AETC AIDS Education & Training Center Program Mountain West

HIV PRIMARY CARE

AIDS Clinical Conference

Jehan Budak, MD
Assistant Professor
Division of Allergy & Infectious Diseases
University of Washington

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Disclosures

No conflicts of interest or relationships to disclose.

Data presented in this presentation offer a limited glimpse of health inequities that exist within a larger social context. Racism, not race, creates and perpetuates health disparities.

The MWAETC, in alignment with the American Medical Association, encourages characterizing race as a social construct, rather than an inherent biological trait, and supports ending the practice of using race as a proxy for biology in medical education, research and clinical practice.

https://www.ama-assn.org/press-center/press-releases/new-ama-policies-recognize-race-social-not-biological-construct

January 2022

HIVMA Primary Care Guidance

Clinical Infectious Diseases

MAJOR ARTICLE

Primary Care Guidance for Persons With Human Immunodeficiency Virus: 2020 Update by the HIV Medicine Association of the Infectious Diseases Society of America

Melanie A. Thompson,[1,a] Michael A. Horberg,[2,a] Allison L. Agwu,[3] Jonathan A. Colasanti,[4] Mamta K. Jain,[5] William R. Short,[6] Tulika Singh,[7] and Judith A. Aberg[8]

[1]AIDS Research Consortium of Atlanta, Atlanta, Georgia, USA, [2]Mid-Atlantic Permanente Research Institute, Kaiser Permanente Mid-Atlantic Permanente Medical Group, Rockville, Maryland, USA, [3]Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [4]Division of Infectious Diseases, Emory University, Atlanta, Georgia, USA, [5]Division of Infectious Diseases, University of Texas Southwestern Medical Center, Dallas, Texas, USA, [6]Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, [7]Internal Medicine, HIV and Infectious Disease, Desert AIDS Project, Palm Springs, California, USA, and [8]Division of Infectious Diseases, Mount Sinai Health System, New York, New York, USA

Objectives

By the end of this session, the participant will be able to:

1. Describe an approach to osteoporosis screening and treatment in PWH
2. Define low level viremia and describe options for its management
3. Recognize the relationship between ART and weight gain

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Osteoporosis and HIV

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At what age should screening for osteoporosis in a cisgender man with HIV begin?

A. 45

B. 50

C. 55

D. 60

Case #1

- A 50-year-old man with well controlled HIV is switched from BIC/TAF/FTC to TDF/3TC/DOR after experiencing weight gain. Approximately one year later, a DXA scan is ordered.

- DXA Results
  - Lumbar spine: T-score: -2.6
  - Left total hip: T-score -2.5
  - Left femoral neck: T-score -2.7

- Workup for secondary causes included Vitamin D level 23 and normal free T

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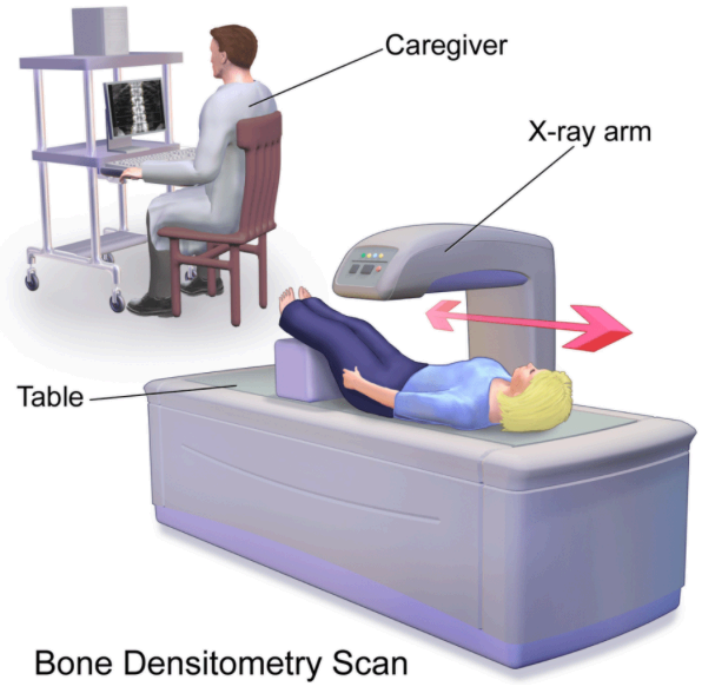
Background

- Osteoporosis Definition[1]
  - Systemic skeletal disorder characterized by:
    - Low bone mass
    - Micro architectural deterioration of bone tissue (bone quality)
  - With a consequent increase in bone fragility and fractures

- Diagnosed based on DXA (dual-energy x-ray absorptiometry)
  - Normal: T-score > -1.0
  - Osteopenia: T-score -1.0 to -2.4
  - Osteoporosis: T-score ≤ -2.5



Bone Densitometry Scan

- What is a Z-score? Used in men < 50 and pre-menopausal women, abnormal if ≤ -2.0

1-Consensus Conference Am J Med 1993. 2-Image: https://www.americanmedicalcoding.com/new-dexa-bone-density-cpt-code-2015/

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Relationship between HIV and Osteoporosis

- Osteoporosis is more common in PWH compared to age-matched individuals without HIV[1]
  - PWH have a higher risk of low bone mineral density (BMD) and fragility fractures[2]
- Reasons are multifactorial
  - ART contributes as well, specifically tenofovir disoproxil fumarate and protease inhibitors
  - ART initiation leads to 2-6% loss in BMD during the first 2 years of therapy[3]
  - HIV-1 can infect osteoclast precursors and increase bone resorption[4]
- Increased risk of osteoporosis with hepatitis C, commonly seen in PWH[5]

1-Todd Brown, Ryan White Provider Conference, 2020. 2-McComsey GA, CID, 2010. 3-Brown TT, CID, 2015. 4-Raynaud-Messina B, PNAS, 2018. 5-Wijarnpreecha K, Saudi J Gastroenterol, 2017.

