic failure (CVF) in ATLAS, FLAIR, ATLAS-2M
- Risk factors for CVF identified
- 96.7% had 0 or 1 risk factor for CVF
  - 0.4% of them had CVF

Parameter	OR
RPV RAM(s) at baseline	40.36
Week 8 RPV trough concentration	5.00
Baseline HIV-1 subtype A1/A6	5.92
BMI (kg/m2) at baseline	1.13

Cutrell A et al, AIDS, 2021

Prevalence of Genotypic Risk Factors for CAB/RPV Failure: France

- ART naïve patients between 2010 and 2020 in Paris (n=4212)
- 10.1% of sequences had genotypic risk factor for CAB/RPV failure (RPV resistance or HIV A1/A6 subtype)
- Only 0.4% had 2 genotypic risk factors for CAB/RPV failure

--- INDICATIONS AND USAGE----------
CAB/RPV … is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

Charpentier C, IAS 2021, Abstract OAB0303

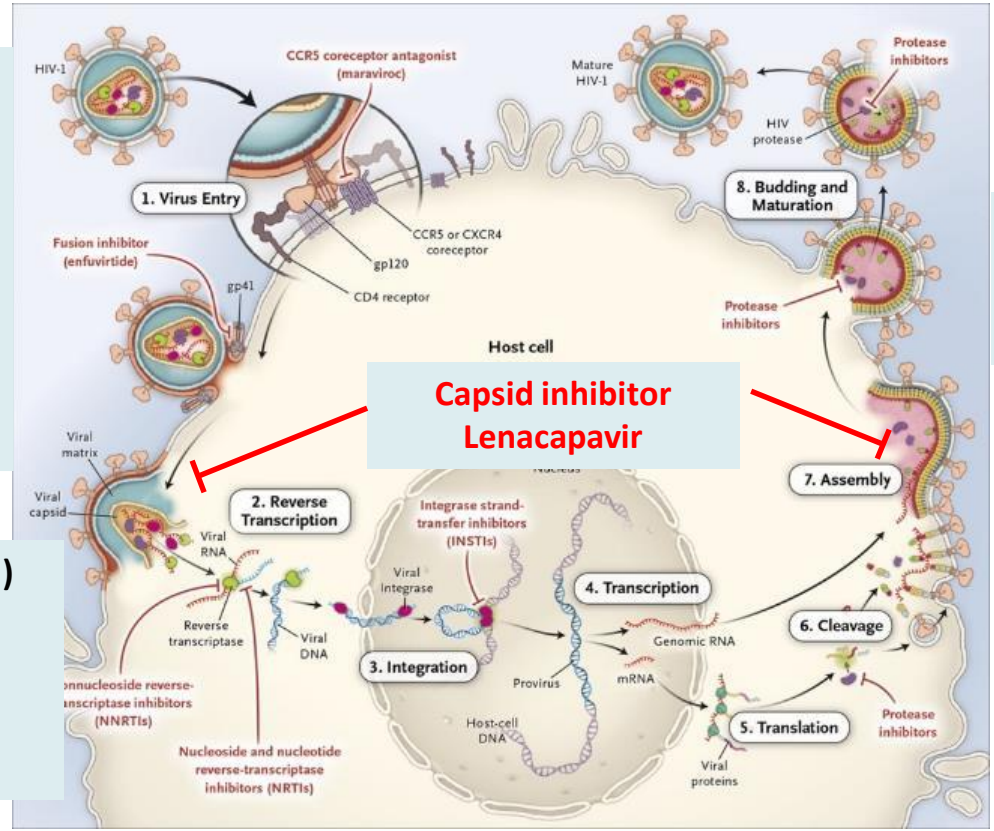
New Drugs in Development

Entry inhibitors:

- Attachment inhibitor:
  - UB-421
- CCR5 Antagonist:
  - Leronlimab
- Fusion Inh.: Albuvirtide
- Multisite: Combinectin
- Broadly neutralizing Abs

Reverse Transcriptase Inh. (RTI)

- Nonnucleoside RTI (NNRTIs)
  - MK-8507
- Nucleoside RT translocation inhibitor: Islatravir



