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MANAGING HIV IN THE NEW DECADE –

Are You Treating Like the Experts?

This continuing medical education activity is provided by

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CME INFORMATION

Target Audience

The intended audience for this activity is infectious disease specialists and other health care professionals involved in the management of patients with human immunodeficiency virus (HIV).

Learning Objectives

Upon successful completion of this activity, participants will be able to:

- Implement treatment regimens for patients with HIV based on the latest clinical evidence as well as individual patient characteristics and preference.
- Select appropriate treatment for patients with HIV who may benefit from switching treatment due to comorbidities, preferences, and/or side effects.
- Review the latest evidence regarding emerging long-acting formulations for HIV management.
- Examine gender issues that may impact choice of ART.
- Incorporate strategies for optimizing adherence to ARTs in patients with HIV.

CME INFORMATION *(continued)*

Accreditation

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CME INFORMATION *(continued)*

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Reviewer: Ronald A. Codario, MD, EMBA, FACP, FNLA, RPVI, CHCP
No relevant financial relationships to disclose.

Vindico Medical Education staff have no relevant financial relationships to disclose.

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CME INFORMATION *(continued)*

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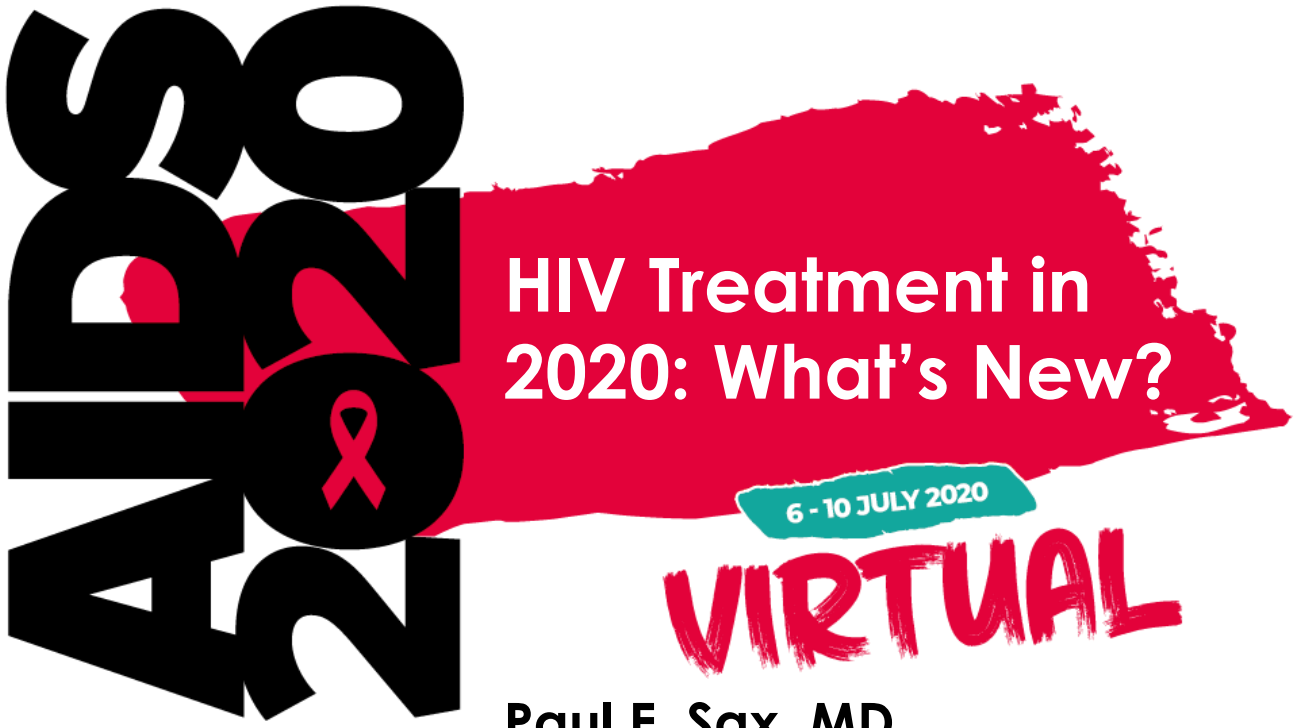

Paul E. Sax, MD
Clinical Director, Division of Infectious Diseases
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Professor of Medicine
Harvard Medical School
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Treatment Update 2020

- What is new over the past year, and why are the following important?
  - **HIV and novel coronavirus disease 2019 (COVID-19)**
  - Latest guidelines for initial therapy
  - Two-drug switch options – what is new?
  - Latest on ART and pregnancy, with new data on DTG + TAF/FTC
  - Cabotegravir versus TDF/FTC for PrEP

ART = antiretroviral therapy; DTG = dolutegravir; PrEP = pre-exposure prophylaxis; TAF/FTC = tenofovir alafenamide/emtricitabine.

COVID-19 and CROI 2020

- February 21: United States with only 30 confirmed cases of COVID-19; Boston with 1 case
- February 26: Biogen executive conference in Boston
- March 2: Biogen notifies employees that many who attended have become sick – later confirmed to be COVID-19 (more than 100 cases)
- March 5: CROI converted from in-person meeting to "virtual" 2 days before it was scheduled to start

How a Premier U.S. Drug Company Became a Virus 'Super Spreader'

Biogen employees unwittingly spread the coronavirus from Massachusetts to Indiana, Tennessee and North Carolina.

New York Times, April 12, 2020

CROI = Conference on Retroviruses and Opportunistic Infections.

THE CORONAVIRUS CRISIS

'Everything Broke Loose': A Doctor And COVID-19 Survivor Recalls His Ordeal

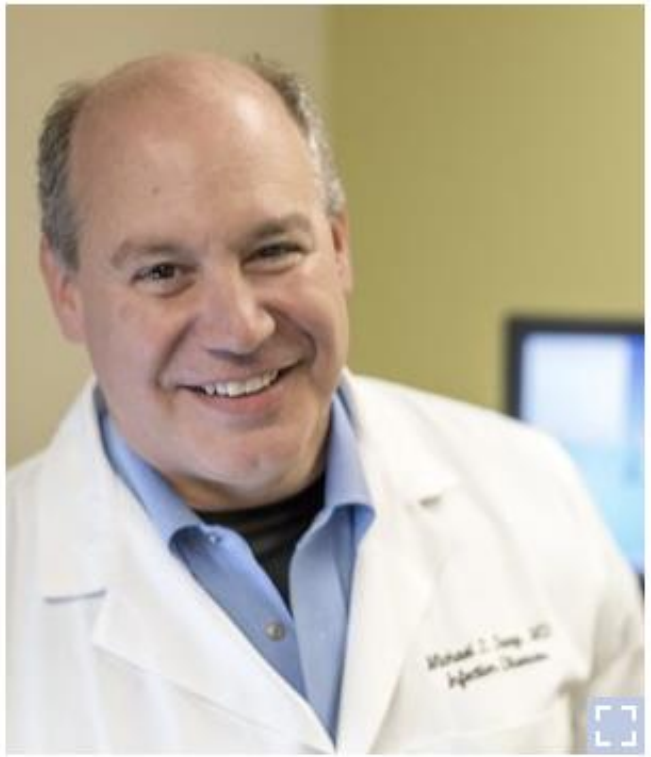
April 11, 2020 · 3:57 PM ET

COLIN DWYER

Dr. Michael Saag studies diseases for a living. The epidemiologist at the University of Alabama, Birmingham, specializes in HIV and AIDS research, so he's familiar with the toll a deadly infection can take on the human body.

No amount of study, however, could have adequately prepared him for having the coronavirus himself.

Almost one month ago, Saag and his son, who is also a physician, came down with symptoms of COVID-19 within days of each other. What came next was days of pain, anxiety and repeatedly dashed hope — until, at last, both men recovered fully.



Dr. Michael Saag, seen at his clinic at the University of Alabama, Birmingham.

Dwyer C. Accessed June 9, 2020. https://www.npr.org/sections/coronavirus-live-updates/2020/04/11/832529963/everything-broke-loose-a-doctor-and-covid-19-survivor-recalls-the-ordeal

COVID-19 in HIV-infected Individuals

Single-center, prospective cohort (Madrid)
51 COVID-19 cases were diagnosed among 2873 HIV-infected individuals (incidence 1.8% [95% CI 1.3–2.3])
COVID-19 presented similar clinical, laboratory, and radiographical features in HIV-infected individuals vs. general population
Those with COVID-19 had a significantly higher prevalence of comorbidities
Lower CD4 cell counts affected disease severity and viral kinetics

Implications

- ✓ HIV-infected individuals should *not* be considered protected from SARS-CoV-2 infection or as having lower risk of severe disease
- ✓ Globally, HIV-infected individuals should receive the same treatment approach as that applied to general population

Vizcarra P, et al. Accessed June 9, 2020. https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(20)30164-8/fulltext

Guidance on COVID-19 for People With HIV

- The limited data available do *not* indicate that HIV is a risk factor for more severe disease
- Older adults (>60 years) and people with a serious underlying medical condition may be at higher risk for severe illness
- Risk for people with HIV getting very sick may be greater for those with advanced HIV (CD4 <200 cells/mm^3) not on ART
- Maintain on-hand at least a 30-day supply of antiretroviral (ARV) drugs and other medications
  - Request a 90-day supply if possible
  - Consider mail order to avoid public pharmacies
- Consider delaying laboratory monitoring and planned switches in therapy
- No indication to change ART based on possible activity of ARVs on SARS-CoV-2

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

US Department of Health and Human Services. Interim Guidance for COVID-19 and persons with HIV. Updated April 21, 2020. Accessed June 9, 2020. https://aidsinfo.nih.gov/guidelines/html/8/covid-19-and-persons-with-hiv--interim-guidance-/0

HIV Treatment Update 2020

- What is new over the past year, and why are the following important?
  - HIV and novel coronavirus disease 2019 (COVID-19)
  - **Latest guidelines for initial therapy**
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  - Cabotegravir versus TDF/FTC for PrEP

DHHS: Recommended Initial Regimens

DHHS (December 2019) Recommended for Most People With HIV
Bictegravir/FTC/TAF
Dolutegravir/ABC/3TC Dolutegravir + FTC/TDF or FTC/TAF Dolutegravir + 3TC*
Raltegravir + FTC/TAF or FTC/TDF

*If HIV RNA <500,000 copies/mL, HBsAg negative, and genotype results available

3TC = lamivudine; ABC = abacavir; HBsAg = hepatitis B surface antigen; TDF = tenofovir disoproxil fumarate.

US Department of Health and Human Services (DHHS). Updated December 18, 2019. Accessed June 9, 2020. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

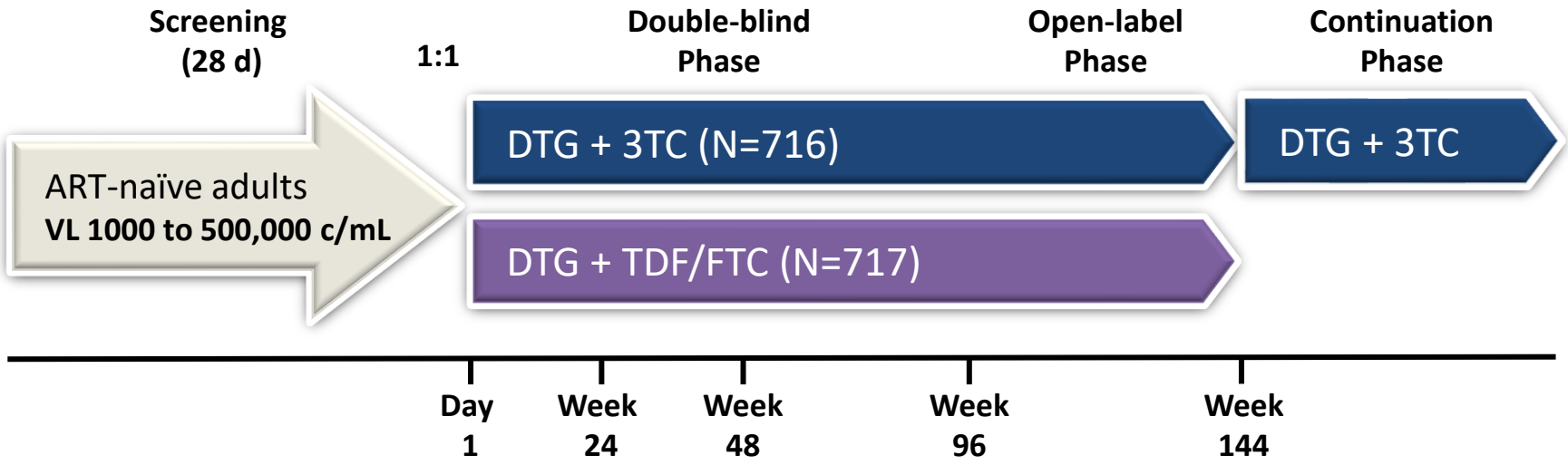
DHHS: Recommended Initial Regimens – With Personal Edits

DHHS (December 2019) Recommended for Most People With HIV
Bictegravir/FTC/TAF
~~Dolutegravir/ABC/3TC~~
Dolutegravir + FTC/TDF or FTC/TAF
Dolutegravir + 3TC*
~~Raltegravir + FTC/TAF or FTC/TDF~~

*If HIV RNA <500,000 copies/mL, CD4 >200 cells/mm^3, HBsAg negative, and genotype results available

US Department of Health and Human Services (DHHS). Updated December 18, 2019. Accessed June 9, 2020. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

GEMINI-1 and GEMINI-2:
Dolutegravir Plus 3TC Versus DTG Plus TDF/FTC



Eligibility criteria

- ≤10 days of prior ART
- No evidence of preexisting viral resistance based on presence of any major resistance-associated mutation
- No HBV infection or need for HCV therapy

Identically designed, randomized, double-blind, parallel-group, multicenter, non-inferiority studies
HBV = hepatitis B virus; HCV = hepatitis C virus; VL = viral load.
Cahn P, et al. *Lancet*. 2019;393(10167)143-155.

