Clinical Impact of New Data From IAS 2019

CCO Official Conference Coverage

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Faculty Disclosures

The ***faculty*** reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME/CE activity:

Brenda E. Crabtree Ramírez, MD, has disclosed that she has received consulting fees from Merck Sharp & Dohme and ViiV Healthcare and funds for research support from Merck Sharp & Dohme.

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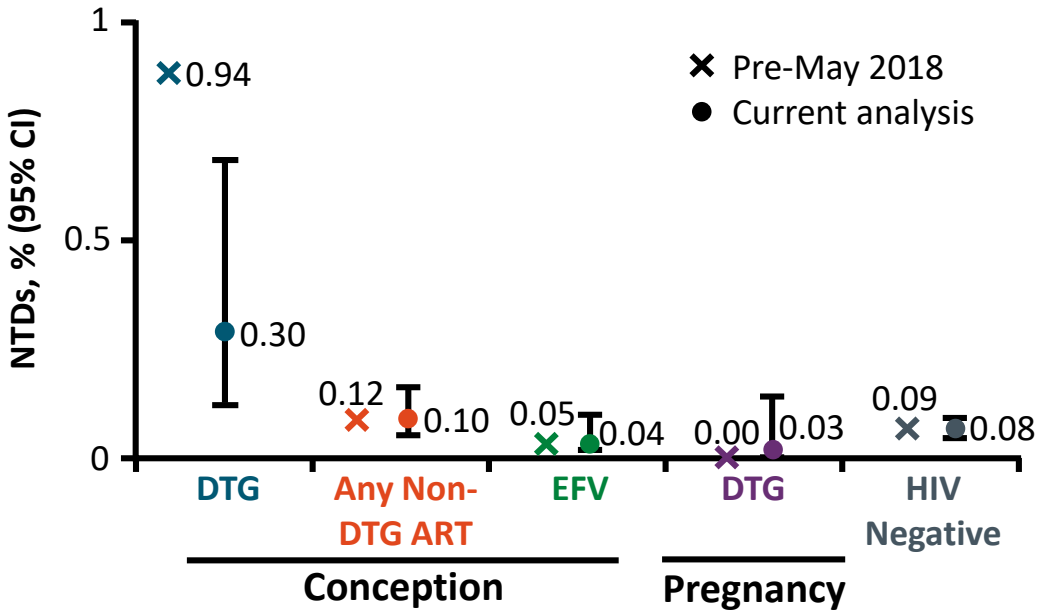
NTD Risk and Pregnancy

Tsepamo: Neural Tube Defects and DTG Exposure

- Birth outcomes surveillance study among Botswanan women ± HIV infection
  - Initial findings in May 2018 found apparent increase in NTD incidence among women who conceived while receiving DTG[1]
  - Warnings issued from WHO, EMA, FDA regarding use of DTG at time of conception[2-4] and some countries halted plans to use DTG-based ART as preferred first-line therapy
- Current analysis reports updated birth outcomes as of March 2019[5,6]
  - From July to September 2018, surveillance area expanded to capture ~ 72% of all births in Botswana; data abstracted from obstetric cards of all in-hospital deliveries
  - Government midwives trained to assess congenital abnormalities performed infant surface exams; abnormalities photographed with maternal consent and reviewed by external medical geneticist (blinded to drug exposure history)

1. Zash. NEJM. 2018;379:979. 2. WHO Statement. May 2018. 3. EMA Statement. May 2018.
4. FDA. Sep 2018. 5. Zash. IAS 2019. Abstr MOAX0105LB. 6. Zash. NEJM. 2019;[Epub].

Tsepamo: NTD Prevalence by ARV Exposure



- **As of March 2019, rate of NTDs with DTG at conception lower than initially signaled[1,2]**
- No significant difference in major external structural malformations with DTG vs non-DTG ART[1,2]
- WHO released updated recommendations reconfirming use of DTG-based ART as preferred first-line and second-line therapy[3]

Outcome	At Conception			DTG in Pregnancy (n = 3840)	HIV Negative (n = 89,372)
	DTG (n = 1683)	Non-DTG (n = 14,792)	EFV (n = 7959)		
NTDs per exposures, n/N	5/1683	15/14792	3/7959	1/3840	70/89372
▪ Prevalence difference, % (95% CI)	Reference	0.20 (0.01-0.59)	0.26 (0.07-0.66)	0.27 (0.06-0.67)	0.22 (0.05-0.62)
NTDs per exposures since May 2018, n/N	1/1275	1/3492	0/2172	1/1028	9/23,315

1. Zash. IAS 2019. Abstr MOAX0105LB. 2. Zash. NEJM. 2019;[Epub]. 3. WHO ARV Policy Update. July 2019.

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Tsepamo: Additional Adverse Birth Outcomes

- No difference between DTG and EFV for any single adverse birth outcome, including preterm/very preterm birth (< 37/< 32 wks), small gestational age, stillbirth, in-hospital neonatal death
- Analysis included single births since October 2016

Birth Outcome, n (%)	DTG at Conception (n = 1271)	EFV at Conception (n = 4430)	Adjusted RR (95% CI)*
Any adverse	422 (33.2)	1550 (35.0)	0.94 (0.86-1.02)
Any severe (SB, NND, vPTB, vSGA)	151 (11.9)	568 (12.8)	0.89 (0.74-1.05)

*Adjusted for maternal age, education, gravida.

Additional NTD Data From Botswana and Brazil

- Prospective birth outcomes surveillance study among Botswanan women commissioned by Botswana Ministry of Health and Wellness in response to May 2018 Tsepamo findings[1]
  - Surveillance area included 22 facilities not covered by Tsepamo (October 2018 to March 2019); potential NTDs evaluated by trained midwives prior to discharge with suspected NTDs reviewed by blinded geneticist

Outcome	HIV Positive			HIV Negative (n = 2328)
	DTG (n = 152)	Any Non-DTG ART (n = 381)	EFV (n = 261)	
NTDs, n (%) [95% CI]	1 (0.66) [0.02 to 3.69]	0 (0) [0 to 0.79]	0 (0) [0 to 1.15]	2 (0.09) [0.01 to 0.31]
Prevalence difference, % (95% CI)	Reference	0.66 (-0.73 to 4.16)	0.66 (-1.25 to 4.16)	0.58 (-0.10 to 4.10)

- Retrospective cohort of Brazilian women with HIV found no NTDs among births to women with possible exposure to DTG at conception from 2017-2018 (n = 384)[2]

1. Raesima. IAS 2019. Abstr MOAX0106LB. 2. Pereira. IAS 2019. Abstr MOAX0104LB.

PrEP Approaches

ImPREP: Same-Day PrEP With TDF/FTC for High-Risk MSM and TGW in Brazil, Mexico, and Peru

- Prospective, open-label demonstration study of same-day PrEP in MSM and TGW at high risk of HIV infection (≥ 1 risk criteria)
- Eligible participants were screened and enrolled on the same day to receive a 30-day supply of TDF/FTC
  - Study enrolled 5019 MSM (94%) and 335 TGW (6%)
- Primary outcomes
  - **PrEP early continuation:** attendance to the first 2 follow-up visits within 120 days of PrEP initiation
  - **PrEP adherence:** ≥ 16 days of PrEP medication filled per 30-day period (medication possession ratio ≥ 0.53)

Veloso. IAS 2019. Abstr TUAC0404LB.

