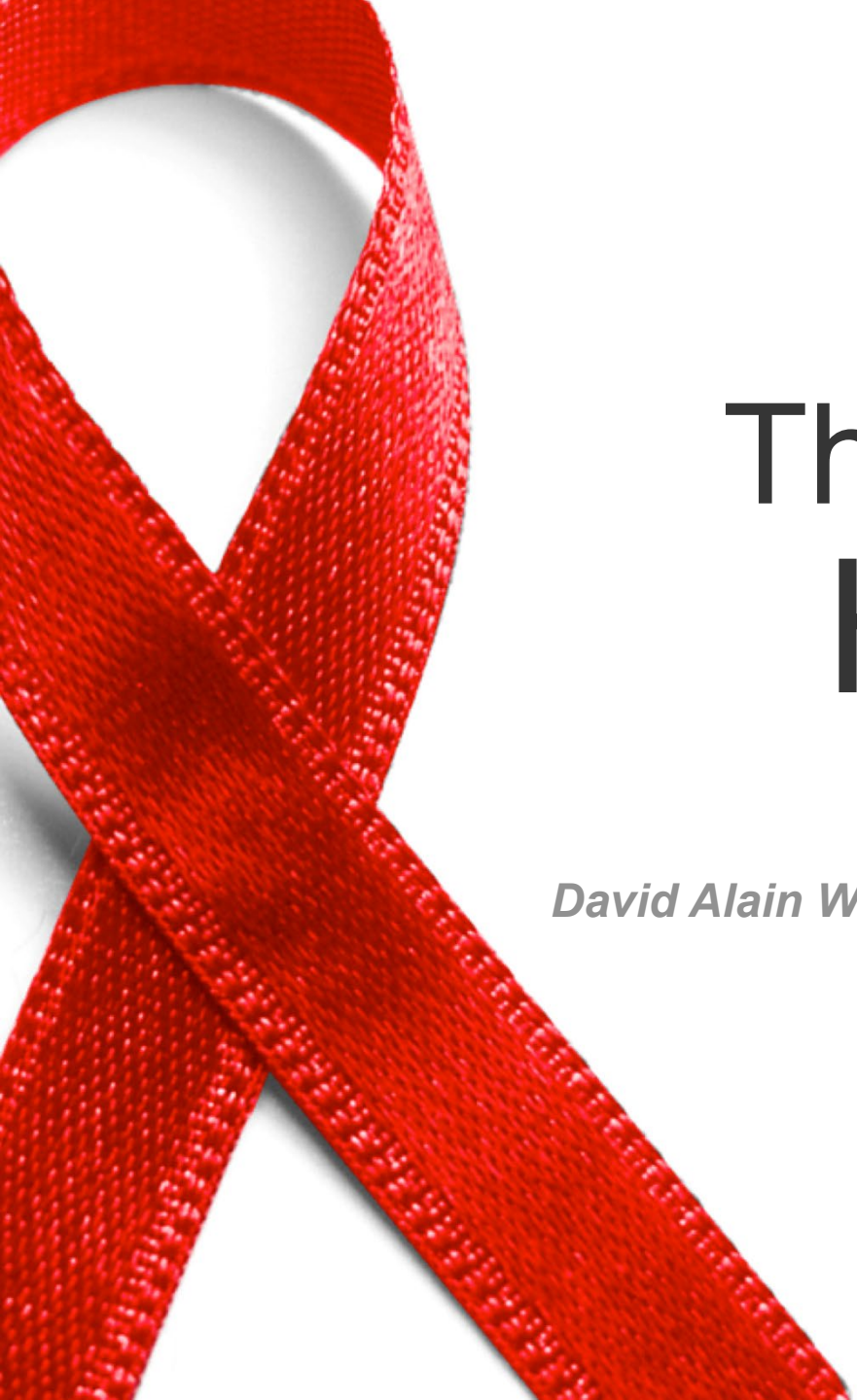


UNC
INSTITUTE FOR GLOBAL HEALTH
& INFECTIOUS DISEASES

The top 5 HIV Stories For 2018

David Alain Wohl, MD – The University of North Carolina

Webcast Wednesday

February, 6 2019

David Alain Wohl, MD

Professor of Medicine

Site Leader, The Global HIV Prevention and Treatment Research Site
Co-Director, North Carolina AIDS Training & Education Center
Co-Director, Viral Hemorrhagic Fever Clinical Research Group

Institute for Global Health & Infectious Diseases
The University of North Carolina (UNC) at Chapel Hill
School of Medicine

Dr. Wohl serves as UNC site PI for studies funded by Gilead Sciences, Merck, and ViiV. Additional research funding is received from the NIH.

He participates in advisory boards for Gilead, Merck, Janssen, and ViiV.

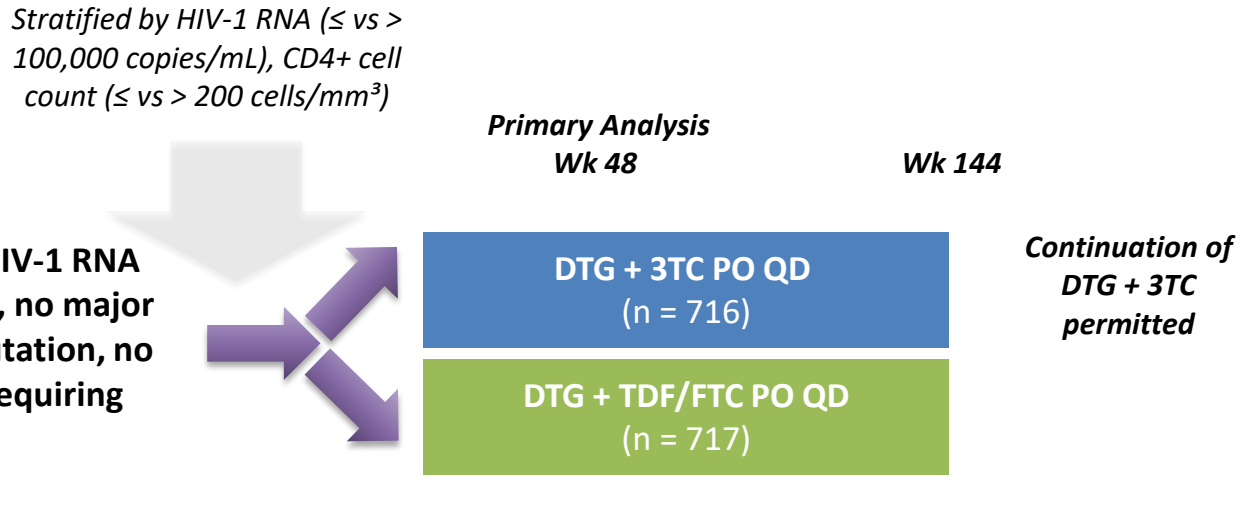
Objective and Caveats

- Describe major developments in the world of clinical HIV care from 2018

- The selection of top stories is completely subjective and reflects personal biases and experiences rooted in the clinical care of people living with and at risk for HIV in the US South
- It is fully acknowledged that a completely different selection could be generated others with different biases and experiences that would be just as good as, and probably better, than that presented here

GEMINI-1 and -2: DTG + 3TC vs DTG + TDF/FTC in Treatment-Naive Patients

Parallel, international, randomized, **double-blind** phase III noninferiority studies



Primary endpoint: HIV-1 RNA < 50 copies/mL at Week 48 by FDA Snapshot analysis

- Noninferiority margin: -10%

Cahn P, et al. AIDS 2018. Abstract TUAB0106LB; Lancet 2018.

GEMINI-1 and -2: Baseline Characteristics

Articles

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Background Effective two-drug regimens could decrease long-term drug exposure and toxicity with HIV-1 antiretroviral therapy (ART). We therefore aimed to evaluate the efficacy and safety of a two-drug regimen compared with a three-drug regimen for the treatment of HIV-1 infection in ART-naive adults

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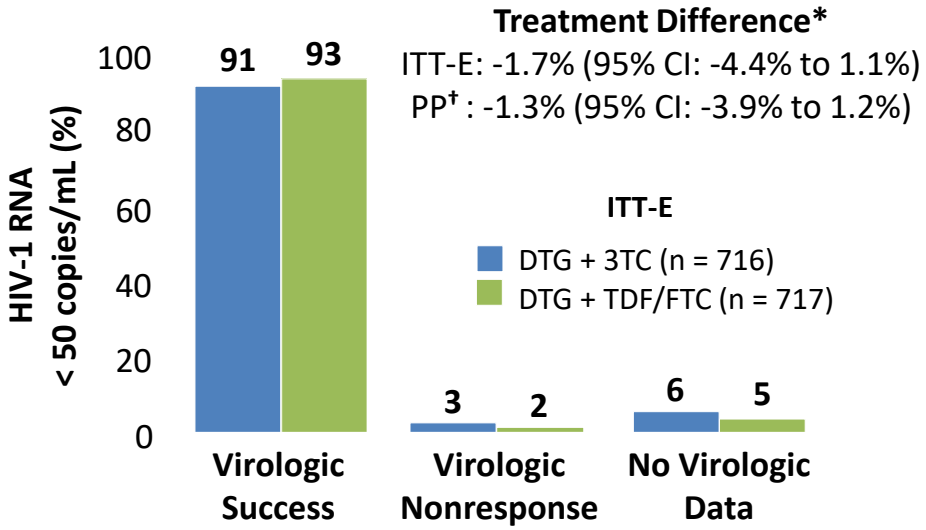
	Two-drug regimen group (n=716)	Three-drug regimen group (n=717)
Age (years)	32·0 (26–40)	33·0 (26–42)
<35	420 (59%)	408 (57%)
35 to <50	231 (32%)	229 (32%)
≥50	65 (9%)	80 (11%)
Sex		
Female	113 (16%)	98 (14%)
Male	603 (84%)	619 (86%)
Ethnicity		
Hispanic or Latino	215 (30%)	232 (32%)
Not Hispanic or Latino	501 (70%)	485 (68%)
Race		
White	480 (67%)	497 (69%)
African	99 (14%)	76 (11%)
Asian	71 (10%)	72 (10%)
American Indian or Alaskan Native	49 (7%)	52 (7%)
Multiracial	15 (2%)	15 (2%)
Native Hawaiian or Pacific Islander	2 (<1%)	5 (<1%)
HIV-1 RNA (log_{10} copies per mL)	4·42 (0·66)	4·45 (0·65)
≤100 000 copies per mL	576 (80%)	564 (79%)
>100 000 copies per mL	140 (20%)	153 (21%)
CD4+ cell count (cells per µL)	462·0 (219·2)	461·3 (213·1)
≤200 cells per µL	63 (9%)	55 (8%)
>200 cells per µL	653 (91%)	662 (92%)

GEMINI-1 and -2: DTG + 3TC Noninferior to DTG + TDF/FTC in Treatment-Naive Patients at Wk 48



*Adjusted for HIV-1 RNA (≤ vs > 100,000 copies/mL), CD4+ cell count(≤ vs > 200 cells/mm^3), and study (GEMINI-1 vs GEMINI-2). †PP = the ITT-E population excluding significant protocol violations.

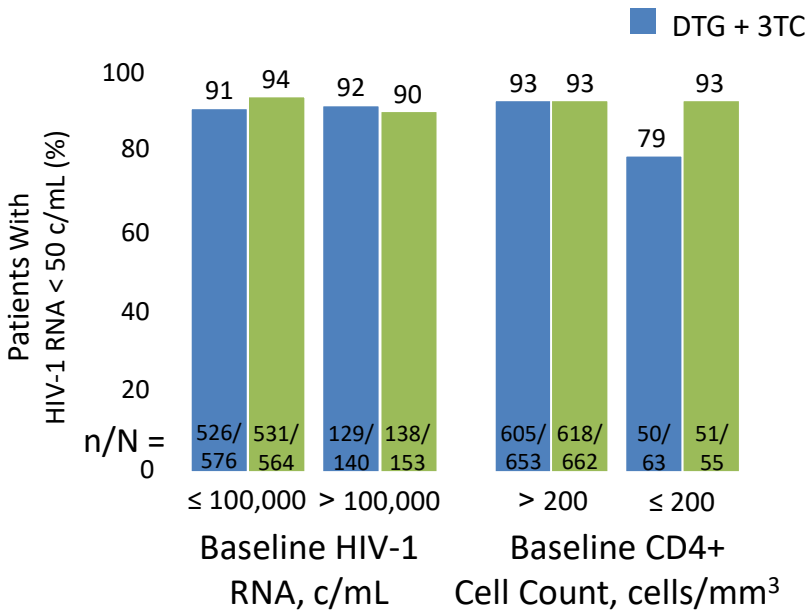
- No treatment-emergent INSTI or NRTI mutations in patients with VF in either arm
- Confirmed VF with DTG+3TC: n=6
- Confirmed VF with DTG+TDF/FTC: n=4
- Bone and kidney safety markers more favorable with DTG + 3TC vs DTG + TDF/FTC

DTG + 3TC was noninferior vs 3-drug therapy, no resistance in either arm

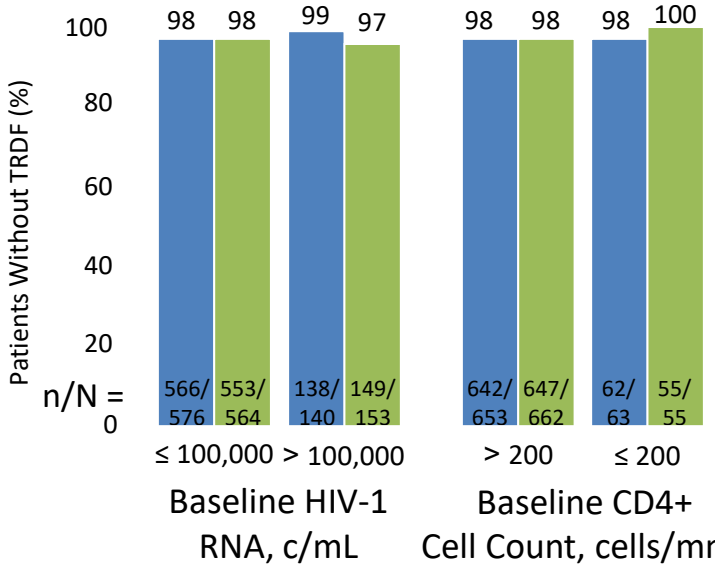
Cahn P, et al. AIDS 2018. Abstract TUAB0106LB.

GEMINI-1 and -2: Virologic Response at Wk 48 by Baseline HIV-1 RNA and CD4+ Cell Count

Virologic Outcomes by FDA Snapshot Analysis



Virologic Outcomes by TRDF Analysis



Treatment Related Discontinuation = Failure (TRDF) includes confirmed virologic withdrawal, withdrawal for lack of efficacy or treatment-related AEs, and participants meeting protocol-defined stopping criteria

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GEMINI-1 and -2: Non-response in low CD4+ cell count stratum

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	Two-drug regimen (n=63)	Three-drug regimen (n=55)
HIV-1 RNA ≥50 copies per mL*	3 (5%)	1 (2%)
Discontinued because of non-treatment-related adverse event	2 (3%)	0
Protocol violations	2 (3%)	0
Lost to follow-up	2 (3%)	1 (2%)
Confirmed virological withdrawal	1 (2%)	0
Withdrew consent	1 (2%)	1 (2%)
Withdrew to start HCV treatment	1 (2%)	0
Unplanned change in ART	1 (2%)	0
Investigator discretion	0	1 (2%)

Data are n (%). HCV=hepatitis C virus. ART=antiretroviral therapy. *Two of three participants in the two-drug regimen group and one participant in the three-drug regimen group resuppressed.

Table 4: **Reasons for Snapshot non-response in the subgroup of participants with baseline CD4+ cell count of 200 cells per µL or less**

GEMINI-1 and -2: Adverse events

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	Two-drug regimen (n=716)	Three-drug regimen (n=717)
Any adverse event	543 (76%)	579 (81%)
Adverse events occurring in ≥4% of participants in either group		
Headache	71 (10%)	75 (10%)
Diarrhoea	68 (9%)	77 (11%)
Nasopharyngitis	55 (8%)	78 (11%)
Upper respiratory tract infection	56 (8%)	44 (6%)
Pharyngitis	36 (5%)	32 (4%)
Back pain	35 (5%)	31 (4%)
Nausea	27 (4%)	53 (7%)
Insomnia	27 (4%)	45 (6%)
Syphilis	27 (4%)	27 (4%)
Bronchitis	28 (4%)	21 (3%)
Influenza	22 (3%)	28 (4%)
Arthralgia	15 (2%)	26 (4%)
Fatal adverse events (grade 5)	2 (<1%)*	0
Drug-related adverse events	126 (18%)	169 (24%)
Grade 2–5†	42 (6%)	47 (7%)
Serious adverse events	50 (7%)	55 (8%)
Drug-related‡	4 (1%)	4 (1%)
Adverse events leading to permanent discontinuation of treatment or withdrawal from study§	15 (2%)	16 (2%)
Drug-related	6 (1%)	9 (1%)

A5353: DTG + 3TC as initial ART

Single-arm phase II study

Primary Endpoint
Wk 24

ART-naive with
HIV-1 RNA ≥ 1000 and < 500,000 copies/mL;
no RT, INSTI, major PI resistance mutations
(N = 120)

→ **DTG 50 mg + 3TC 300 mg**

Virologic Outcome at Wk 24, n (%)	Baseline HIV-1 RNA, copies/mL		Total (N = 120)
	> 100,000 (n = 37)	≤ 100,000 (n = 83)	
Success*	33 (89)	75 (90)	108 (90)
Nonsuccess	3 (8)	2 (2)	5 (4)
No data	1 (3)	6 (7)	7 (6)

*HIV-1 RNA < 50 copies/mL.

