AETC AIDS Education & Training Center Program Mountain West

Antiretroviral Therapy Controversies

Brian R. Wood, MD
Medical Director, Mountain West AETC HIV Telehealth Program
Associate Professor, Division of Infectious Diseases
University of Washington, Seattle

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Disclosures

I have no financial disclosures or conflict of interest.
I will be discussing investigational therapies.

For more on any of the topics discussed today:

National HIV Curriculum (www.hiv.uw.edu)

HIV ECHO Talks (youtube, MWAETC: Project ECHO)

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HIV Treatment Controversies

- Do the latest ARV's lead to more weight gain than older agents?
- Does dolutegravir increase the risk of neural tube defects?
- What are the advantages of dual (2-drug) ART?
- A few other questions and conundrums

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DHHS and IAS-USA
Recommended Initial ART Options

DHHS (Oct 2018)[1] Recommended for Most People With HIV	IAS-USA (July 2018)[2] Recommended Initial Regimens
BIC/FTC/TAF	BIC/FTC/TAF
DTG/ABC/3TC (if B*5701 neg) DTG + FTC/TAF or FTC/TDF	DTG/ABC/3TC (if B*5701 neg) DTG + FTC/TAF
RAL + FTC/TAF or FTC/TDF	

Abbreviations:
BIC – bictegravir, DTG – dolutegravir, ABC – abacavir, 3TC – lamivudine, FTC – emtricitabine
TDF – tenofovir disoproxil fumarate, TAF – tenofovir alafenamide

1. DHHS: http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Revision Oct 25, 2018
2. IAS-USA: Saag MS, et al. *JAMA.* 2018;320:379-396.

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Frequent Clinical Question

- Should all persons with HIV taking a “second-line” ARV switch to a recommended option? Examples:
  - TDF
  - Elvitegravir/cobicistat
  - Efavirenz
  - Atazanavir + ritonavir

- What factors should be considered before making a switch? What is the best option for an “update?”

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Do the newest ARV's (dolutegravir, bictegravir, TAF) lead to more weight gain compared to older agents?

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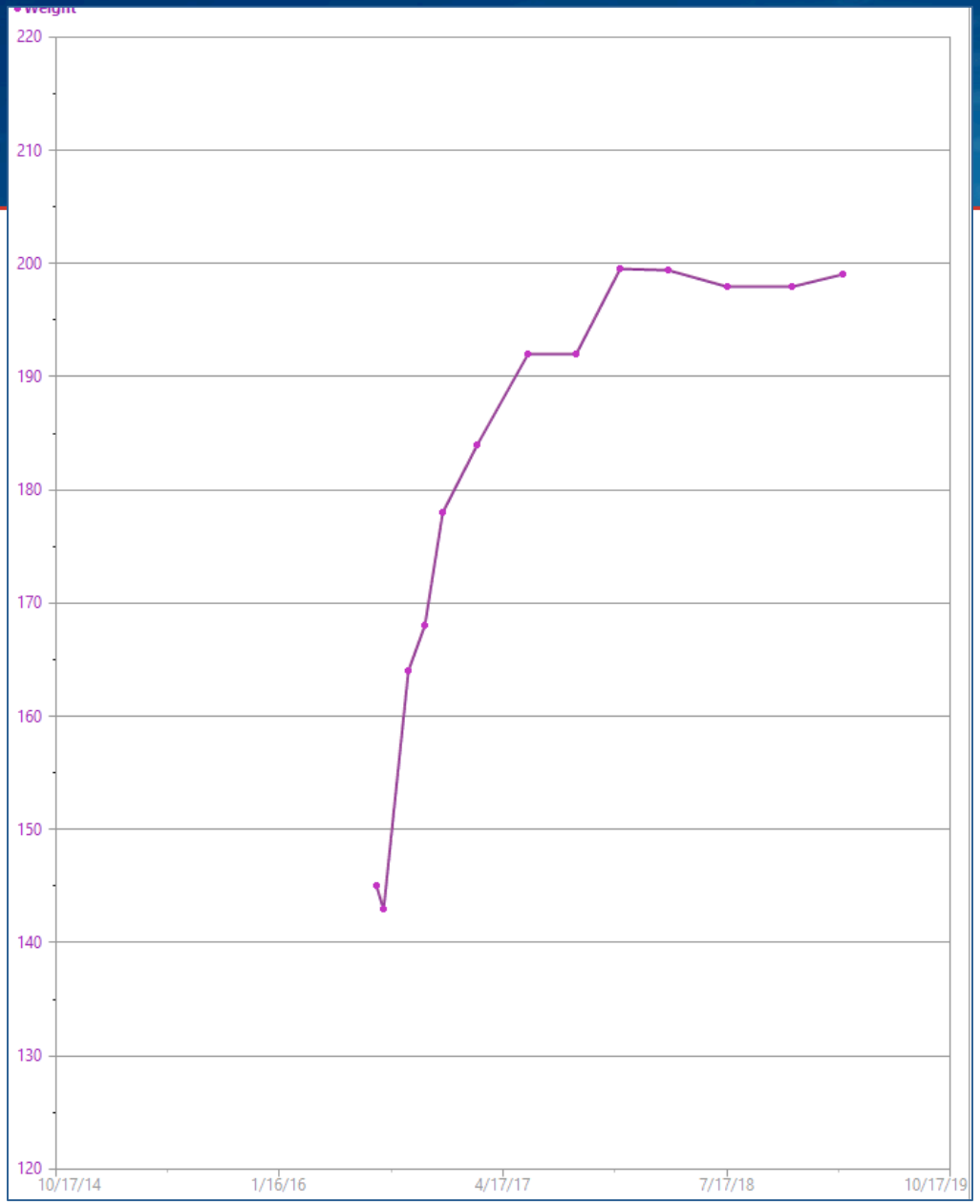
Case