ImPREP: Levels of Early Continuation and Adherence

Population	Early Continuation, %	Medication Possession Ratio ≥ 0.53, %	Follow-up, PY	HIV Incidence per 100 PY (95% CI)
Brazil	85.4	98.7	1438.6	0.2 (0.1-0.6)
Mexico	84.0	98.0	344.0	0.6 (0.2-2.3)
Peru	52.7	91.0	286.4	2.4 (1.2-5.1)
Overall	79.6	97.2	2069.0	0.6 (0.3-1.0)
▪ TGW	55.7	88.7	--	--

Veloso. IAS 2019. Abstr TUAC0404LB.

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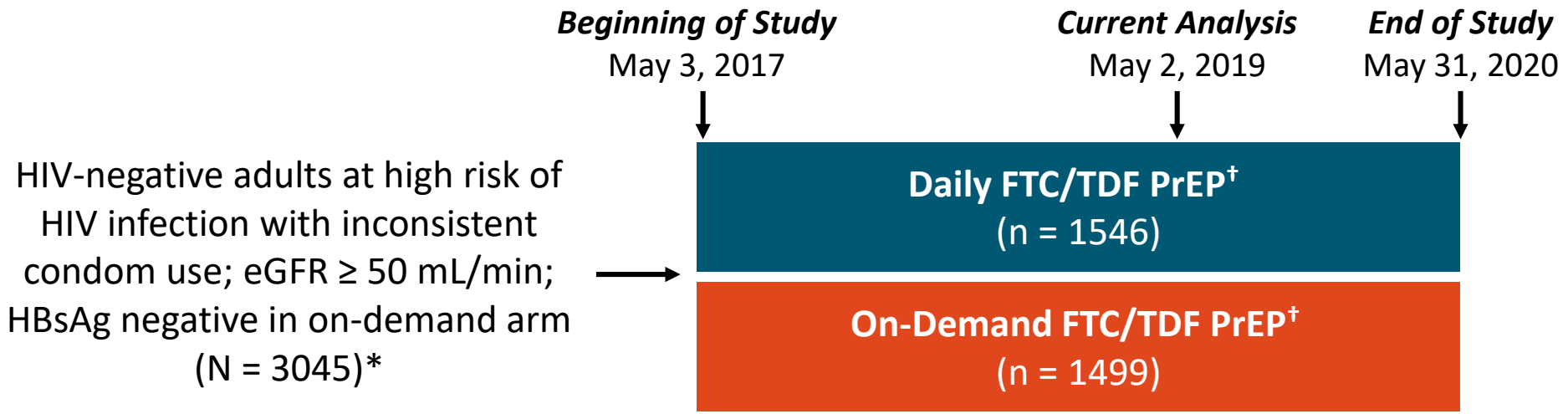
ANRS Prevenir: Daily vs On-Demand PrEP With FTC/TDF

- Multicenter, open-label, prospective cohort study mainly in MSM (98.6%) from Paris



*Participants enrolled on arm of their choice with ability to switch. †Plus condoms, gels, risk reduction and adherence counseling, questionnaire on sexual behavior. Follow-up every 3 mos with STI and/or HIV testing, plasma creatinine measurement.

- Primary endpoint: ≥ 15% reduction in new HIV diagnoses among MSM in Paris vs rate reported by National Surveillance network in 2016
- Secondary endpoints: PrEP adherence, sexual behavior, safety

Molina. IAS 2019. Abstr TUAC0202.

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ANRS Prevenir: HIV Incidence

mITT Analysis	Daily PrEP (1072.9 PYFU)	On-Demand PrEP* (1132.7 PYFU)	*P* Value
HIV incidence/100 PY (95% CI)	0 (0-0.3)	0.2 (0-0.6)	.132

*On-demand PrEP strategy not FDA or EMA approved.

- Global HIV incidence: 0.09/100 PY (n = 2)
  - PrEP stopped 7-10 wks before infection in both cases
- Mean follow-up: 8.7 mos
- Overall HIV infections averted: n = 143
  - Assuming incidence of 6.6/100 PY as reported for placebo arm in ANRS IPERGAY study
- Rate of study discontinuation: 8.9/100 PY (n = 196)

Molina. IAS 2019. Abstr TUAC0202.

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ANRS Prevenir: PrEP Adherence, Sexual Behavior, Safety

At Last Sexual Encounter, n (%)	Daily PrEP (3806 Acts)	On-Demand PrEP (3879 Acts)
PrEP use	3705 (97.3)	3188 (82.2)
▪ Correct*	3613 (97.5)	3072 (96.4)
Condom use	716 (18.8)	851 (21.9)

Participants with adherence data, n = 2134.
*Per protocol, or at least 1 pill before and after within 24 hrs.

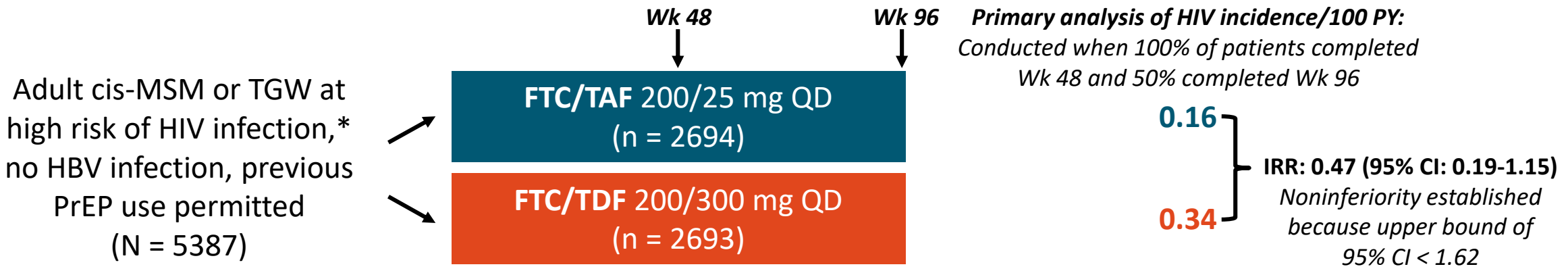
- Daily PrEP users had:
  - More sexual partners
  - More frequent condomless sex
  - Higher incidence of bacterial STIs