- n = 3 with protocol defined virologic failure
  - **1 with emergent M184V and R263R/K mixture**
  - All 3 pts had DTG levels reflective of suboptimal adherence

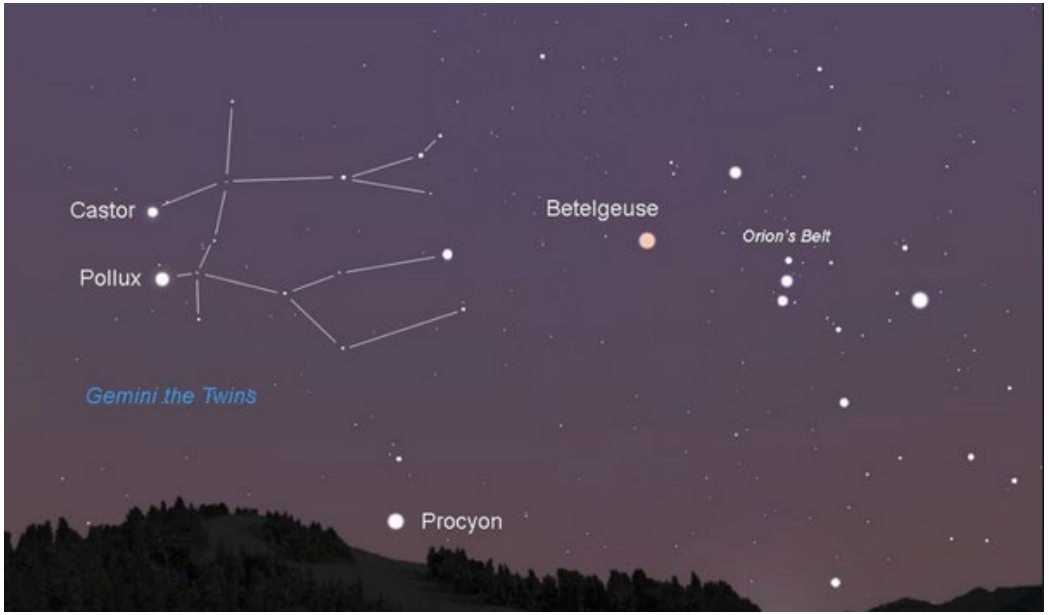
Two Drug HIV Therapy: Initial and Switch Therapy

Study	Initial or Switch	N	Regimen	Results
GEMINI-1, -2	Initial	1433	DTG + 3TC	Noninferior efficacy vs DTG + FTC/TDF; no resistance at VF
ACTG 5353	Initial	120	DTG + 3TC	Encouraging efficacy; 1 patient with resistance at VF
LAMIDOL	Switch	110	DTG + 3TC	Encouraging efficacy
SALT	Switch	286	ATV/RTV + 3TC	Similar efficacy as ATV/RTV + 2 NRTIs
ATLAS-M	Switch	266	ATV/RTV + 3TC	Noninferior and superior efficacy vs ATV/RTV + 2 NRTIs
NEAT001/ANRS14	Initial	805	DRV/RTV + RAL	Similar efficacy as DRV/RTV + FTC/TDF except in hi VL, low CD4
ANDES	Initial	145	DRV/RTV + 3TC	Similar efficacy as DRV/RTV + 3TC/TDF at interim
SWORD-1, -2	Switch	1024	DTG + RPV	Non-inferior to continued ART

Cahn P, et al. AIDS 2018. Abstract TUAB0106LB.; Taiwo BO, et al. IAS 2017. Abstract MOAB0107LB; Joly V, et al. CROI 2017. Abstract 458; Perez-Molina JA, et al. Lancet Infect Dis. 2015;15:775-784; Di Giambenedetto S, et al. J Antimicrob Chemother. 2017;72:1163-1171; Sued O, et al. IAS 2017. Abstract MOAB0106LB; Raffi F, et al. Lancet. 2014;384:1942-1951; Llibre JM, et al. Lancet. 2018;391:839-849

Significance of GEMINI

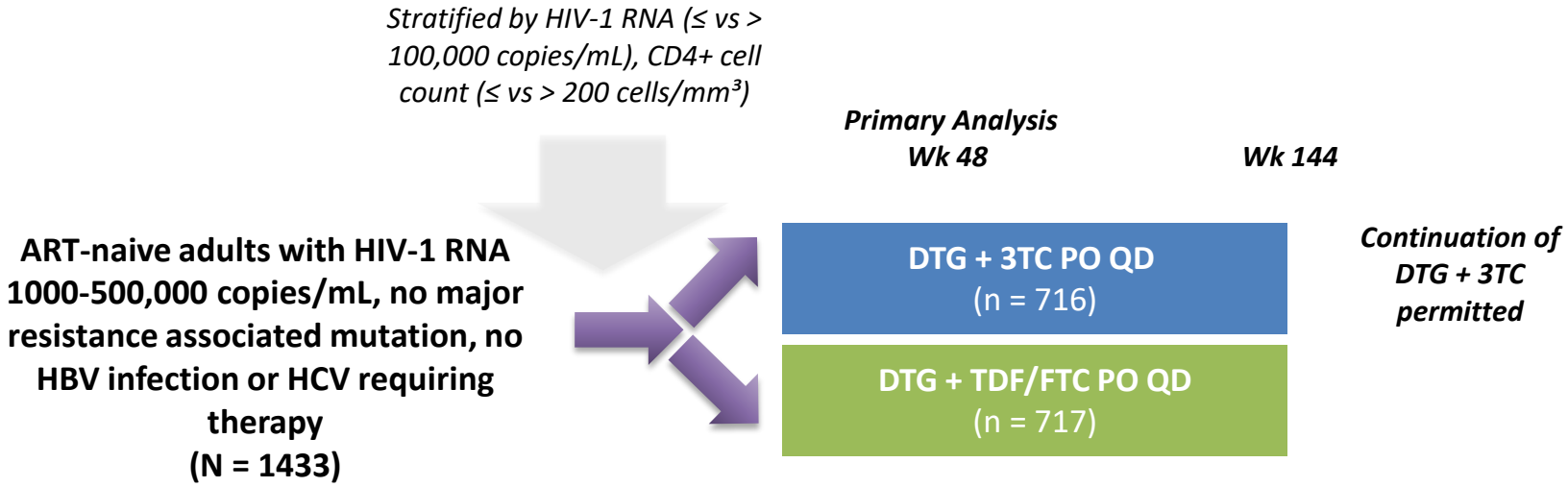
- **Will HIV care providers embrace two-drug therapy as initial therapy?**
- **What will the drivers be?**
  - **Toxicity**
  - **Cost**
- **Will patients care?**



2

Dolutegravir and Neural Tube Birth Defects

Parallel, international, randomized, **double-blind** phase III noninferiority studies



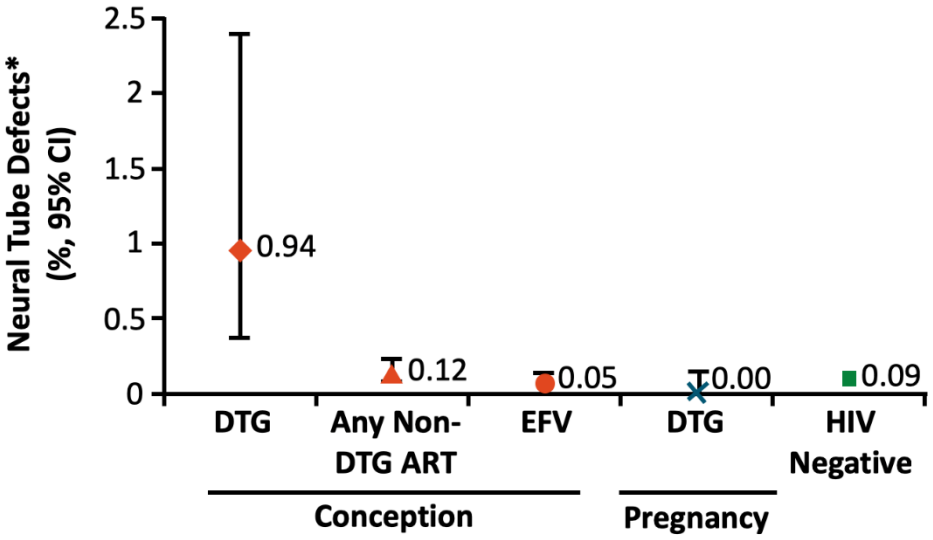
Primary endpoint: HIV-1 RNA < 50 copies/mL at Week 48 by FDA Snapshot analysis

- Noninferiority margin: -10%

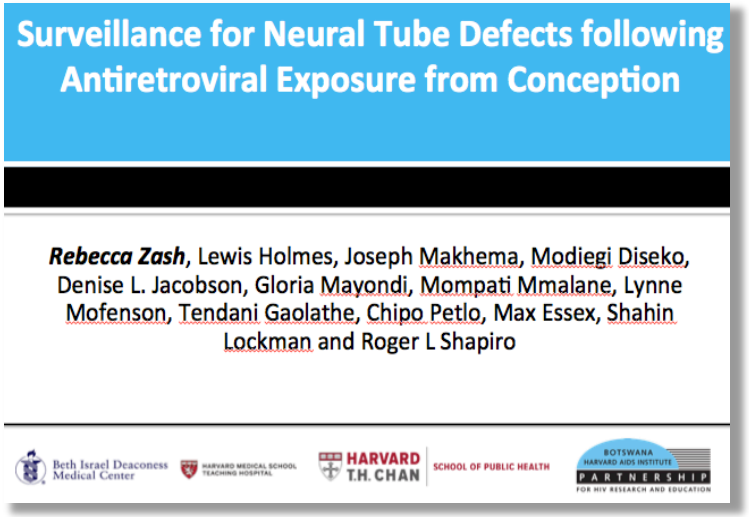
Cahn P, et al. AIDS 2018. Abstract TUAB0106LB; Lancet 2018.

Tsepamo: Neural Tube Defects (NTD) and DTG Exposure

Unplanned analysis of ongoing birth outcomes surveillance study among Botswanan women ± HIV infection[1,2]



*In 89,064 births as of **May 1, 2018.**



1. Zash R, et al. N Engl J Med. 2018;[Epub ahead of print]. 2. Zash R, et al. AIDS 2018. Session TUSY15.

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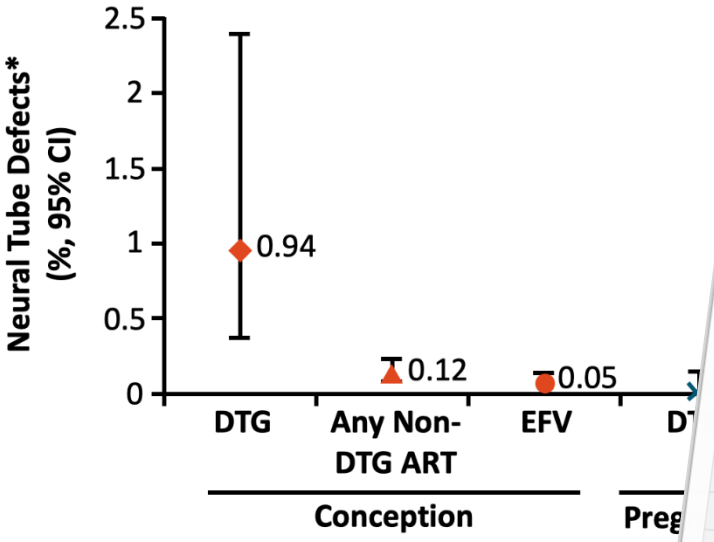

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1. Zash R, et al. N Engl J Med. 2018;[Epub ahead of print]. 2. Zash R, et al. AIDS 2018. Session TUSY15.

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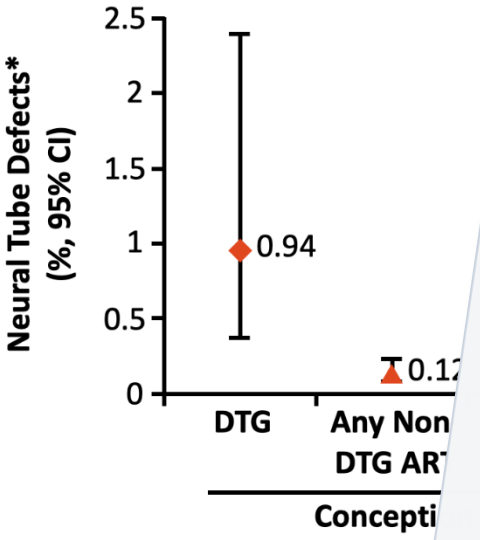

*In 89,064 births as of **May 1, 20**

1. Zash R, et al. N Engl J Med. 2018;[Epub ahead of

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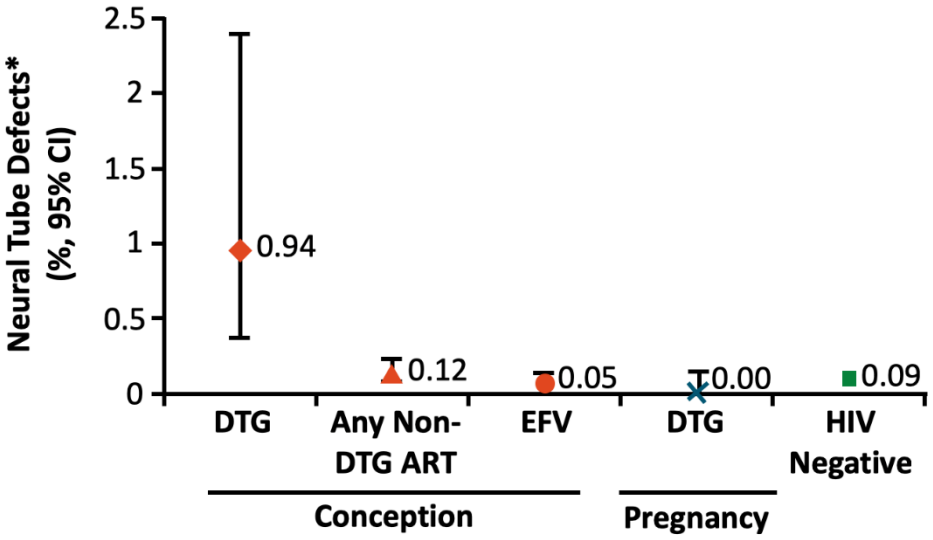


*In 89,064 births as of **May 1, 2018.**

- At latest analysis on **July 15, 2018**[2]
  - NTD prevalence with DTG exposure **at conception**: 4/596 (0.67%; 95% CI: 0.26% to 1.7%)
  - NTD prevalence with DTG started **during pregnancy**: 1/3104 (0.03%; 95% CI: 0.01% to 0.18%)
- Next formal analysis to occur after **March 31, 2019,** which will include 72% of national births

1. Zash R, et al. N Engl J Med. 2018;[Epub ahead of print]. 2. Zash R, et al. AIDS 2018. Session TUSY15.

What is Tsepamo?

Background

- **The Tsepamo Study started in August 2014**
  - Birth Outcomes Surveillance
  - Funding: NIH/NICHD (R01, R Shapiro PI)

- **Primary aims:**
  - (1) Evaluate adverse birth outcomes by HIV-status and ART regimen
  - **(2) Determine if there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception**

What is Tsepamo?

Background

Study Setting: Botswana

1. Ability to capture outcomes

- Antenatal record available at delivery for >99% of women
- >95% of women deliver in a healthcare facility
- Early termination extremely rare

2. Large # of exposures

- High HIV prevalence (~25%)
- High uptake of ART in pregnancy (>90%)
- Multiple ART regimens in use concurrently
  - 52% start prior to conception

What is Tsepamo?

Background

Study Setting: Botswana

Study Population: Methods

Tsepamo takes place at 8 of the largest maternity wards in Botswana

- **~45% of the total births in the country**

Research assistants abstract data from the obstetric cards for all in-hospital deliveries.

What is Tsepamo?