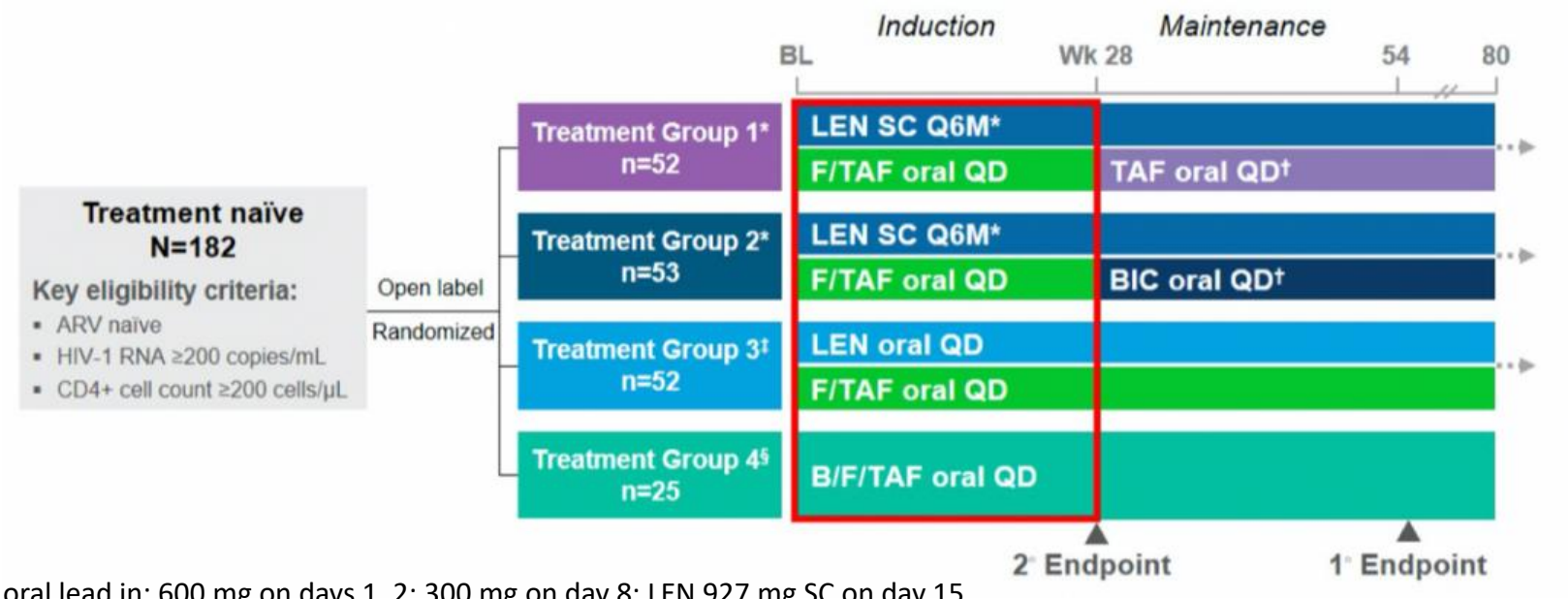
Maturation inhibitor

GSK3640254 (non-boosted)

Gandhi M, Gandhi RT. NEJM 2014;371:248-259.

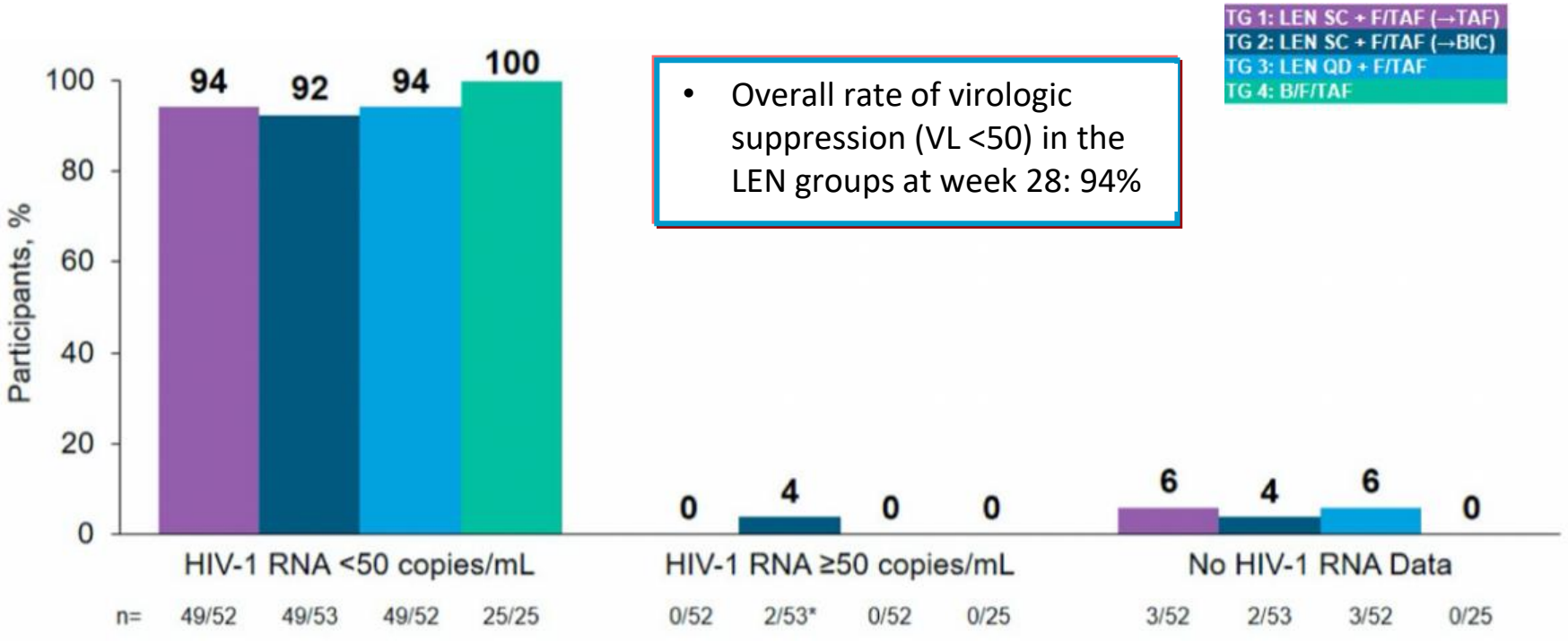
CALIBRATE: Lenacapavir (LEN) in Treatment Naive

- Investigational capsid inhibitor. Oral formulation: median half-life 11-13 d; subcutaneous injection: every 6 months
- CALIBRATE: LEN in treatment naïve PWH: induction/maintenance with SC or oral LEN



*LEN oral lead in: 600 mg on days 1, 2; 300 mg on day 8; LEN 927 mg SC on day 15

CALIBRATE: Lenacapavir (LEN) in Treatment Naïve: Wk 28

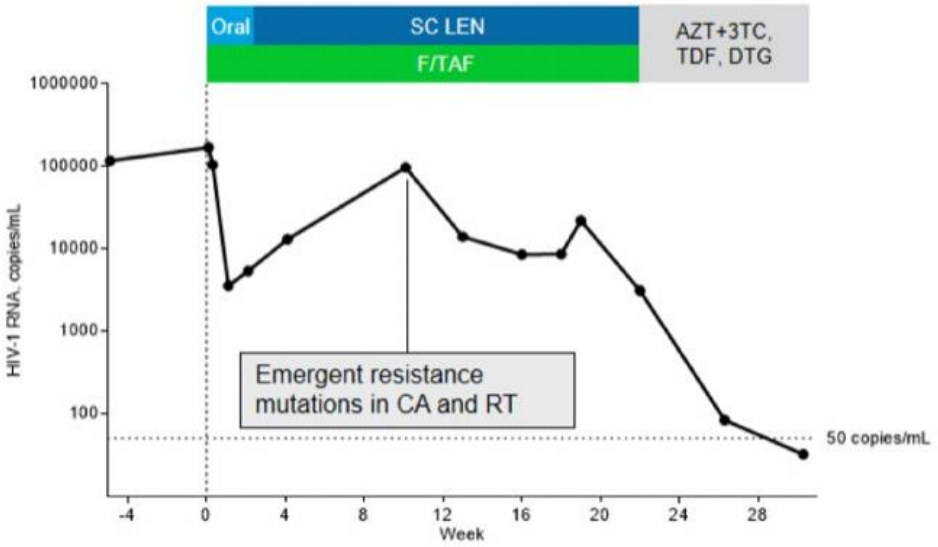


- Overall rate of virologic suppression (VL <50) in the LEN groups at week 28: 94%