Incidence/100 PY (95% CI)	Daily PrEP (1072.9 PYFU)	On-Demand PrEP (1132.7 PYFU)
Drug-related AEs†	11.4 (9.4-13.6)	13.2 (11.2-15.5)
▪ Leading to d/c	0 (0-0.3)	0.3 (0-0.8)‡
Grade 3/4 AEs	5.3 (4.0-6.9)	4.4 (3.3-5.8)
Viral hepatitis	0.9 (0.5-1.7)	1.2 (0.6-2.0)
ALT abnormality	13.0 (10.9-15.3)	10.3 (8.5-12.4)
▪ Grade 3/4	0.8 (0.4-1.6)	0.6 (0.3-1.3)
Grade 1 creatinine	15.4 (13.1-17.9)	15.6 (13.4-18.1)
CrCl		
▪ 50-70 mL/min	17.7 (15.3-20.4)	18.5 (16.1-21.2)
▪ < 50 mL/min	0.8 (0.4-1.6)	0.8 (0.4-1.5)

†Most were gastrointestinal. ‡Grade 3 vomiting, grade 1 diarrhea, grade 1 nausea/headache/dizziness; each n = 1.

DISCOVER: FTC/TAF vs FTC/TDF as PrEP in MSM, TGW

- International, randomized, double-blind, active-controlled phase III trial



*Defined as ≥ 2 episodes of condomless anal sex within past 12 wks or rectal gonorrhea, chlamydia, or syphilis within past 24 wks.

- Current analysis assessed whether adherence, PK, sexual behavior, or STI incidence could account for observed differences in HIV infection rates

Spinner. IAS 2019. Abstr TUAC0403LB. Hare. CROI 2019. Abstr 104LB.

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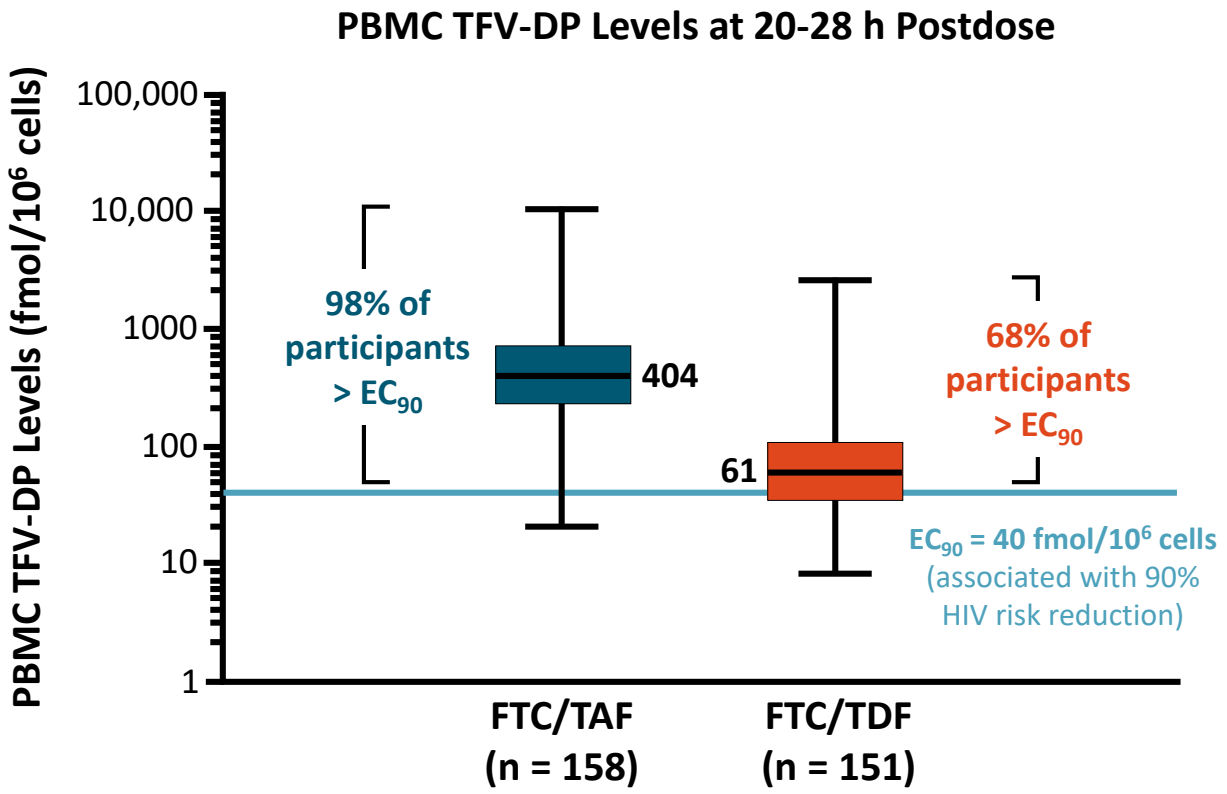
DISCOVER: Onset and Duration of Protection With FTC/TAF vs FTC/TDF as PrEP

- Adherence comparable between arms by self-report over time, pill count (median adherence: 98% in each arm), and TFV-DP levels in DBS
- **Steady-state PBMC TFV-DP levels were 6.3-fold higher with FTC/TAF vs FTC/TDF**
- Modeling found that concentrations > EC_{90} would last for 16 days after final dose of FTC/TAF vs 10 days after FTC/TDF