Background

Study Setting: Botswana

Study Population: Methods

Data Collection: Congenital Abnormalities

- Hospital-based midwives trained by Tsepamo staff on infant surface exam/congenital abnormalities using materials developed by the WHO

- When an abnormality is noted, the midwife contacts the Tsepamo research assistant who consents mother for a photograph of the abnormality
  - Photographs are reviewed by an experienced medical geneticist, blinded to exposure information

What is Tsepamo?

Background

Study Setting: Botswana

Study Population: Methods

Data Collection: Congenital Abnormalities

Analysis Plan: 2014

- Original plan was for a 4-year analysis in August 2018 to compare the prevalence of neural tube defects in live-born and stillbirths (combined) among women on EFV at conception and other exposure groups
- In 2016, Botswana switched first line ART from TDF/FTC/EFV to TDF/FTC/dolutegravir (DTG) for all adults (including pregnant women)

Recent results from DTG started *during* pregnancy

- Compared to EFV, no increased risk of adverse birth outcomes (stillbirth, preterm birth, small for gestational age, or neonatal death) among 1729 women who started DTG *during pregnancy*[1]
  - No increased risk of major congenital abnormalities identified in the small number (N=280) who started DTG during the first trimester

1. Zash et al *Lancet GH* 2018

Recent results from DTG started *during* pregnancy

Analysis Update

- Asked to provide any preliminary data available for May 2018 WHO HIV guidelines committee for outcomes among women ***who started DTG before pregnancy (pre-conception)***
  - Upon review of data we identified more neural tube defects than expected

- We then performed an unplanned analysis of NTDs comparing births to women on DTG-based ART started prior to conception to other exposure groups

1. Zash et al *Lancet GH* 2018

Recent results from DTG started *during* pregnancy

Analysis Update

Results: Neural Tube Defects

- **86 NTDs identified in 88,755 births**
  - 0.10% (95% CI 0.08%, 0.12%)
  - 42 meningocele/myelomeningocele, 30 anencephaly, 13 encephalocele and 1 iniencephaly
  - 57% had photos, 43% descriptions
- **N=22 (25%) of all NTDs occurred among stillbirths**
- Among live-born babies with NTDs, 25 (39%) died within 28 days, and 1 had unknown vital status

Recent results from DTG started *during* pregnancy

Analysis Update

Results: Neural Tube Defects

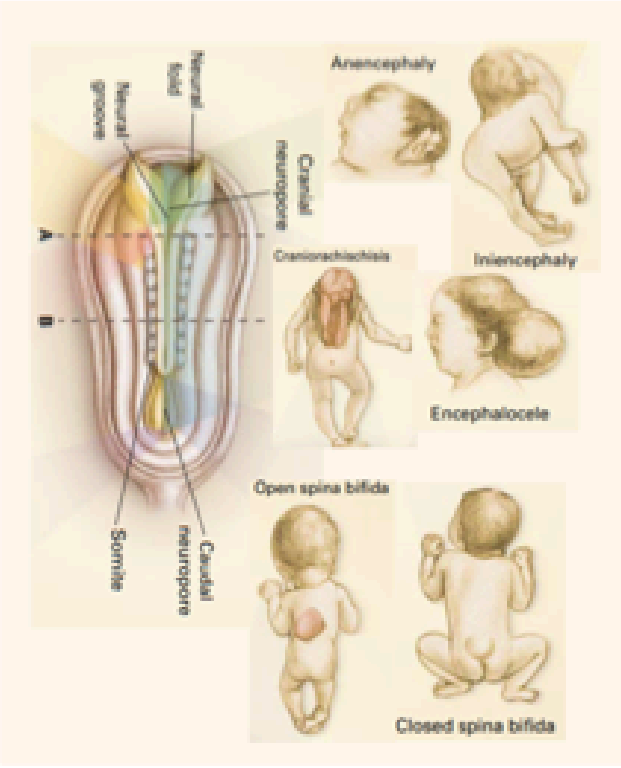
Results: Neural Tube Defect by Exposure

Deliveries up to 1 MAY 2018

- **DTG at conception**:
  - 4/426 (0.94%; 95%CI 0.37%, 2.4%)
- **Non-DTG ART at conception:**
  - 14/11,300 (0.12%; 95%CI 0.07%, 0.21%)
- **EFV at conception:**
  - 3/5787 (0.05%; 95%CI 0.02%, 0.15%)
- **DTG started during pregnancy:**
  - 0/2812 (0.00%; 95%CI 0.0%, 0.13%)
- **Non-DTG ART started during pregnancy:**
  - 3/5624 (0.05%, 95% CI 0.02%, 0.16%)
- **HIV-uninfected**
  - 61/66057 (0.09%, 95%CI 0.07%, 0.12%)

Neural Tube Defects on DTG at conception

- The 4 defects identified were all pre-specified as NTDs, and included:
  - encephalocele (with photo)
  - anencephaly (no photo)
  - myelomeningocele (with photo)
  - iniencephaly (with photo)
- None of the women were reported to be on folate supplementation PRIOR to pregnancy
  - Botswana does not fortify grains with folate
- Review of maternal data found no other risk factor for NTD present



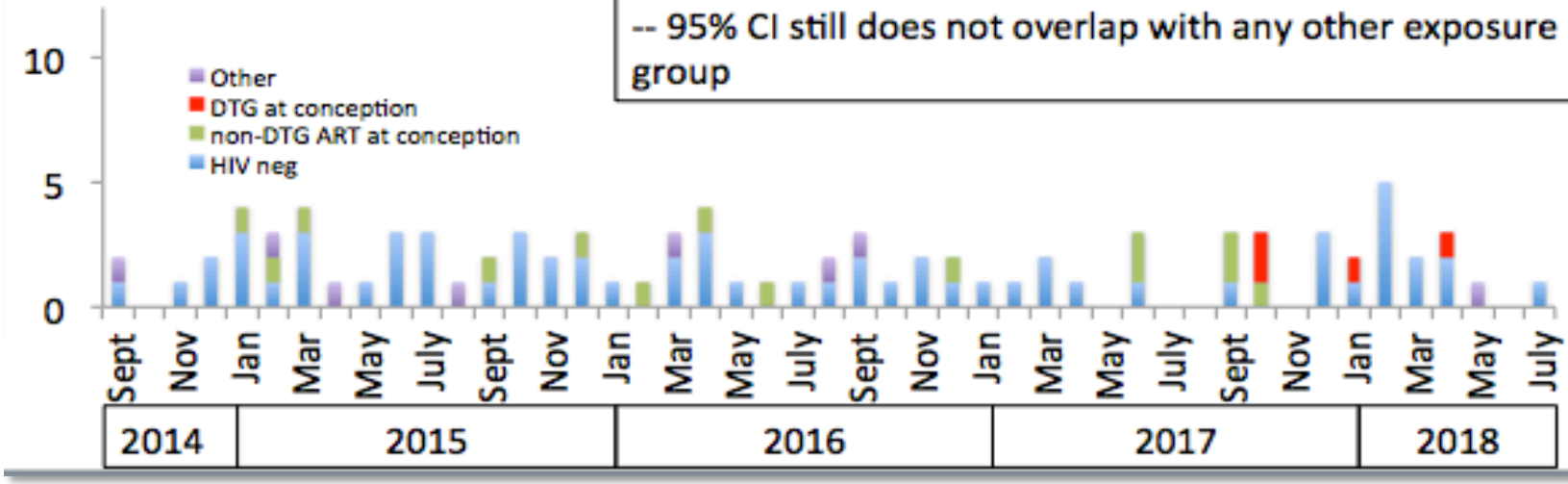
NEJM Botto 1999

Neural Tube Defects on DTG at conception

Update since 1 May 2018

- From 1 May-15 July, there were **2 more NTDs;** 1 in an infant exposed to **DTG *started during pregnancy*** (8 weeks GA) and 1 birth to an **HIV-uninfected** woman
  - NTDs in DTG started in pregnancy: 1/3104 (0.03%, 95% CI 0.01%, 0.18%)

Updated prevalence of DTG exposure at conception is 4/596 (0.67%, 95% CI 0.26%, 1.7%)
-- 95% CI still does not overlap with any other exposure group



Neural Tube Defects on DTG at conception

Update since 1 May 2018

Projections for March 2019

- **With expanded surveillance to 18 sites, we estimate ~ 1226 births with exposure to DTG from conception by end of March 2019**

With 0 more NTDs, the lower CI overlaps with the upper CI for other ART at conception (0.21%), EFV at conception (0.15%) and with HIV-uninfected (0.13%)

With 1 more NTD, the lower CI overlaps with the upper CI for other ART at conception (0.21%)

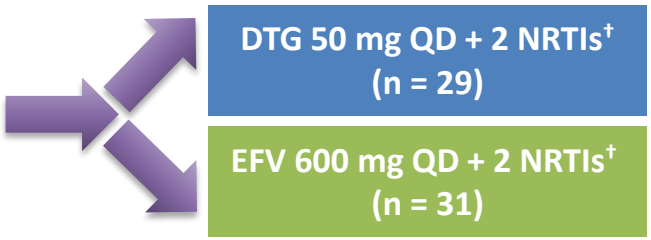
Number of total NTDs	Prevalence	95% Confidence Interval
4 in 1226	0.33%	0.13%, 0.84%
5 in 1226	0.41%	0.18%,0.95%
6 in 1226	0.49%	0.22%, 1.1%
7 in 1226	0.57%	0.28%, 1.2%
8 in 1226	0.65%	0.33%,1.3%
9 in 1226	0.73%	0.38%, 1.4%
10 in 1226	0.82%	0.45%,1.5%

DolPHIN-1: DTG or EFV + NRTIs in Pregnant Women Initiating ART During Third Trimester

- Randomized, open-label phase II/III pilot study in South Africa and Uganda
- Primary endpoint: maternal pharmacokinetics of DTG
- Secondary endpoints: HIV-1 RNA < 50 copies/mL at 2 wks postpartum, safety

Adult women with untreated HIV presenting to antenatal clinics at ≥ 28-36 wks of gestation;
no ARVs in prior 6 mos or INSTI experience;
no depression; Hb ≥ 8 g/dL, eGFR ≥ 50 mL/min, ALT ≤ 5 x ULN; no active HBV*
(N = 60)

2 wks postpartum

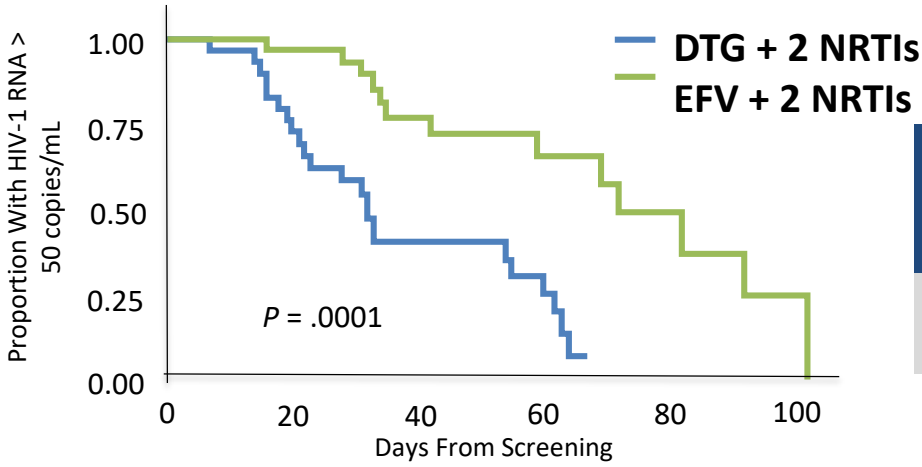


All patients subsequently received EFV + 2 NRTIs; post-switch follow-up for up to 6 mos

*EFV-based regimen begun immediately at diagnosis per national guidelines, randomization at a median of 3 days (range: 1-8) later.
†TDF/FTC in South Africa; TDF/3TC in Uganda.

Orrell C, et al. AIDS 2018. Abstract THAB0307LB. Waitt C, et al. CROI 2018. Abstract 807. ClinicalTrials.gov. NCT02245022.

DolPHIN-1: Virologic Response



HIV-1 RNA < 50 copies/mL, n (%)	DTG + 2 NRTIs (n = 29)	EFV + 2 NRTIs (n = 31)	P Value
2 wks postpartum	20 (69.0)	12 (38.7)	.02

Median time to virologic suppression approximately halved with DTG vs EFV

Orrell C, et al. AIDS 2018. Abstract THAB0307LB.

Significance of Tsepamo

DTG may be used | Use DTG or another option | Do not use DTG

Currently Receiving DTG?	Pregnancy Status	Recommendation on DTG		
		DHHS[1]	BHIVA[2]	WHO[3]
No	Early pregnancy*			
	Late pregnancy†			
	Childbearing potential, no contraception			
	Childbearing potential, effective contraception			
Yes	Early pregnancy*			
	Late pregnancy†			
	Childbearing potential, no contraception			
	Childbearing potential, effective contraception			

*DHHS: < 8 wks from last menstrual period; BHIVA and WHO: first trimester.
†DHHS: ≥ 8 wks from last menstrual period; BHIVA and WHO: second and third trimesters.

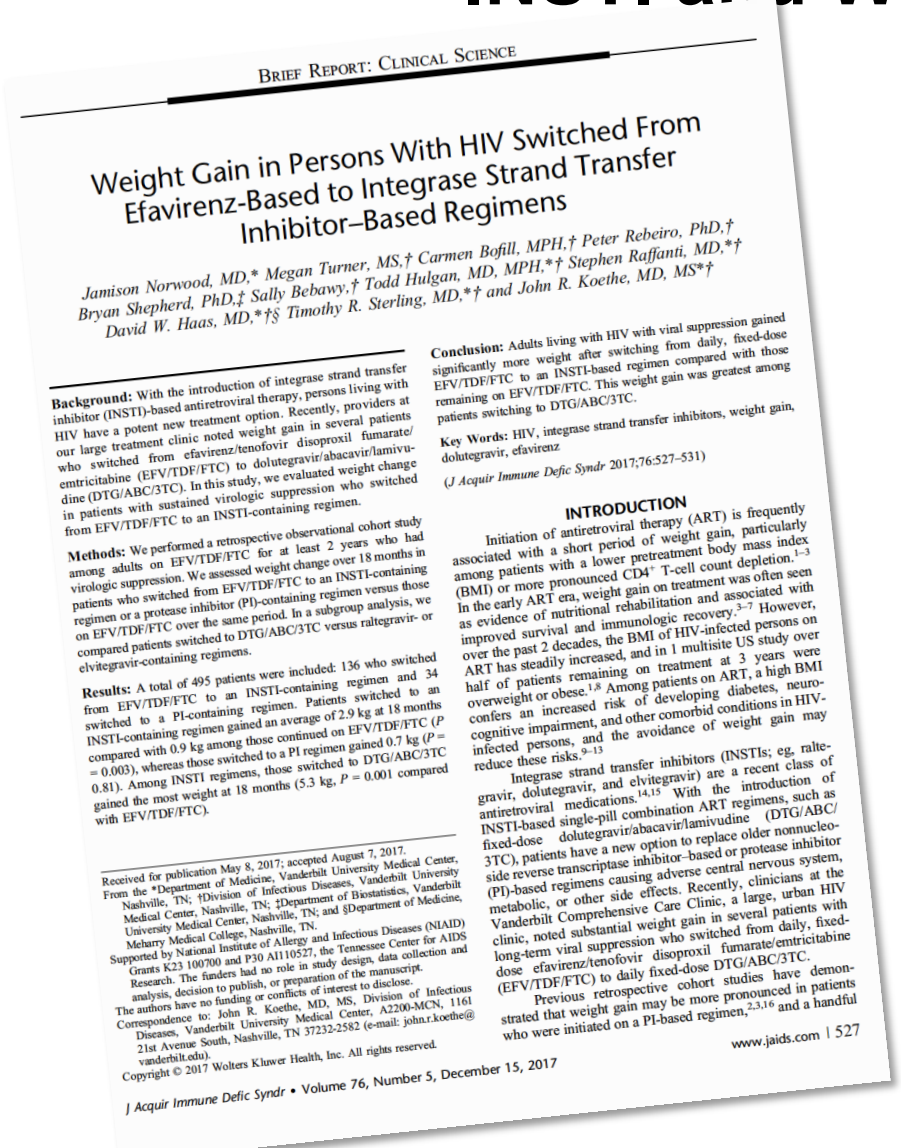
1. DHHS. Recommendations regarding the use of dolutegravir in adults and adolescents with HIV who are pregnant or of child-bearing potential. Available at: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential.
2. BHIVA. Statement on potential safety signal in infants born to women conceiving on dolutegravir (on behalf of the BHIVA HIV in Pregnancy Guidelines Committee). Available at: http://www.bhiva.org/BHIVA-statement-on-Dolutegravir.aspx.
3. WHO. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidance. Available at: http://www.who.int/hiv/pub/guidelines/ARV2018update/en/.