GEMINI-1 and -2 Studies: Confirmed Virologic Withdrawals Through Week 96

- Comparable numbers of patients met confirmed virologic withdrawal (virologic failure) criteria in both arms
  - Dolutegravir + 3TC (n=11) and dolutegravir + FTC/TDF (n=7)
  - Similar numbers across treatment arms by baseline HIV RNA level or CD4 count
- No emergent resistance
- Viral load trajectories among treatment failures in both arms suggested nonadherence or treatment interruptions rather than loss of virologic control

Confirmed Virologic Withdrawals

	Dolutegravir + 3TC (n=11)	Dolutegravir + FTC/TDF (n=7)
Timing of withdrawal (number)		
Weeks 12 to 24	5	4
Weeks 4 to 60	3	1
Weeks 72 to 96	3	2
HIV RNA (copies/mL)		
Confirmed virologic withdrawal	206 to 88,000	232 to 7800
At withdrawal visits	59 to 1513	46 to 3011
Reason for confirmed virologic withdrawal (number)		
Nonadherence	5	1
Treatment interruption	2	0
Unknown	4	6

Underwood M, et al. *Top Antivir Med*. 2020;28(1):170. CROI Abstract 483.

HIV Treatment Update 2020

- What is new over the past year, and why are the following important?
  - HIV and novel coronavirus disease 2019 (COVID-19)
  - Latest guidelines for initial therapy
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  - Latest on ART and pregnancy, with new data on DTG + TAF/FTC
  - Cabotegravir versus TDF/FTC for PrEP

DHHS Guidelines: Switch Strategies to Optimize ART to Reduce AEs or DDIs

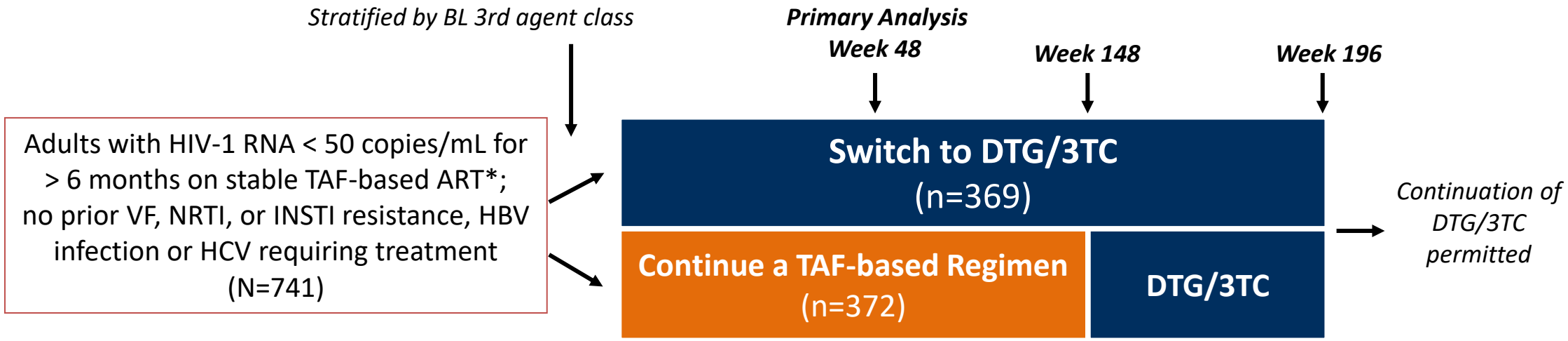
- Assess prior resistance, interactions with concomitant therapies, and the need to decrease or increase concomitant medications
- Strategies to “de-escalate” ART in patients with no drug resistance
  - Switch if suppressed to DTG/RPV or DTG/3TC if no drug–drug interactions (DDIs) that might lower the levels of either drug, no resistance to either drug, no hepatitis B
- If limited drug resistance, recommendations are extrapolated from other studies
  - Within class switch from 1 high-resistance barrier drug to another (DTG to BIC)
  - Between-class switch from 1 high-resistance barrier drug to another (boosted PI to BIC or DTG + at least 1 fully active NRTI)
  - Could extend these considerations to 2-drug therapy if both drugs are fully active
- Limited data and guidance for patients with complex underlying resistance

AEs = adverse events; BIC = bictegravir; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; RPV = rilpivirine.

US Department of Health and Human Services (DHHS). Updated December 18, 2019. Accessed June 9, 2020. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

TANGO: Study Design
Switch to DTG/3TC Versus Continuing a TAF-Based 3-Drug Regimen

- International, randomized, open-label phase 3 noninferiority study



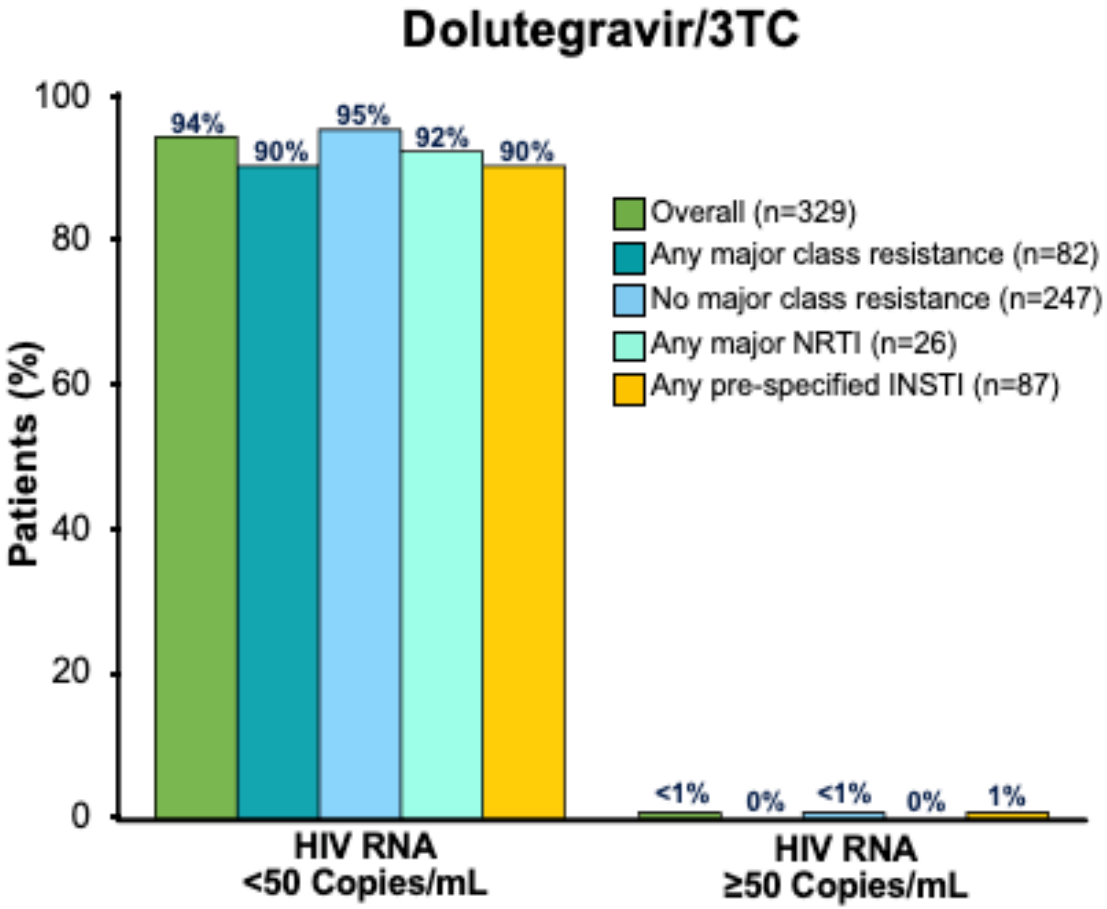
*Initial regimen of FTC/TAF + PI, NNRTI, or INSTI, or TDF switched to TAF ≥ 3 months prior to screening with no other regimen changes.

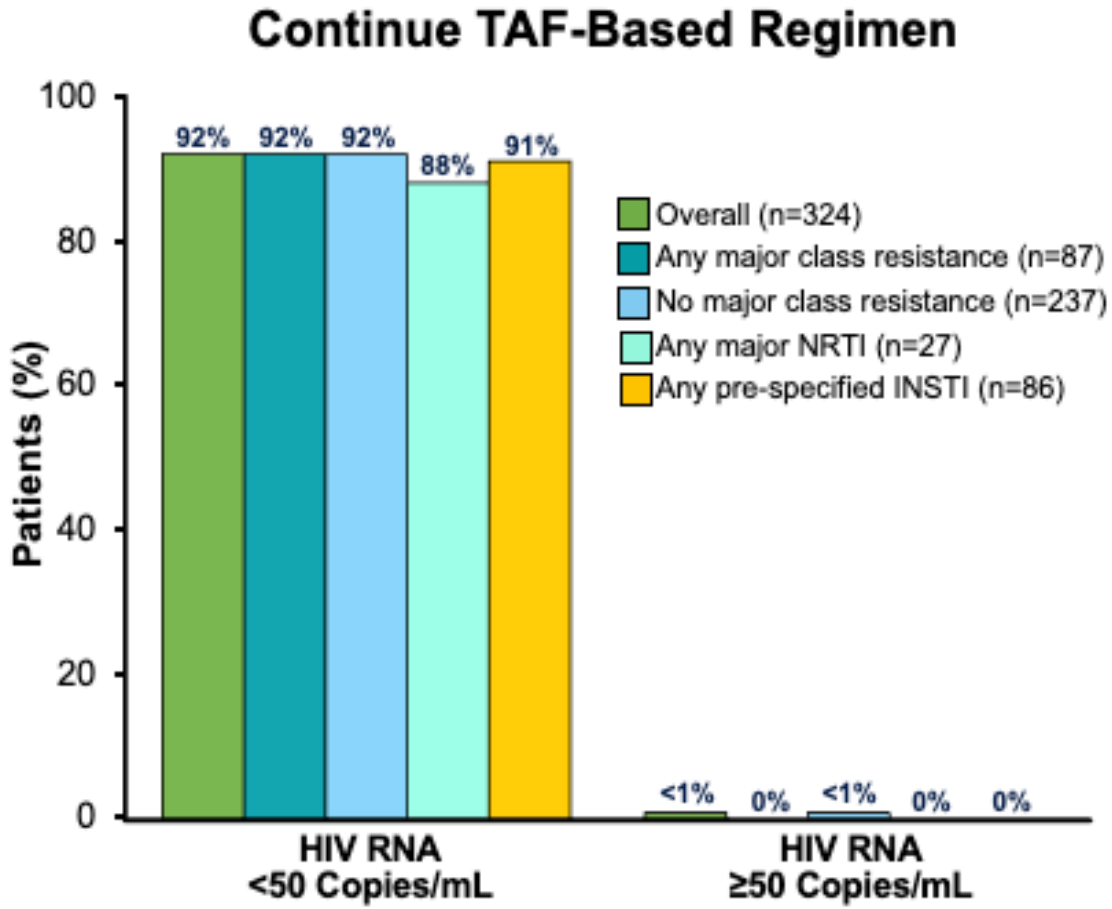
- **Primary endpoint:** VF at week 48 by FDA Snapshot analysis (ITT-E)
  - Noninferiority margin: 4%
  - Secondary endpoint: safety
- **Results:** DTG/3TC was non-inferior in maintaining virologic suppression vs a TAF-based regimen at Week 48, with no virologic failure or emergent resistance reported in the DTG/3TC group

NNRTI = non-nucleoside reverse-transcriptase inhibitor; NRTI = nucleoside reverse-transcriptase inhibitor; PI = protease inhibitor; VF= virologic failure.

van Wyk J, et al. Published January 6, 2020. *Clin Infect Dis*. doi:10.1093/cid/ciz1243

TANGO Study: Archived Resistance Subanalysis



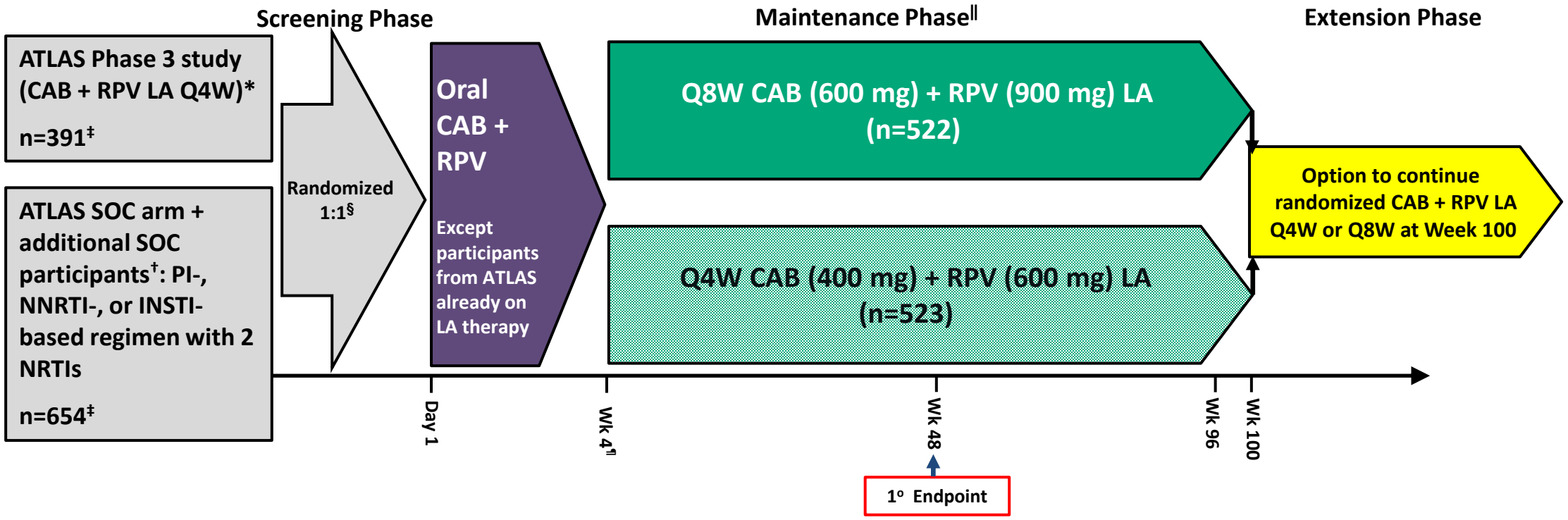


INSTI = integrase stand transfer inhibitor.