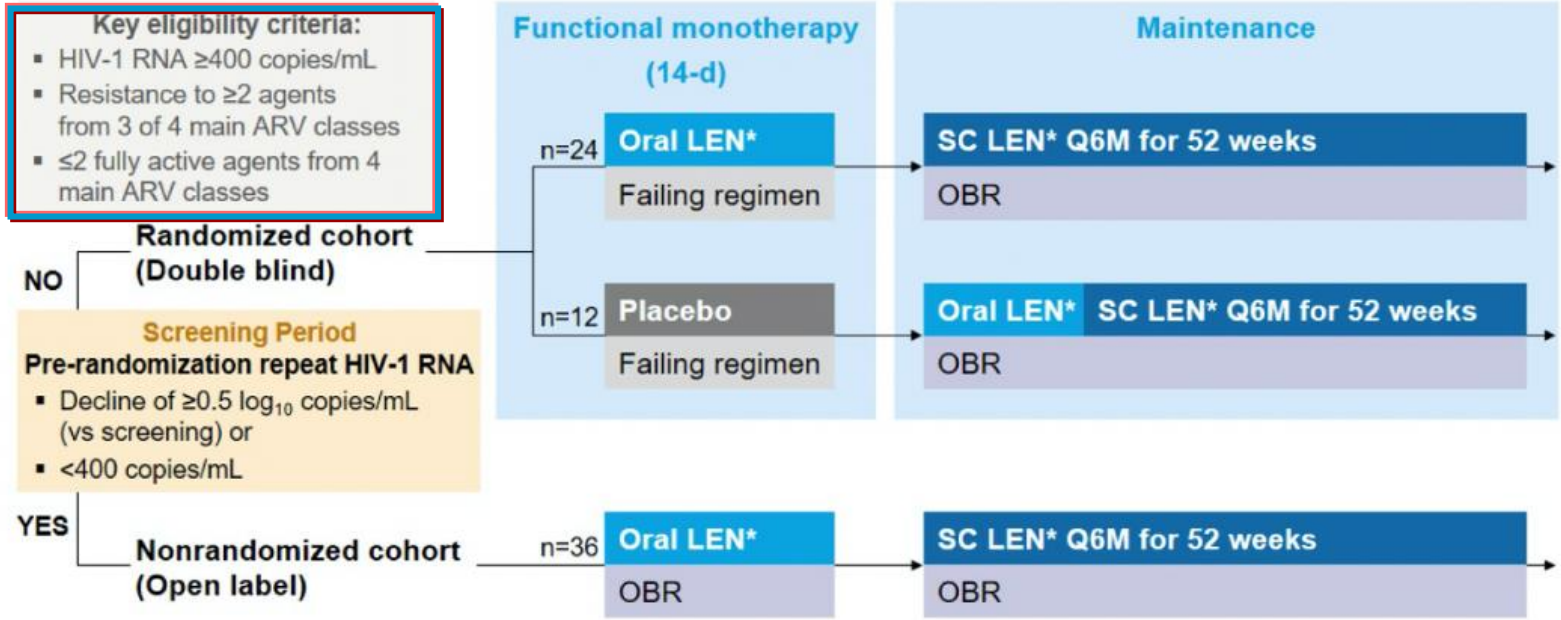
CALIBRATE: Lenacapavir (LEN) in Treatment Naive

- One participant in TG 2 had emergent resistance mutations at Week 10
  - CA: Q67H+K70R

    (LEN fold change=20)
  - RT: M184M/I
- Plasma LEN concentrations were consistently in target range†



CAPELLA: LEN in People with Drug Resistant HIV



OBR: optimized background regimen

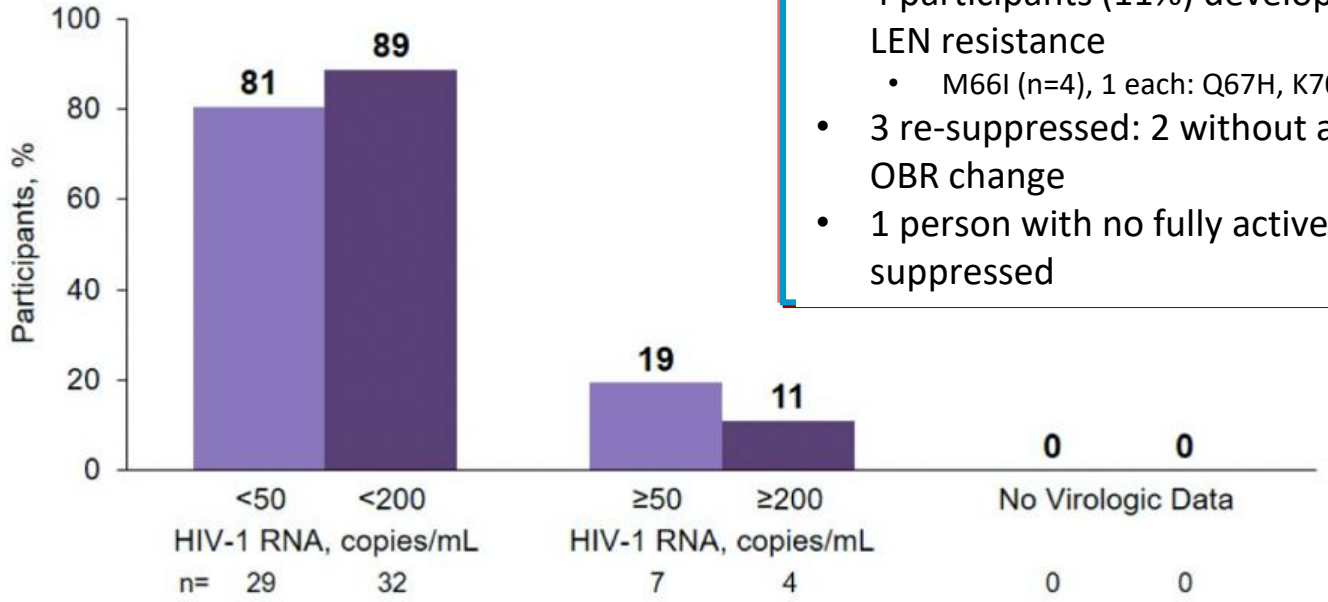
CAPELLA: LEN in People with Drug Resistant HIV