Significance of Tsepamo

- How do we use DTG in women who are able to become pregnant?
  - Already on DTG
  - Initiating therapy
- Do these results extend to other INSTI?
- What are best treatment options for women who are pregnant or planning to be?

3

INSTI and Weight Gain



BRIEF REPORT: CLINICAL SCIENCE

Weight Gain in Persons With HIV Switched From Efavirenz-Based to Integrase Strand Transfer Inhibitor–Based Regimens

Jamison Norwood, MD, Megan Turner, MS,† Carmen Bofill, MPH,† Peter Rebeiro, PhD,† Bryan Shepherd, PhD,‡ Sally Bebawy,† Todd Hulgan, MD, MPH,*† Stephen Raffanti, MD,*† David W. Haas, MD,*†§ Timothy R. Sterling, MD,*† and John R. Koethe, MD, MS*†*

Background: With the introduction of integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy, persons living with HIV have a potent new treatment option. Recently, providers at our large treatment clinic noted weight gain in several patients who switched from efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) to dolutegravir/abacavir/lamivudine (DTG/ABC/3TC). In this study, we evaluated weight change in patients with sustained virologic suppression who switched from EFV/TDF/FTC to an INSTI-containing regimen.

Methods: We performed a retrospective observational cohort study among adults on EFV/TDF/FTC for at least 2 years who had virologic suppression. We assessed weight change over 18 months in patients who switched from EFV/TDF/FTC to an INSTI-containing regimen or a protease inhibitor (PI)-containing regimen versus those on EFV/TDF/FTC over the same period. In a subgroup analysis, we compared patients switched to DTG/ABC/3TC versus raltegravir- or elvitegravir-containing regimens.

Results: A total of 495 patients were included: 136 who switched from EFV/TDF/FTC to an INSTI-containing regimen and 34 switched to a PI-containing regimen. Patients switched to an INSTI-containing regimen gained an average of 2.9 kg at 18 months compared with 0.9 kg among those continued on EFV/TDF/FTC ($P = 0.003$), whereas those switched to a PI regimen gained 0.7 kg ($P = 0.81$). Among INSTI regimens, those switched to DTG/ABC/3TC gained the most weight at 18 months (5.3 kg, $P = 0.001$ compared with EFV/TDF/FTC).

Conclusion: Adults living with HIV with viral suppression gained significantly more weight after switching from daily, fixed-dose EFV/TDF/FTC to an INSTI-based regimen compared with those remaining on EFV/TDF/FTC. This weight gain was greatest among patients switching to DTG/ABC/3TC.

Key Words: HIV, integrase strand transfer inhibitors, weight gain, dolutegravir, efavirenz

(*J Acquir Immune Defic Syndr* 2017;76:527–531)

INTRODUCTION

Initiation of antiretroviral therapy (ART) is frequently associated with a short period of weight gain, particularly among patients with a lower pretreatment body mass index (BMI) or more pronounced $CD4^+$ T-cell count depletion.[1–3] In the early ART era, weight gain on treatment was often seen as evidence of nutritional rehabilitation and associated with improved survival and immunologic recovery.[3–7] However, over the past 2 decades, the BMI of HIV-infected persons on ART has steadily increased, and in 1 multisite US study over half of patients remaining on treatment at 3 years were overweight or obese.[1,8] Among patients on ART, a high BMI confers an increased risk of developing diabetes, neurocognitive impairment, and other comorbid conditions in HIV-infected persons, and the avoidance of weight gain may reduce these risks.[9–13]

Integrase strand transfer inhibitors (INSTIs; eg, raltegravir, dolutegravir, and elvitegravir) are a recent class of antiretroviral medications.[14,15] With the introduction of INSTI-based single-pill combination ART regimens, such as fixed-dose dolutegravir/abacavir/lamivudine (DTG/ABC/3TC), patients have a new option to replace older nonnucleoside reverse transcriptase inhibitor–based or protease inhibitor (PI)-based regimens causing adverse central nervous system, metabolic, or other side effects. Recently, clinicians at the Vanderbilt Comprehensive Care Clinic, a large, urban HIV clinic, noted substantial weight gain in several patients with long-term viral suppression who switched from daily, fixed-dose efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) to daily fixed-dose DTG/ABC/3TC.

Previous retrospective cohort studies have demonstrated that weight gain may be more pronounced in patients who were initiated on a PI-based regimen,[2,3,16] and a handful

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From the *Department of Medicine, †Division of Infectious Diseases, ‡Department of Biostatistics, §Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; and Meharry Medical College, Nashville, TN.
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3

INSTI and Weight Gain

BRIEF REPORT: CLINICAL SCIENCE

Weight Gain in Persons With
Efavirenz-Based to Integra
Inhibitor–Based

Jamison Norwood, MD,* Megan Turner, MS,† Carm
Bryan Shepherd, PhD,‡ Sally Bebawy,† Todd Hulgan,
David W. Haas, MD,*†§ Timothy R. Sterling, MD,

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The authors have no funding or conflicts of interest to disclose.
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Journal of Antimicrobial Chemotherapy

Obesity following ART initiation is common and influenced by both traditional and HIV-/ART-specific risk factors

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Background: Obesity rates are increasing among HIV-infected individuals, but risk factors for obesity development on ART remain unclear.

Objectives: In a cohort of HIV-infected adults in Rio de Janeiro, Brazil, we aimed to determine obesity rates before and after ART initiation and to analyse risk factors for obesity on ART.

Methods: We retrospectively analysed data from individuals initiating ART between 2000 and 2015. BMI was calculated at baseline (time of ART initiation). Participants who were non-obese at baseline and had ≥90 days of ART exposure were followed until the development of obesity or the end of follow-up. Obesity incidence rates were estimated using Poisson regression models and risk factors were assessed using Cox regression models.

Results: Of participants analysed at baseline ($n = 1794$), 61.3% were male, 48.3% were white and 7.9% were obese. Among participants followed longitudinally ($n = 1567$), 66.2% primarily used an NNRTI, 32.9% a PI and 0.9% an integrase strand transfer inhibitor (INSTI); 18.3% developed obesity and obesity incidence was 37.4 per 1000 person-years. In multivariable analysis, the greatest risk factor for developing obesity was the use of an INSTI as the primary ART core drug (adjusted HR 7.12, $P < 0.0001$); other risk factors included younger age, female sex, higher baseline BMI, lower baseline CD4+ T lymphocyte count, higher baseline HIV-1 RNA, hypertension and diabetes mellitus.

Conclusions: Obesity following ART initiation is frequent among HIV-infected adults. Key risk factors include female sex, HIV disease severity and INSTI use. Further research regarding the association between INSTIs and the development of obesity is needed.

Introduction

Advancements in ART have led to vast improvements in the general health and life expectancy of HIV-infected individuals.[1–3] Among individuals on suppressive ART, wasting has become less common and recent studies from both upper- and lower-income countries report weight gain irrespective of ART type.[4–8] Additionally, many countries have reported an increasing prevalence of overweight and obese states in HIV-infected persons even prior to ART initiation, consistent with trends in the general population.[6,9] As obesity rates rise, so does the risk for obesity-related complications.[10–13] This is particularly worrisome as, even in the absence of obesity, HIV-infected individuals are already at high risk of non-AIDS events such as cardiovascular and fatty liver disease.[14–16]

Among HIV-infected individuals initiating ART, female sex,[4,17] lower baseline CD4+ T lymphocyte counts[4,17,18] and a lower baseline BMI[4,6] have been associated with subsequent weight gain. However, associations between specific ART regimens and weight gain/obesity remain controversial.[5,17–19]

In a large cohort of HIV-infected, ART-treated adults in Rio de Janeiro, Brazil, we aimed to calculate the prevalence of obesity prior to ART initiation and the incidence of obesity after ART initiation. Additionally, we aimed to determine specific risk factors associated with the development of obesity after ART initiation,

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INSTI and Weight Gain

BRIEF REPORT: CLINICAL SCIENCE

Weight Gain in Persons With
Efavirenz-Based to Integra
Inhibitor–Based

Jamison Norwood, MD,* Megan Turner, MS,† Carm
Bryan Shepherd, PhD,‡ Sally Bebawy,† Todd Hulgan,
David W. Haas, MD,*†§ Timothy R. Sterling, MD,

Background: With the introduction of integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy, persons living with HIV have a potent new treatment option. Recently, providers at our large treatment clinic noted weight gain in several patients who switched from efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) to dolutegravir/abacavir/lamivudine (DTG/ABC/3TC). In this study, we evaluated weight change in patients with sustained virologic suppression who switched from EFV/TDF/FTC to an INSTI-containing regimen.

Methods: We performed a retrospective observational cohort study among adults on EFV/TDF/FTC for at least 2 years who had virologic suppression. We assessed weight change over 18 months in patients who switched from EFV/TDF/FTC to an INSTI-containing regimen or a protease inhibitor (PI)-containing regimen versus those on EFV/TDF/FTC over the same period. In a subgroup analysis, we compared patients switched to DTG/ABC/3TC versus raltegravir- or elvitegravir-containing regimens.

Results: A total of 495 patients were included: 136 who switched from EFV/TDF/FTC to an INSTI-containing regimen and 34 switched to a PI-containing regimen. Patients switched to an INSTI-containing regimen gained an average of 2.9 kg at 18 months compared with 0.9 kg among those continued on EFV/TDF/FTC ($P = 0.003$), whereas those switched to a PI regimen gained 0.7 kg ($P = 0.81$). Among INSTI regimens, those switched to DTG/ABC/3TC gained the most weight at 18 months (5.3 kg, $P = 0.001$ compared with EFV/TDF/FTC).

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Obesity following ART initiation is common
traditional and HIV-/ART-specific

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Valdilea G. Veloso[2], Jordan E. Lake[1,3]† and Beatri

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Methods: We retrospectively analysed data from individuals initiating ART
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INSTI as the primary ART core drug (adjusted HR 7.12, $P < 0.0001$); other
female sex, higher baseline BMI, lower baseline CD4+ T lymphocyte count, hi
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Conclusions: Obesity following ART initiation is frequent among HIV-infecte
male sex, HIV disease severity and INSTI use. Further research regarding the
development of obesity is needed.

Introduction

Advancements in ART have led to vast improvements in the general health and life expectancy of HIV-infected individuals.[1–3] Among individuals on suppressive ART, wasting has become less common and recent studies from both upper- and lower-income countries report weight gain irrespective of ART type.[4–8] Additionally, many countries have reported an increasing prevalence of overweight and obese states in HIV-infected persons even prior to ART initiation, consistent with trends in the general population.[6,9] As obesity rates rise, so does the risk for obesity-related complications.[10–13] This is particularly worrisome as, even in the absence of obesity, HIV-infected individu
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gain/obesity remain
In a large cohort
Janeiro, Brazil, we c
prior to ART initiatio
ation. Additionally,
associated with the

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VIEWPOINT

Are new antiretroviral treatments increasing the risks of clinical obesity?

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Abstract

There is growing evidence that the use of integrase inhibitors could lead to statistically significant increases in body weight and even clinical obesity, although it is unclear whether these changes are clinically significant. The effects of integrase inhibitors on body weight need to be analysed for women and by race, because current evidence suggests different effects. Potential additional effects of NRTIs on body weight need to be evaluated. Combined, standardised analyses of Phase 3 and independent clinical trials, with endpoints following the US Food and Drug Administration (FDA) guidelines where feasible, should be conducted to answer this question definitively. Analyses should also include a range of laboratory markers of cardiovascular risk, as proposed by the FDA.

Keywords: antiretroviral therapy, integrase inhibitors, obesity, raltegravir, dolutegravir, bictegravir

Introduction

There is growing evidence that the use of integrase inhibitors could lead to statistically significant increases in body weight and even clinical obesity. These effects seem to be most pronounced in black people and women; the use of tenofovir disoproxil fumarate (tenofovir DF) seems to lessen these effects, compared to the use of tenofovir alafenamide (tenofovir AF), abacavir or nucleoside analogue- (NRTI) sparing treatments.

Before the widespread introduction of integrase inhibitors, the US NA-ACCORD study, including over 14,000 individuals, described weight gains on first-line ART in a 2015 analysis. After 3 years on ART, 22% of individuals with a normal body mass index (BMI, 18.5–24.9 kg/m^2) at baseline had become overweight (BMI 25–29.9 kg/m^2) and 18% of those overweight at baseline had become obese (BMI >30). These increases in BMI were largest for women and, for some subgroups, greater than age-matched population controls [1]. Among people without HIV, life expectancy is 4 years shorter for those with a BMI >30, compared with people with a normal BMI [2]. However, an increase in weight after initiating ART is a well-described phenomenon, considered part of the 'return to health' effect [3]. Additionally, much of the world is dealing with rising rates of obesity in the general population [4]. Analysing weight change in randomised trials and among individuals switching ART may be more informative.

Results from observational studies

In 2017–2018, results from four observational cohort studies suggested that the use of integrase inhibitors was associated with greater increases in body weight, particularly among women. In a French study of 517 individuals (most already virologically suppressed on ART), there was a mean increase of 4 kg among men. Increases in body weight and BMI were also greater for people given dolutegravir in combination with abacavir, compared to tenofovir. Four individuals discontinued dolutegravir-based treatment because of abnormal weight gain [5]. Similar results were seen in a US observational study of 495 individuals, comparing those switched from tenofovir DF/emtricitabine/efavirenz to either an integrase-based regimen or a protease inhibitor- (PI) based regimen. Patients switched to integrase-based treatment showed a mean rise in body weight of 2.9 kg at 18 months, compared with a rise of 0.9 kg among those switched to PIs. Among those switched to integrase-based treatment, those switched to abacavir/lamivudine/dolutegravir showed the greatest increases in body weight, with a mean increase of 5.3 kg by month 18 of treatment [6]. A Brazilian study of 1794 individuals who started ART also showed similar trends: development of clinical obesity was seven times more likely for individuals starting integrase-based treatment, compared with non-nucleoside reverse-transcriptase inhibitor- (NNRTI) or PI-based treatment. In this study, females were more likely to develop clinical obesity [7]. Finally, a study of 4048 individuals treated in Texas, USA, showed the largest increases in BMI for non-white females, especially if treated with integrase inhibitors [8]. The increases in BMI were greater for people treated with PIs than for NNRTIs.

These observational studies were not randomised, and so the differences between treatment classes in body weight might be explained by other factors. There was a prospective trial of dolutegravir monotherapy conducted at the same time, including eight individuals stable on ART switched to dolutegravir monotherapy. Among these individuals, there was a mean increase in body weight of 4kg over 24 weeks [9].

Results from randomised studies

Results from five randomised studies support the association between use of integrase inhibitors and increases in weight. Summary results are shown in Table 1. Two studies have evaluated raltegravir, with three evaluating dolutegravir. In the ACTG 5257 trial, including 1809 individuals, those randomised to first-line treatment with raltegravir were significantly more likely to become either overweight or obese than individuals given either atazanavir/r or darunavir/r (all combined with a tenofovir DF/emtricitabine backbone). In addition, black participants were 5 more likely to become either overweight or obese, compared to white participants [10]. The results suggested that these weight changes were associated with abdominal fat, as waist circu

INSTI and Weight Gain

BRIEF REPORT: CLINICAL SCIENCE

Weight Gain in Persons With HIV Switched From Efavirenz-Based to Integrase Strand Transfer Inhibitor–Based Regimens

Jamison Norwood, MD, Megan Turner, MS,† Carmen Bofill, MPH,† Peter Rebeiro, PhD,† Bryan Shepherd, PhD,‡ Sally Bebawy,† Todd Hulgan, MD, MPH,*† Stephen Raffanti, MD,*† David W. Haas, MD,*†§ Timothy R. Sterling, MD,*† and John R. Koethe, MD, MS*†*

Background: With the introduction of integrase strand transfer inhibitor (INSTI)-based antiretroviral therapy, persons living with HIV have a potent new treatment option. Recently, providers at our large treatment clinic noted weight gain in several patients who switched from efavirenz/tenofovir disoproxil fumarate/emtricitabine (EFV/TDF/FTC) to dolutegravir/abacavir/lamivudine (DTG/ABC/3TC). In this study, we evaluated weight change in patients with sustained virologic suppression who switched from EFV/TDF/FTC to an INSTI-containing regimen.

Methods: We performed a retrospective observational cohort study among adults on EFV/TDF/FTC for at least 2 years who had virologic suppression. We assessed weight change over 18 months in patients who switched from EFV/TDF/FTC to an INSTI-containing regimen or a protease inhibitor (PI)-containing regimen versus those on EFV/TDF/FTC over the same period. In a subgroup analysis, we compared patients switched to DTG/ABC/3TC versus raltegravir- or elvitegravir-containing regimens.