Wang R, et al. *Top Antivir Med*. 2020;28(1):173. CROI Abstract 489.

ATLAS-2M Study Design[a]

Phase 3, randomized, multicenter, parallel-group, noninferiority, open-label study

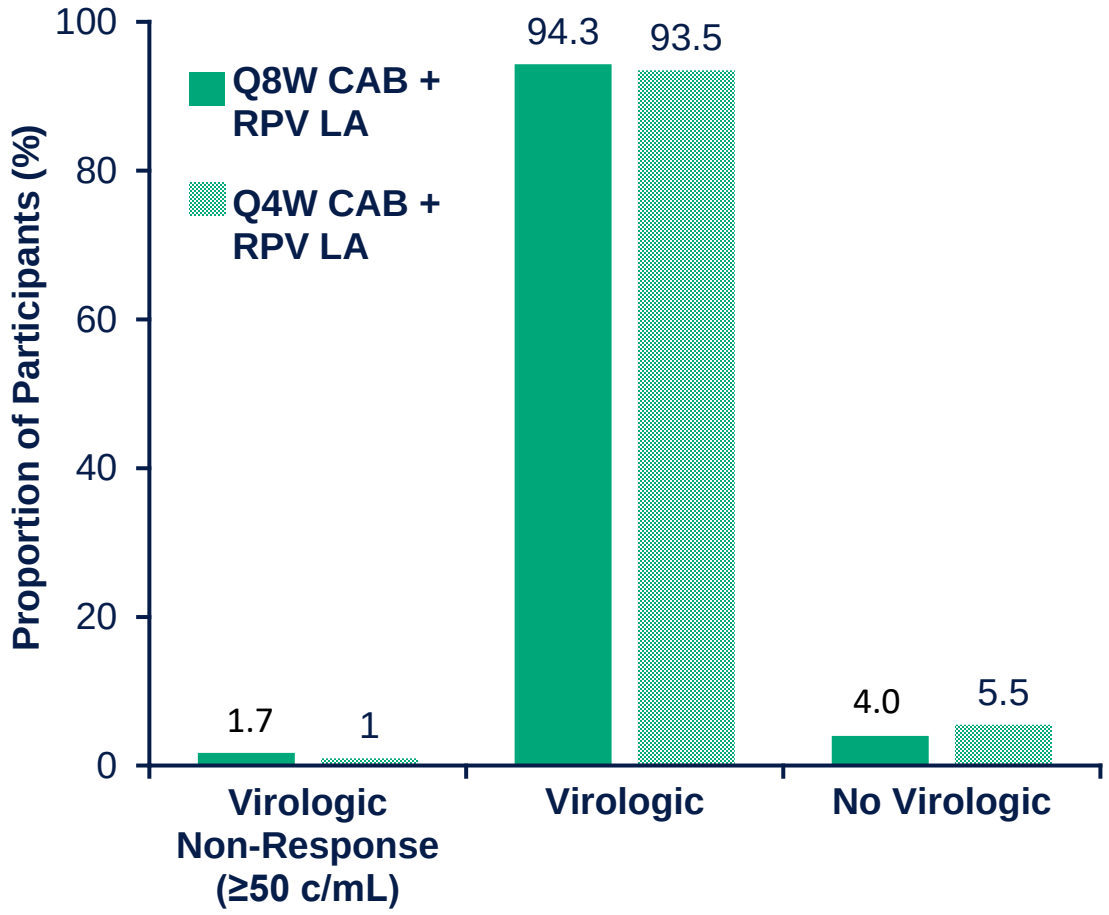


[a]Refer to the presentation for definition of the *, †, ‡, ‖, §, and ¶.

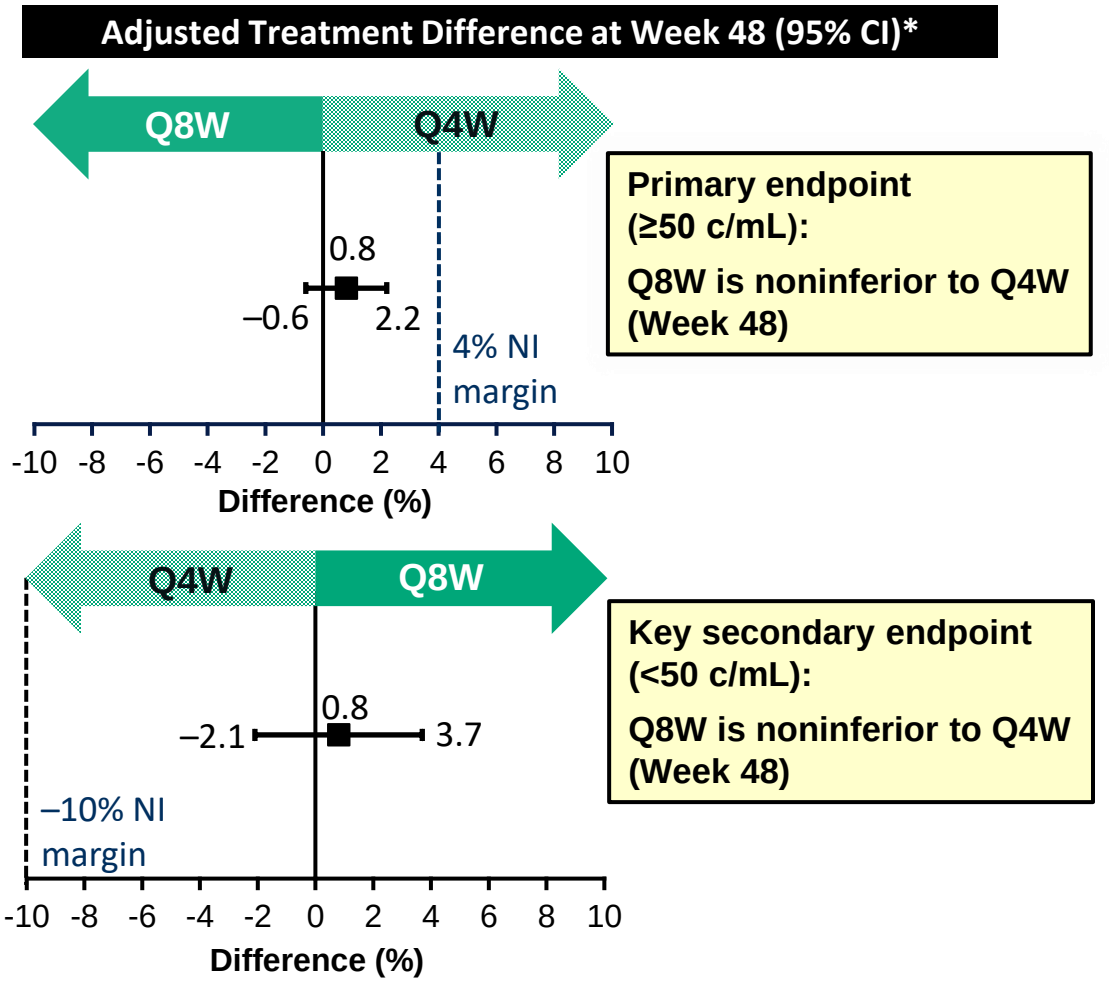
CAB = cabotegravir; LA = long-acting; NRTI = nucleoside reverse transcriptase inhibitor; NNRT = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; Q4W = every 4 weeks; Q8W = every 8 weeks; RPV = rilpivirine; SOC = standard of care; Wk = week.

Overton ET, et al. Presented virtually at CROI 2020. Abstract 34. Accessed June 10, 2020. http://www.croiwebcasts.org/console/player/44585?mediaType=slideVideo&

ATLAS-2M: Results



Participant numbers: n=522 Q8; n=523 Q4.



*Based on CMH stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1–24 weeks, >24 weeks).

CMH = Cochran–Mantel–Haenszel; NI = noninferiority.

Overton ET, et al. Presented virtually at CROI 2020. Abstract 34. Accessed June 10, 2020. http://www.croiwebcasts.org/console/player/44585?mediaType=slideVideo&

ATLAS-2M: Virologic Failure, Resistance, and Injection Site Reactions (ISRs), and Patient Preferences

Outcome	CAB LA + RPV LA Q8W (n=522)	CAB LA + RPV LA Q4W (n=523)
CVF, n (%)	8 (1.5)	2 (0.4)
CVF with RPV RAMs,* n/N	6/8	1/2
Treatment-emergent RPV RAMs	K101E, E138E/K, E138A, Y188L	K101E, M230L
CVF with INSTI RAMs,* n/N	5/8	2/2
Treatment-emergent INSTI RAMs	Q148R, N155H†	E138E/K, Q148R, N155N/H

*Post hoc BL PBMC HIV-1 DNA testing. †Or a mixture.

- CAB LA + RPV LA well tolerated
  - 98% of ISRs were grade 1/2; median duration was 3 days
- Patients preferred CAB LA + RPV LA over oral therapy
- Patient preference
  - No prior CAB/RPV: 98% preferred injectable to oral therapy
  - Prior Q4 week CAB/RPV: 94% preferred Q8 week

CVF = confirmed virologic failure; PBMC = peripheral blood mononuclear cell; RAM = resistance associated mutation.

Overton ET, et al. Presented virtually at CROI 2020. Abstract 34. Accessed June 10, 2020. http://www.croiwebcasts.org/console/player/44585?mediaType=slideVideo&

Question for Panel

When injectable cabotegravir/rilpivirine is approved, how will you prescribe it?

A. Every 4 weeks

B. Every 8 weeks

C. Every 4 weeks initially, then every 8 weeks

HIV Treatment Update 2020

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  - Cabotegravir versus TDF/FTC for PrEP

What to Start in Pregnancy: DHHS Guidelines April 14, 2020

Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection *and* Interventions to Reduce Perinatal HIV Transmission in the United States

Developed by the HHS Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission—A Working Group of the Office of AIDS Research Advisory Council (OARAC)

Two NRTIs

Abacavir/3TC

or

TDF/FTC or TDF/3TC

Plus

DO NOT USE:

TAF (insufficient data)
Bictegravir (insufficient data)
Elvitegravir/cobi (PK concerns)
DRV/cobi (PK concerns)
ATV/cobi (PK concerns)
DOR (insufficient data)
Two-drug regimens

Integrase inhibitor:

Raltegravir (twice daily) or

Dolutegravir (regardless of trimester)

or

Protease inhibitor:

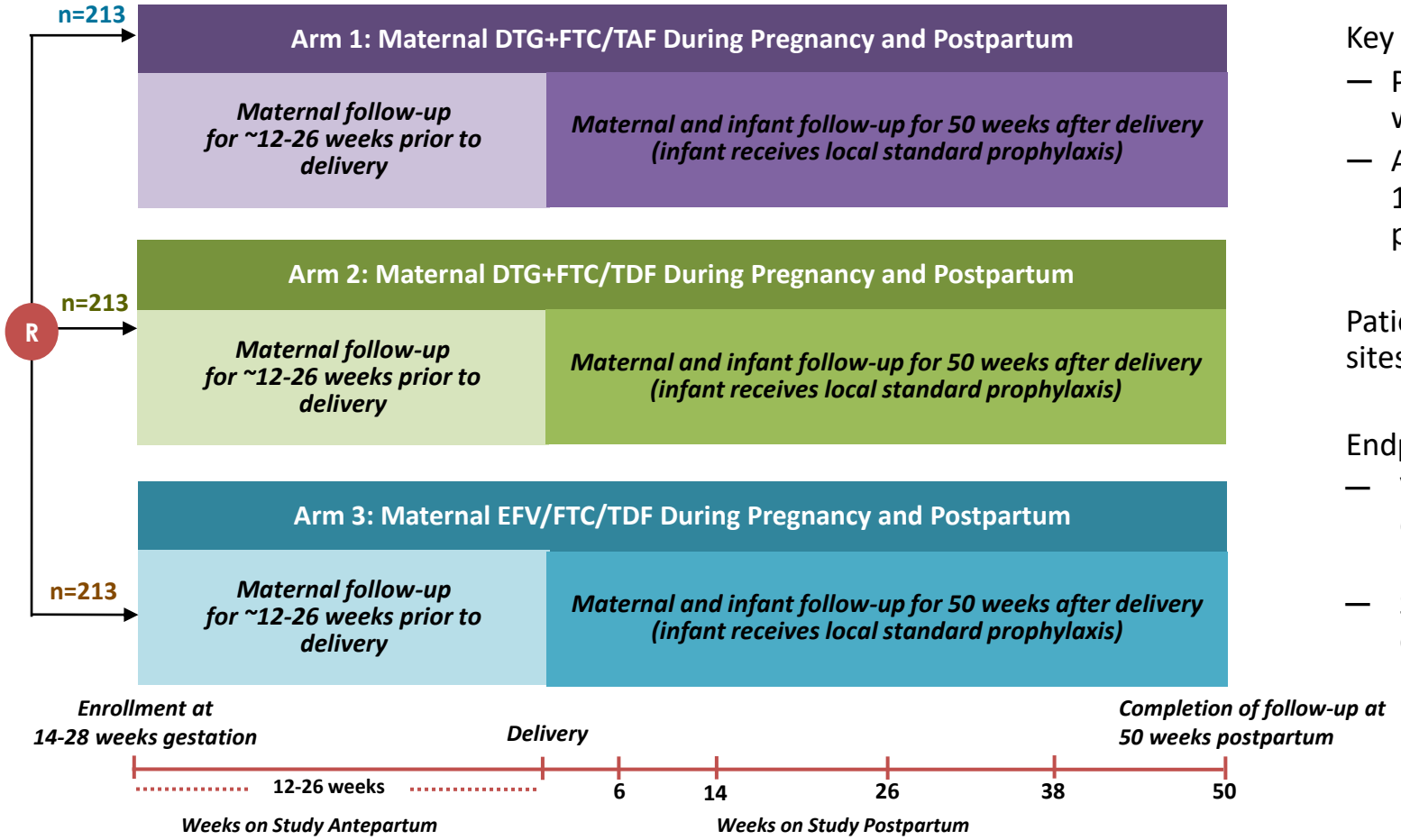
Darunavir/ritonavir (twice daily) or

Atazanavir/ritonavir

cobi = cobicistat; DOR = doravirine; PK = pharmacokinetics.