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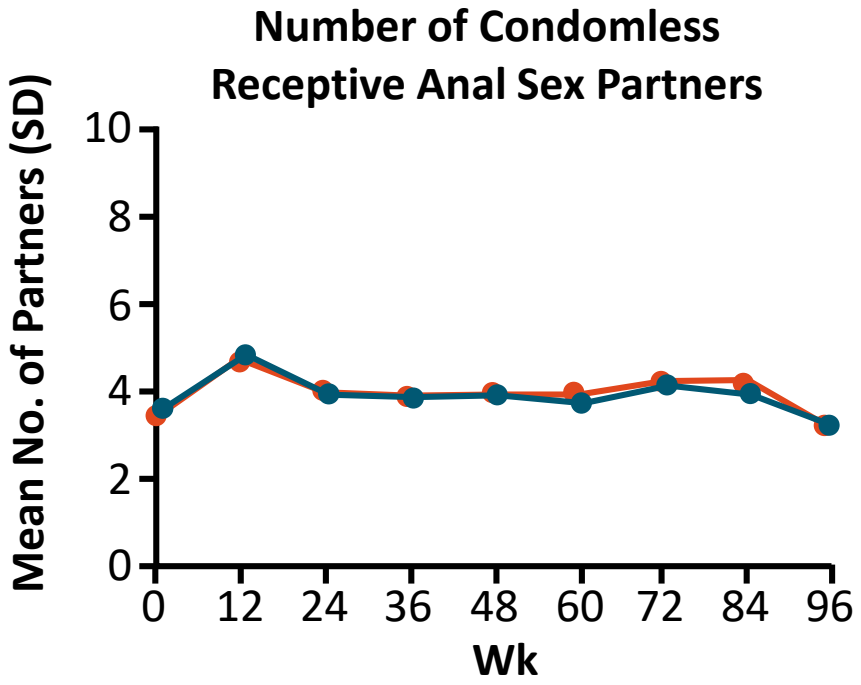
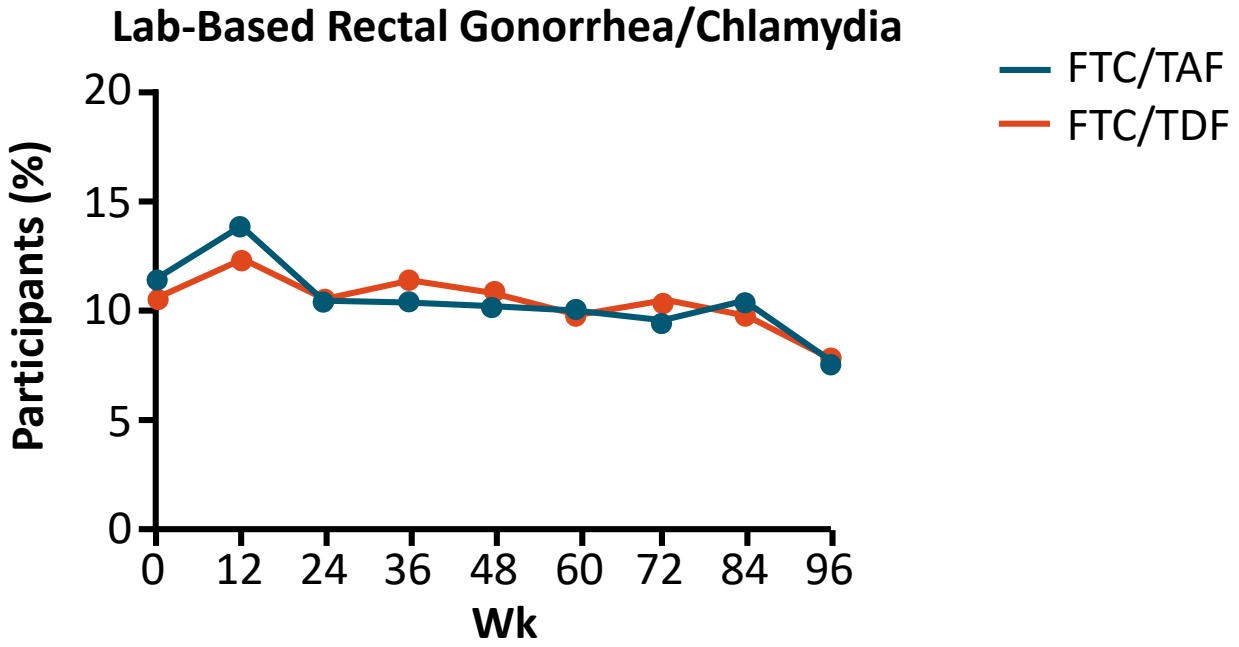
DISCOVER: Sexual Behaviors and STI Incidence

- Sexual behavior and STI incidence comparable between arms
  - AE-based incidence of chlamydia, gonorrhea, and syphilis: 145/100 PY with FTC/TAF, 139/100 PY with FTC/TDF





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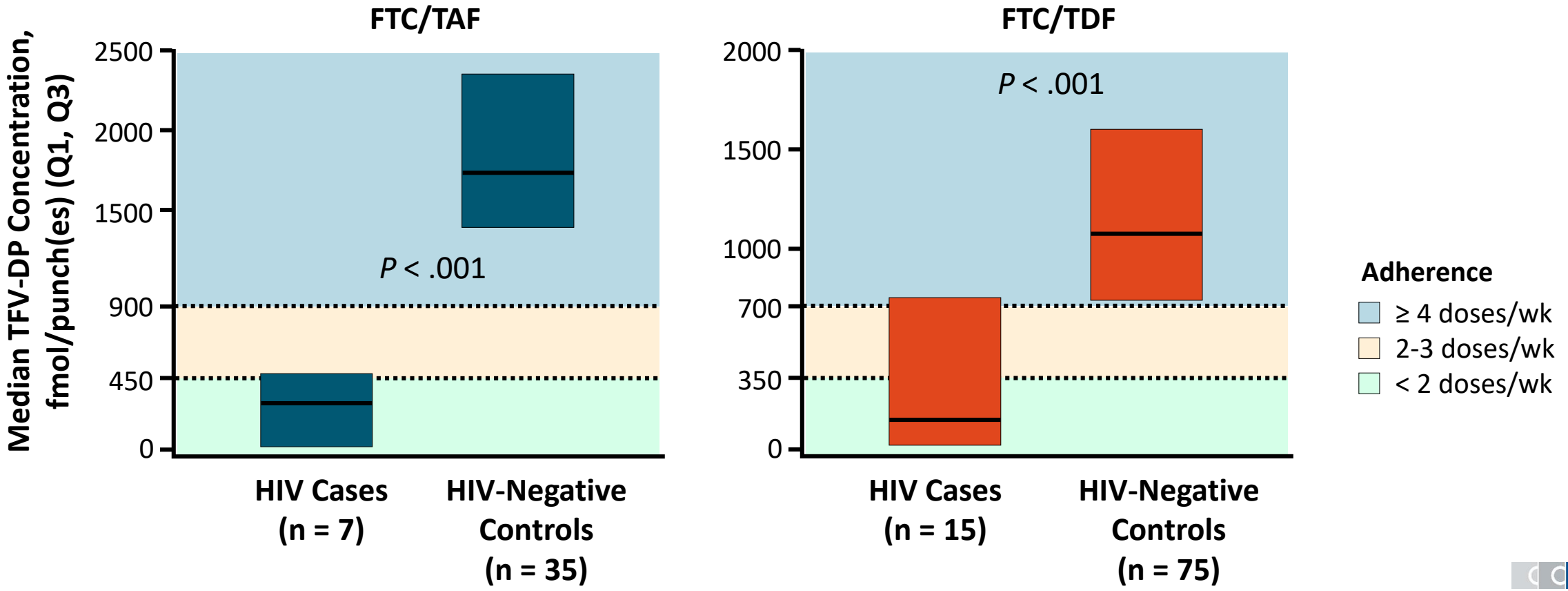
DISCOVER: Adherence by DBS at HIV Diagnosis Visit in Nested Case-Control Study