Results: A total of 495 patients were included: 136 who switched from EFV/TDF/FTC to an INSTI-containing regimen and 34 switched to a PI-containing regimen. Patients switched to an INSTI-containing regimen gained an average of 2.9 kg at 18 months compared with 0.9 kg among those continued on EFV/TDF/FTC ($P = 0.003$), whereas those switched to a PI regimen gained 0.7 kg ($P = 0.81$). Among INSTI regimens, those switched to DTG/ABC/3TC gained the most weight at 18 months (5.3 kg, $P = 0.001$ compared with EFV/TDF/FTC).

Conclusion: Adults living with HIV with viral suppression gained significantly more weight after switching from daily, fixed-dose EFV/TDF/FTC to an INSTI-based regimen compared with those remaining on EFV/TDF/FTC. This weight gain was greatest among patients switching to DTG/ABC/3TC.

Key Words: HIV, integrase strand transfer inhibitors, weight gain, dolutegravir, efavirenz

J Acquir Immune Defic Syndr 2017;76:52

INTRODUCTIO

Initiation of antiretroviral thera associated with a short period of w among patients with a lower pretrea (BMI) or more pronounced CD4+ T In the early ART era, weight gain on as evidence of nutritional rehabilita improved survival and immunolog over the past 2 decades, the BMI o ART has steadily increased, and in half of patients remaining on tr overweight or obese.[1,8] Among pat confers an increased risk of de cognitive impairment, and other co infected persons, and the avoid reduce these risks.[9–13]

Integrase strand transfer in gravir, dolutegravir, and elvitegr antiretroviral medications.[14,15] INSTI-based single-pill combina fixed-dose dolutegravir/abacav 3TC), patients have a new optio side reverse transcriptase inhibit (PI)-based regimens causing ac metabolic, or other side effec Vanderbilt Comprehensive Ca clinic, noted substantial weigh long-term viral suppression w dose efavirenz/tenofovir dis (EFV/TDF/FTC) to daily fixe

Previous retrospective strated that weight gain may who were initiated on a PI-b

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From the *Department of Medicine, Vanderbilt University Medical Center, Nashville, TN; †Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, TN; ‡Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN; and §Department of Medicine, Meharry Medical College, Nashville, TN.

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Retrospective cohort in TN

- 495 patients on EFV/FTC/TDF (suppressed 2+ y)
  - 136 switched to INSTI
    - 58 to DTG/3TC/ABC
    - 78 to EVG or RAL
  - 34 switched to PI
  - 325 remained of EFV/FTC/TDF

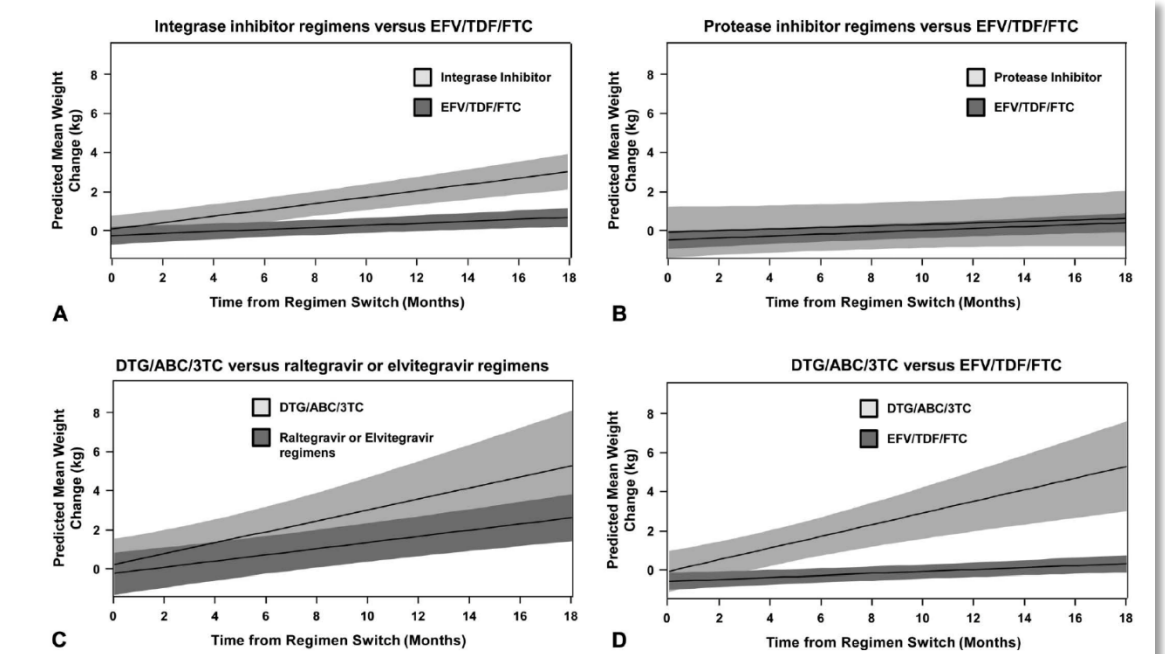

FIGURE 1. Weight change at 18 months among patients switching to an integrase inhibitor-based regimen versus remaining on EFV/TDF/FTC (panel A), switching to a protease inhibitor-based regimen versus remaining on EFV/TDF/FTC (panel B), switching to DTG/ABC/3TC versus a raltegravir or elvitegravir-based regimen (panel C), or switching to DTG/ABC/3TC versus remaining on EFV/TDF/FTC (panel D). Models adjusted for age, sex, race, total duration of ART, and baseline CD4+ T-cell count and weight.

INSTI and Weight Gain

ART Initiation with Integrase Inhibitors is Associated with Greater Weight Gain than with PI- or NNRTI-Based ART in the US and Canada

JE Lake, CA Jenkins, PF Rebeiro, K Bourgi, TR Sterling, MA Horberg, WC Mathews, A Willig and JR Koethe

Study Population

	NNRTI (n=10,711)	PI (n=7063)	INSTI (n=4093)	Overall (21,867)
Age	43 (32, 52)	42 (32, 50)	41 (30, 51)	42 (32, 51)
Black race	40%	41%	38%	40%
Hispanic ethnicity	8%	9%	9%	8%
Male sex	91%	81%	87%	87%
Baseline BMI (kg/m^2)	25 (23, 29)	25 (22, 28)	25 (22, 29)	25 (22, 29)
Year ART start	2010 (2008, 2012)	2010 (2008, 2011)	2013 (2011, 2014)	2010 (2009, 2012)
Baseline CD4$^+$ T cell count (cells/μL)	311 (178, 451)	261 (107, 405)	346 (171, 516)	303 (154, 451)
Baseline HIV-1 RNA (copies/mL)	40,480 (11,198, 120,016)	52,405 (12,830, 169,824)	42,657 (11,939, 144,709)	44,054 (11,796, 139,374)
ART agent				
RAL	--	--	51%	10%
EVG	--	--	37%	7%
DTG	--	--	12%	2%
ATV	--	43%	--	14%
DRV	--	35%	--	11%
EFV	87%	--	--	43%

Median (interquartile range) or percent reported

INSTI and Weight Gain

Results

	NNRTI		PI		INSTI	
Years since ART initiation	Weight (kg)	95% CI	Weight (kg)	95% CI	Weight (kg)	95% CI
0.0	78.988	(78.820, 79.178)	79.025	(78.744, 79.288)	79.247	(78.899, 79.561)
0.5	80.491	(80.355, 80.620)	81.134	(80.985, 81.313)	81.538	(81.315, 81.751)
1.0	81.630	(81.488, 81.770)	82.695	(82.513, 82.890)	83.183	(82.934, 83.491)
2.0	82.247	(82.062, 82.425)	83.332	(83.113, 83.519)	83.656	(83.322, 84.033)
3.0	82.537	(82.370, 82.732)	83.494	(83.275, 83.693)	84.059	(83.625, 84.646)
4.0	82.881	(82.694, 83.124)	83.790	(83.507, 84.073)	84.740	(84.046, 85.551)
5.0	83.111	(82.878, 83.374)	83.981	(83.683, 84.259)	85.096	(84.165, 86.149)

	NNRTI		PI		INSTI	
	Weight, kg (95% CI)	Weight Change, kg	Weight, kg (95% CI)	Weight Change, kg	Weight, kg (95% CI)	Weight Change, kg
Year 0	79.0 (78.8, 79.2)	0.0	79.0 (78.7, 79.3)	0.0	79.2 (78.9, 79.6)	0.0
Year 1	81.6 (81.5, 81.8)	2.6	82.7 (82.5, 82.9)	3.7	83.2 (82.9, 83.5)	4.0
Year 2	82.2 (82.1, 82.4)	3.3	83.3 (83.1, 83.5)	4.3	83.7 (83.3, 84.0)	4.4
Year 5	83.1 (82.9, 83.4)	4.1	84.0 (83.7, 84.3)	5.0	85.1 (84.2, 86.1)	5.8

INSTI vs NNRTI: p=<0.0001

INSTI vs PI: p=0.68

PI vs NNRTI: p<0.001

INSTI and Weight Gain

Results

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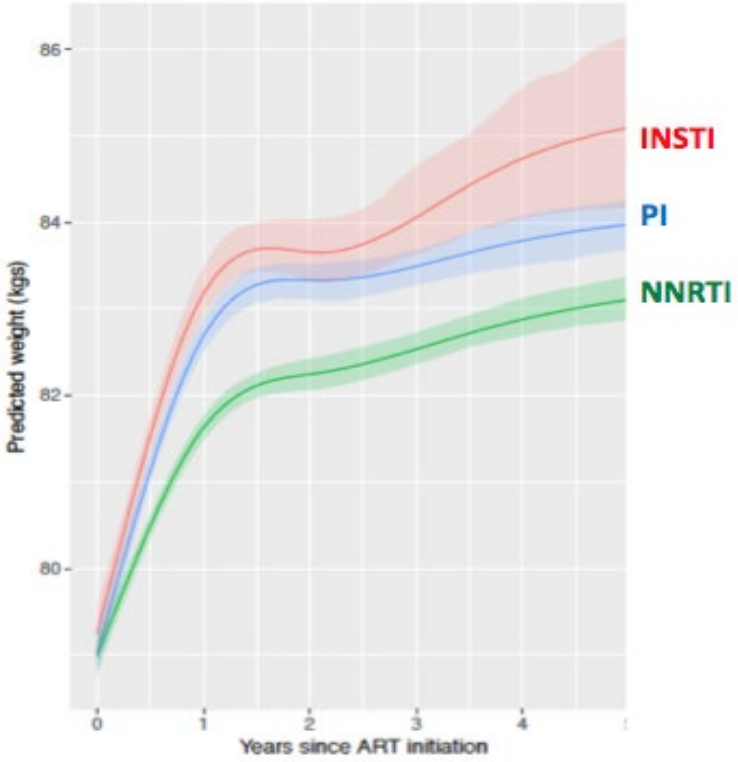

PI		INSTI	
ht, kg % CI)	Weight Change, kg	Weight, kg (95% CI)	Weight Change, kg
9.0 , 79.3)	0.0	79.2 (78.9, 79.6)	0.0
2.7 , 82.9)	3.7	83.2 (82.9, 83.5)	4.0
3.3 , 83.5)	4.3	83.7 (83.3, 84.0)	4.4
4.0 , 84.3)	5.0	85.1 (84.2, 86.1)	5.8

)=<0.0001
=0.68
<0.001

INSTI and Weight Gain

Results

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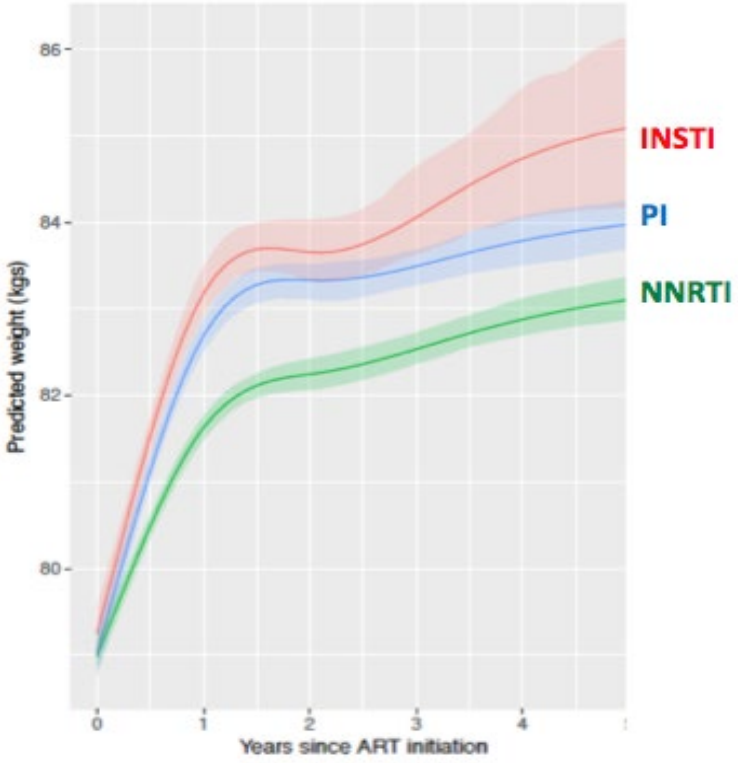

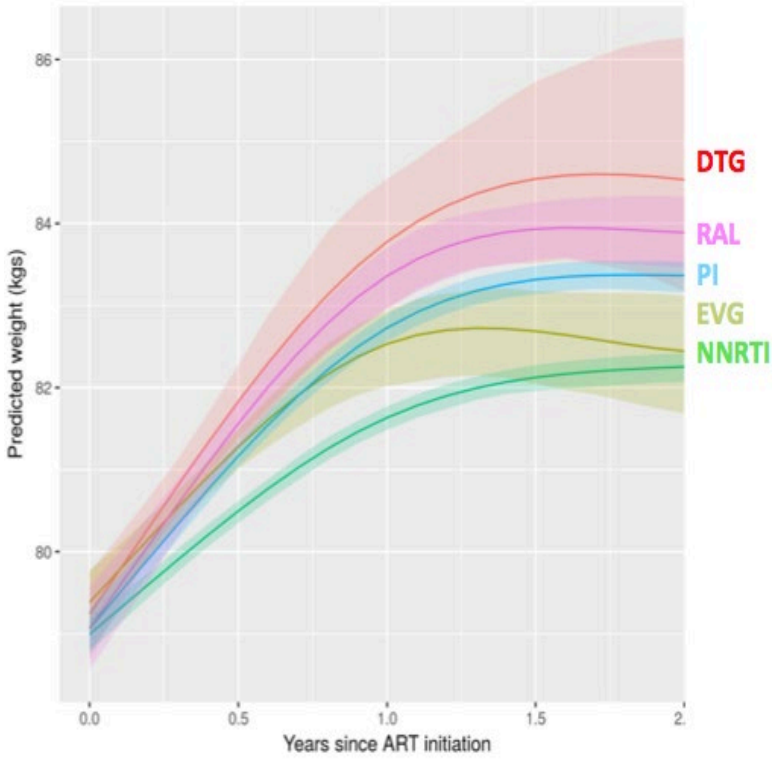

INSTI and Waist Circumference

Open Forum Infectious Diseases
MAJOR ARTICLE

Changes in Waist Circumference in HIV-Infected Individuals Initiating a Raltegravir or Protease Inhibitor Regimen: Effects of Sex and Race

Priya Bhagwat,[1] Ighovwerha Ofotokun,[2] Grace A. McComsey,[3] Todd T. Brown,[4] Carlee Moser,[5] Catherine A. Sugar,[1] and Judith S. Currier[1]

[1]University of California, Los Angeles, Los Angeles, California; [2]Emory University School of Medicine, Department of Medicine, Atlanta, Georgia; [3]Case Western University, Cleve
Hopkins University School of Medicine, Baltimore, Maryland; [5]Harvard T. H. Chan School of Public Health, Boston, Massachusetts

Background. This study investigates the association of clinical and demographic predictors with abdominal fat ga
using waist circumference (WC) and self-reported abdominal size.

Methods. We analyzed data from ACTG A5257, a clinical trial that randomized treatment-naïve HIV-infected
1 of 3 antiretroviral regimens: raltegravir (RAL) or the protease inhibitors (PIs) atazanavir/ritonavir (ATV/r) or dar
vir (DRV/r), each in combination with tenofovir disoproxil fumarate/emtricitabine. Associations of treatment and
graphic characteristics with 96-week WC change were assessed using repeated-measures models. Ordinal logistic
used to examine the associations of predictors with week 96 self-reported abdominal changes.

Results. The study population (n = 1809) was 76.0% male and predominantly black non-Hispanic (41.9%) and
panic (34.1%). Mean baseline WC was 90.6 cm, with an average 96-week increase of 3.4 cm. WC increases were hi
arm compared with DRV/r ($P = .0130$). Females experienced greater increases in WC on RAL vs ATV/r than m
Similarly, a larger difference in WC change was found for RAL vs DRV/r for black vs nonblack individuals ($P = .$
multivariable model found that in addition to the treatment regimen, higher baseline viral load and lower CD4+ we
with WC increases.