	Randomized		Nonrandomized	
	LEN n=24	Placebo n=12	LEN n=36	Total N=72
Age, median (range), years	55 (24 – 71)	54 (27 – 59)	49 (23 – 78)	52 (23 – 78)
Sex, % female at birth	29	25	22	25
Race, % Black	42	55	31	38
Ethnicity, % Hispanic/Latinx	25	36	14	21
HIV-1 RNA, median (range), $\log_{10}$ copies/mL	4.2 (2.3 – 5.4)	4.9 (4.3 – 5.3)	4.5 (1.3 – 5.7)	4.5 (1.3 – 5.7)
>75,000 copies/mL, %	17	50	28	28
CD4 count, median (range), cells/μL	172 (16 – 827)	85 (6 – 237)	195 (3 – 1296)	150 (3 – 1296)
≤200 cells/μL, %	67	92	53	64
Years since HIV diagnosis, median (range)	27 (13 – 39)	26 (14 – 35)	23 (9 – 44)	24 (9 – 44)
Number of prior ARV agents, median (range)	9 (2 – 24)	9 (3 – 22)	13 (3 – 25)	11 (2 – 25)
Number of ARV agents in failing regimen, median (range)	3 (1 – 7)	3 (2 – 6)	4 (2 – 7)	3 (1 – 7)
Known resistance to ≥2 drugs in class, %				
NRTI	96	100	100	99
NNRTI	92	100	100	97
PI	83	67	83	81
INSTI	83	58	64	69

Molina JM et al, IAS 2021, Abstract OALX01LB02

CAPELLA: LEN in People with Drug Resistant HIV

Virologic efficacy at week 26 in the randomized cohort (n=36)



- 4 participants (11%) developed emergent LEN resistance
  - M66I (n=4), 1 each: Q67H, K70N/R/S N74D
- 3 re-suppressed: 2 without and 1 with OBR change
- 1 person with no fully active agent never suppressed

Lenacapavir

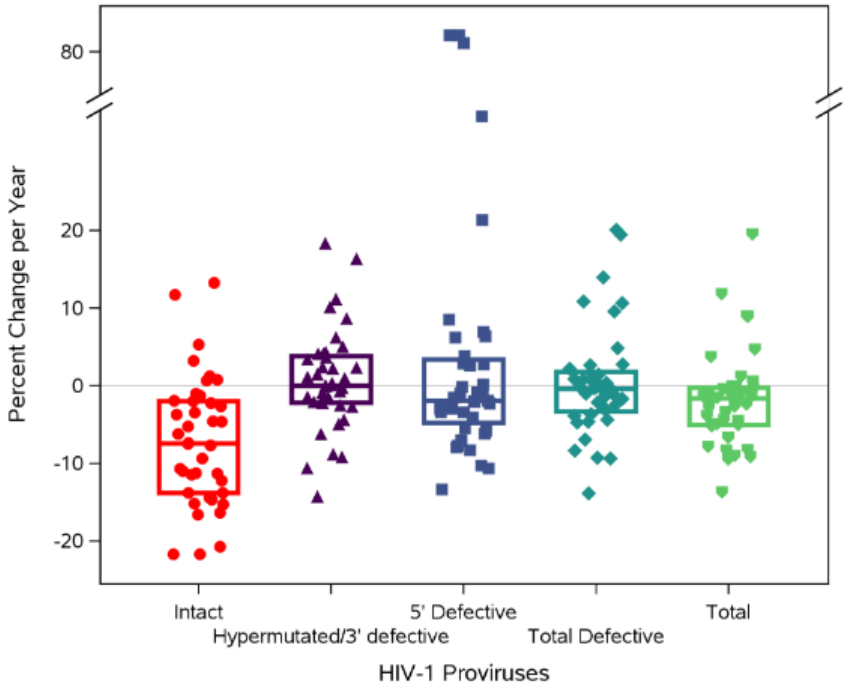
- New drug application filed with US FDA for treatment of heavily treatment experienced people with multi-drug resistant HIV

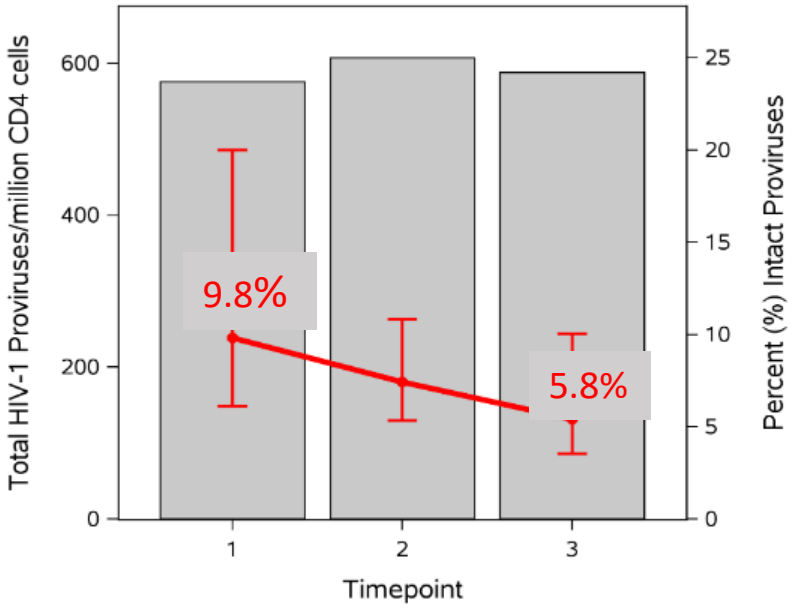
- Studies to be done in treatment-naïve and experienced patients in combination with other long-acting agents (islatravir, broadly neutralizing antibodies, others)