- Low adherence (< 2 doses/wk) associated with significantly increased risk of HIV infection in both arms (both *P* < .001)



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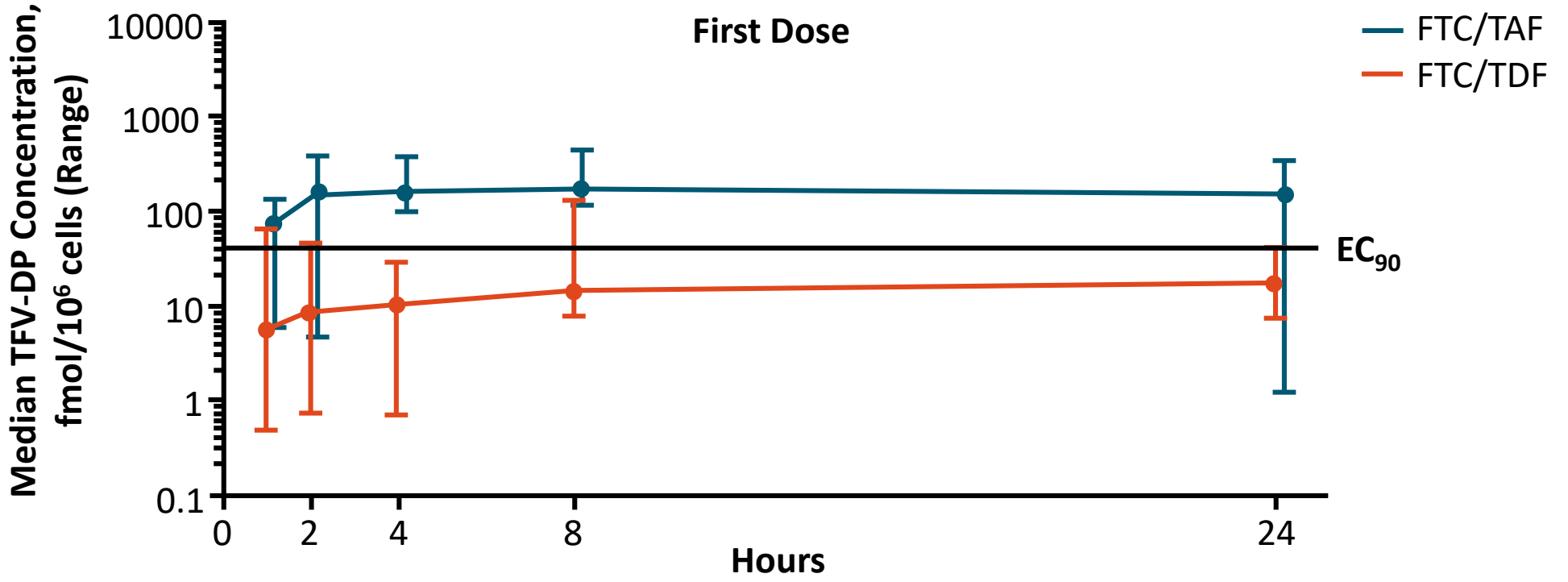
DISCOVER: Rapidity in Achieving EC_{90}

- In a phase I study in healthy volunteers, median PBMC TFV-DP concentration > EC_{90} reached within **1-2 hrs (all within 4 hrs) of dosing with FTC/TAF** vs **3 days of dosing with FTC/TDF**



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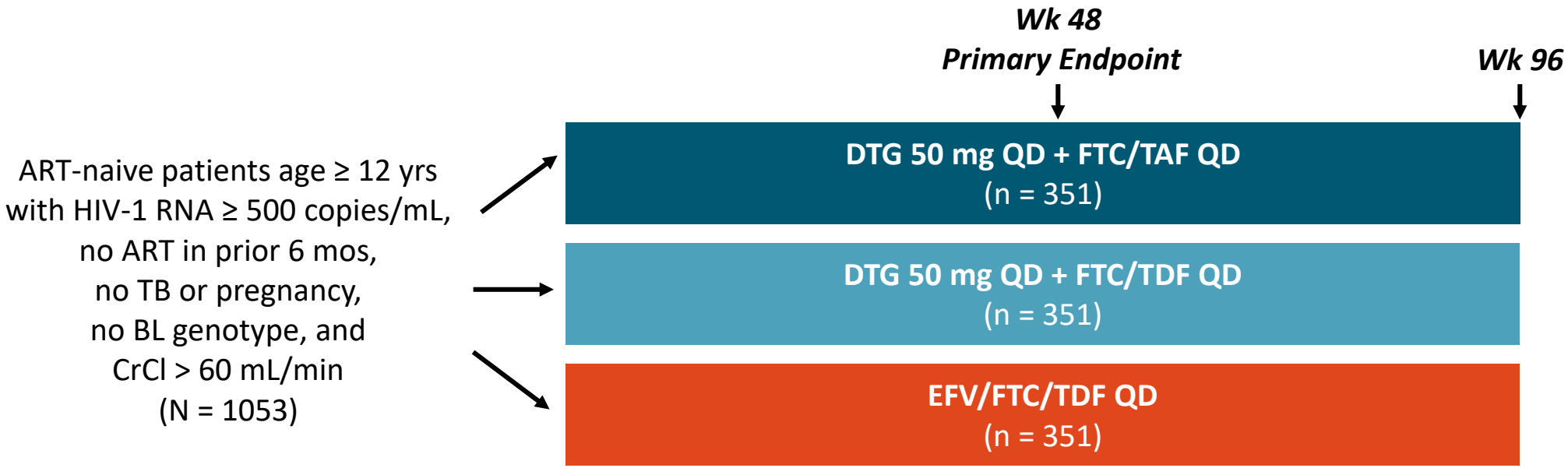
ADVANCE: First-line DTG + FTC/TAF vs DTG + FTC/TDF vs EFV/FTC/TDF

- Multicenter, randomized, open-label phase III trial conducted in South Africa



- Primary endpoint: HIV-1 RNA < 50 c/mL, d/c, or missing data at Wk 48 (FDA Snapshot in ITT)
  - Noninferiority margin: -10%
- Secondary endpoints: safety

Venter. IAS 2019. Abstr WEAB0405LB. Venter. NEJM. 2019;[Epub].