- Patient in their 40's
- Re-engaged in care 3 years ago, CD4 21
- New ART: DTG + RPV/FTC/TAF
- Approx. 55 lb. weight gain over 2 years (BMI 25 → 35)
- *Would you change ART due to weight gain?*



Case credit to Dr. Elizabeth Duke.

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Weight Change in Treatment-Naïve Studies
Retrospective Analyses

Authors (Source)	N	Cohort	Findings
Bourgi et al. (CID, May 2019)	21,886	NA-ACCORD	More weight gain with INSTI start than NNRTI start; esp. dolutegravir or raltegravir
Rebeiro et al. (ID Week 2019, #LB9)	21,506	NA-ACCORD	INSTI or PI initiation may increase diabetes risk compared to NNRTI (approx. 25% increased risk)
Kline et al. (ID Week 2019, #335)	496	Military	Greatest weight gain: black participants with BMI $\geq$25 at baseline and starting an INSTI

Adapted from slides from Dr. Jehan Budak.

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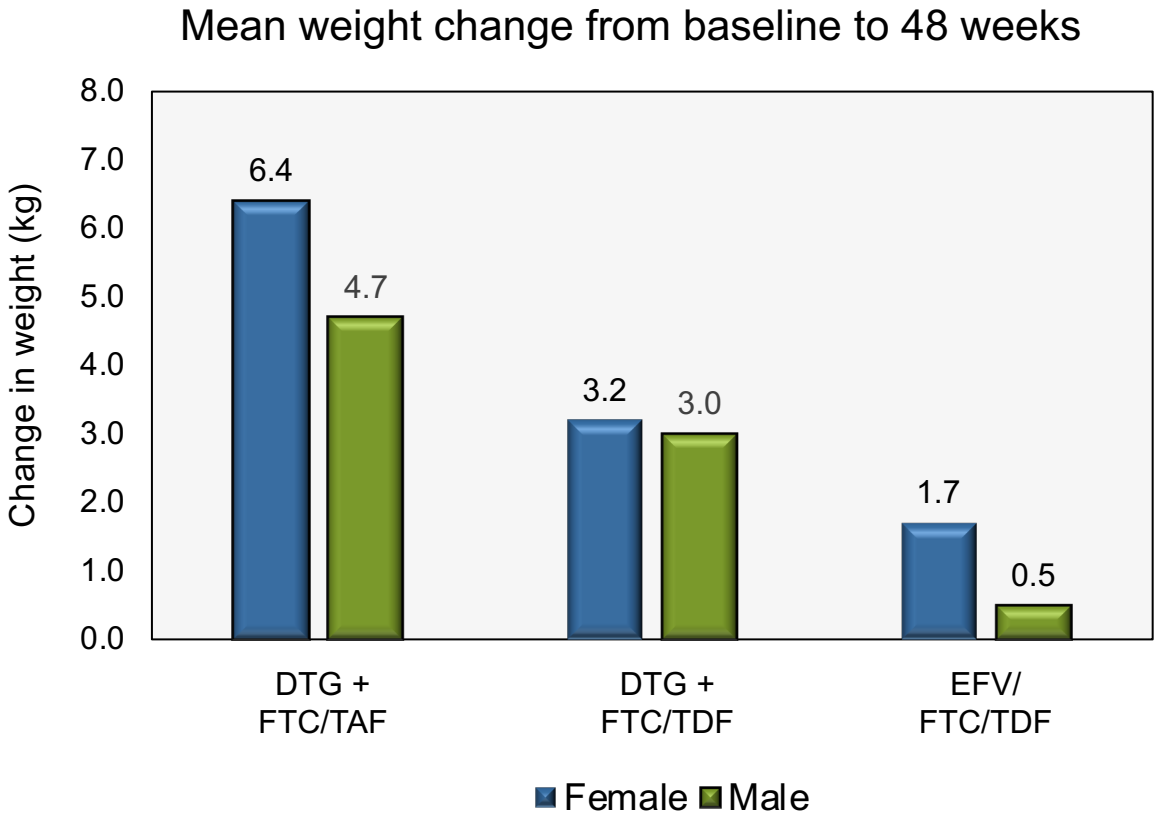
ADVANCE Trial
Comparison of Three First-Line Regimens

- Phase 3 RCT in South Africa
- Initial ART: DTG + FTC/TDF, DTG + FTC/TAF, EFV/FTC/TDF
- DTG arms non-inferior with fewer discontinuations; TAF led to fewer bone/renal AE's



Ventner WDF et al. NEJM, August 2019.