US Department of Health and Human Services. Updated April 14, 2020. Accessed June 10, 2020. https://aidsinfo.nih.gov/guidelines/html/3/perinatal/224/whats-new-in-the-guidelines

IMPAACT 2010: DTG+FTC/TAF vs DTG+FTC/TDF vs EFV/FTC/TDF in Pregnancy



Key eligibility criteria:

- Pregnant WLHIV 14-28 weeks gestation
- ART-naïve (up to 14 days ART in current pregnancy allowed)

Patients were enrolled at 22 sites in 9 countries

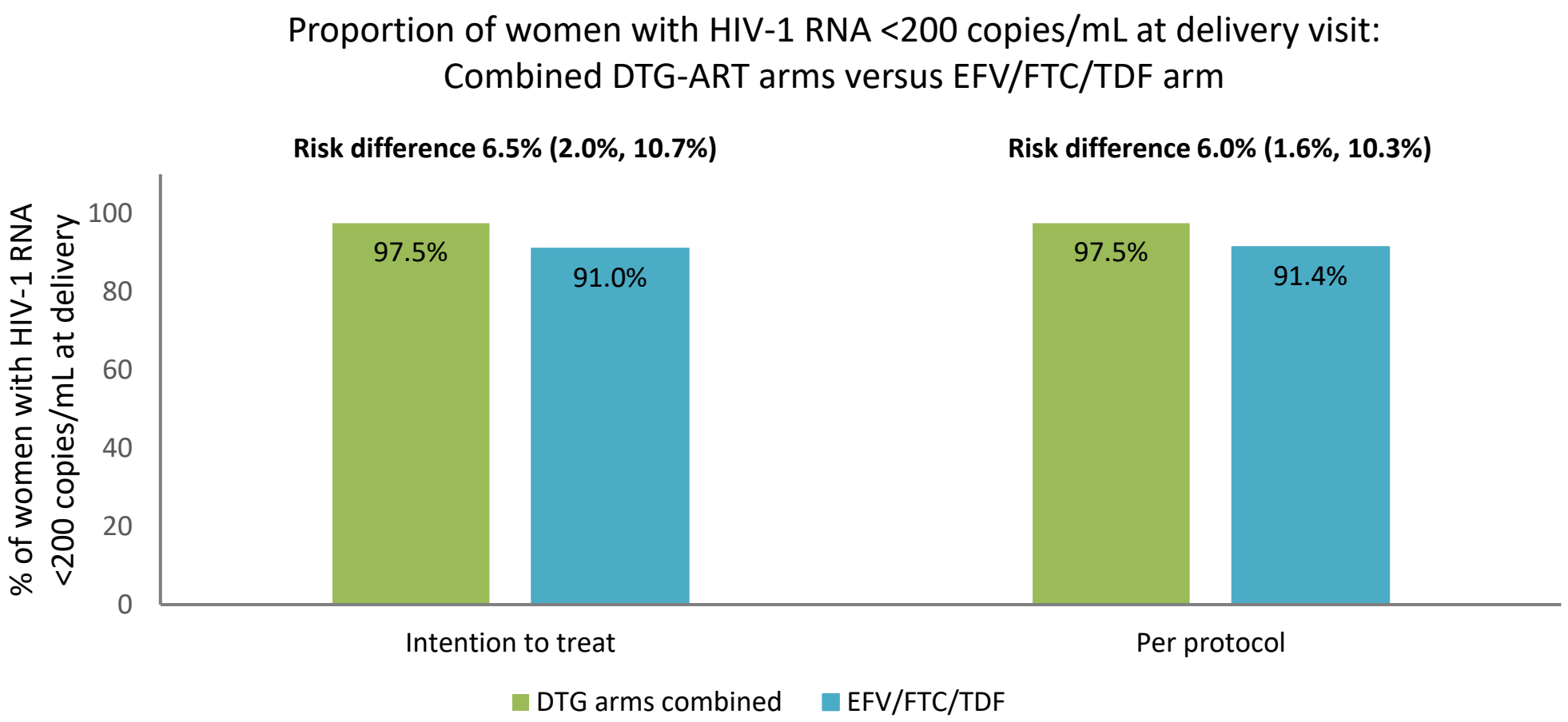
Endpoints:

- Viral: VL <200 c/mL at delivery (10% noninferiority
- Safety: adverse pregnancy or infant outcomes

EFV = efavirenz; WLHIV = women living with HIV

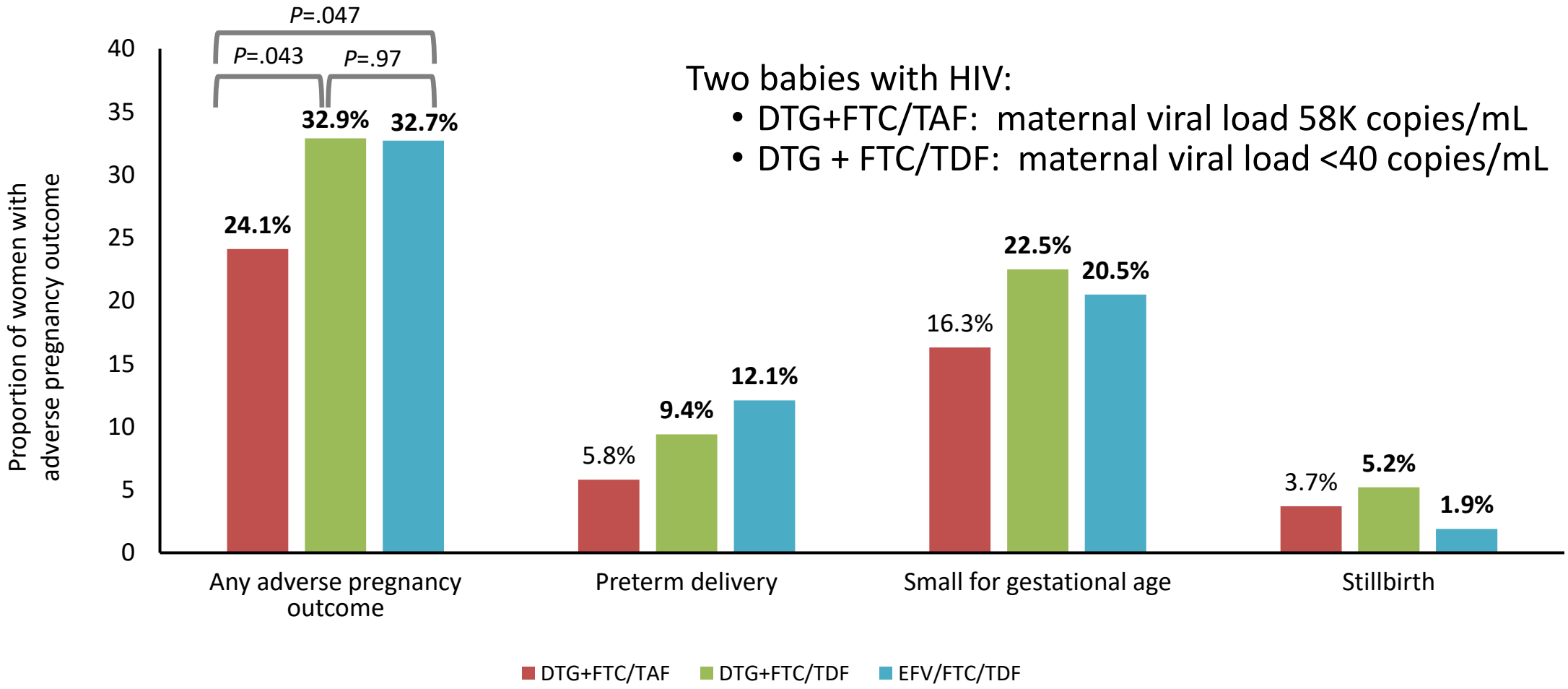
Chinula L, et al. *Top Antivir Med*. 2020;28(1):42. CROI Abstract 130LB.

IMPAACT 2010: DTG Superior to EFV in Pregnancy



Chinula L, et al. *Top Antivir Med*. 2020;28(1):42. CROI Abstract 130LB.

IMPAACT 2010: Adverse Pregnancy Outcomes by Arm



Two babies with HIV:

- DTG+FTC/TAF: maternal viral load 58K copies/mL
- DTG + FTC/TDF: maternal viral load <40 copies/mL

Chinula L, et al. *Top Antivir Med*. 2020;28(1):42. CROI Abstract 130LB.

IMPAACT 2010: Practice-Changing Results

- For women diagnosed with HIV during pregnancy, DTG preferred over EFV-based regimens due to higher viral suppression at the time of delivery
  - Does not address the DTG and risk of neural tube defects issue, which relates to DTG at the time of conception
- TAF/FTC better than TDF/FTC for pregnancy outcomes (preterm delivery, small for gestational age) – change in guidelines warranted?
- Weight greatest with DTG + TAF/FTC but closest to recommended weight gain during pregnancy

Chinula L, et al. *Top Antivir Med*. 2020;28(1):42. CROI Abstract 130LB.

HIV Treatment Update 2020

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  - Latest on ART and pregnancy, with new data on DTG + TAF/FTC
  - **Cabotegravir versus TDF/FTC for PrEP**

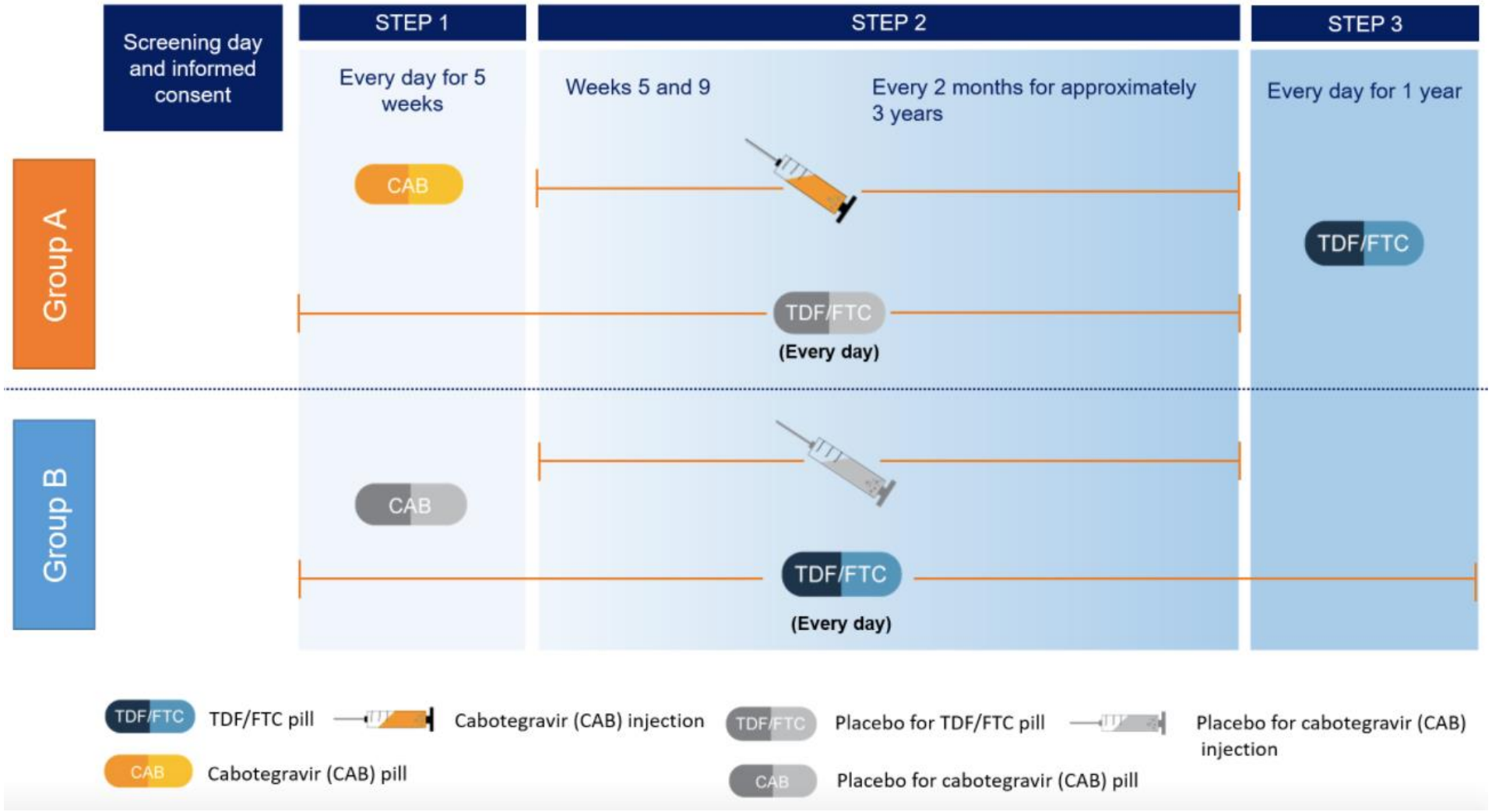
HPTN 083: Cabotegravir (CAB) Versus TDF/FTC for PrEP

- Placebo-controlled, double-blind trial comparing injectable CAB every 8 weeks with daily TDF/FTC
- *Inclusion criteria*
  - MSM and transgender women who have sex with men
  - Age >18 years
  - High-risk for HIV acquisition: Reported sexual behavior, stimulant drug use, rectal gonorrhea/chlamydia or syphilis in prior 6 months
  - HIV, HBV, HCV negative
  - "Good health" based on CBC, CMP
- *Exclusion criteria*
  - Positive HIV screening test
  - IDU within 90 days
  - Medical comorbidities: cardiovascular disease, seizure disorder, liver disease, coagulopathy
  - Condition that would interfere with injections or evaluation for injection site reactions
- Targeted highest risk individuals – Age <30 years, black MSM, transgender women

CBC = complete blood count; CMP = comprehensive metabolic panel; HBV = hepatitis B virus; HCV = hepatitis C virus; IDU = injection drug user; HPTN = HIV Prevention Trials Network; MSM = men who have sex with men.