Conclusions. With antiretroviral therapy initiation, higher WC increases in the RAL arm compared with P
nounced in female and black participants, and a more advanced baseline HIV disease state was a strong predicto
inal increases. Understanding factors predisposing individuals to abdominal fat gain could inform health manag
initiation.

Keywords. abdominal fat; central adiposity; lipodystrophy; metabolic complications; waist circumference.

Central fat gain remains a prevalent issue for HIV-infected patients in the contemporary antiretroviral therapy (ART) era [1–7]. Central fat gain often includes increases in visceral adipose tissue (VAT), which is a known risk factor for cardiovascular disease (CVD) [8, 9]. CVD is an important cause of morbidity and mortality in HIV-infected individuals, and infection with HIV has been associated with a higher risk of CVD [10–12]. This increase in risk of CVD associated with VAT may be higher especially in HIV-infected individuals compared with HIV-uninfected individuals [13]. VAT has also been shown to be associated with elevated cardiometabolic risk. In HIV-infected individuals, increased VAT has been fou
with increased insulin resistance and to l
onary calcification [14–18]. This highlig
further investigating the underlying risk
associated with central fat gain, especiall
In general, antiretroviral therapy ha
weight gain; however, therapy effects o
to vary by regimen. Atazanavir has bee
with larger increases in abdominal fa
regimens including darunavir, and ra
associated with smaller increases in
with efavirenz in treatment-naïve in
apy [5, 6, 19–23]. A previous analys
substudy of A5257 comparing ataz
darunavir/ritonavir (DRV/r), and
there were significant increases in
3 treatments from entry to week 9
between the arms in the magnitu
found that higher baseline viral load
gains in central fat [24]. A metabolic analysis of the A5257
study, with a larger full cohort sample size, found larger waist

Received 9 February 2018; editorial decision 5 August 2018; accepted 11 October 2018.
Correspondence: P. Bhagwat, PhD, Center for HIV Identification, Prevention, and Treatment Services (CHIPTS), University of California, Los Angeles, 10920 Wilshire Blvd., Suite 350, Los Angeles, CA 90024, USA (pbhagwat@ucla.edu).

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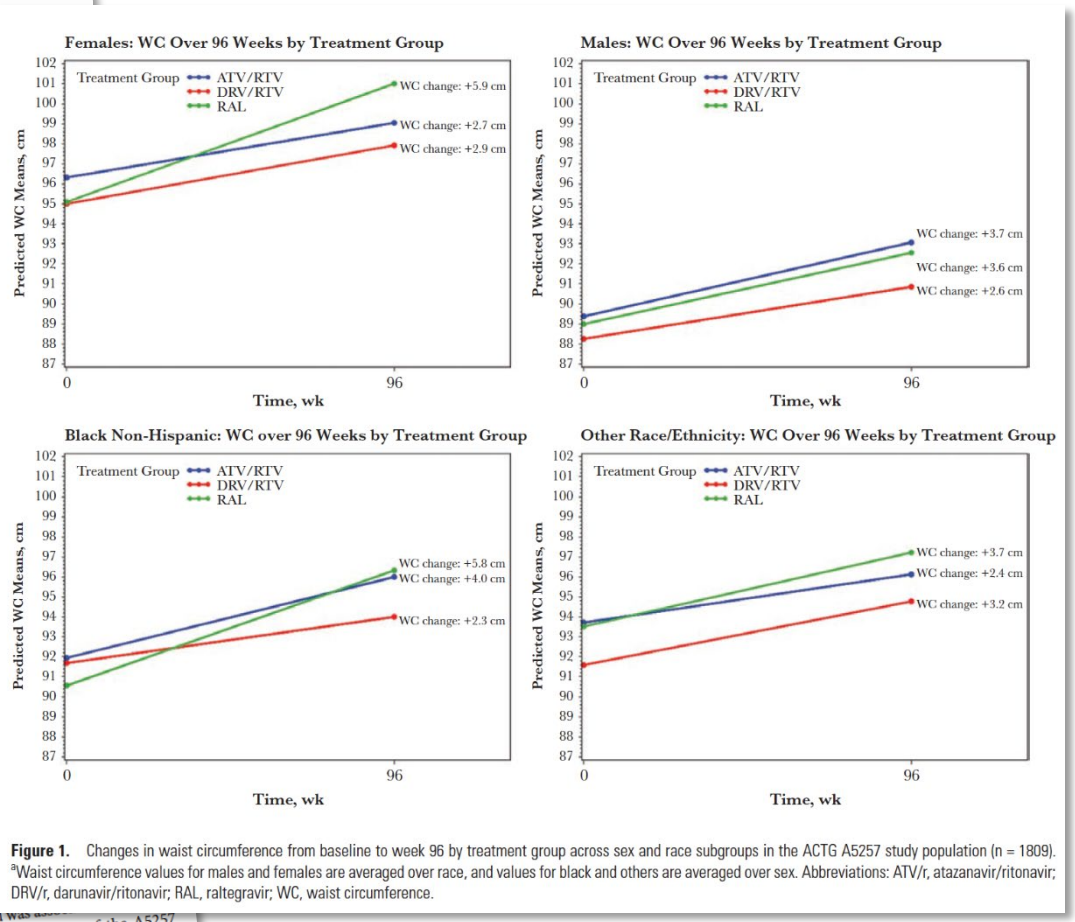


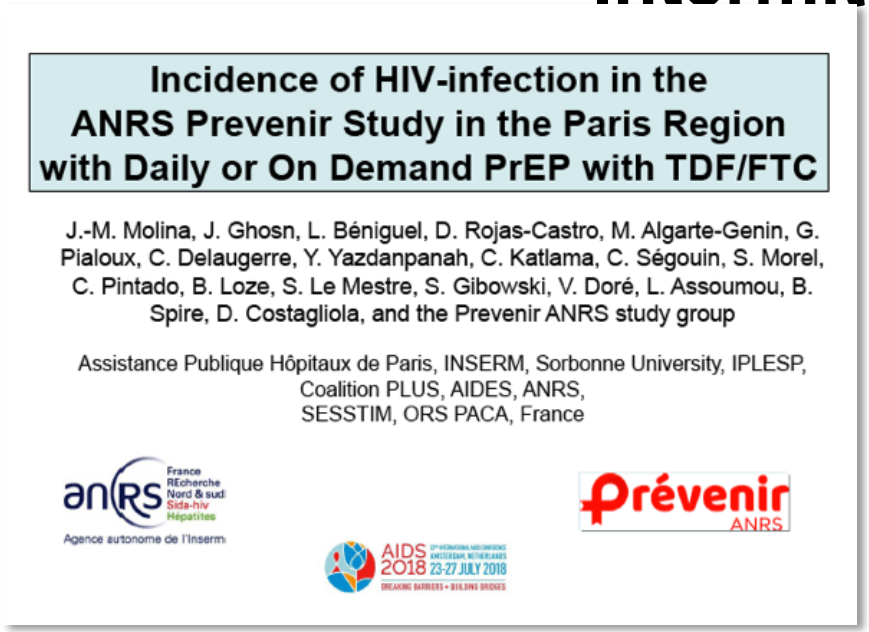
Figure 1. Changes in waist circumference from baseline to week 96 by treatment group across sex and race subgroups in the ACTG A5257 study population (n = 1809). [a]Waist circumference values for males and females are averaged over race, and values for black and others are averaged over sex. Abbreviations: ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; RAL, raltegravir; WC, waist circumference.

INSTI and Weight Gain

- Are the increases in weight different between ART classes/agents?
- Are any differences clinically significant?
- Are they noticed by patients?
- Will standardized measures of weight become the next thing to include in clinical trials (i.e., DXA, lipids, proteinuria)?

4

Intermittent PrEP



Incidence of HIV-infection in the ANRS Prevenir Study in the Paris Region with Daily or On Demand PrEP with TDF/FTC

J.-M. Molina, J. Ghosn, L. Béniguel, D. Rojas-Castro, M. Algarte-Genin, G. Pialoux, C. Delaugerre, Y. Yazdanpanah, C. Katlama, C. Ségouin, S. Morel, C. Pintado, B. Loze, S. Le Mestre, S. Gibowski, V. Doré, L. Assoumou, B. Spire, D. Costagliola, and the Prevenir ANRS study group

Assistance Publique Hôpitaux de Paris, INSERM, Sorbonne University, IPLESP, Coalition PLUS, AIDES, ANRS, SESSTIM, ORS PACA, France

4

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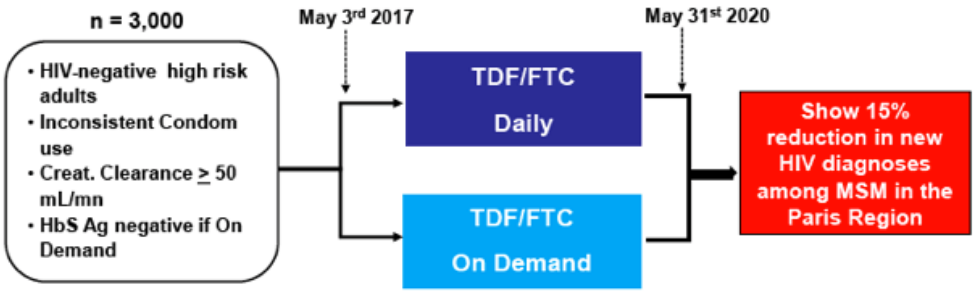
Assistance Publique Hôpitaux de Paris, INSERM, Sorbonne University, IPLESP, Coalition PLUS, AIDES, ANRS, SESSTIM, ORS PACA, France

Prévenir ANRS
http://prevenir.anrs.fr/

Study Design

Open-Label Prospective Cohort Study in the Paris Region



- **Participants opted for either Daily or On Demand PrEP and could switch regimens**
- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine
- STI screening at physicians' discretion (Guidelines recommend every 3 months in MSM)
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

4

Intermittent PrEP

Incidence of HIV-infection in the ANRS Prevenir Study in the Paris Region with Daily or On Demand PrEP with TDF/FTC

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Prévenir ANRS

http://prevenir.anrs.fr/

Study Objectives

Primary Objective

- To show ≥ 15% reduction of new HIV diagnoses among MSM in the Paris region in comparison with the numbers provided by the National Surveillance network in 2016 (mandatory notification of HIV diagnoses in France)

Secondary Objectives

- Participants characteristics
- Overall HIV incidence and by dosing regimen (Daily or On Demand)
- PrEP adherence and coverage of sex events (self-report, dried blood spots)
- Impact of peer counseling on adherence and retention
- Sexual behavior (condom use, Nb of sexual acts, Nb of partners, STIs)
- Safety, tolerability

3,000 pts to be enrolled (85% MSM) with the hypothesis of PrEP efficacy: 80%
July 2, 2018: 1628 pts enrolled across 22 sites

Open-Label Prosp

n = 3,000

- HIV-negative high risk adults
- Inconsistent Condom use
- Creat. Clearance ≥ 50 mL/mn
- HbS Ag negative if On Demand

Daily

TDF/FTC On Demand

Show 15% reduction in new HIV diagnoses among MSM in the Paris Region

- **Participants opted for either Daily or On Demand PrEP and could switch regimens**
- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine
- STI screening at physicians' discretion (Guidelines recommend every 3 months in MSM)
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

Intermittent PrEP

Prévenir ANRS

Baseline Characteristics

Characteristics (Median, IQR) or (n, %)	Daily n = 724 (45.4%)	On Demand n= 870 (54.6%)	P-value
Age (years)	36 (30-44)	36 (30-44)	0.10
MSM	708 (98)	865 (99.4)	
Heterosexual men or women	7 (0.1)	5 (0.6)	<.01
Transgender	8 (1.1)	0 (0)	
No regular sex partner	380 (53)	437 (51)	0.41
History of PrEP use	408 (56.5)	515 (59.2)	0.28
Use of Chemsex*	128 (17.7)	124 (14.3)	0.06
No. condomless sex acts in prior 4 weeks	**3** (1-8)	**2** (0-4)	<.001
No. sexual partners in prior 3 months	**15** (7-25)	**10** (5-15)	<.001

* at last sexual intercourse : cocaine, GHB, MDMA, mephedrone..

anrs France Recherche Nord & sud Sida-hiv Hépatites

Agence autonome de l'Inserm

Intermittent PrEP

Adherence to PrEP / Condoms

PrEP / Condom use at last sexual intercourse

2279 sexual acts assessed in 1102 participants ≥ M3

(n, %)	Daily n = 1088 acts	On Demand n = 1191 acts	Total n= 2279
Total PrEP use	1068 (98.2)	967 (81.2)	2035 (89.2)
Correct use*	1024 (95.8)	931 (96.2)	1955 (96.1)
Suboptimal	44 (4.1)	36 (3.7)	80 (3.9)
No PrEP	20 (1.8)	224 (18.8)	244 (10.7)
Condoms	206 (18.9)	258 (21.6)	464 (20.4)

* According to the protocol, or at least one pill before (<24h) and one pill after sex (<24h)

Over time, participants largely remained on chosen PrEP strategy

HIV Incidence (mITT Analysis)

Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)
TDF/FTC (Daily)	443	0 (0-0.8)
TDF/FTC (On Demand)	506	0 (0-0.7)

Mean Follow-up in this Open-Label Cohort: 7 months (SD: 4)

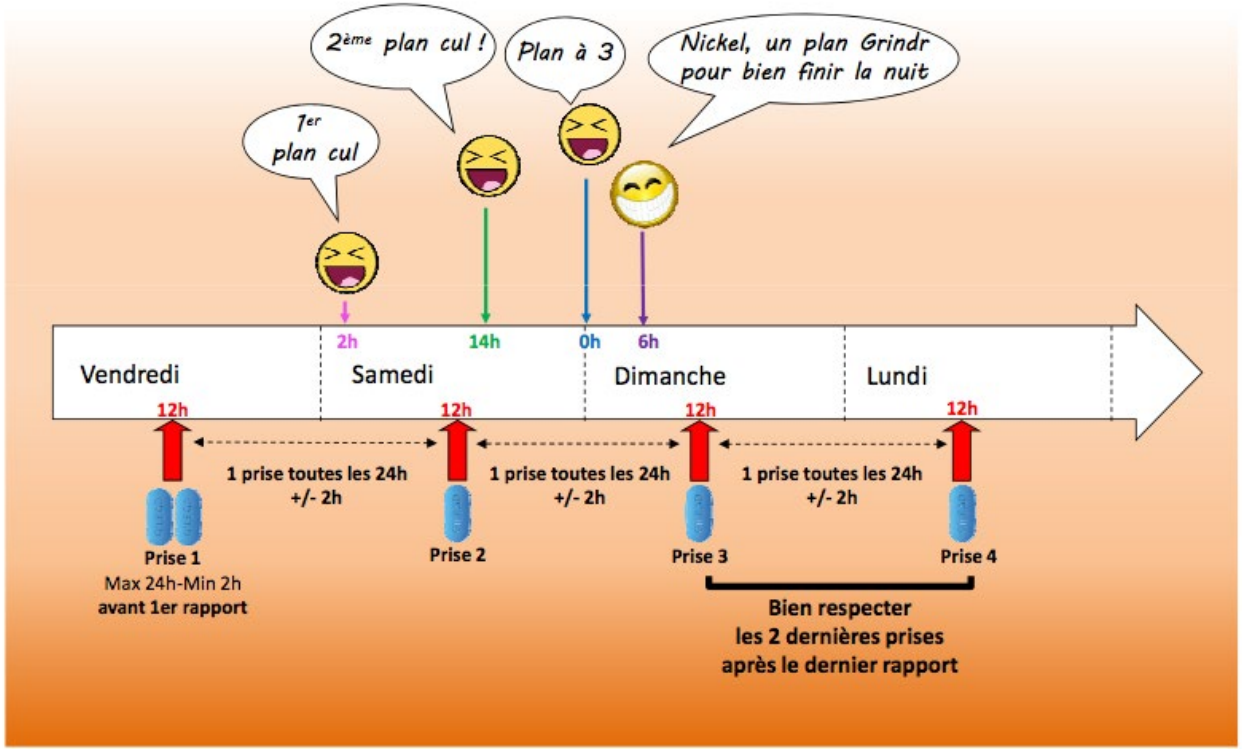
Incidence of study discontinuation:
3.3/100 PY including 1.5/100 PY who discontinued PrEP

85 HIV-infections averted*

* assuming an incidence of 9.17/100 PY as observed in the ANRS Ipergay study in Paris

Significance of Intermittent PrEP

- **Do you have faith that in practice, intermittent PrEP works as well as daily PrEP?**
- **Anyone you would not recommend use intermittent PrEP?**



5

Bictegravir Lands

www.natap.org

U.S. Food and Drug Administration Approves Gilead's Biktarvy® (Bictegravir, Emtricitabine, Tenofovir Alafenamide) for Treatment of HIV-1 Infection

– In Clinical Trials, Biktarvy Demonstrated High Efficacy, Few Interactions With Other Drugs and a High Barrier to Resistance Through 48 Weeks –

FDA label

FOSTER CITY, Calif.--(BUSINESS WIRE)--Feb. 7, 2018-- Gilead Sciences, Inc. (NASDAQ:GILD) today announced that the U.S. Food and Drug Administration (FDA) has approved Biktarvy® (bictegravir 50mg/emtricitabine 200mg/tenofovir alafenamide 25mg, BIC/FTC/TAF), a once-daily single tablet regimen (STR) for the treatment of HIV-1 infection. Biktarvy combines the novel, unboosted integrase strand transfer inhibitor (INSTI) bictegravir, with the demonstrated safety and efficacy profile of the Descovy® (FTC/TAF) dual nucleoside reverse transcriptase inhibitor (NRTI) backbone, and is the smallest INSTI-based triple-therapy STR available.