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Pooled Analysis of Weight Change in Treatment-Naïve RTC's ART Initiation 2003 to 2015

- >5,000 individuals, >10,000 person-years follow up
- 96-week median weight gain: 2.0 kg (IQR: -1.0, 5.8)

Risk factors any weight gain:	Risk factors weight gain ≥10% body weight:
Lower CD4	**Lower CD4**
Higher HIV RNA	Higher HIV RNA
No injection drug use	Normal baseline BMI
Age <50	**Female sex**
Female sex	**Black race**
Black race	**BIC/DTG vs EFV**
INSTI's vs PI's or NNRTI's	**ELV/c vs EFV**
BIC/DTG vs ELV/c	**RPV vs EFV**
RPV vs EFV	**TAF vs TDF, ABC, or AZT**
TAF vs TDF, ABC, or AZT	

Sax et al. Clin Infect Dis. 2019 Oct 14. pii: ciz999. doi: 10.1093/cid/ciz999.

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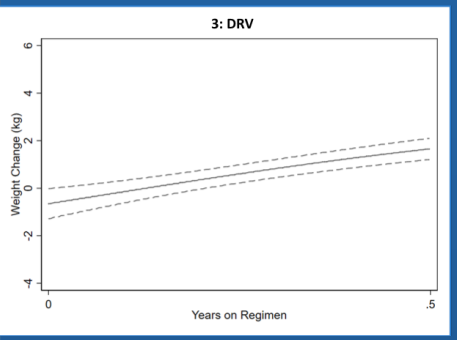
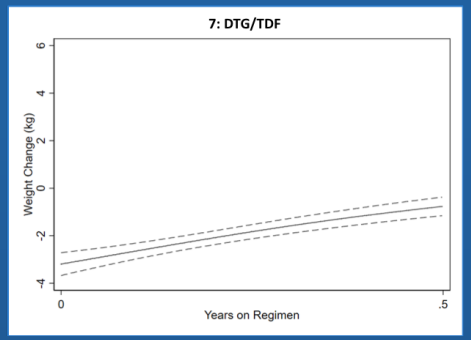
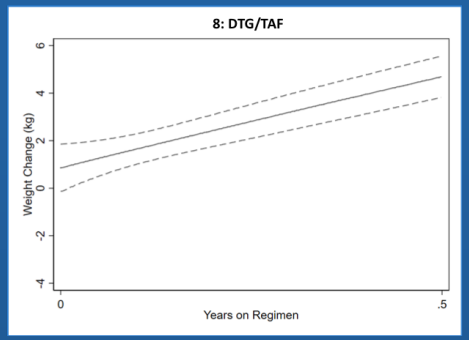
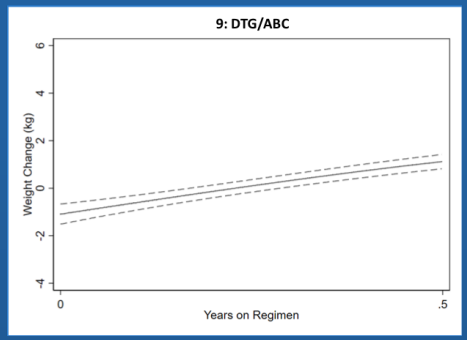
Weight Change Following ART Initiation in CNICS
Presented at EACS Nov 2019

Short term weight change in kg (6 months)