HPTN 083. https://www.hptn.org/research/studies/hptn083;
HPTN 083 FAQ. https://www.hptn.org/sites/default/files/inline-files/HPTN%20083%20FAQ_A4_May2020_0.pdf. Accessed June 11, 2020.

HPTN 083: Study Design



HPTN 083 FAQ. https://www.hptn.org/sites/default/files/inline-files/HPTN%20083%20FAQ_A4_May2020_0.pdf. Accessed June 11, 2020.

HPTN 083: May 2020 Data Safety Monitoring Board Meeting

- 50 incident HIV infections
  - TDF/FTC arm: 38 (incidence 1.21%)
  - CAB arm: 12 (incidence 0.38%)
- Both substantially lower than the anticipated 4.5% incidence for this group
- Blinded portion of the study stopped due to 3-fold fewer cases in CAB arm
- Full data to be presented at this AIDS 2020 conference!

NIAID Newsroom. May 18, 2020. Accessed June 10, 2020. https://www.hiv.gov/blog/nih-study-long-acting-injectable-drug-prevents-hiv-among-men-who-have-sex-men-and-transgender
HPTN 083 FAQ. https://www.hptn.org/sites/default/files/inline-files/HPTN%20083%20FAQ_A4_May2020_0.pdf. Accessed June 11, 2020.

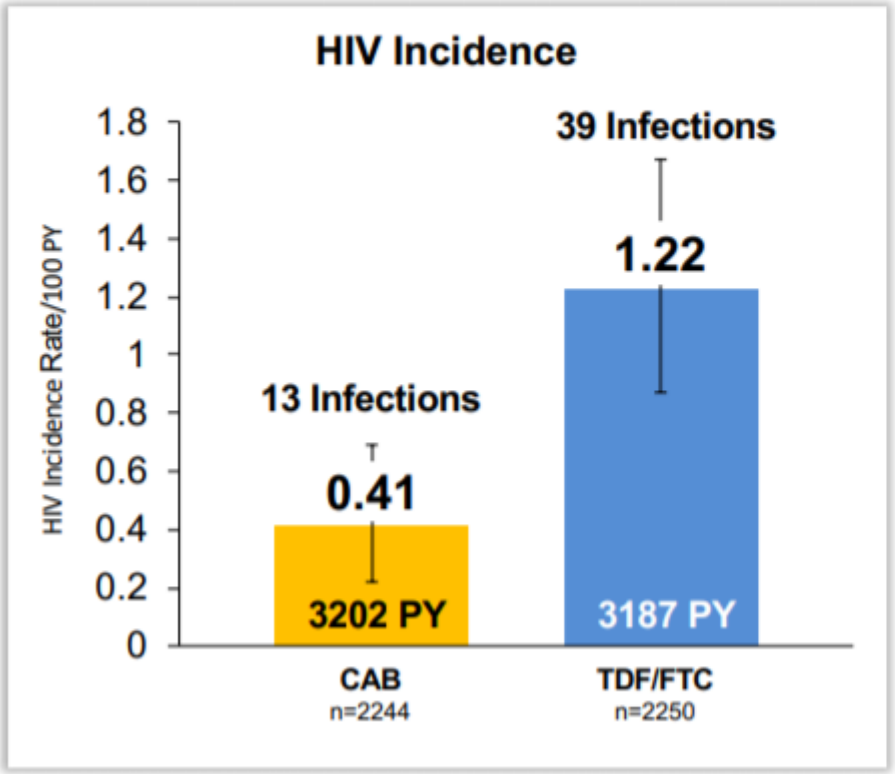
HPTN 083: Update from AIDS2020

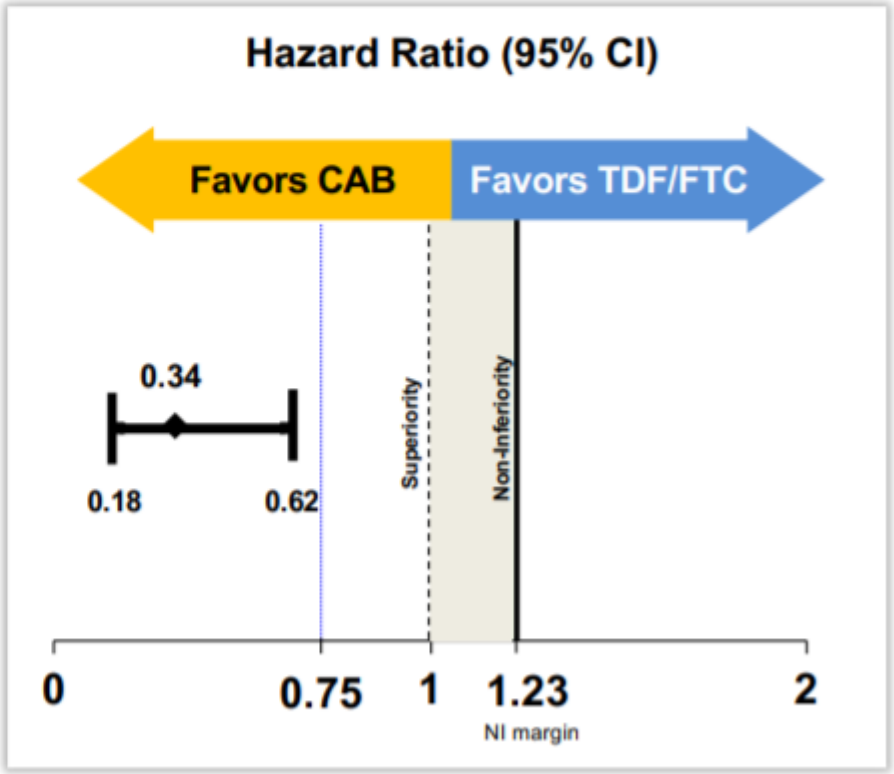
HIV Incidence CAB vs. TDF/FTC

52 HIV infections in 6389 PY of follow-up

1.4 (IQR 0.8-1.9) years median per-participant follow-up

Pooled incidence 0.81 (95%CI 0.61-1.07) per 100 PY





PrEP regimen containing CAB-LA was superior to a daily oral regimen of TDF/FTC in HPTN 083, with a 66% reduction in risk of HIV infection observed in participants receiving CAB compared to TDF/FTC

Awaiting results for cisgender women (HPTN 084)

CI, confidence interval

HPTN 083 Study Demonstrates Superiority of Cabotegravir for the Prevention of HIV. https://www.hptn.org/news-and-events/announcements/hptn-083-study-demonstrates-superiority-cabotegravir-prevention-hiv Accessed July 7, 2020.

Results: https://www.hptn.org/sites/default/files/inline-files/HPTN083_PrimaryAIDS2020_Landovitz-Final_web.pdf. Landovitz RJ et al. AIDS 2020, #OAXLB01.

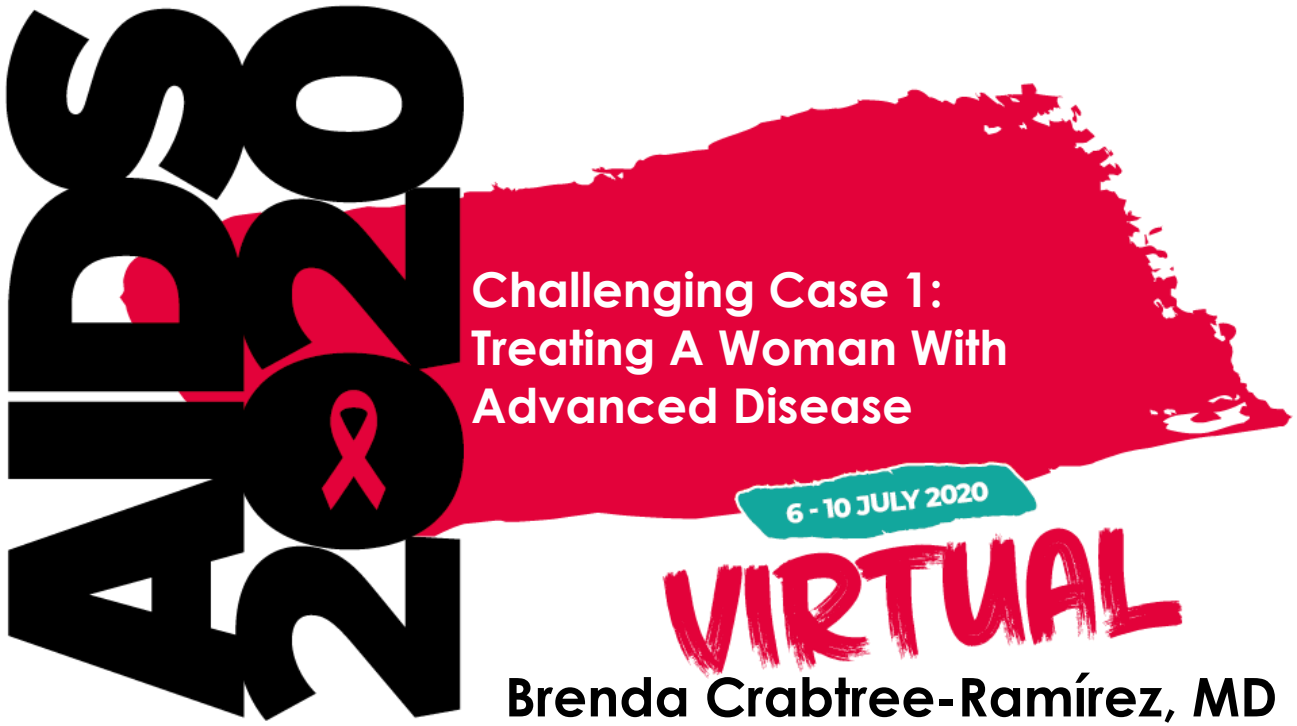
Advances in HIV Treatment: Summary

- COVID-19: No apparent increased severity among stable people with HIV
- Recommended initial regimens now include a 2-drug option: DTG/3TC
  - Comparable efficacy to 3-drug regimens, with low resistance risk
  - Not intended for chronic HBV, HIV RNA >500,000 copies/mL, and possibly CD4 <200 cells/mm^3
- Injectable CAB/RPV every 8 weeks is noninferior to every 4 weeks
- In women starting ART during pregnancy, TAF/FTC plus DTG highly effective and associated with best pregnancy outcomes
- CAB for PrEP highly promising

Moderated by Anton Pozniak MD, FRCP
Consultant Physician
Professor Clinical Research
Chelsea and Westminster Hospital and LSHTM
United Kingdom

Questions for Panel

- In what clinical situations will LA therapy be most useful?
- Do you think moving appointments from every 6 months to every 2 months is going to be a barrier to LA therapy?
- Do you think that injections will reduce stigma in patients with HIV?
- Is LA therapy the solution for all patients with adherence issues?
- What tools may assist providers in implementing LA injectables into their clinic?

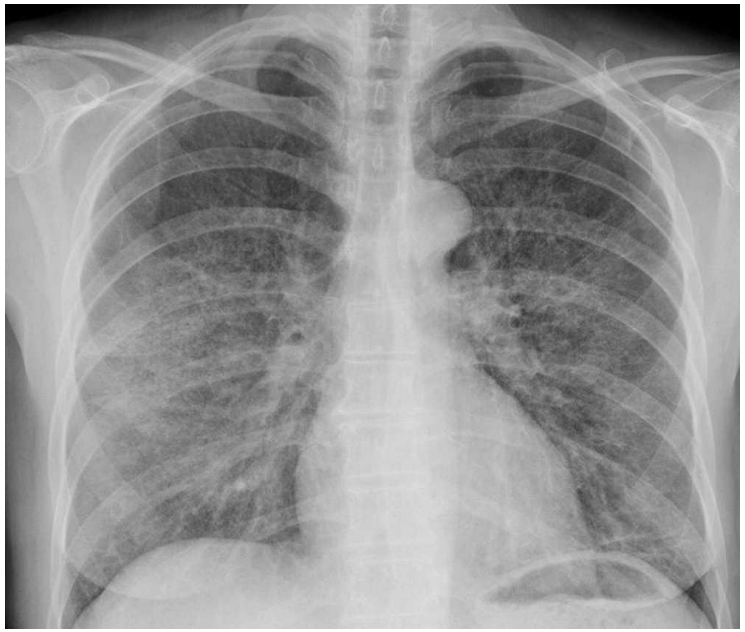


Brenda Crabtree-Ramírez, MD
Assistant Professor
HIV Program at Universidad Nacional Autónoma de México
Department of Infectious Diseases
Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán
Mexico City, Mexico

Case 1: Woman With Advanced Disease

A 25-year-old woman was recently diagnosed with HIV and *Pneumocystis jirovecci* pneumonia (April 2020). At that time, she had a CD4 cell count of 110 cells/mm^3 and an HIV RNA viral load of 840,780 copies/mL. She also has hypothyroidism that is treated with levothyroxine.

- She was hospitalized in April 2020 with pneumonia.
- A PCR test for SARS-CoV-2 was performed, which was negative. Therefore, she was tested for HIV, and PCP was suspected.
- She was treated with TMP/SMZ, with clinical improvement. Other opportunistic infections were ruled out.
- She attended her follow-up visit after hospital discharge, and it was decided to start her on ART.
- She indicated her desire to become pregnant in the future.



ART = antiretroviral therapy; CD4 = T-helper cells; HIV = human immunodeficiency virus; PCP= *Pneumocystis jirovecci* pneumonia; PCR = polymerase chain reaction; TMP/SMZ = trimethoprim/sulfamethoxazole.

Question for Panel

In women of childbearing age, with the possibility of becoming pregnant, and advanced HIV disease…

<u>Which antiretroviral therapy would be appropriate?</u>

Guidelines: First-line ART Regimens

DHHS (2019)	IAS-USA (2018)	CENSIDA (2019)
• BIC/TAF/FTC • DTG/ABC/3TC, if HLA-B*5701 negative • DTG + TAF or TDF/FTC or 3TC • RAL + TAF or TDF/FTC or 3TC • DTG/3TC, except for individuals with HIV-1 RNA >500,000 c/mL, with HBV or for whom results of HIV genotypic resistance testing or HBV testing are not yet available	• BIC/TAF/FTC • DTG/ABC/3TC, if HLA-B*5701 negative • DTG + TAF/FTC	Coformulated • BIC/TAF/FTC • DTG/ABC/3TC Not coformulated • DTG + TAF/FTC or TDF/XTC or TDS/XTC

3TC = lamivudine; ABC = abacavir; BIC = bictegravir; CENSIDA = Centro Nacional para la Prevención y el Control del VIH y el sida; DHHS = US Department of Health and Human Services; DTG = dolutegravir; FTC = emtricitabine; HBV = hepatitis B virus; IAS = International Antiviral Society; RAL = raltegravir; TAF = tenofovir alafenamide fumarate; TDF = tenofovir disoproxil fumarate; TDS = tenofovir disoproxil succinate; XTC = lamivudine or emtricitabine.