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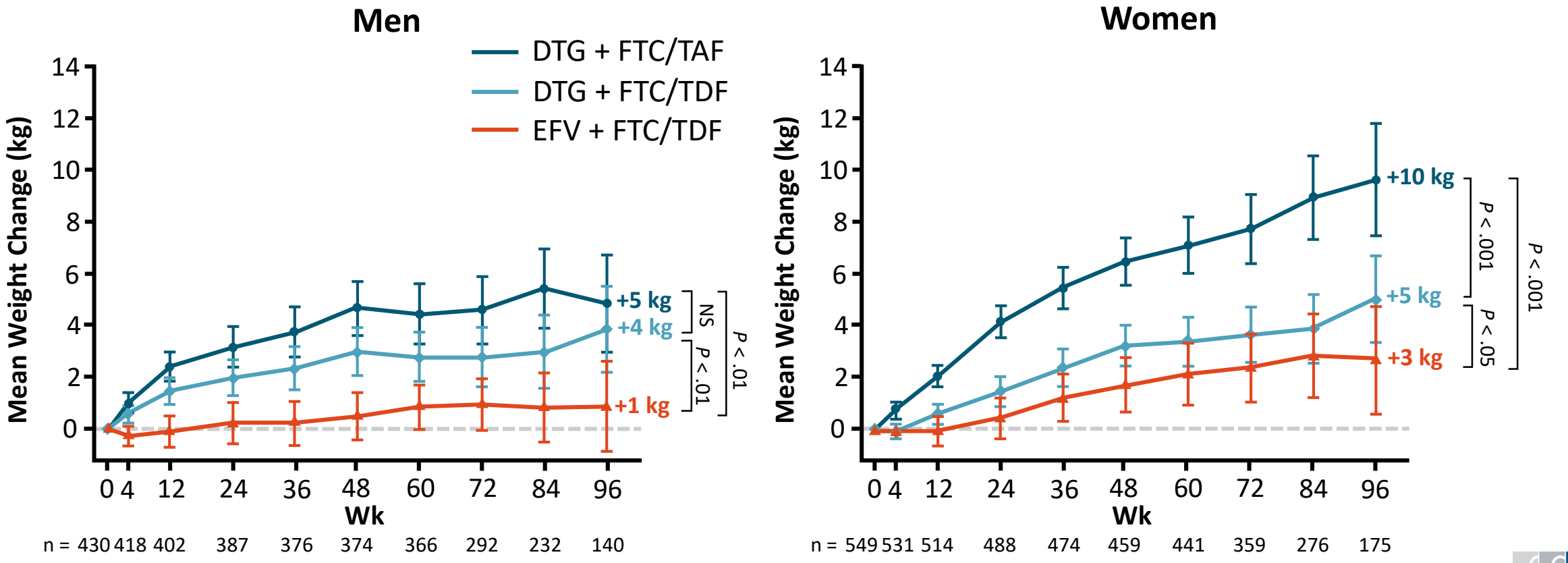
ADVANCE: Mean Change in Weight to Wk 96 by Sex

- Significantly greater weight increase* with DTG vs EFV, with TAF vs TDF; plateauing in weight gain after Wk 48 observed in men but not in women



Hill. IAS 2019. Abstr MOAX0102LB. Reproduced with permission.

*Wilcoxon rank-sum comparison at Wk 96.

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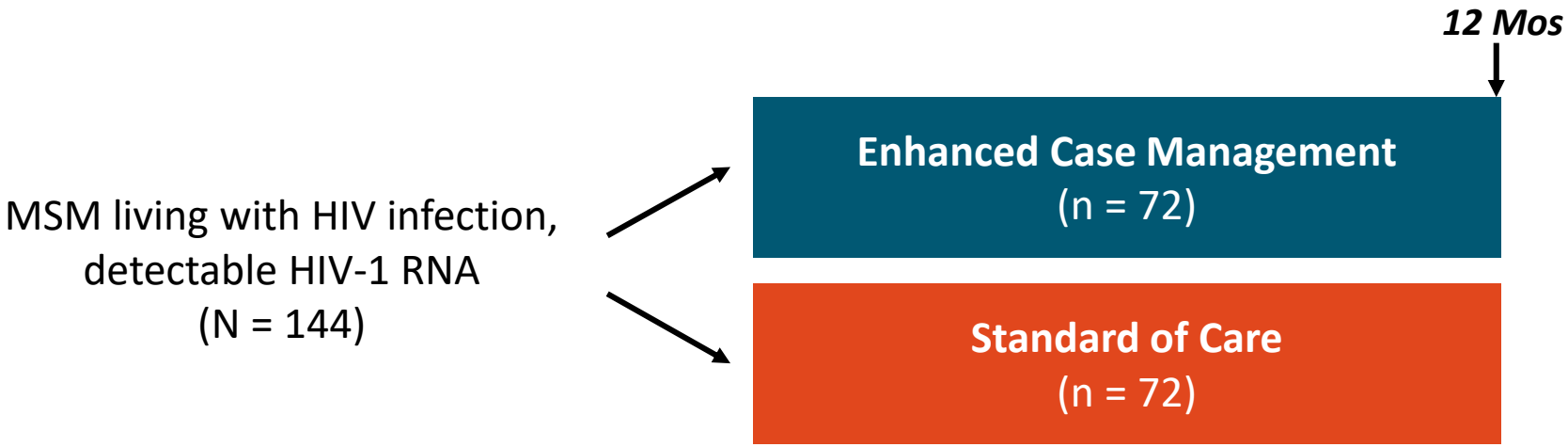
Other Issues in HIV Care

HPTN 078: Intervention to Engage Virologically Unsuppressed MSM Living With HIV



- **Enhanced case management:** access to a case manager and referral services, counseling using motivational interviewing, and automated adherence and motivational messaging
  - Intervention intensity was participant driven (by choosing frequency and content of interactions)
- **Study population:** predominantly black (84%), educated (≥ 90% had high school diploma), low income (65% earned < $20,000 annually), and ART experienced (86%)
  - Median HIV-1 RNA at baseline: 19,459 copies/mL

Remien. IAS 2019. Abstr MOAX0101LB.