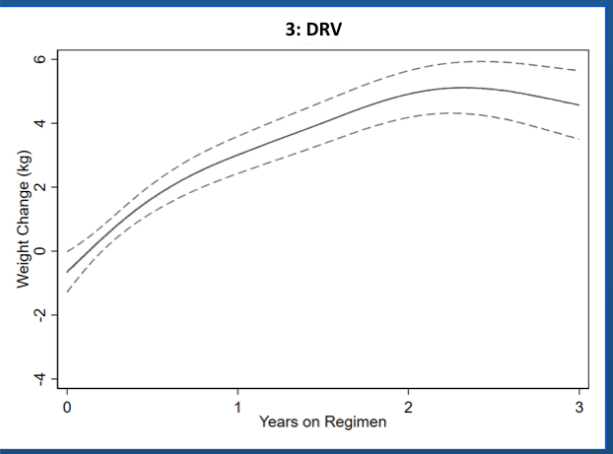


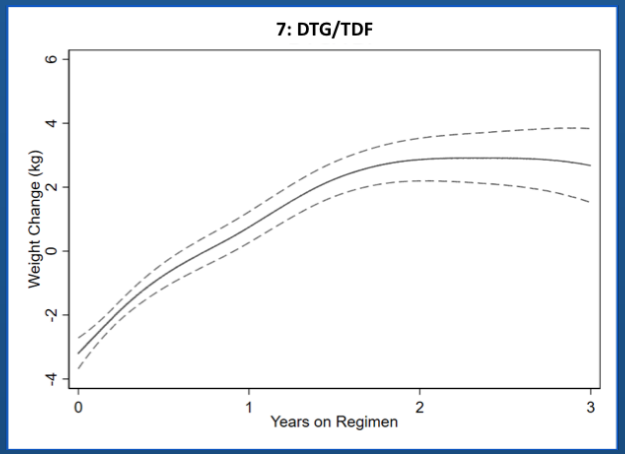


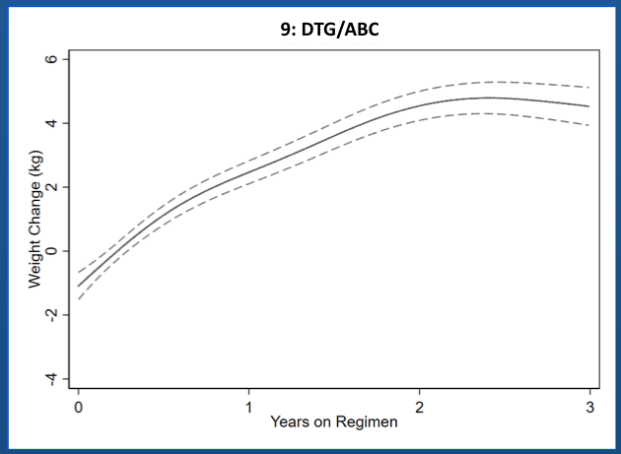




Longer term weight change in kg (mean follow up 2.0 years)







Ruderman SA et al. EACS 2019, Basel, Switzerland. Abstract PE2/55.

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Weight Change in Treatment-Naïve Studies
Bictegravir (BIC) vs Dolutegravir (DTG)

Study	Weight Change Baseline to 96 Weeks	
1489 (mean increase)	BIC/FTC/TAF **3.5 kg**	DTG + FTC/TAF **3.9 kg**
1490 (median increase)	BIC/FTC/TAF **3.6 kg**	DTG/ABC/3TC **2.4 kg**

Study 1489- Stellbrink. Lancet HIV. 2019;6:e364. Study 1490 - Wohl. Lancet HIV. 2019;6:e355.

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Summary
Weight Change in Treatment-Naïve Studies

- Most individuals gain weight in first 1-2 years of ART
  - Some gain more than others and may surpass goal BMI
  - Key factors: CD4 count, sex, race/ethnicity
- Newer ARV's associated with more weight gain than older comparators (most occurs with DTG or BIC + TAF)
  - Reason? **Tolerability?** Toxicity? Faster VL suppression?
  - Consequences? Statistical significance vs clinical significance?
- *Should this affect choice of initial ART?*

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Case

- Young cisgender woman
- Stable on efavirenz/FTC/TDF for 4 years
- Switches to DTG + FTC/TAF to reduce toxicity risk
- Experiences 25 lb weight gain over 18 months and requests a switch back to prior regimen
- *How would you counsel her? Would you recommend a switch back, or to something else?*

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Weight Change After Switch to an INSTI
Retrospective Studies

Authors (Abstract #)	N	Cohort	Switch Associated with Weight Gain?
Lake et al. (CROI 2019, 669)	972	A5001, A5322	YES
Mounzer et al. (ID Week 2019, 978)	972	OPERA	YES
Aldredge (ID Week 2019, 980)	881	WIHS (WLH)	YES
Zimmerman (ID Week 2019, 981)	90	Single center	YES
Bernstein et al. (ID Week 2019, 334)	260	Single center	YES
Hsu et al. (ID Week 2019, 341)	7,494	OPERA	YES
Kerchberger et al. (CROI 2019, 671)	1118	WIHS (WLH)	YES
Palella et al. (CROI 2019, 674)	653	HOPS	YES
Mugglin et al. (EACS 2019)	2,186	Swiss Cohort	YES
McComsey et al. (CROI 2019, 670)	3468	TRIO	NO
Verboeket S et al. (EACS 2019)	595	AGEhIV	NO

Adapted from slides from Dr. Jehan Budak.

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Weight Change After TDF to TAF Switch
Retrospective Studies

Authors	N	Cohort	Retrospective Analysis Findings
Schafer et al. (OFID 2019)	110	Single center	In the year after TDF to TAF switch, median BMI increases 0.5 kg/m^2 and ASCVD risk increases average 13%
Gomez et al. (Infection 2019)	241	Single center	Mean weight increase weight 3.17% over 1 year after TDF to TAF switch; only 0.55% with continued TDF
Lee et al. (EACS 2019)	191	Single center	No significant weight change after TDF to TAF switch for individuals over 60 years old

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Summary
Weight Change in Switch Studies

- Retrospective studies suggest weight gain occurs after switch to an INSTI (especially dolutegravir) or TAF
  - Data lacking for switch to bictegravir
- Methods, follow-up, definitions of weight gain, participant demographics all highly variable
- Long-term consequences unclear
- *How should we incorporate this data into counseling and decisions about ART switches/updates?*

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Does dolutegravir increase the risk of neural tube defects?

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Case

- 38 year-old cisgender woman with HIV, well-controlled on dolutegravir + FTC/TDF, wishes to conceive
- Her husband has HIV with a suppressed viral load on ART
- She is going to seek assisted reproductive services
- *Would you recommend a change of dolutegravir to a different agent?*

Dolutegravir (DTG) and Concern for Neural Tube Defects (NTD's)
Background

- DTG has many advantages, however, prelim analysis of a birth surveillance study in Botswana (May 2018) found:
  - 4 neural tube defects (NTD's) out of 426 infants born to women who initiated DTG prior to conception (**rate 0.94% vs. 0.12% with non-DTG ART) → FDA Alert**
  - IAS July 2018: updated incidence **4/596 (0.67%)**

Sources: 1. Zash R et al. N Engl J Med. 2018 Sep 6;379(10):979-981. 2. Zash R et al. IAS 2018, Amsterdam. Session TUSY15.