Biktarvy is indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no antiretroviral treatment history or to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA <50 c/mL) on a stable antiretroviral regimen for at least three months with no history of treatment failure and no known substitutions associated with resistance to the individual components of Biktarvy. No

Box 2. Selected Recommendations for Initial ART Regimens[a]

Generally Recommended Initial Regimens (Listed in Alphabetic Order by InSTI Component)

- Bictegravir/TAF/emtricitabine (evidence rating AIa)[b]
- Dolutegravir/abacavir/lamivudine (evidence rating AIa)[c,d]
- Dolutegravir plus TAF/emtricitabine (evidence rating AIa)[c,e]

Recommended Initial Regimens for Individuals for Whom Generally Recommended Regimens Are Not Available or Not an Option (Listed in Alphabetic Order by First Component)

- Darunavir/cobicistat plus TAF (or TDF)/emtricitabine (evidence rating AIa)[e]
- Darunavir boosted with ritonavir plus TAF (or TDF)/emtricitabine (evidence rating AIa)[e]
- Efavirenz/TDF/emtricitabine (evidence rating AIa)
- Elvitegravir/cobicistat/TAF (or TDF)/emtricitabine (evidence rating AIa)[e]
- Raltegravir plus TAF (or TDF)/emtricitabine (evidence rating AIa for TDF)[e]
- Rilpivirine/TAF (or TDF)/emtricitabine (if pretreatment HIV RNA level is <100 000 copies/mL and CD4 cell count is >200/μL) (evidence rating AIa)[e]

TDF is not recommended for individuals with or at risk for kidney or bone disease (osteopenia or osteoporosis) (evidence rating BIII).

Initial 2-drug regimens are only recommended in the rare situations in which a patient cannot take abacavir, TAF, or TDF (evidence rating BIa).

Pregnant individuals with HIV infection should initiate ART for their own health and to reduce the likelihood of HIV transmission to the infant (evidence rating AIa).

Regimens for the Antiretroviral-

, 2018; last reviewed October 25, 2018)

mmendations

erally consists of two nucleoside reverse transcriptase inhibitors from one of three drug classes: an integrase strand transfer (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic (PK) urpose are cobicistat and ritonavir).

otential prior to the initiation of antiretroviral therapy **(AIII)**.

(the Panel) classifies the following regimens as Recommended

HLA-B*5701 negative **(AI)**

roxil fumerate, **BII** for tenofovir alafenamide)

neural tube defects in infants born to people who were receiving r INSTI, please refer to Table 6b for specific recommendations on

also provides a list of Recommended Initial Regimens in Certain

regimen for a particular patient should be guided by factors such as interaction potential, resistance test results, comorbid conditions, regimen based on selected clinical case scenarios. Table 9 ents in a regimen.

a from well-designed nonrandomized trials, observational cohort alence studies, or regimen comparisons from randomized switch

are two forms of tenofovir that are approved by the Food and Drug while TDF is associated with lower lipid levels. Safety, cost, and ese drugs.

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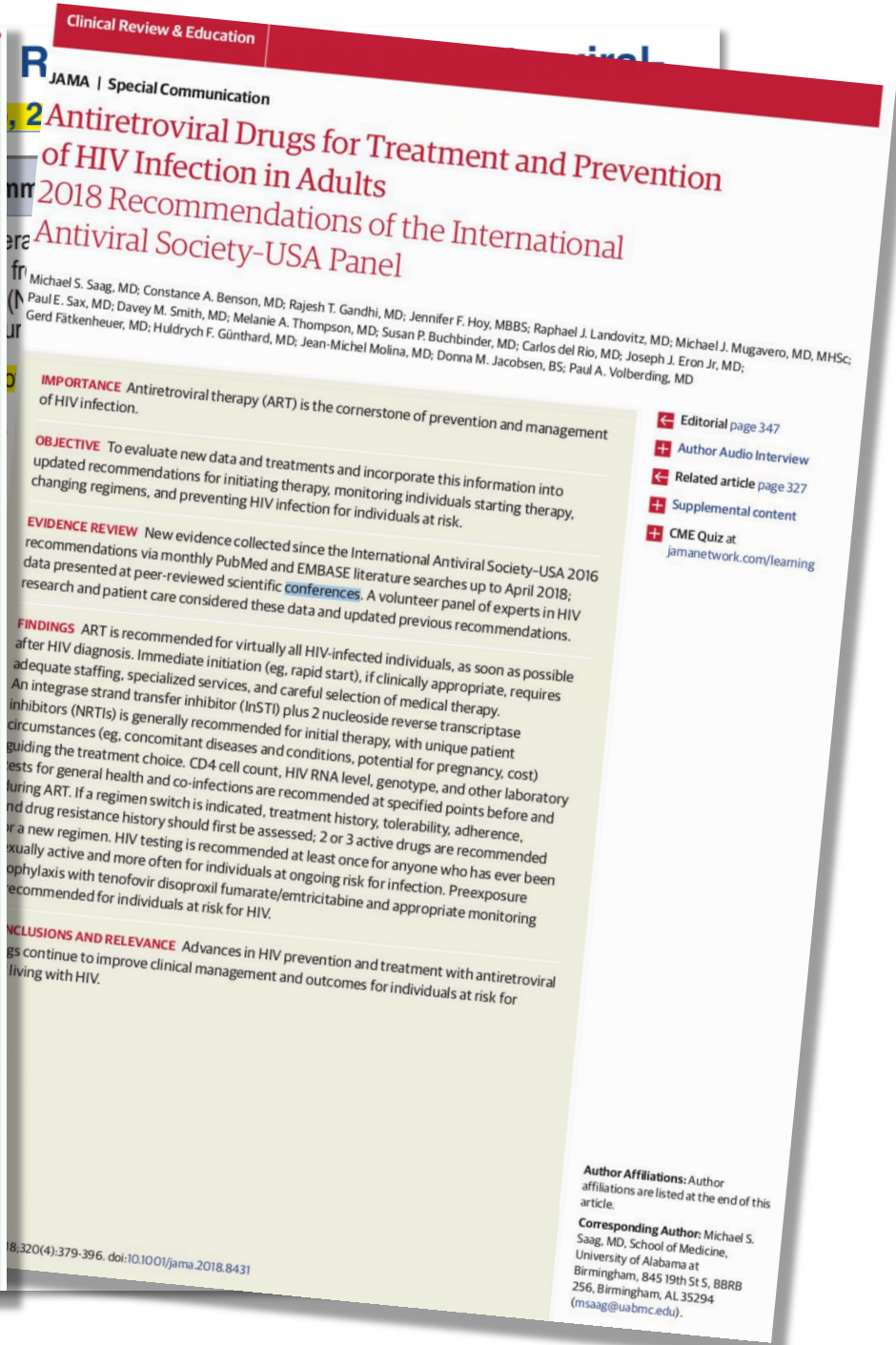

Clinical Review & Education

JAMA | Special Communication

Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2018 Recommendations of the International Antiviral Society–USA Panel

Michael S. Saag, MD; Constance A. Benson, MD; Rajesh T. Gandhi, MD; Jennifer F. Hoy, MBBS; Raphael J. Landovitz, MD; Michael J. Mugavero, MD, MHSc; Paul E. Sax, MD; Davey M. Smith, MD; Melanie A. Thompson, MD; Susan P. Buchbinder, MD; Carlos del Rio, MD; Joseph J. Eron Jr, MD; Gerd Fätkenheuer, MD; Huldrych F. Günthard, MD; Jean-Michel Molina, MD; Donna M. Jacobsen, BS; Paul A. Volberding, MD

IMPORTANCE Antiretroviral therapy (ART) is the cornerstone of prevention and management of HIV infection.

OBJECTIVE To evaluate new data and treatments and incorporate this information into updated recommendations for initiating therapy, monitoring individuals starting therapy, changing regimens, and preventing HIV infection for individuals at risk.

EVIDENCE REVIEW New evidence collected since the International Antiviral Society–USA 2016 recommendations via monthly PubMed and EMBASE literature searches up to April 2018; data presented at peer-reviewed scientific conferences. A volunteer panel of experts in HIV research and patient care considered these data and updated previous recommendations.

FINDINGS ART is recommended for virtually all HIV-infected individuals, as soon as possible after HIV diagnosis. Immediate initiation (eg, rapid start), if clinically appropriate, requires adequate staffing, specialized services, and careful selection of medical therapy. An integrase strand transfer inhibitor (InSTI) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) is generally recommended for initial therapy, with unique patient circumstances (eg, concomitant diseases and conditions, potential for pregnancy, cost) guiding the treatment choice. CD4 cell count, HIV RNA level, genotype, and other laboratory tests for general health and co-infections are recommended at specified points before and during ART. If a regimen switch is indicated, treatment history, tolerability, adherence, and drug resistance history should first be assessed; 2 or 3 active drugs are recommended for a new regimen. HIV testing is recommended at least once for anyone who has ever been sexually active and more often for individuals at ongoing risk for infection. Preexposure prophylaxis with tenofovir disoproxil fumarate/emtricitabine and appropriate monitoring is recommended for individuals at risk for HIV.

CONCLUSIONS AND RELEVANCE Advances in HIV prevention and treatment with antiretroviral drugs continue to improve clinical management and outcomes for individuals at risk for and living with HIV.

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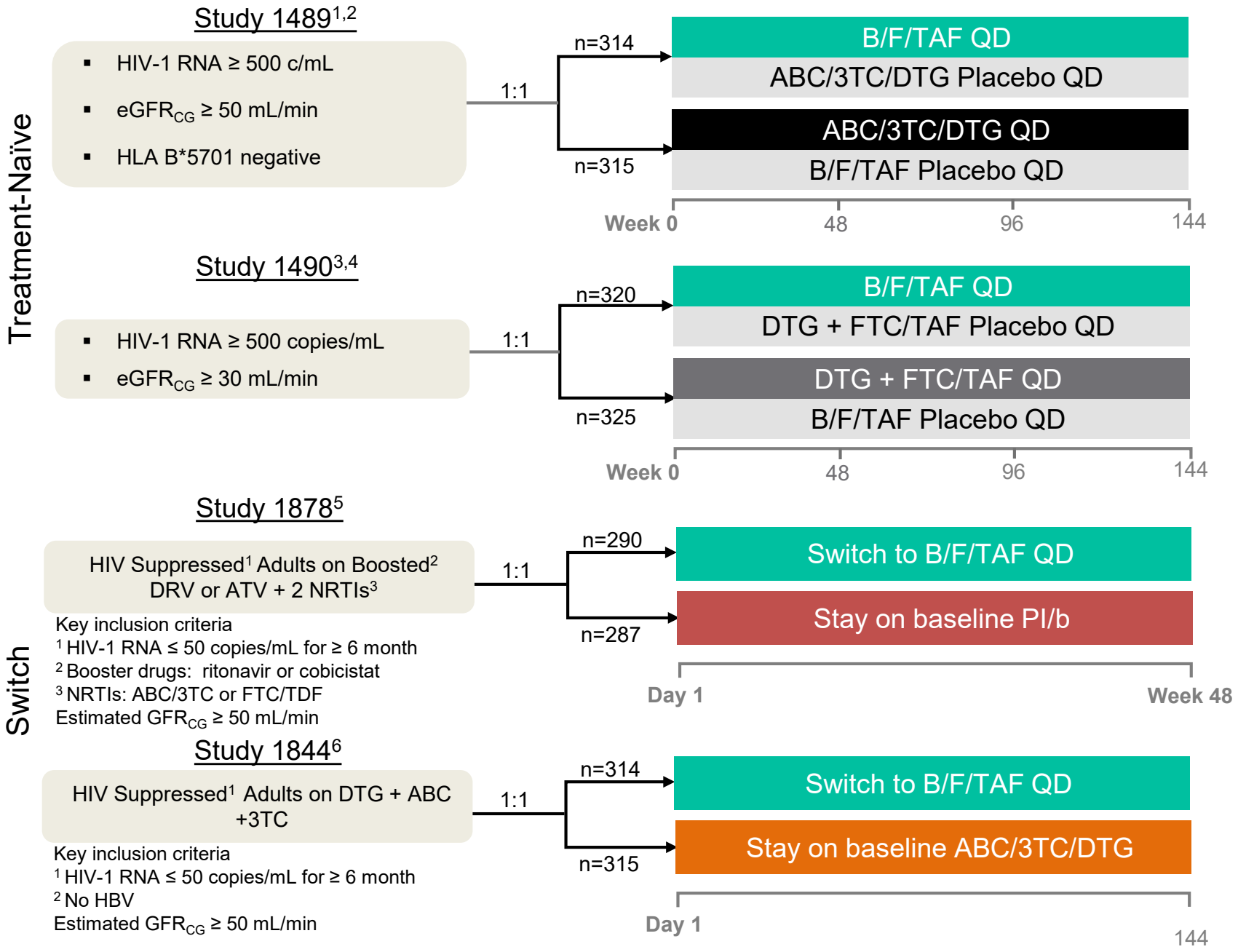
Supplemental content
CME Quiz at jamanetwork.com/learning

Author Affiliations: Author affiliations are listed at the end of this article.

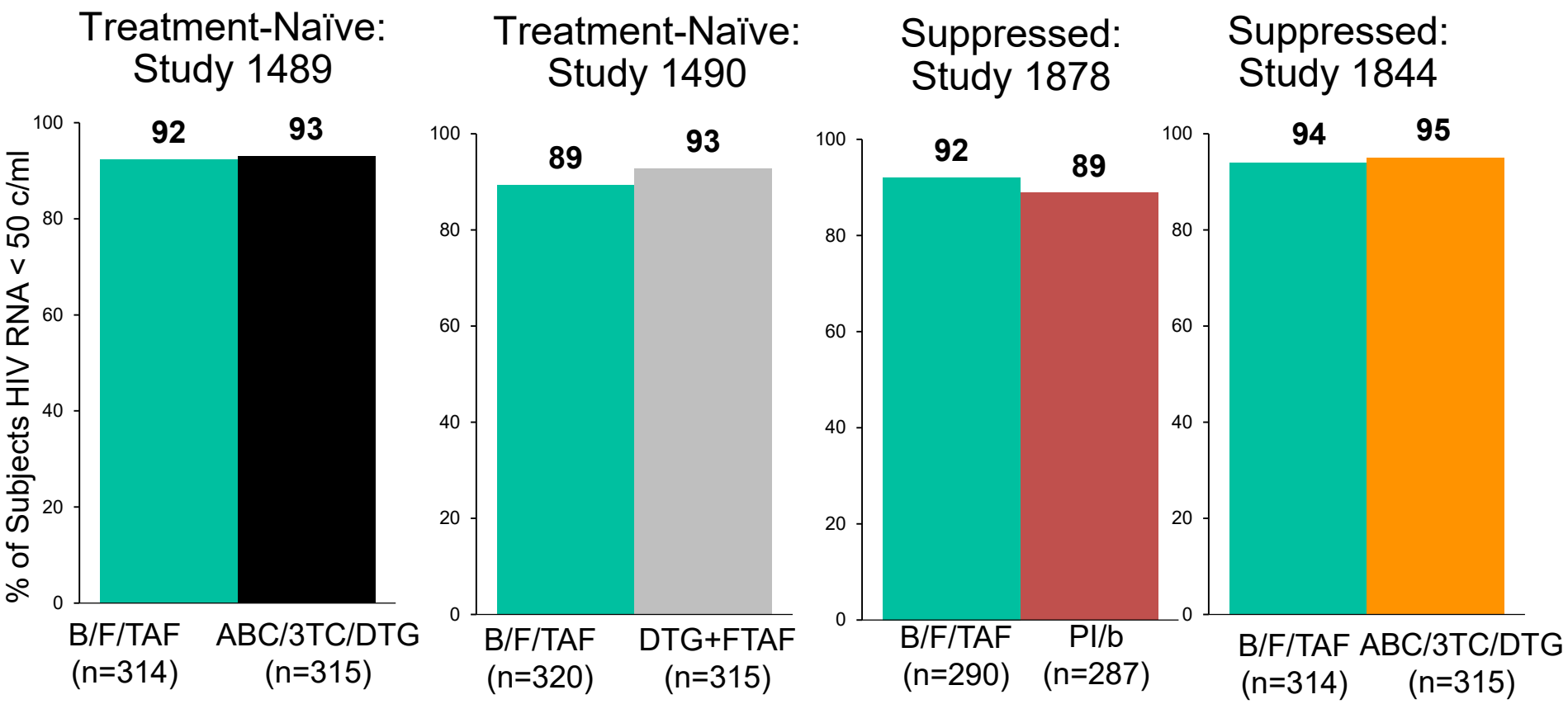
Corresponding Author: Michael S. Saag, MD, School of Medicine, University of Alabama at Birmingham, 845 19th St S, BBRB 256, Birmingham, AL 35294 (msaag@uabmc.edu).