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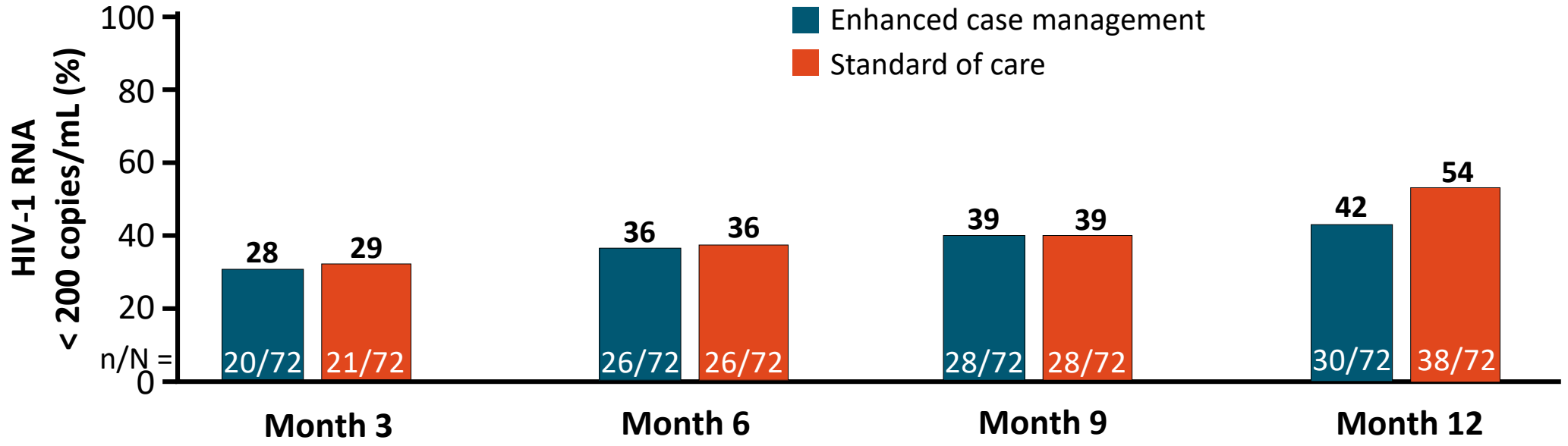
HPTN 078: Virologic Suppression Rates Similar With Enhanced Case Management vs Standard of Care

- At Month 12, 91% of participants were retained and 48% were virologically suppressed
- No significant difference in virologic suppression rates between **enhanced case management** and **standard of care** (OR: 0.615; 95% CI: 0.315-1.197; *P* = .1526)



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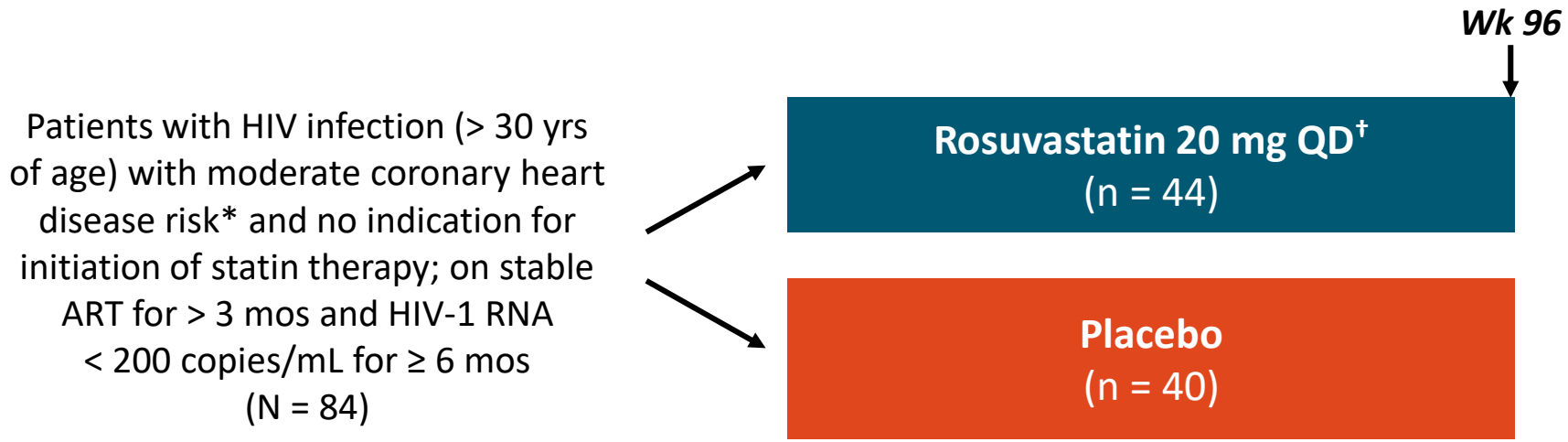
Rosuvastatin for Atherosclerotic Progression in People With HIV at Moderate Cardiovascular Risk

- Randomized, double blind, placebo-controlled, multinational trial



*Framingham risk score: 10-15%.

†Participants on a boosted PI or COBI received 10 mg rosuvastatin.

- Study population consisted primarily of white males; mean age: 54 years
- Approximately one third of participants were current smokers, and approximately one third had a family history of heart attack
- Approximately one quarter of participants were receiving abacavir

Trevillyan. IAS 2019. Abstr MOAB0201.

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Rosuvastatin vs Placebo: Outcomes at Wk 96

Mean Common Carotid IMT (SD)	Rosuvastatin (n = 44)	Placebo (n = 40)	*P* Value†
Baseline	0.722 (0.032)	0.772 (0.033)	.115
48 wks	0.726 (0.032)	0.771 (0.033)	.158
96 wks (primary endpoint)	0.726 (0.032)	0.779 (0.033)	.097
P value*	.319	.115	

*Baseline vs Wk 96 within each arm.

†Difference between arms at each time point.

- Decreases in total and LDL cholesterol with rosuvastatin vs placebo
- Greater incidence of adverse events in rosuvastatin vs placebo arm
  - 75% vs 27% of participants experienced ≥ 1 AE
  - 16% vs 0% experienced grade 3/4 AEs

Trevillyan. IAS 2019. Abstr MOAB0201.

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BRAHMS: STIs Among MSM in Germany

- Multicenter, prospective study in MSM aged 18-45 yrs at risk of HIV infection (N = 1040)
  - Eligibility criteria: in last 24 wks, documented syphilis, rectal gonorrhea, or chlamydia OR condomless anal intercourse with ≥ 2 unique male partners whose HIV status was positive or unknown
- Participants screened for STIs every 3 mos by blood, urine, anal swab, and oropharyngeal swab; also given sexual behavior questionnaires
- At BL, 45% were receiving PrEP, 18% initiated PrEP after risk reduction counseling, and 37% chose not to receive PrEP

Streeck. IAS 2019. Abstr TUPDC0106.