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Dolutegravir (DTG) and Concern for Neural Tube Defects (NTD's)
Background

- Unanswered questions:
  - Could DTG cause NTD's directly or could the cause be environmental factors (e.g. no folate supplementation of flour/grains in Botswana)?
    - DTG is a partial antagonist of folate receptor 1 (FOLR1)*
  - As the WHO rolls out TDF/3TC/DTG ("TLD") worldwide, should child-bearing potential be a contraindication?

*Cabrera RM et al. AIDS. 2019 Jun 26.

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Updated Data from the Tsepamo Study
IAS July 2019

Neural Tube Defects According to Maternal HIV Status and ART

	DTG at Conception	Non-DTG ART at Conception	EFV at Conception	DTG Started During Pregnancy	HIV-Negative
# of NTD	**5**	15	3	1	70
# of exposures	**1,683**	14,792	7,959	3,840	89,372
% with NTD (95% CI)	**0.30** (0.13-0.69)	**0.10** (0.06-0.17)	0.04 (0.01-0.11)	0.03 (0.00-0.15)	0.08 (0.06-0.10)
Difference in prevalence (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)

*Compare to IAS July 2018: 4/596 (0.67%)

Source: Zash R et al. N Engl J Med. 2019 Jul 22. and IAS 2019, Mexico City.

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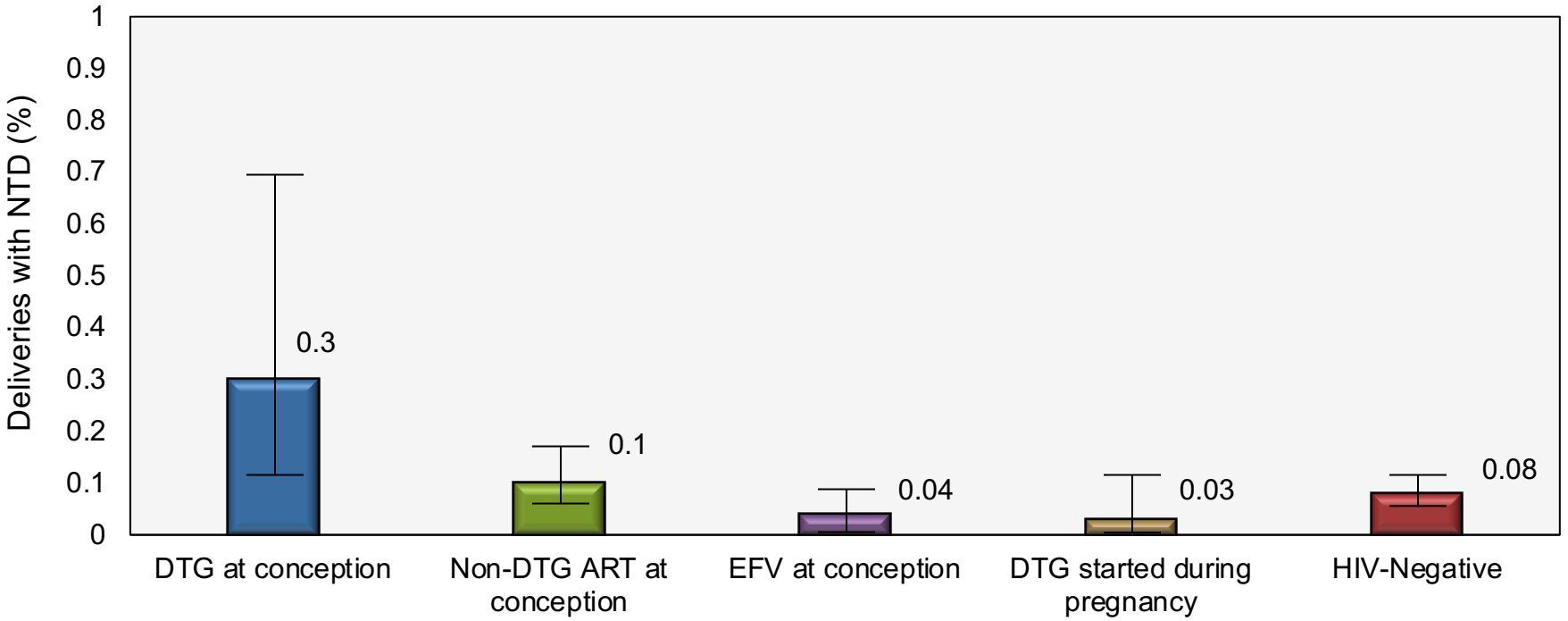
Updated Data from the Tsepamo Study
IAS July 2019

Neural Tube Defects According to Maternal HIV Status and ART



"99.8% of the women for whom folate was prescribed started taking folate during, not before, pregnancy"

Source: Zash R et al. N Engl J Med. 2019 Jul 22. and IAS 2019, Mexico City.