Antiretroviral Management Guide for People with HIV. 2019. National Center for the Prevention and Control of HIV and AIDS. Accessed 5 June 2020. https://www.gob.mx/cms/uploads/attachment/file/470115/Fragmento_Gu_a_de_Manejo_ARV.pdf
US Department of Health and Human Services. Updated December 18, 2019. Accessed June 5, 2020. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf
Saag MS, et al. *JAMA*. 2018;320(4):379-396.

INSTI Efficacy at CD4 <200 cells/mm^3

Regimen	Study	Study efficacy (<200 cells/mm^3), %	Comparator efficacy, %
RAL+ 2 INSTIs vs **EFV + 2 INSTIs**	**STARTMRK**	89	**85**
RAL 400 bid vs **RAL 1200 qd**	**ONCEMRK**	88	**85**
DTG + 2 INSTIs vs **RAL 2 INSTIs**	**SPRING-2**	78	**68**
DTG/ABC/3TC vs **EFV/TDF/FTC**	**SINGLE**	79	**77**
DTG + 2 INSTIs vs **DRV/r + 2 INSTIs**	**FLAMINGO**	91	**79**
BIC/FTC/TAF vs **DTG/ABC/3TC**	**Study 1489**	83	**81**
BIC/FTC/TAF vs **DTG/FTC/TAF**	**Study 1490**	95	**100**
DTG + 1 INSTI vs **DTG + 2 INSTIs**	**GEMINI-1 and -2**	79	**93**

bid = twice daily; EFV = efavirenz; INSTI = integrase stand transfer inhibitor; qd = once per day.

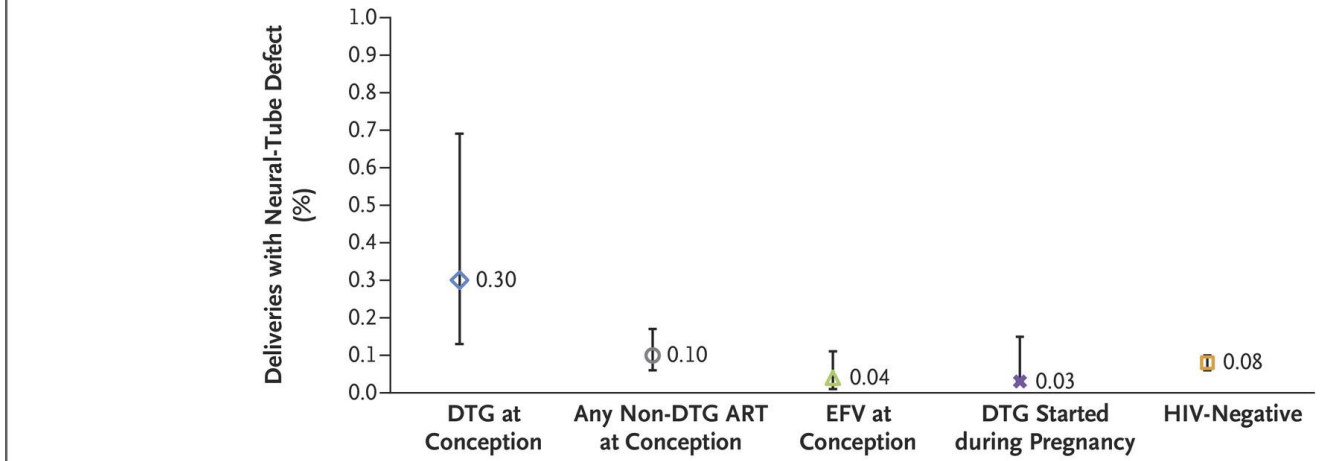
Lennox JL, et al. *J Acquir Immune Defic Syndr*. 2010;55(1):39-48; Cahn P, et al. *J Acquir Immune Defic Syndr*. 2018;78(5):589-598; Raffi F, et al. *Lancet*. 2013;381(9868):735-743; Walmsley SL, et al. *N Engl J Med*. 2013;369(19):1807-1818; Clotet B, et al. *Lancet*. 2014;383(9936):2222-2231; Gallant J, et al. *Lancet*. 2017;390(10107):P2063-P2072; Sax PE, et al. *Lancet*. 2017;390(10107):P2073-P2082; Cahn P, et al. *Lancet*. 2019;393(10167):143-155.

When Initiating ART in Women, Circumstances Must Be Taken Into Consideration

Conception and contraception

Pregnancy and lactation

Adolescents and post-menopausal women



	DTG at Conception	Any Non-DTG ART at Conception	EFV at Conception	DTG Started during Pregnancy	HIV-Negative
No. of Neural-Tube Defects	5	15	3	1	70
No. of Exposures	1683	14,792	7959	3840	89,372
Percent with Defect (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) — Percentage Points	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)

Data 2019: 0.3% DTG vs 0.1% non-DTG ART;
estimated difference: 0.20% to 0.27%

From Zash R, et al. *N Engl J Med*. 2019;381(9):827-840.

Case 1 (cont'd)

- After family planning counseling, the patient decided to use an intrauterine device as her contraception method
- Since 2019, Mexico has made massive purchases of BIC/TAF/FTC for first-line regimen, and the patient was started on that regimen, with adequate tolerance and adherence
- 5 weeks later, she developed fever and an enlarged cervical lymph node. An aspirate biopsy was performed and GeneXpert testing for TB was positive

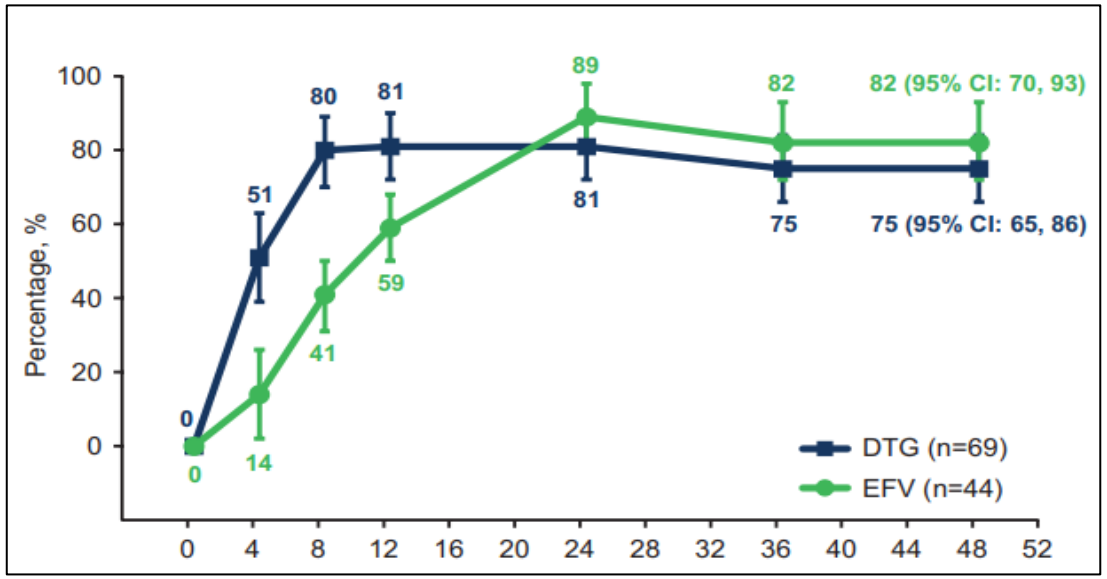
TB = tuberculosis.

Question for Panel

In the context of unmasked TB, what would you do about the current ART…

<u>Which antiretroviral therapy would be appropriate?</u>

ART and Tuberculosis Treatment



Proportion of participants in the ITT-E population with Snapshot HIV-1 RNA ≤50 copies/mL, by week following initiation of antiretroviral therapy with DTG or EFV.

Summary of Snapshot Study Outcomes, by Visit, Treatment Group, and Study Population

Arm	ITT-E 24 weeks	ITT-E 48 weeks	PP 48 weeks
Dolutegravir	**56/69 (81%)** 95% CI 72–90%	**52/69 (75%)** 95% CI 65–86%	**49/62 (79%)** 95% CI 69–89%
Efavirenz	**39/44 (89%)** 95% CI 79–98%	**36/44 (82%)** 95% CI 70–93%	**33/41 (80%)** 95% CI 68–93%

Outcomes data indicate participants with plasma HIV-1 RNA <50 copies/mL.

Participants on rifampicin-based tuberculosis treatment ≤8 weeks were randomized (3:2) to receive DTG (50 mg twice daily both during and 2 weeks after tuberculosis therapy, then 50 mg once daily) or efavirenz (EFV; 600 mg daily) with 2 nucleoside reverse transcriptase inhibitors for 52 weeks.
ITT-E = intent-to-treat exposed; PP = per protocol.
Dooley KE, et al. *Clinical Infect Dis*. 2020;70(4):549-556. Open Access.

Case 1 (cont'd)

- The patient was switched to DTG + TDF/FTC and placed on anti-TB therapy, with good tolerability and clinical improvement

Case 1b: Transgender Woman With Advanced Disease

A 25-year-old transgender woman was recently diagnosed with HIV and *Pneumocystis jirovecci* pneumonia (April 2020). At that time, she had a CD4 cell count of 110 cells/mm^3 and an HIV RNA viral load of 840,780 c/mL.

She has a BMI of 30 kg/m^2 and is on hormone therapy (estradiol and spironolactone), without removal of testicles.

She received treatment for PCP, with great clinical improvement.

BMI = body mass index.

Question for Panel

In transgender women with hormone therapy…

<u>Which ART would be appropriate?</u>

Drug Interactions

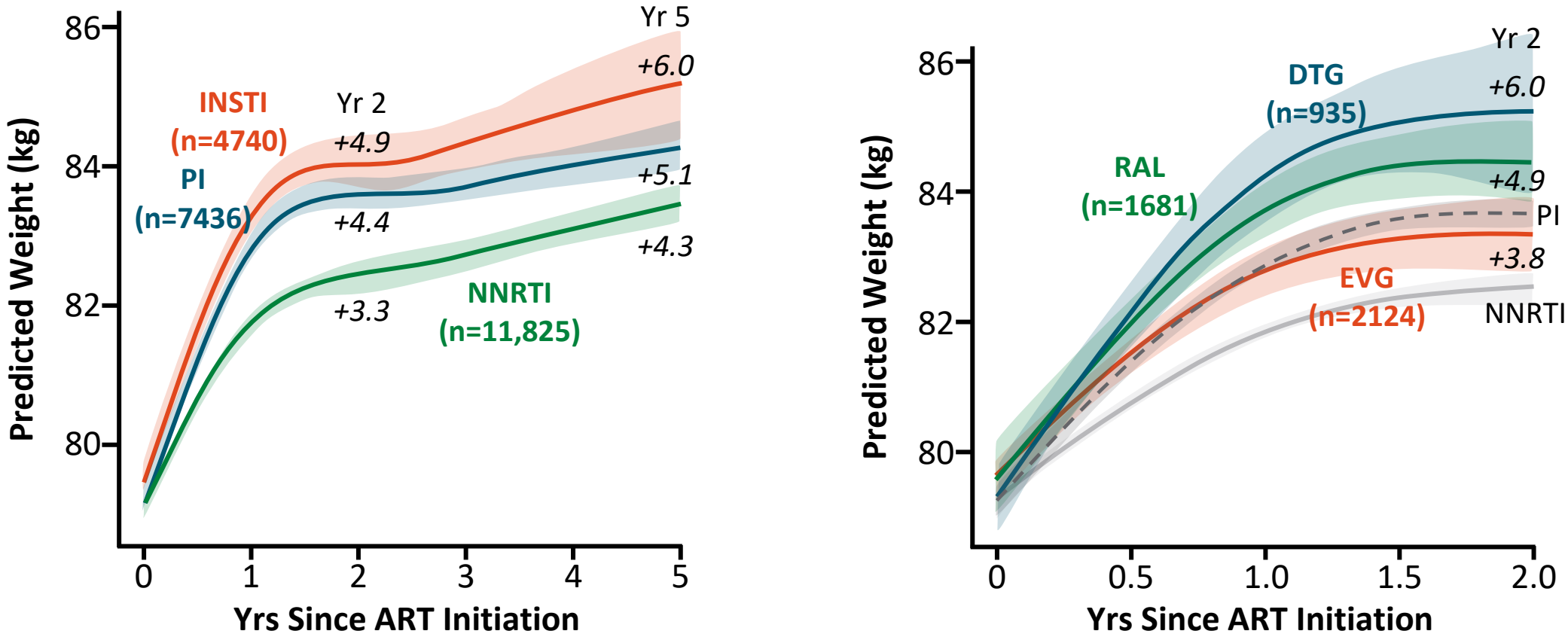
ART Agent	Hormone	Interaction
BIC/FTC/TAF	**Estradiol** **Spironolactone**	**No interaction expected**
DTG/3TC	Estradiol Spironolactone	No interaction expected
DTG/ABC/3TC	Estradiol Spironolactone	No interaction expected
DTG/FTC/TAF	Estradiol Spironolactone	No interaction expected
DRV/c	Estradiol Spironolactone	**Potential interaction with DRV/c and estradiol**
DRV/r	Estradiol Spironolactone	**Potential interaction with DRV/r and estradiol**

c = cobicistat; DAR = darunavir; r = ritonavir.