- Phase 3 studies of lenacapavir for pre-exposure prophylaxis initiated

HIV Cure Research

Intact Proviruses Decline Over Time on ART Whereas Defective Proviruses Do Not

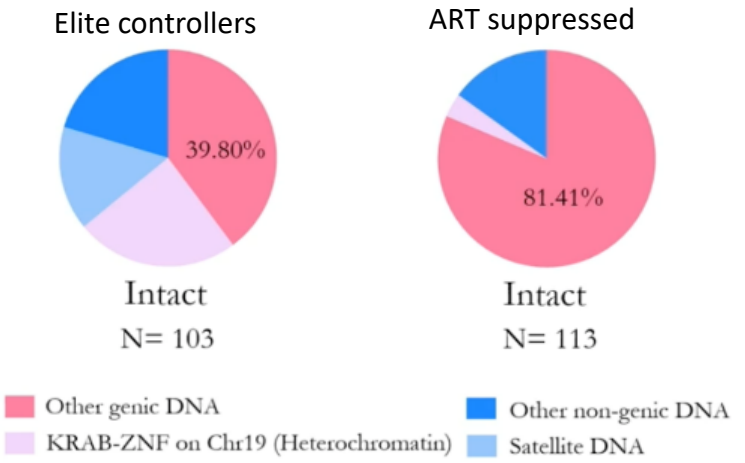




Peluso M/Deeks S et al, JCI Insight 2020; Antar AA/Siliciano RF et al, JCI, 2020; Gandhi RT/Mellors JW et al, JID, 2021

Intact Proviruses: Quality and Location Matter

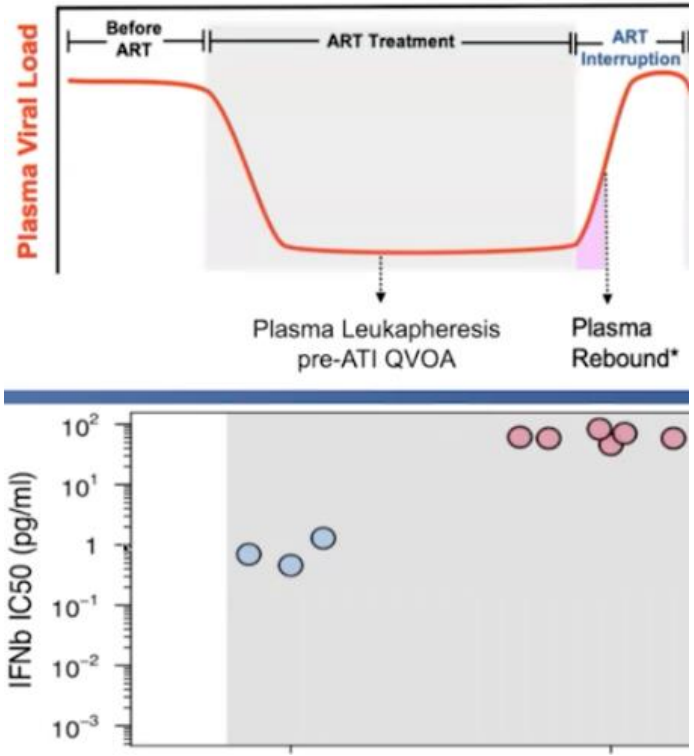
- Elite controllers more likely than ART suppressed patients to have intact proviruses integrated into quiescent regions of genome (”gene deserts”) --> is this the basis for ART-free control?
- Two exceptional elite controllers: no detectable intact proviruses or virus outgrowth
  - California and Esperanza (Hope) patients
  - Natural cures?
- Can one achieve ART-free remission by inducing a more quiescent reservoir?



Yu X, IAS 2021

HIV that rebounds during treatment interruption is highly interferon resistant

Example:

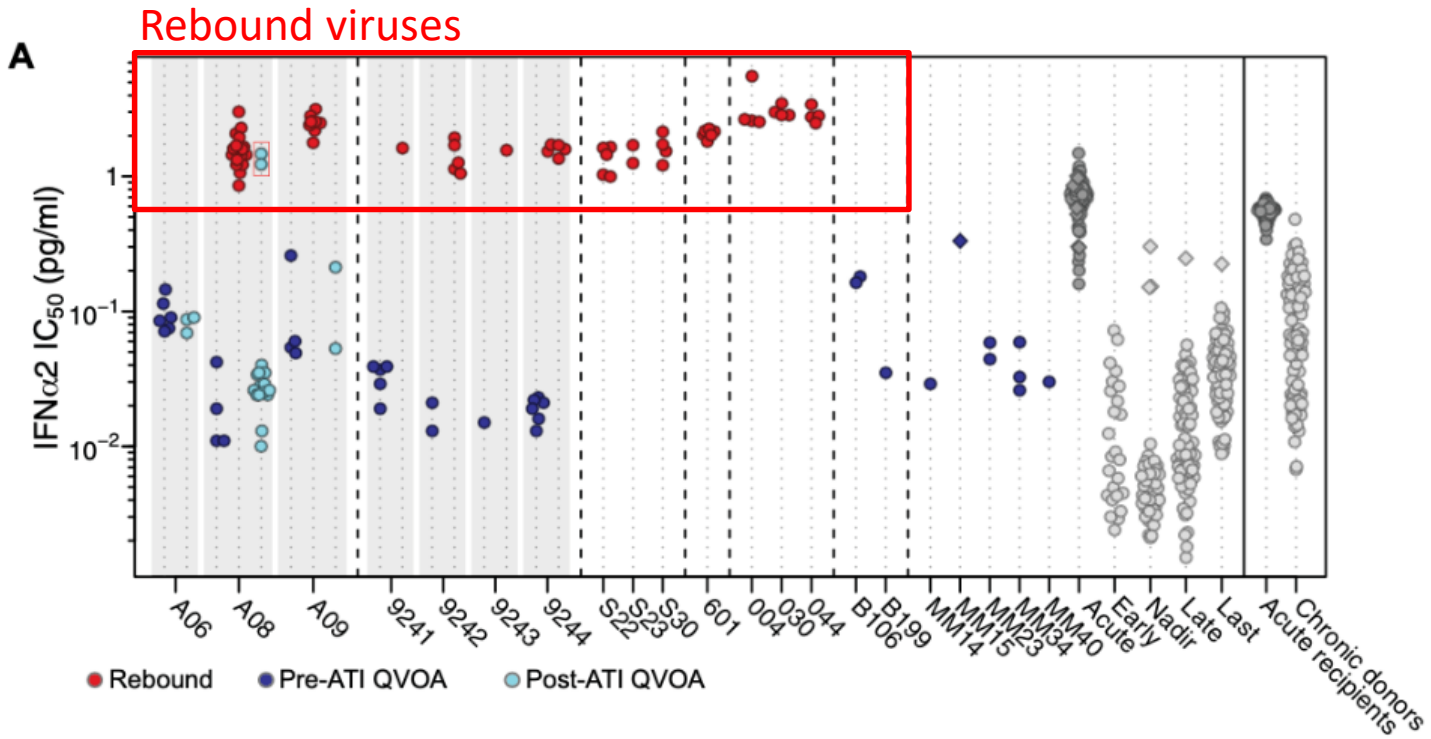


- Compared interferon sensitivity of HIV obtained from pre-treatment interruption quantitative virus outgrowth assay to HIV isolate during ART treatment interruption
- Rebound isolates highly resistant to type 1 interferon

Hahn B, IAS 2021

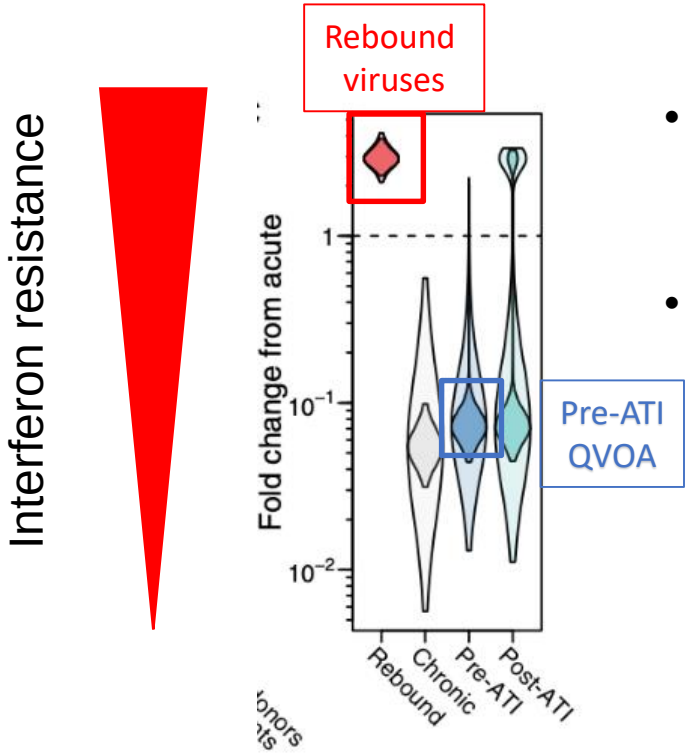
HIV that rebounds during treatment interruption is highly interferon resistant

Interferon resistance



Gondim MV et al, Science Translational Medicine, 2021; Hahn B, IAS 2021

HIV that rebounds during treatment interruption is highly interferon resistant



- Rebound virus more interferon resistant than virus obtained from pre-treatment interruption viral outgrowth assays
- Possible explanations:
  - "Rebound competent" reservoir may consist of interferon resistant viruses
  - ART interruption and HIV rebound may stimulate an innate interferon response that selects for interferon resistant virus

Gondim MV et al, Science Translational Medicine, 2021; Hahn B, IAS 2021

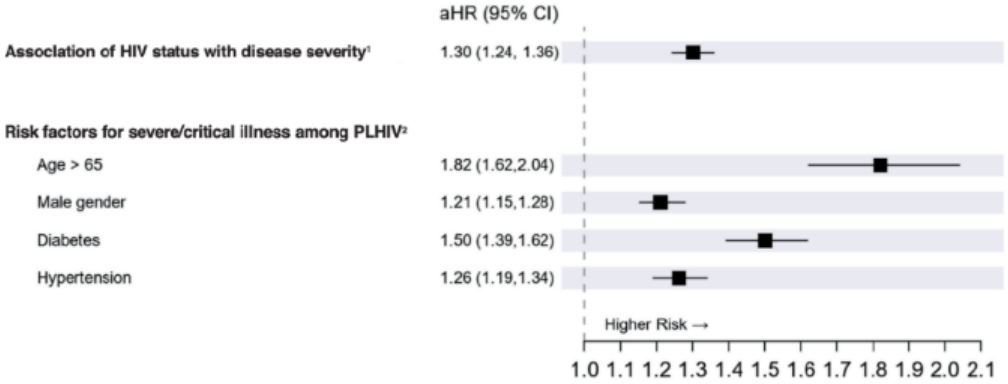
COVID-19

- COVID-19 Outcomes in People with HIV
- COVID-19 Vaccines in People with HIV

HIV Associated with Worse COVID-19 Outcomes: WHO Analysis

- Clinical data from 268,412 hospitalized patients in 24 countries (most data were from South Africa)
- 15,522 people with HIV
  - 92% on ART (no information on VL, CD4)
- HIV associated with increased risk of severe/critical COVID (aOR 1.13) after adjusting for age, sex, underlying conditions
- HIV associated with increased risk of in-hospital mortality (aOR 1.3)