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Interpretation

- Investigator conclusion: “The prevalence of NTD’s was slightly higher in association with DTG exposure at conception than with other types of ART exposure”
  - **Relative risk higher (3/1000 versus 1/1000); absolute risk low (2 excess NTD’s per 1000 births)**
- Limitations: observational, small # NTD’s overall, can’t control for all confounders, lacking comparison data for other INSTI’s, lacking robust data from other countries

Source: Zash R et al. N Engl J Med. 2019 Jul 22. and IAS 2019, Mexico City.

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Additional Neural Tube Defect Data
IAS & EACS 2019

Studies From Countries with Folate Food Fortification

	NTD per deliveries with DTG at conception	Comparison
Brazil[1]	0/382	EFV or RAL at conception: 0/1086
United States APR[2,3]	1/312 (0.30%)	Any ART: 3/8546 (0.03%); Any INSTI: 1/714 (0.14%); RAL: 0/268; EVG: 0/217

Antiretroviral Pregnancy Registry (APR): http://www.apregistry.com/

1. Pereira G et al. IAS 2019, #MAX0104LB. 2. Mofenson LM et al. IAS #TUAB0101.
3. Vannappagari V et al, EACS 2019.

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WHO Recommendation
July 2019

WHO recommends dolutegravir as preferred HIV treatment option in all populations

22 July 2019 | News release | Mexico City

Based on new evidence assessing benefits and risks, the WHO recommends the use of the HIV drug dolutegravir (DTG) as the preferred first-line and second-line treatment for all populations, including pregnant women and those of childbearing potential.

Source: https://www.who.int/news-room/detail/22-07-2019-who-recommends-dolutegravir-as-preferred-hiv-treatment-option-in-all-populations

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What is the optimal ART regimen during conception/early pregnancy?

A) Dolutegravir + FTC/TDF

B) Raltegravir + FTC/TDF

C) Efavirenz/FTC/TDF

D) Rilpivirine/FTC/TDF

E) Atazanavir + ritonavir + FTC/TDF

F) Darunavir + ritonavir + FTC/TDF

G) Something else

HHS Guidelines to be updated soon!

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What are the advantages of dual ART (2 active drugs)? Should we be recommending these options more often?

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Case

- 54-year-old cisgender man, suppressed HIV RNA on dolutegravir/ABC/3TC
- Comorbidities: BMI 37, hyperlipidemia, hypertension
- Other meds: HCTZ, lisinopril, atorvastatin
- Normal renal function; ASCVD risk estimate 10.3%
- What would be the best update to his ART?
  - A) Dolutegravir + FTC/TAF
  - B) Bictegravir/FTC/TAF
  - C) Rilpivirine/FTC/TAF
  - D) Dolutegravir/rilpivirine
  - E) Dolutegravir/3TC
  - F) No update, continue DTG/ABC/3TC

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Oral 2-Drug Maintenance ART
Prospective RCT's

DUAL ART	MAINTENANCE ART STUDIES
Dolutegravir/rilpivirine[1]	SWORD (n=1,028, comparator: TDF-based 3-drug ART)
Dolutegravir/3TC[2]	TANGO (n=750, comparison: TAF-based 3-drug ART)
Dolutegravir + FTC[3]	SIMPL'HIV (n=188, comparison: TAF, TDF, ABC-based 3-drug ART)
Boosted darunavir + 3TC[4]	DUAL GESIDA (n=249, comparator: TDF-based 3-drug ART)
Boosted darunavir + dolutegravir[5]	DUALIS (n=263, comparison: TDF-based 3-drug ART)

1. 148 Week Data: van Wyck, BHIVA, April 2019.
2. 48 Week Data: van Wyck, IAS, July 2019.
3. 48 Week Data: Sculier, EACS, Nov 2019.
4. 48 Week Data: Pulido, CID, 2017.
5. 48 Week Data: Spinner C, IAS 2019.

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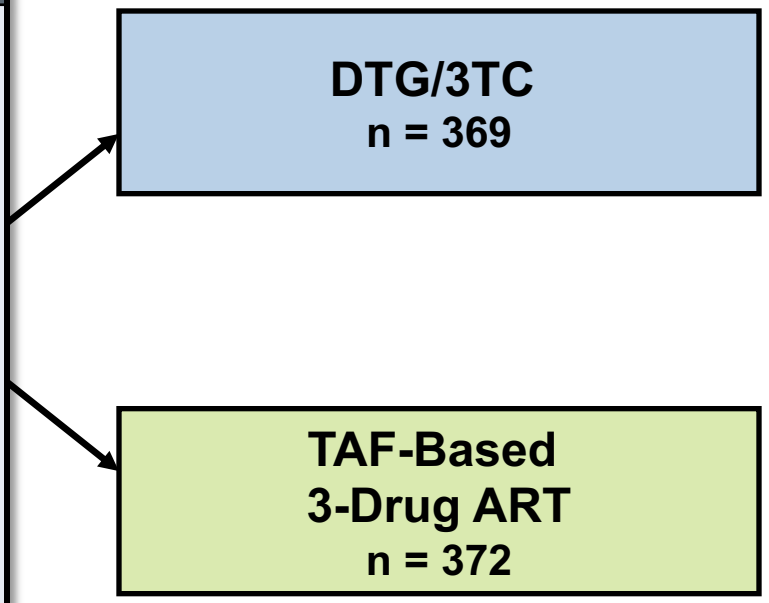
Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART
TANGO: Background