;320(4):379-396. doi:10.1001/jama.2018.8431



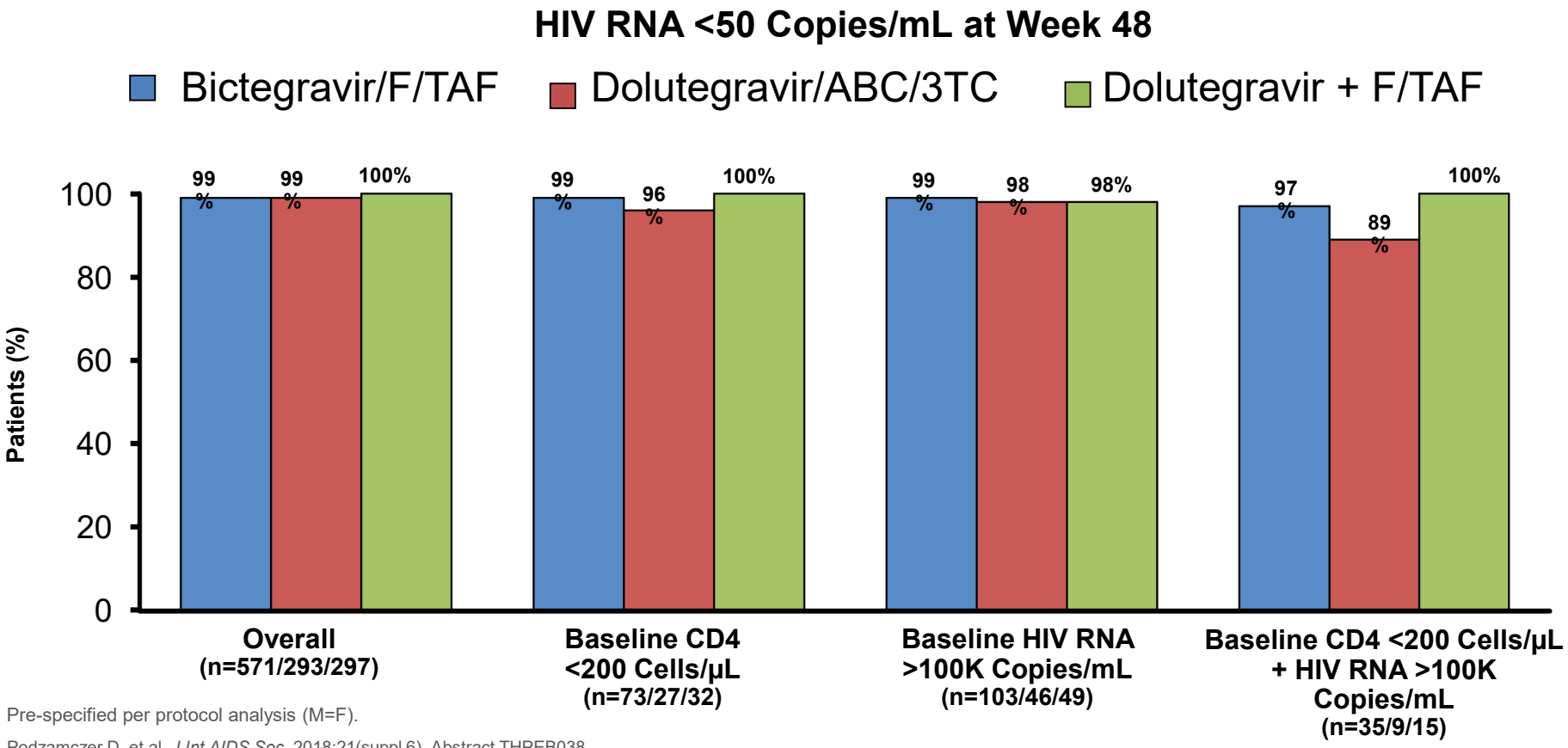
1. Gallant J, et al. IAS 2017. Paris, France. Oral #MOAB0105LB
2. Gallant J, et al. Lancet 2017;390:2063-72.
3. Sax P, et al. IAS 2017. Paris, France. Poster Discussion #TUPDB0201LB
4. Sax P, et al. Lancet 2017;390:2073-82.
5. Daar E, et al. ID Week 2017. San Diego, CA. Oral LB-4
6. Molina JM, et al. *Lancet HIV*. 2018;5:e357-e365.

Virologic Outcome at Week 48 (FDA Snapshot)



BFTAF was non-inferior to comparator arms
B/F/TAF has NO resistance development

Studies 1489 and 1490: Virologic Outcomes by Low CD4, High Viral Load, or Both



Pre-specified per protocol analysis (M=F).

Podzamczer D, et al. *J Int AIDS Soc*. 2018;21(suppl 6). Abstract THPEB038.

Study 1489: Safety Outcomes With Bictegravir/FTC/TAF Versus Dolutegravir/ABC/3TC at Week 48

- Both regimens were well tolerated
  - No deaths
  - No discontinuations due to adverse events in the bictegravir/F/TAF arm
  - Nausea was more common in the dolutegravir/ABC/3TC arm
- No discontinuations due to renal adverse events
- Similar changes in eGFR: -11 mL/min
- Both treatment arms had similar changes in BMD and lipid parameters

Safety Results

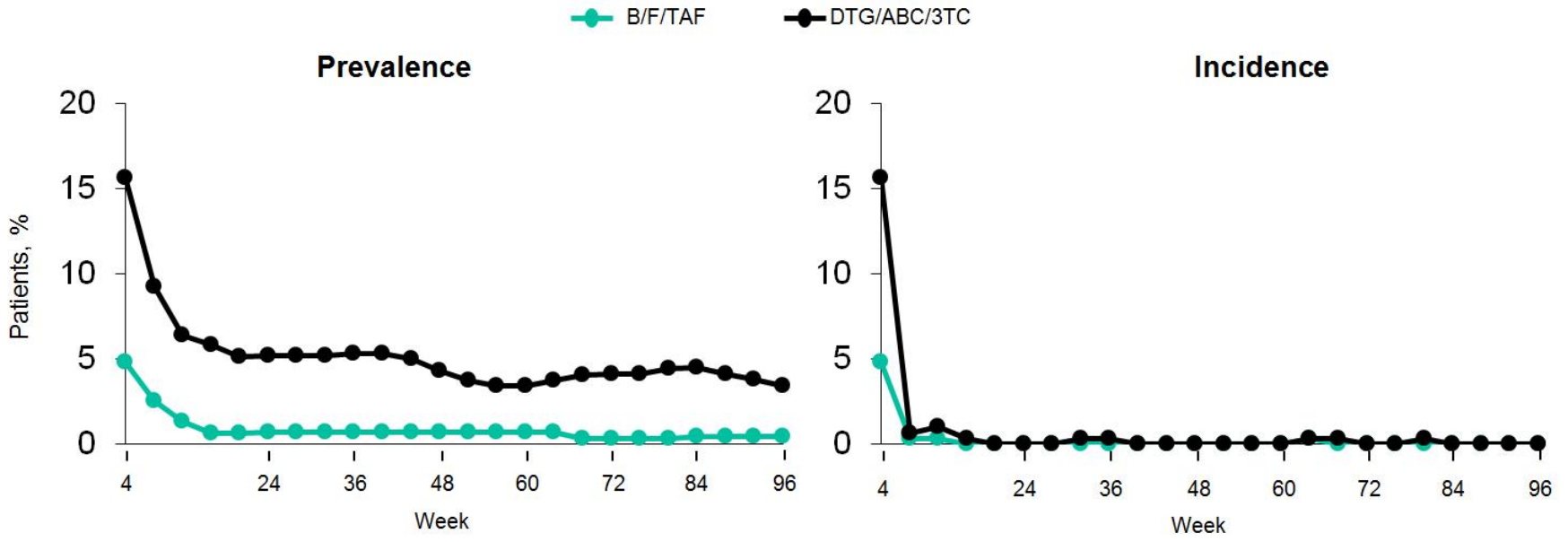
	Bictegravir/ FTC/TAF (n=314)	Dolutegravir/ ABC/3TC (n=315)
Discontinuations due to adverse events (%)	0	1.3
Adverse events, all grades (%)	13	13
Diarrhea	12	14
Headache	10	23*
Nausea		
Change in BMD (%)		
Spine	-0.8	-0.6
Hip	-0.8	-1.0
Lipid changes (mg/dL)		
Total cholesterol	13	11
LDL-C	7	4
HDL-C	5	5
Triglycerides	9	3

*$P<0.001$ versus bictegravir/FTC/TAF.

Gallant J, et al. *Lancet.* 2017;390:2063-2072.

Study 380-1489

Prevalence and Incidence of Nausea



B/F/TAF, n=	314	307	300	296	293	288	282	281	314	307	300	296	293	288	282	281
DTG/ABC/3TC, n=	315	310	303	300	297	295	292	292	315	310	303	300	297	295	292	292

Summary of Bothersome Symptoms: B/F/TAF vs ABC/DTG/3TC

	Treatment-naïve (Study 1489)				Virologically suppressed (Study 1844)			
	Week			Longitudinal Model	Week			Longitudinal Model
HIV-SI Bothersome Symptom	4	12	48		4	12	48	
Fatigue/loss of energy	✓	✓	✓	✓	✓			
Dizzy/lightheadedness	✓		✓		✓			✓
Nausea/vomiting	✓	✓		✓		✓	✓	✓
Loss of appetite		✓		✓		✓		✓
Sad/down/depressed					✓		✓	✓
Nervous/anxious					✓	✓	✓	✓
Difficulty sleeping		✓	✓			✓		✓

✓ = statistically significant ($p<0.05$) based on adjusted logistic regression favoring B/F/TAF

Note: Only symptoms where at least two or more timepoints/models showed significance in either study are presented.

Wohl D, et al. Patient. 2018; 11(5): 561–573.

Study 1490: Safety Outcomes With Bictegravir/FTC/TAF Versus Dolutegravir + FTC/TAF at Week 96

- Overall, both treatment arms were well tolerated
  - Deaths (n=6 [3 in each arm]; none were related to study drugs)
  - Low rate of discontinuations due to adverse events (2%)
- No discontinuations due to renal adverse events and no cases of renal tubulopathy
- Similar changes in lipid parameters in the bictegravir and dolutegravir arms

Safety Results

	Bictegravir/ FTC/TAF (n=320)	Dolutegravir + FTC/TAF (n=325)
Discontinuations due to adverse events (%)	2	2
Adverse events, all grades (%)	18	16
Diarrhea	16	15
Headache	8	11
Nausea		
Grade 3/4 creatine elevation (%)	5	3
Lipid changes (mg/dL)		
Total cholesterol	17	16
LDL-C	19	16
HDL-C	4	5
Triglycerides	6	6
Total cholesterol:HDL-C	0	-0.1

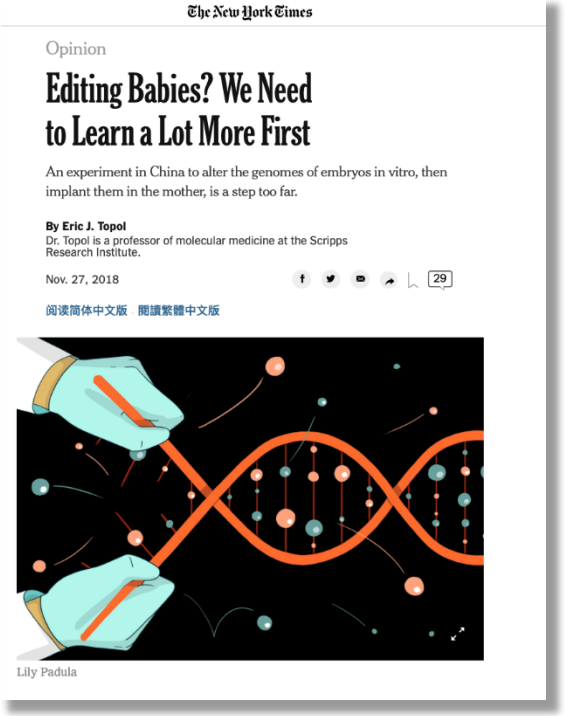
Sax PE, et al. *Lancet*. 2017;390:2073-2082.
Stellbrink H, et al. *J Int AIDS Soc*. 2018;21(suppl 8):8. Abstract O211.

Significance of Bictegravir

- Is B/F/TAF the default initial ART regimen?
- Should those on boosterd regimens switch to INSTIs?

Runner's Up

- **Deleting CCR5 with CRISPR-Cas9**



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Opinion

Editing Babies? We Need to Learn a Lot More First

An experiment in China to alter the genomes of embryos in vitro, then implant them in the mother, is a step too far.

By Eric J. Topol
Dr. Topol is a professor of molecular medicine at the Scripps Research Institute.

Nov. 27, 2018 29

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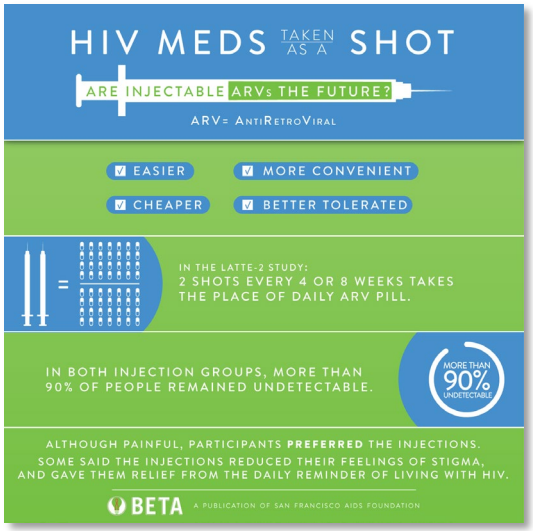

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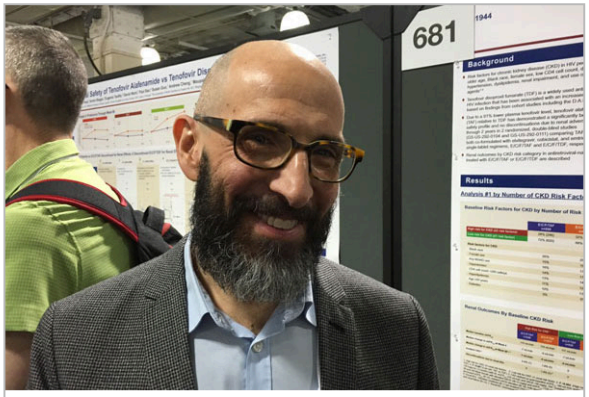
FEATURE

Top 10 HIV Clinical Developments of 2018

By David Alain Wohl, M.D.
From TheBodyPRO

December 18, 2018



David Alain Wohl, M.D. (Credit: Warren Tong)

It's the beginning of the end. Not in some apocalyptic way, but rather in how we think about the prevention and management of HIV.

A tea-leaf reader of the stories that made heads turn this past year could reasonably predict that the antiretroviral regimens of tomorrow will come in pairs, be delivered via a route other than the gastrointestinal tract, or both. The next great leap in HIV prevention will also involve novel ways of getting drugs where they need to be when they need to be there.

Until then, we remain stuck trying to get providers to prescribe pre-exposure prophylaxis (PrEP), and to get those who can benefit from PrEP to take it. All we are saying is: Give PrEP a chance.

Less mutable are racial and socioeconomic influences on HIV outcomes. Inequities in HIV care are intractable, and will remain so as long as society is stacked to shower preference and privileges on some while it thwarts and threatens others. The advocacy that is woven into the fabric of HIV care has supported great progress: The Ryan White Care Act and, in some places, the Affordable Care Act have ensured access to health care for many living with or at risk of HIV acquisition. But these efforts mitigate, and do not obviate, the inherent injustices that make the difference for staying HIV negative or undetectable.

Any recap of where we are really is a preamble to speculation about where we are going. Beyond innovations in medications, the year closed with a sour taste of things to come from a physicist in China who appears to believe he is servicing humanity by messing with it at its most basic level to fix a problem that can be solved more compassionately and ethically in other ways. That this scientist chose, among the options, to re-engineer the genes of babies to make them resistant to the HIV their father carries speaks to an ignorance and fear that no tweaking of a molecule can cure.

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