HIV and Risk of In-hospital Mortality



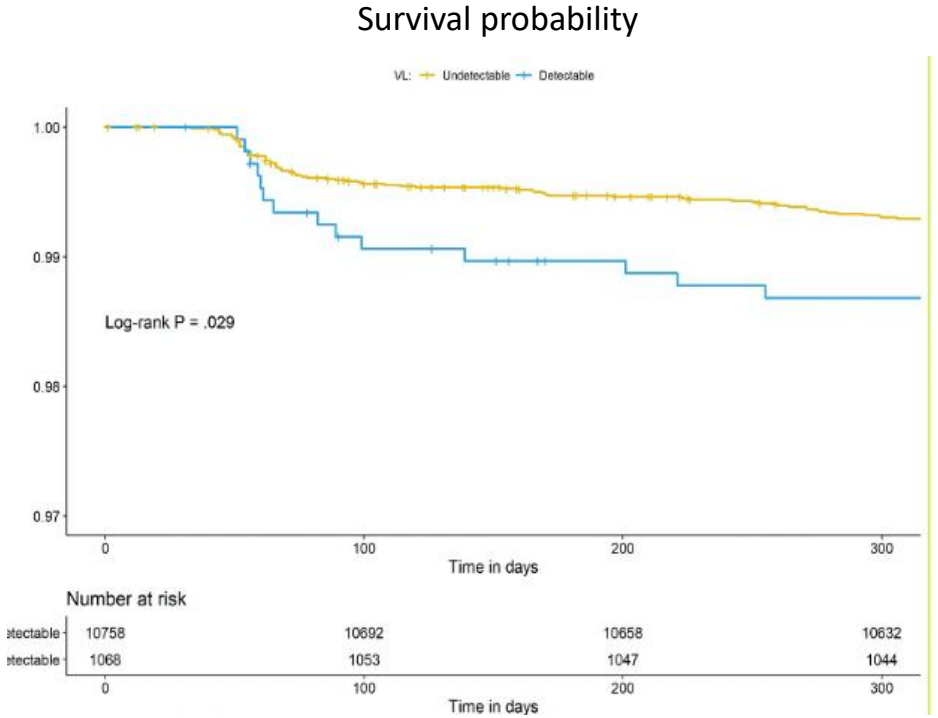
[1] Adjusted hazard ratio for HIV infection as a significant independent risk factor for in-hospital mortality of COVID-19, after adjusting for age, sex, disease severity and burden of underlying conditions.

[2] Adjusted hazard ratio for each risk factor for in-hospital mortality among PLHIV, after controlling for the other risk factors in the model.

Bertagnolio S., IAS 2021, Abstract PEBLB20

Unsuppressed HIV RNA Associated with Worse COVID-19 Outcomes

- Cohort study of PWH (n=13,142)
  - 82% VL undetectable
  - 8% VL detectable, 10% VL missing
- 749 PWH tested positive for SARS CoV-2
  - 103 hospitalized, 13 deaths
- Severe outcomes more frequent among those with detectable HIV RNA
- Limitation: very few participants with unsuppressed HIV RNA



Potential Reasons Why PWH May Have Worse COVID-19 Outcomes

- **Immunodeficiency or immune dysregulation**
  - Patients with immunodeficiency, such as organ transplant recipients, are at increased risk for severe COVID-19
  - Prolonged SARS CoV-2 replication reported in immunocompromised hosts
  - Suggests PWH with low CD4 cell counts may be at increased risk for severe COVID (as they are for influenza)
  - Residual inflammation in PWH on ART
    - Most pronounced in PWH with low CD4 cell count nadirs, incomplete CD4 cell reconstitution, low CD4/CD8 ratio
    - Immune dysregulation "legacy effect": impact on COVID-19 not certain
- **Comorbidities**
  - PWH have high rates of comorbidities that are also risk factors for severe COVID-19
- **Social determinants of health**
  - PWH more likely to be racial/ethnic minorities, poor – risk factors for worse COVID-19 outcomes

Triant V and Gandhi R, JID 2021

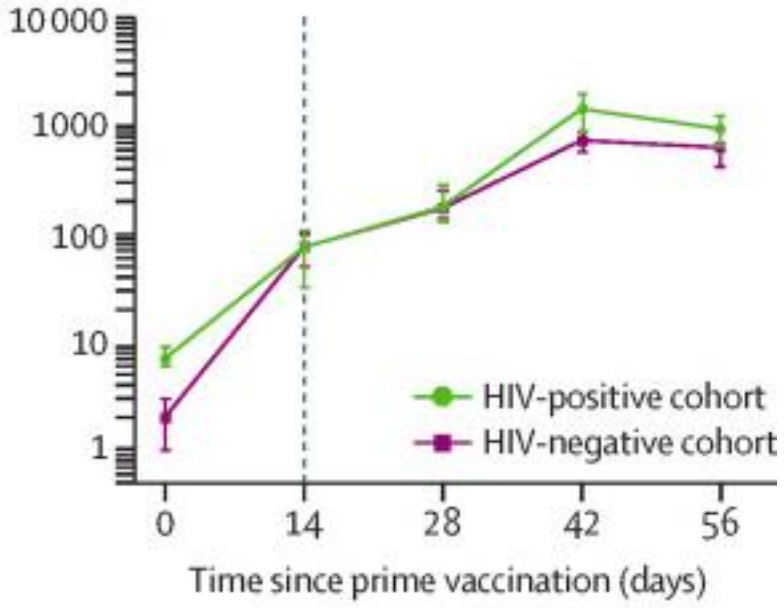
People with HIV (PWH) in FDA authorized COVID-19 vaccine Phase 3 Clinical Trials