Study Design: TANGO

- **Background**:
  - Ongoing, phase 3, randomized, open label, multicenter, non-inferiority trial
- **Enrollment Criteria:**
  - Adults with HIV RNA <50 copies/mL for >6 months on stable 3-drug TAF-based ART (ok if started TDF but switched to TAF ≥3 months before screening)
  - No HBV or need for HCV treatment
  - No prior virologic failure or documented NRTI or INSTI resistance resistance



Primary endpoint: virologic response at 48 weeks by FDA snapshot

Source: van Wyk J et al. IAS July 2019, Mexico City.

Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART
TANGO: Baseline Characteristics

Characteristic	DTG/3TC (n = 369)	TAF-Based 3-Drug ART (n = 372)
Age, years, median (range)	40 (20-74)	39 (18-73)
Female, n (%)	25 (7)	33 (9)
White, n (%)	296 (80)	289 (78)
Black/African American, n (%)	51 (14)	13 (3)
CD4 cell count, mean (range)	682 (133-1904)	720 (119-1810)
CD4 cell count <350, n (%)	35 (9)	30 (8)
Months on ART, median (range)	33.8 (7.1-201.2)	35.1 (7.0-160.8)
Baseline third agent class		
INSTI	289 (78)	296 (80)
NNRTI	51 (14)	48 (13)
PI	29 (8)	28 (8)

Source: van Wyk J et al. IAS July 2019, Mexico City.

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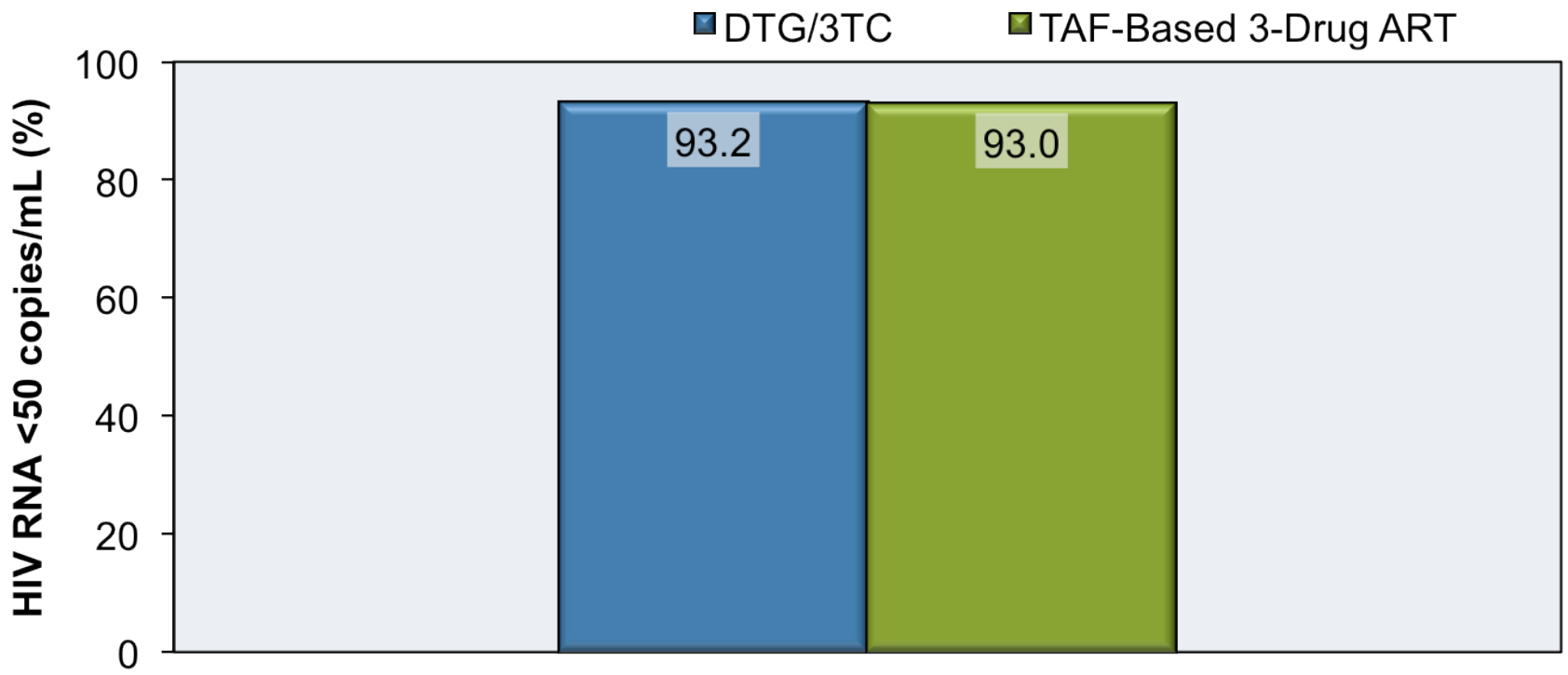
Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART
TANGO: Results

Week 48 Virologic Response (Intention-to-Treat Analysis)



- Confirmed withdrawal for virologic failure: 0 in DTG/3TC arm, 1 in TAF-based ART arm
- No new resistance mutations occurred
- 4 with baseline M184V/I in DTG/3TC arm (by proviral genotype) suppressed at week 48

Source: van Wyk J et al. IAS July 2019, Mexico City.