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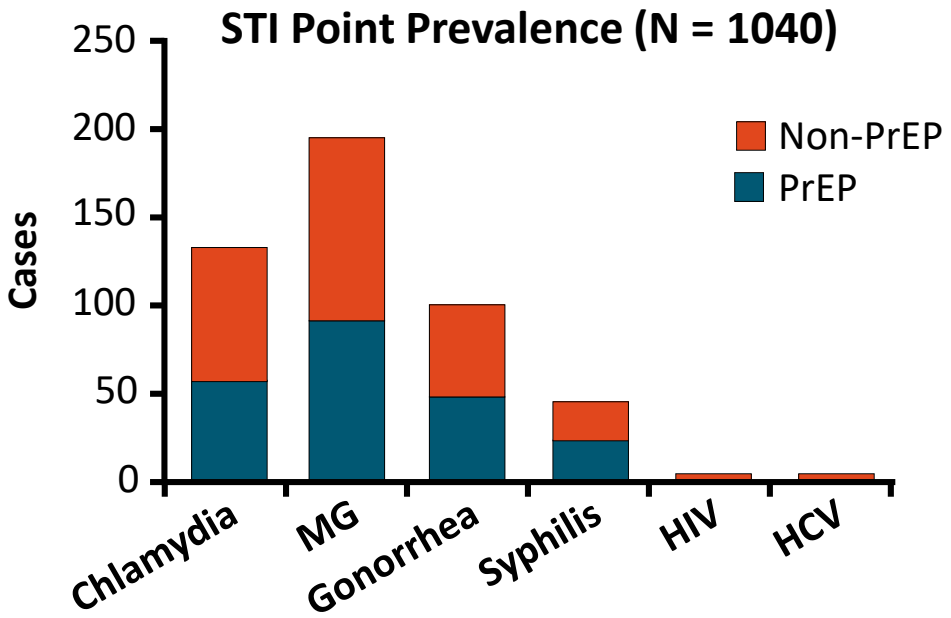
BRAHMS: STI Prevalence

- No difference in STI point prevalence by PrEP status; all cases of HIV in non-PrEP users



Point Prevalence, %	12	19	9.2	4.6	0.4	0.4	Overall
	12.6	18.5	8.5	4	0.7	0.6	Non-PrEP
	11.4	19.7	10.2	5.5	0.2	0.2	PrEP

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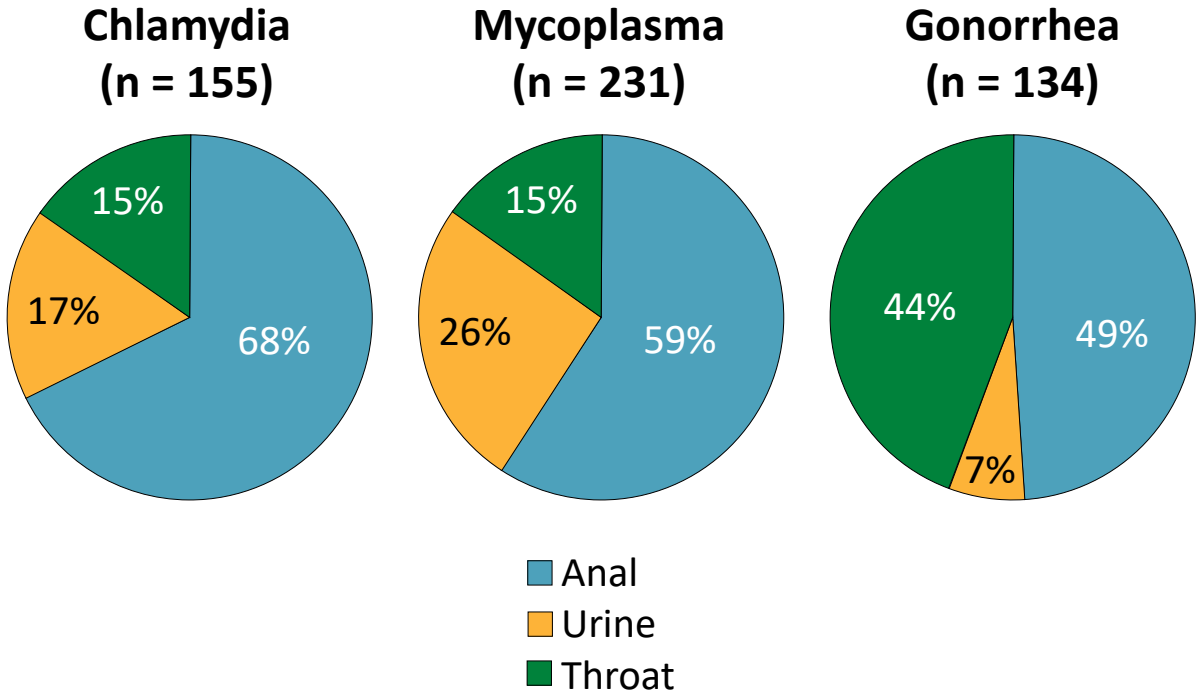
- 25% of participants had > 1 STI
- Most STIs were rectal, asymptomatic



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Early-Phase Investigational ART

Select Agents Under Early Investigation For the Prevention and Treatment of HIV

Agent	MOA	Phase	n	Key Findings
Ad26.Mos4.HIV and either clade C gp140 or bivalent gp140[1]	Vaccine	I/IIa	126	▪ Both regimens induced immune responses against a broad range of HIV-1 subtypes in healthy adults; well tolerated
Islatravir (ISL; MK-8591)[2]	NRTTI	I	12	▪ Drug-eluting implants projected to provide HIV prophylaxis for ≥ 1 yr; well tolerated. ISL + DOR tx regimen in phase IIb[3]
2-hydroxypropyl-β-cyclodextrin cabotegravir nanochannel delivery implant[4]	INSTI	PK	6 (rats)	▪ Clinically-relevant plasma CAB concentrations and drug penetration into relevant tissues; no AEs observed
GS-6207[5]	HIV-1 capsid inhibitor	Ib	18	▪ Single SC 50-450 mg dose provided potent antiviral activity, well tolerated in PLWH naive to capsid and integrase inhibitors
VRC01LS and VRC07-523LS[6]	HIV-1 bNAbs	I	16	▪ Decreased HIV-1 RNA following 1 IV dose in viremic PLWH; well tolerated
Vesatolimod (GS-9620)[7]	TLR 7 agonist	Ib	36	▪ Induced immune activation at doses ≥ 4 mg in virologically-suppressed PLWH; well tolerated

1. Stieh. IAS 2019. Abstr TUAC0402LB. 2. Matthews. IAS 2019. Abstr TUAC0401LB. 3. Molina. IAS 2019. Abstr WEAB0402LB. 4. Pons-Faudoa. IAS 2019. Abstr TUPEA106. 5. Daar. IAS 2019. Abstr LBPEB13. 6. Chen. IAS 2019. Abstr WEAA0305LB. 7. Riddler. IAS 2019. Abstr WEAA0304.

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