Data from HIV Drug Interactions; University of Liverpool. Updated June 15, 2020. Accessed June 15, 2020. https://www.hiv-druginteractions.org/checker

NA-ACCORD: Weight Gain Among 24,001 ART-Naïve Patients Initiating Treatment

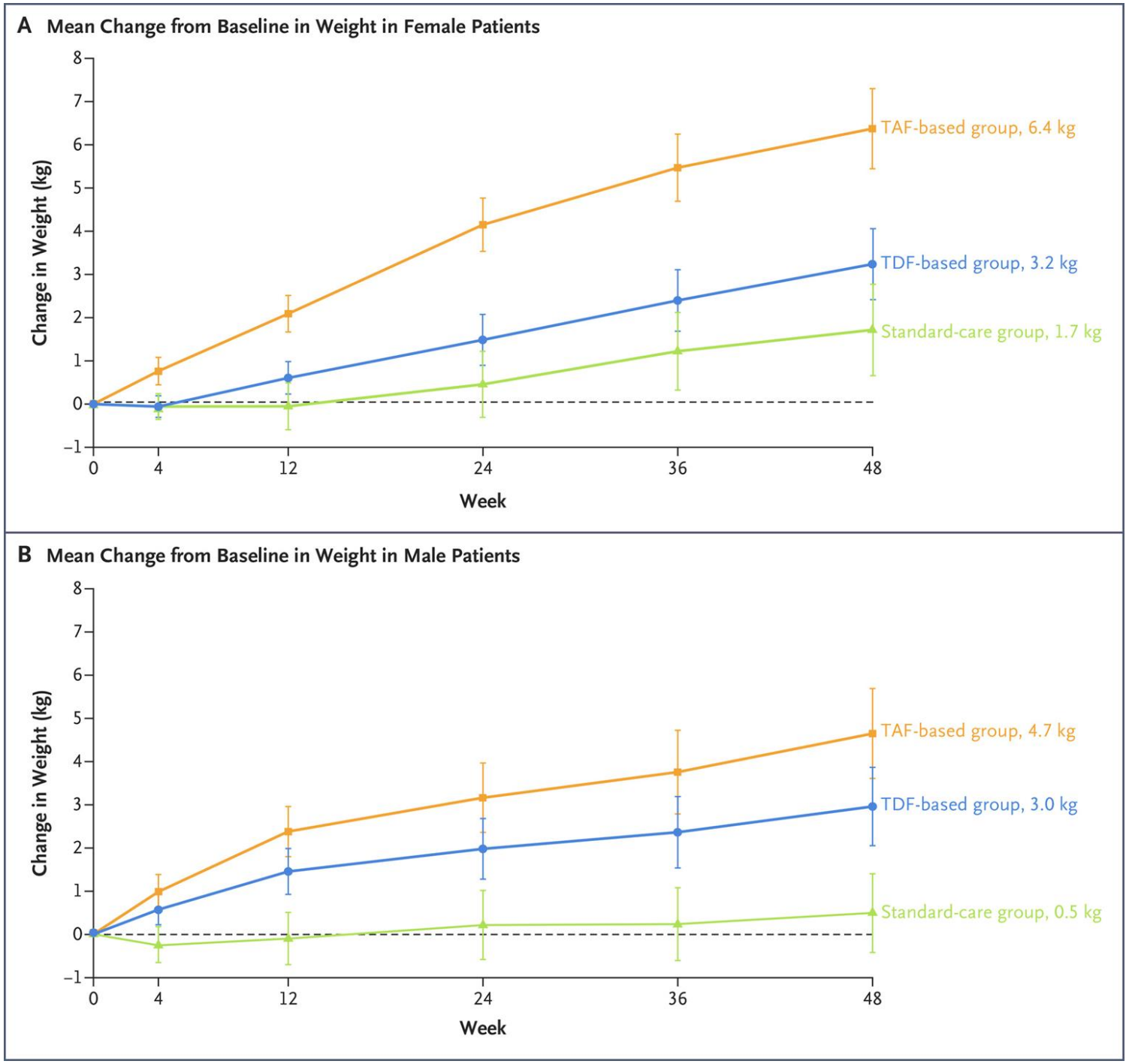
Multivariate analysis of weight gain in patients initiating ART from 2007-2016



NA-ACCORD = North American AIDS Cohort Collaboration on Research and Design; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Bourgi K, et al. *J Int AIDS Soc*. 2020;23(4):e25484. Open Access; Bourgi K, et al. Presented at: CROI 2019; March 4-7, 2019; Seattle, WA. Abstract 670.

Weight Gain Over Time With ART: ADVANCE Study



Shown is the mean change from baseline in weight in female patients (excluding those who were pregnant) (Panel A) and in male patients (Panel B).

From Venter WD, et al. *N Engl J Med.* 2019;381(9):803-815.

ADVANCE Trial: Risks of Metabolic Syndrome, Diabetes, and Cardiovasular Disease

	Metabolic syndrome†		QRISK‡ (Heart attack or stroke)			QDiabetes		
	Baseline	WK 96	Baseline	WK 48	WK 96	Baseline	WK 48	WK 96
DTG + TAF/FTC	16/351 (5%)	20/259 (8%)	0.60%	+0.10%	+0.20%	0.30%	+0.70%§	+0.90%§
DTG + TDF/FTC	21/351 (6%)	15/258 (6%)	0.60%	+0.10%	+0.20%	0.40%	0.40%	+0.50%
EFV + TDF/FTC	14/351 (4%)	8/242 (3%)	0.50%	0.00%	+0.10%	0.30%	+0.60%‖	+0.70%‖

Metabolic syndrome defined as clinical obesity (BMI >30) and any 2 of the following: raised triglycerides, reduced high-density lipoprotein cholesterol, raised blood pressure, raised fasting glucose. †Significant difference between DTG + FTC/TAF vs EFV/FTC/TDF at Wk 96 (*P* = .031). ‡Significantly greater increase in risk between DTG + FTC/TAF vs EFV/FTC/TDF at Wk 96 (*P*=.027). §Significantly greater increase in risk with DTG + FTC/TAF vs DTG + FTC/TDF at Wk 48 (*P*=.008) and at Wk 96 (*P*=.004). ‖Significantly greater increase in risk with EFV/FTC/TAF vs DTG + FTC/TDF at Wk 48 (*P*=.047) and at Wk 96 (*P*=.005).

Hill A, et al.
Presented at: CROI 2020. March 10, 2020. Oral abstract #OL-07. Accessed June 15, 2020. http://www.croiwebcasts.org/console/player/44690?mediaType=audio&

Cardiometabolic Consequences of Weight Gain With ART

NA-ACCORD	D:A:D
ART-naive: INSTI, PI, or NNRTI 2007-2016	All in ART, at least 2 BMI measurements and 1 year of follow-up 1999-2009
Risk of diabetes: INSTI HR 1.22 PI HR 1.3	Increased BMI associated with increased risk of diabetes but no increased risk of cardiovascular disease

D:A:D = Data Collection on Adverse Events of Anti-HIV Drugs; HR = hazard ratio.

Rebeiro PF, et al. *Top Antivir Med*. 2020;28(1):249-250.
Petoumenos K, et al. *Top Antivir Med*. 2020;28(1):28.

Summary

1. When initiating ART in a woman, circumstances of her life have to be taken into consideration.
   - More information regarding the use of BIC/TAF/FTC in women of childbearing age and pregnancy is needed

2. In low-income countries, advanced disease at presenting to care is still comon.

3. Social barriers and times of pandemic complicate care and follow-up, especially in patients with other comorbidities.

4. In transgender women, more studies are urgently needed:
   - No representation in clinical trials
     - More social issues that may impact on adequate access to care, retention, and adherence
     - Drug abuse
     - Polypharmacy
     - Mental health

Chloe Orkin, MBBCh, FRCP
Consultant Physician Barts Health NHS Trust
Clinical Lead for COVID 19 Research at Barts Health NHS Trust
Lead for HIV and HIV/Hep C Research
Athena Swan Chair, Queen Mary, University of London School of Medicine
London, United Kingdom

Case 2: "Clarence"

55-year-old white MSM

- HIV diagnosis in 1990 at age 25 years – then defaulted
- Returned to care in 1994
- Well
- No significant medical history
- Lives alone
- *Habits:* alcohol in excess, heavy smoking, no party drugs (chems)
- Very clear that he does NOT wish to take ART
- Followed up in clinic for next 10 years

Parameter	Lab value on return (year)
HIV-1 RNA, copies/mL	2162 (1996)
CD4+ cell count, cells/mm^3	360 (1994)
Anti-HBs	Positive
Anti-HCV	Negative

ART = antiretroviral therapy; Anti-HBs = Hepatitis B surface antibody; HCV = hepatitis C virus; MSM = men who have sex with men.

I Meet Him 15 Years After Diagnosis

- He comes in for routine 6-month visit
- Now 40 years old and CDC Category C
- *Habits:*
  - Heavy smoking
  - Too much alcohol
  - No party drugs (chems)
- Symptomatic
  - Perianal fistulae, requiring multiple surgeries
  - Oral *Candida*
  - Weight loss

Parameter	Lab value at ART initiation
HIV-1 RNA, copies/mL	200,000
CD4+ cell count, cells/mm^3	42
FBC, U&E, lipid profile	Normal
Hemoglobin A1C	5.1
Blood pressure, mm Hg	125/75
BMI	18
eGFR, mL/min	95

A1C = glycated hemoglobin; BMI = body mass index; CDC = Centers for Disease Control and Prevention; eGFR = estimated glomerular filtration rate; FBC = full blood count; U&E = urea and electrolytes.

I Ask About Reasons For Not Taking ART

- I watched my friends die while on early monotherapy trials
- I am angry at “big pharma” and capitalism
- My mom is a homeopath; we are skeptical of Western medicine
- I am worried about lifelong chemicals in my body
- I don’t want to have bad side effects, especially nausea

ART Options 2005

- Triple NRTI:
  - AZT/3TC/ABC
- NNRTI based:
  - EFV
  - NVP
- PI-based:
  - LOP/R
  - FOS/R
  - ATV/R

3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; EFV = efavirenz; FOS = fosamprenivir; LOP = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitos; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; R = ritonavir.

ART Options 2005

- Triple NRTI:
  - AZT/3TC/ABC
- NNRTI based:
  - EFV
  - NVP
- PI-based:
  - LOP/R
  - FOS/R
  - ATV/R

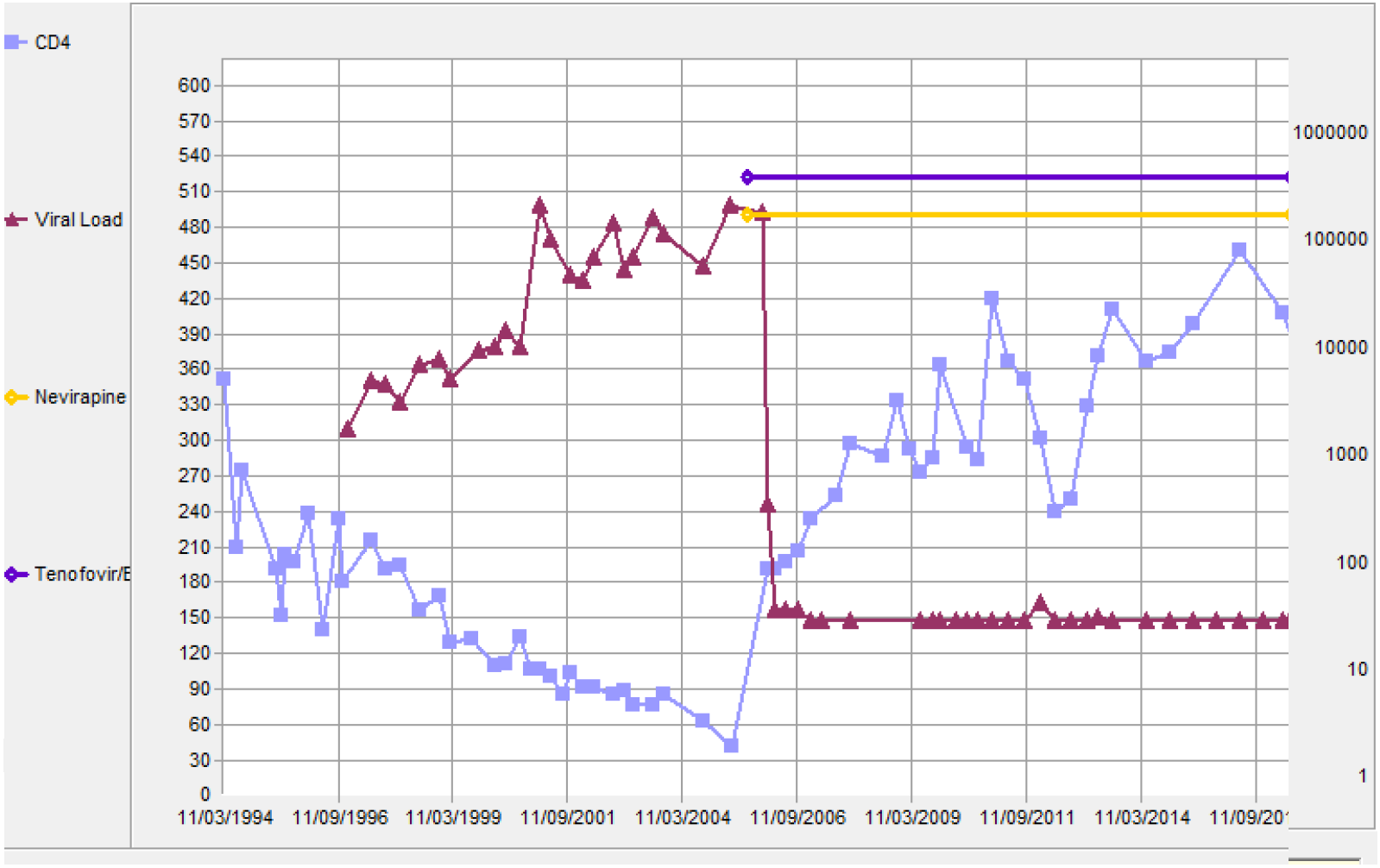
3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; EFV = efavirenz; FOS = fosamprenivir; LOP = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitos; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; R = ritonavir.

ART Options 2005

- Triple NRTI:
  - AZT/3TC/ABC
- NNRTI based:
  - EFV
  - NVP PLUS TDF/FTC
- PI-based:
  - LOP/R
  - FOS/R
  - ATV/R

3TC = lamivudine; ABC = abacavir; ATV = atazanavir; AZT = zidovudine; EFV = efavirenz; FOS = fosamprenivir; LOP = lopinavir; NNRTI = non-nucleoside reverse transcriptase inhibitos; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; R = ritonavir.