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Switch to DTG/3TC vs Continued TAF-Based 3-Drug ART
TANGO: Results

Week 48 Bone, Renal, and Other Side Effects

- Greater declines in estimated GFR in switch group
  - But all switching to dolutegravir, so difficult to interpret
- No clear difference in markers of proximal tubulopathy
- No clear winner in markers of bone turnover
- Mean weight increase similar between arms (0.8 kg)
- Some improvement in lipids & insulin resistance w/switch

Source: van Wyk J et al. IAS July 2019, Mexico City. Ait-Kaled M et al. EACS Nov 2019.

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Interpretation

- What are the advantages of DTG/3TC maintenance compared to continues TAF-based 3-drug ART?
  Answer: "reduced ARV exposure," but what exactly does that mean? What are the long-term benefits?

- Which perspective is best?

  1) Is there a strong indication to switch to 2-drug ART?

  2) Is there a strong indication to continue 3 drugs?

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Dual ART: What's Coming?
Long-Acting IM Cabotegravir (CAB) + Rilpivirine (RPV)

- Phase 3 data:
  - FLAIR:[1] 16 weeks DTG/ABC/3TC, then continue vs 4 weeks oral CAB/RPV then monthly IM CAB/RPV
  - ATLAS:[2] suppressed on standard 3-drug ART continue vs 4 weeks oral CAB/RPV then monthly IM CAB/RPV
  - ATLAS-2M:[3] suppressed on 3-drug ART then 4 weeks oral CAB/RPV then IM CAB/RPV q4 weeks vs q8 weeks

IM cabotegravir

FDA NDA submitted April 2019!

1. Orkin et al, CROI 2019, #140LB. 2. Swindells et al, CROI 2019, #139. 3. Press release Aug 2019 (ViiV, Jannsen).
Image courtesy of Dr. Raphael Landovitz.

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Dual ART: What's Coming?
Long-Acting IM Cabotegravir (CAB) + Rilpivirine (RPV)

- ACTG 5359: LATITUDE:
  - Long-Acting Therapy to Improve Treatment SUccess in Daily LifE
  - Individuals with HIV RNA >200 copies/mL
  - 24-week oral induction with financial incentives
  - If suppress, randomize to continue oral ART vs 4 weeks oral CAB/RPV then monthly IM CAB/RPV
- Outstanding Questions:
  - *Optimal lead in period? Risks of missed doses? Necessary oral tail if stopping? Best candidates?*

Source: clinicaltrials.gov

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Dual ART: What's Coming?
Islatravir (ISL) + Doravirine (DOR)

- Islatravir: first NRTTI (nucleoside reverse transcriptase translocation inhibitor)
  - Prevents nucleotide binding and incorporation into the DNA chain, resulting in immediate chain termination
  - Pros: high barrier to resistance, active with some NRTI resistance mutations, few drug interactions, long half life (120 hours)
- DRIVE2SIMPLIFY: ISL + DOR + 3TC initial ART (n=79)[1]
  - Compared to DOR/TDF/3TC for 24 weeks (n=24)
  - At 24 weeks, those receiving ISL narrow to ISL + DOR
  - At 48 weeks, well tolerated with no VF; comparable efficacy

Sources: 1. Molina JM et al. 2. Matthews R et al. IAS July 2019, Mexico City.

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A few other controversies

Other Controversial ART Questions

1) Are TAF, 3TC, FTC safe with advanced renal disease (eGFR below 15-30 mL/min): *Answer: probably*

- Eron study: individuals with eGFR <15 mL/min & on HD switched to ELV/cobi/FTC/TAF; at 96 weeks, 30/31 remained suppressed (97%)

2) Are DTG + FTC/TAF or BIC/FTC/TAF sufficient in the setting of an isolated M184V? *Answer: probably*

- DAWNING study: NNRTI failure, randomized to DTG + 2 NRTI's vs LPV/r + 2 NRTI's; DTG + 2 NRTI's superior; >80% had M184V/I

3) Are DTG + FTC/TAF or BIC/FTC/TAF sufficient in the setting of advanced HIV disease? *Answer: yes, in most cases*

- 3 case reports of resistance developing to DTG; all had very high viral loads, low CD4, complicating infection; 2 on rifamycins

1. Eron , IAS 2019. 2. Aboud, Lancet ID, Feb 2019. 3. Fulcher CID 2018, Pena OFID 2019, Lubke NEJM 2019.

Returning to Key Questions

- Would you alter your choice of initial ART due to concern for weight gain? Will the data alter counseling about switch or updates to ART regimens?
- What is the optimal ART regimen during conception and early pregnancy?
- Should we be defaulting to 3-drug ART or 2-drug ART?
- *What other ART controversies have come up for you recently?*

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Questions?

Email: bwood2@uw.edu

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