- Participants with stable HIV:
  - Moderna: 176
  - Pfizer: 196
  - J & J: 1218

- No immunogenicity data reported yet

Immune Responses to AstraZeneca COVID-19 Vaccine in people with or without HIV

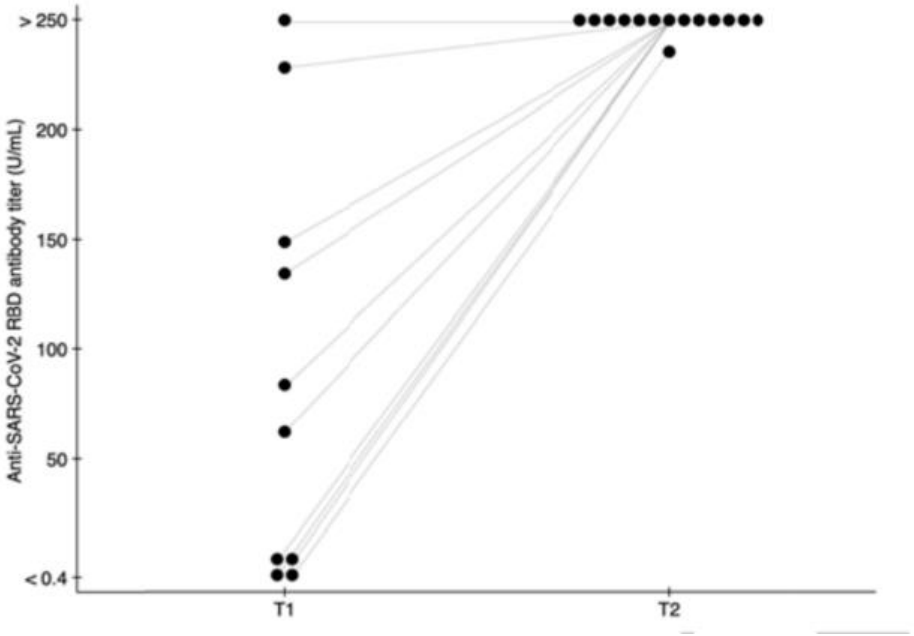
- PWH (n=54)
  - On ART with viral suppression
  - Median CD4 694
- People without HIV (n=50)
- Antibody and T cell responses comparable between people with and without HIV
- Similar results in study of 104 PWH and 70 people without HIV in South Africa after AZ vaccine



Frater J et al., Lancet HIV, 2021
Madhi S et al. *ChAdOx1 nCoV-19 (AZD1222) vaccine in people living with and without HIV.* Research Square pre-print, posted online 17 March 2021.

Antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in persons with HIV

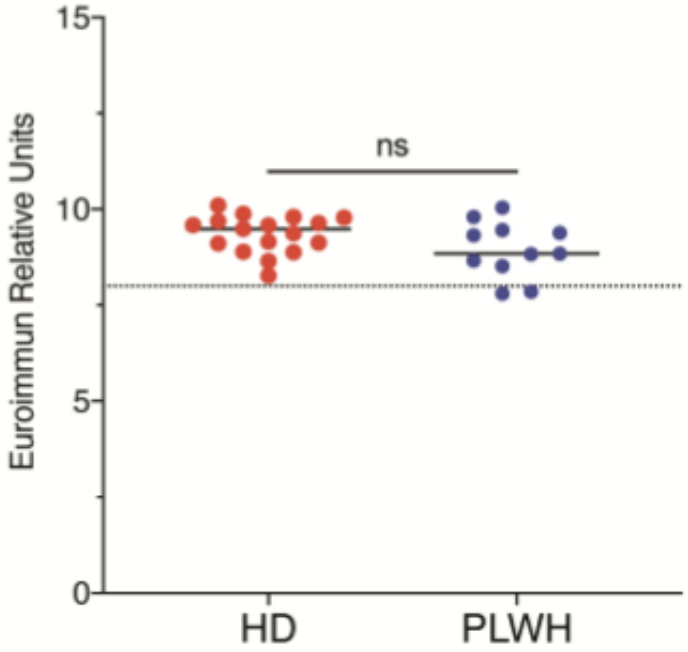
- PWH (n=14)
  - 14/14 on ART for > 6 months
  - 13/14 had undetectable HIV RNA
  - 2 (14%) had CD4 cell count <200
- 5 received Pfizer vaccine, 9 received Moderna vaccine
- Variable antibody titers after 1st dose
- All participants developed high titers of antibodies after 2nd dose



Ruddy JA et al., AIDS, 2021

Antibody responses after Pfizer Vaccine in People With and Without HIV

- PWH (n=12)
  - All on ART
  - Median CD4: 913 (range 649-1678)
- Healthy donors (HD, n=17)
- Similar levels of anti-SARS-CoV-2 spike binding antibodies and T cell responses in both groups after 2nd dose

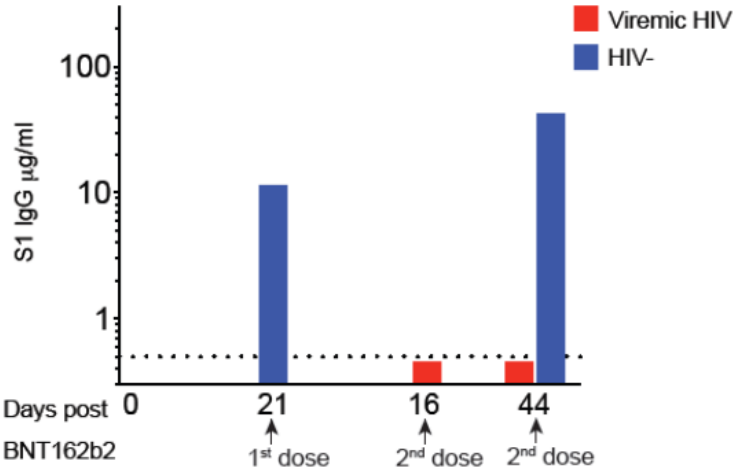


Woldemeskel, CID, 2021

Failure to Seroconvert after COVID-19 Vaccine in a Patient with Uncontrolled HIV

- Patient with uncontrolled HIV who was not on ART
- Received 2 doses of Pfizer vaccine
- About 2 weeks after the 2nd vaccine dose, the CD4 cell count was 20, HIV RNA >800,000; started on ART
- About 6 weeks after 2nd vaccine dose (4 weeks after starting ART), HIV RNA <50, CD4 cell count 70

No anti-spike IgG after 2nd COVID vaccine dose in patient with uncontrolled HIV



Touizer E et al, Lancet HIV, 2021.

Summary

- Additional evidence for DTG/3TC in maintenance therapy
- Lenacapavir submitted to FDA for treatment of highly treatment experienced patients with MDR HIV; will be studied with other long-acting agents for treatment-naïve and –experienced patients; need more information on its barrier to resistance
- HIV cure research advances: quality (not just quantity) of reservoir is important
- COVID-19 outcomes appear to be worse in people with HIV, particularly if not virologically suppressed.
- People with HIV who are on ART appear to have similar immune responses to COVID vaccines as people without HIV
  - People who are not on ART and who have a CD4 cell count <200 may not mount as good an immune response; should they receive a 3rd vaccine dose after starting ART?