2005! Starts ART, Suppresses 11 Years



11 Years Later, Fully Suppressed Since First ART

- Attends for routine blood draws. Viral load is 36,000 copies/mL!
- Misses his clinic review appointment
- Clinic sends another 2 appointments
- Misses those
- Clearly not taking ART; he does not have enough meds to last
- Does not return calls
- I refer to our dedicated LINK clinic

LINK Clinic (Re-engagement Service)

Booked into ONE-STOP SUPPORT clinic
Immediate access to:

Focused holistic support
Physician, specialist nurse, social worker, psychology, peer support, substances

POSITIVELY UK

PositiveEast
better futures for positive people

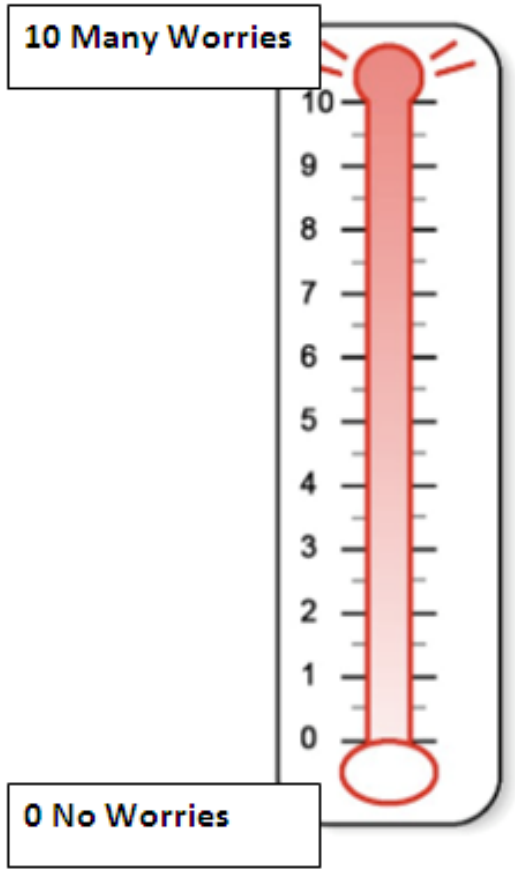
Case management: Dedicated clinic; phone and text message reminder service
Active general practitioner-finding service
Referral to party drug or alcohol services

ARTAS = Anti-Retroviral Treatment and Access to Services, https://www.cdc.gov/hiv/effective-interventions/treat/artas?Sort=Title%3A%3Aasc
Positively UK. https://positivelyuk.org/

Assessing Needs/Priorities

HOSPITAL NO: NAME: DOB:

We would like to know about your worries and concerns today. Please circle a number on the thermometer below and tick any boxes that are relevant to you.



PRACTICAL PROBLEMS

- ☐ Housing
- ☐ Financial
- ☐ Benefits
- ☐ Immigration
- ☐ Employment
- ☐ Childcare
- ☐ Transport

PSYCHOLOGICAL PROBLEMS

- ☐ Loneliness or isolation
- ☐ Depressions or sadness
- ☐ Worries about the future
- ☐ Difficulty accepting your diagnosis
- ☐ Concerns about stigma/confidentiality

SOCIAL PROBLEMS

- ☐ Relationships (family, friends, partner)
- ☐ Difficulty telling others about your diagnosis

SPIRITUAL/RELIGIOUS ISSUES

- ☐ Questioning beliefs and values
- ☐ Conflicts between faith and HIV

MEDICATION PROBLEMS

- ☐ Side effects of medication
- ☐ Difficulty remembering medication

OTHER

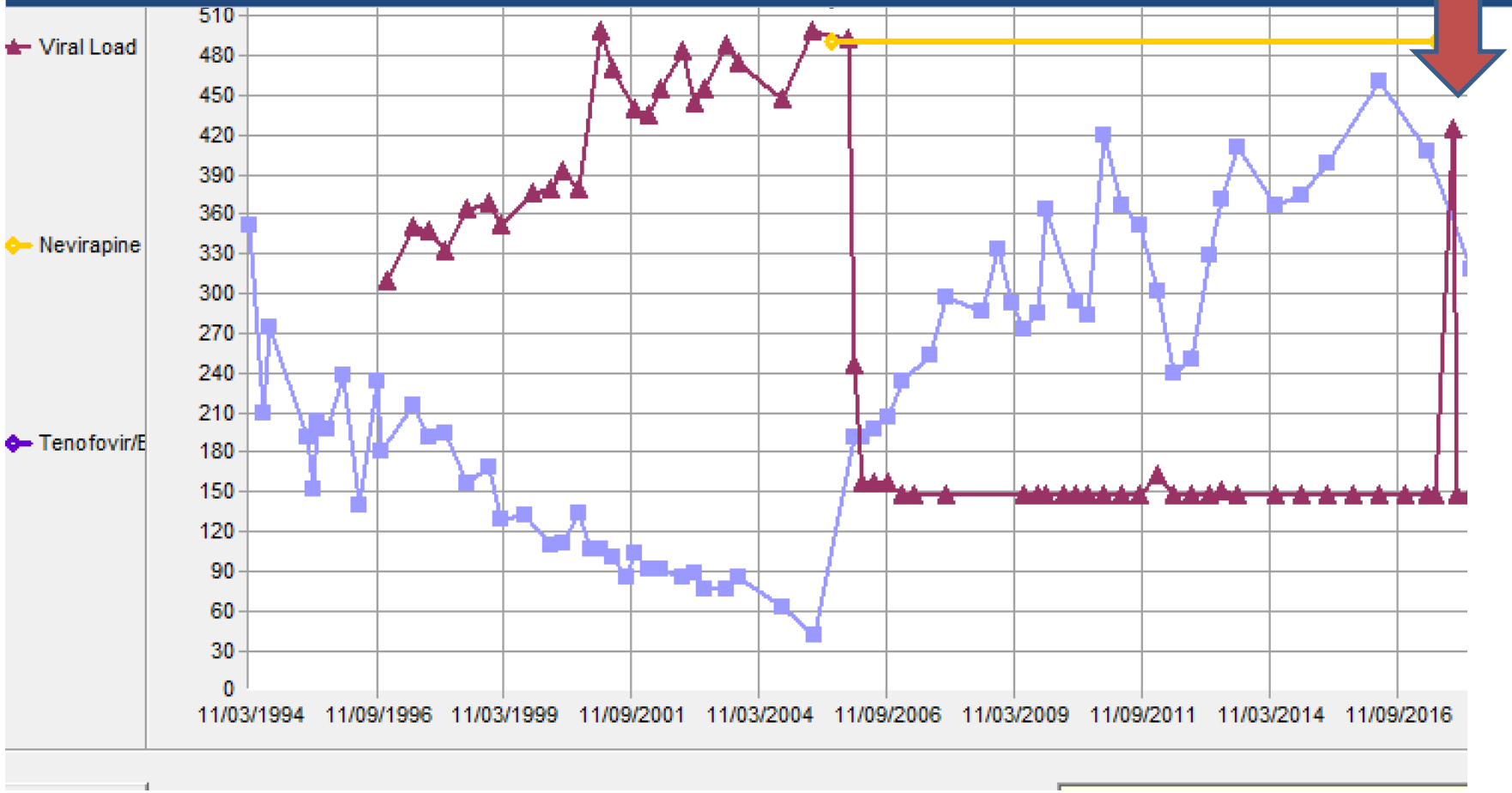
- ☐

Courtesy of Chloe Orkin, MBBCh

Does Not Attend LINK Clinic…Returns to my Clinic

He restarted himself on TDF/FTC/NVP 6 weeks ago, after a 4-month break

He is undetectable!



Refuses LINK Clinic…Returns to my Clinic

He restarted himself on TDF/FTC/ NVP 6 weeks ago, after a 4-month break

He is undetectable!

- Now 55 years old
- Well!
- Heavy smoker

Parameter	Lab value at ART initiation
HIV-1 RNA, copies/mL	<20
CD4+ cell count, cells/mm^3	300
Lipid profile	Normal
Hemoglobin A1C	5.1
Blood pressure, mm Hg	**139/89**
BMI	24
eGFR, mL/min	**70**
Resistance test	No resistance

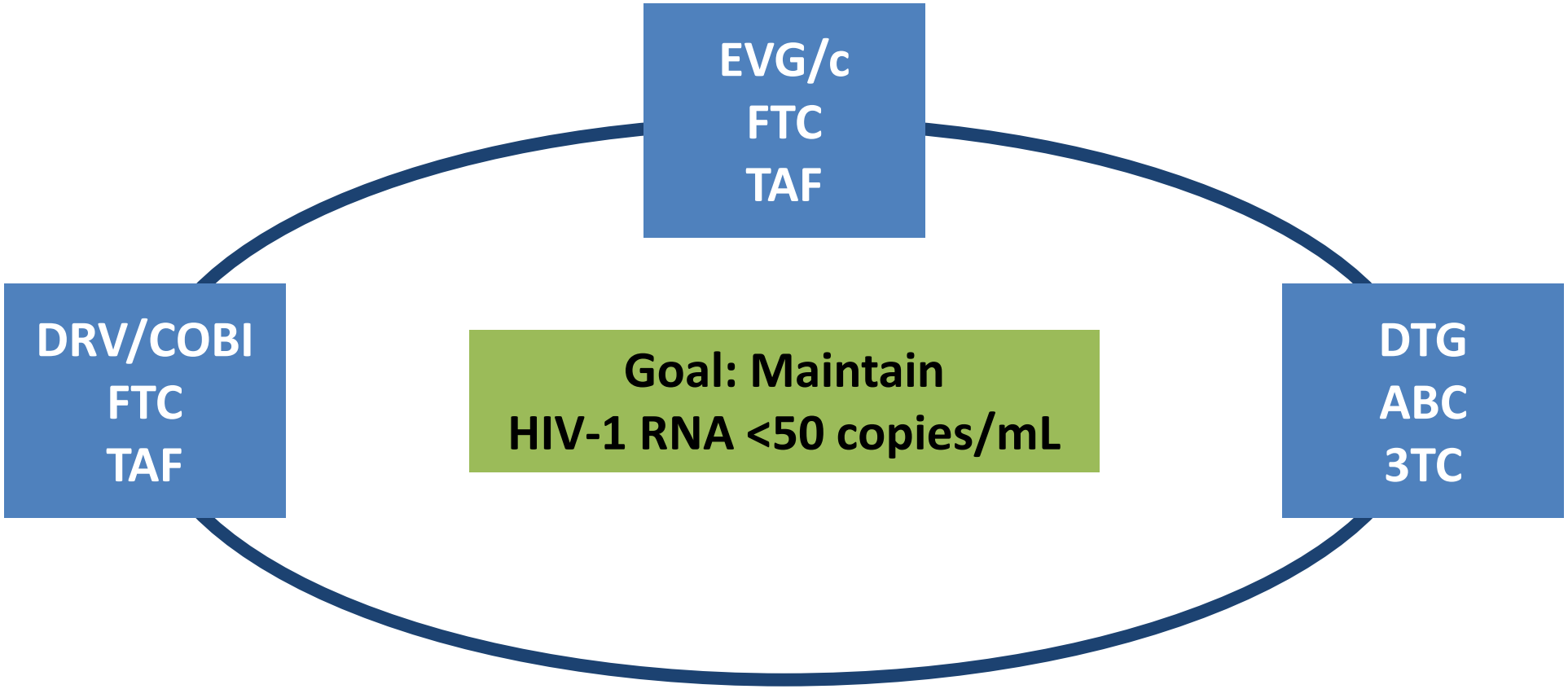
Indications for Switch in Virologically Suppressed Persons

- Documented toxicity or prevention of long-term toxicity
- Avoidance of DDIs
- Aging and/or comorbidity
- Simplification
- Planned pregnancy or women wishing to conceive
- Protection from HBV
- Regimen fortification
- Cost reduction

DDIs = drug–drug interactions; HBV = hepatitis B virus.

EACS Guidelines. November 2019. https://www.eacsociety.org/files/guidelines-10.0_final_2_2.pdf

2019: Modernization – Aim to Avoid TDF and NNRTIs [UK: No B/F/TAF or DTG/3TC STR on NHS Formulary]



3TC = lamivudine; ABC = abacavir; BIC = bictegravir; COBI = cobicistat; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; FTC = emtricitabine; NHS = National Health Service; NNRTIs = non-nucleoside reverse transcriptase inhibitors; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.

EACS Guidelines. November 2019. https://www.eacsociety.org/files/guidelines-10.0_final_2_2.pdf

Question for Panel

Given my options, which antiretroviral therapy would you choose?

1 Year Later

- I prescribe D/C/F/TAF; he suppresses and remains suppressed for 1 year
- Gains 3 kg (6.6 lbs) in 1 year; wants to switch regimen
- Lipids are now high
- Asks about STR 2DR options and injectable ART

Best candidates:

Virologically suppressed for at least 6 months
A need to avoid ABC, TDF, and TAF
HBV-immune

Excellent adherence history
No documented or suspected resistance to regimen components

2DR = 2 drugs; D/C/F/TAF = darunavir/cobicistat/emtricitabine/tenofovir alafenamide.

STR 2DR Options

- I prescribe DTG/3TC
- DTG/RPV (has been on NVP and interrupted therapy) – I avoid
- I tell him “Injectable therapy is not licensed, and he will need to be suppressed for 6 months, but I will bear him in mind. Injections have to be given within 1 week of scheduled appointment”!
- He remains virally suppressed and has lost 0.7 kg (1.5 lbs) in 6 months

RPV = rilpivirine.

FUTURE

THANK YOU

RECOMMEND TO A COLLEAGUE:

The educational content from this activity will post on the Healio and Power-Pak websites within 6 to 8 weeks following this event. To view online and earn CME/CPE credit go to:

Healio CME

www.HealioCME.com

POWER-PAK C.E.

www.PowerPak.com

and search for the title, "**Managing HIV in the New Decade – Are You Treating Like the Experts?**".

MANAGING HIV IN THE NEW DECADE –

Are You Treating Like the Experts?

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