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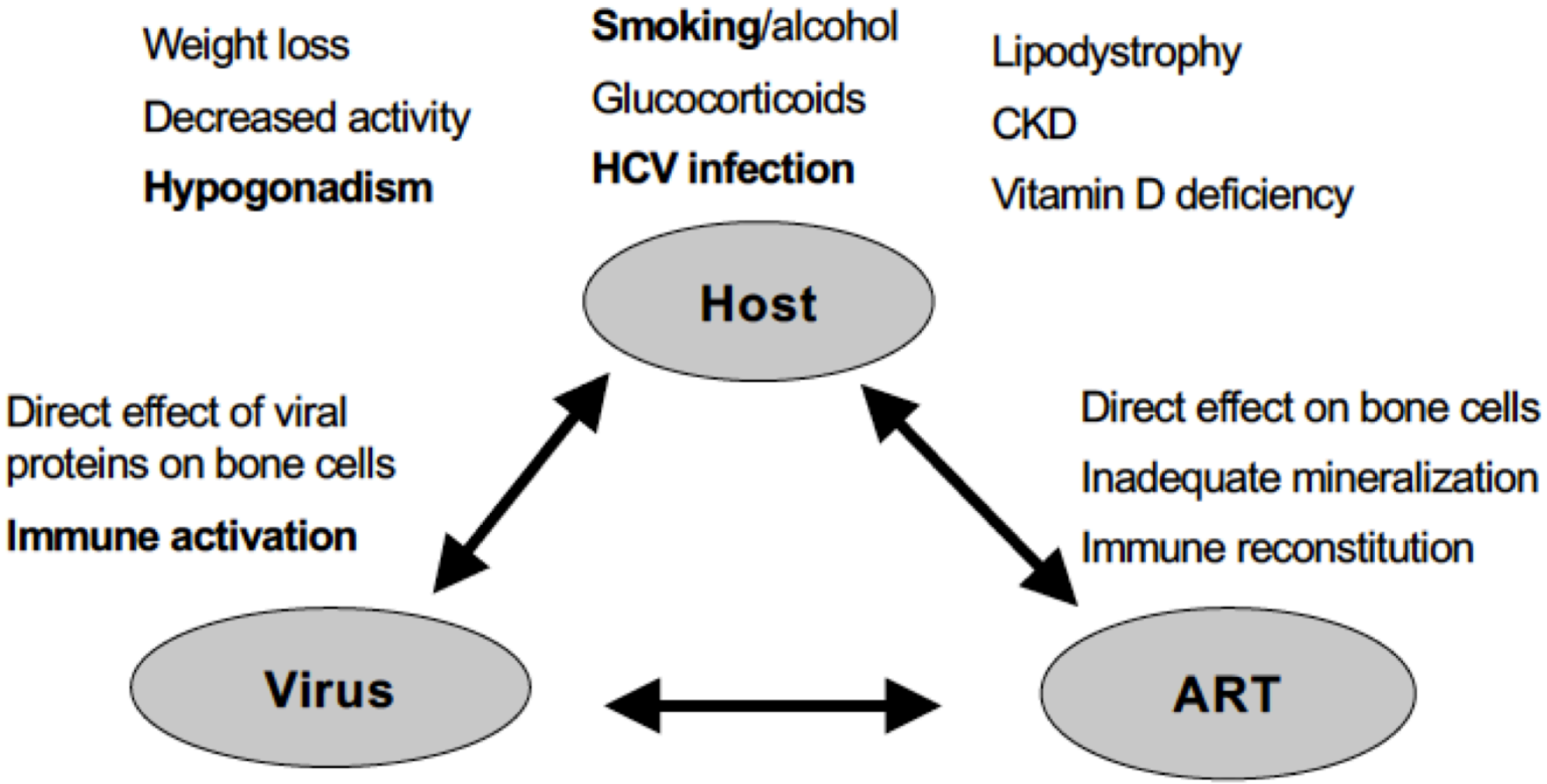
Etiologies of Bone Loss in HIV are Multifactorial



Brown TT, HIV and the Bones.

Bone Disease in HIV Guidance

Recommendations for Evaluation and Management of Bone Disease in HIV

Todd T. Brown,[1] Jennifer Hoy,[2] Marco Borderi,[3] Giovanni Guaraldi,[4] Boris Renjifo,[5] Fabio Vescini,[6] Michael T. Yin,[7] and William G. Powderly[8]

[1]Division of Endocrinology, Diabetes and Metabolism, Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia; [3]Infectious Diseases Unit, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, and [4]Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy; [5]Global Medical Affairs Virology, Global Pharmaceutical Research and Development, AbbVie, North Chicago, Illinois; [6]Endocrinology and Metabolism Unit, University Hospital "Santa Maria della Misericordia," Udine, Italy; [7]Department of Medicine, Columbia University Medical Center, New York, New York; and [8]Division of Infectious Diseases, Washington University School of Medicine, St Louis, Missouri

Brown TT, CID, 2015.

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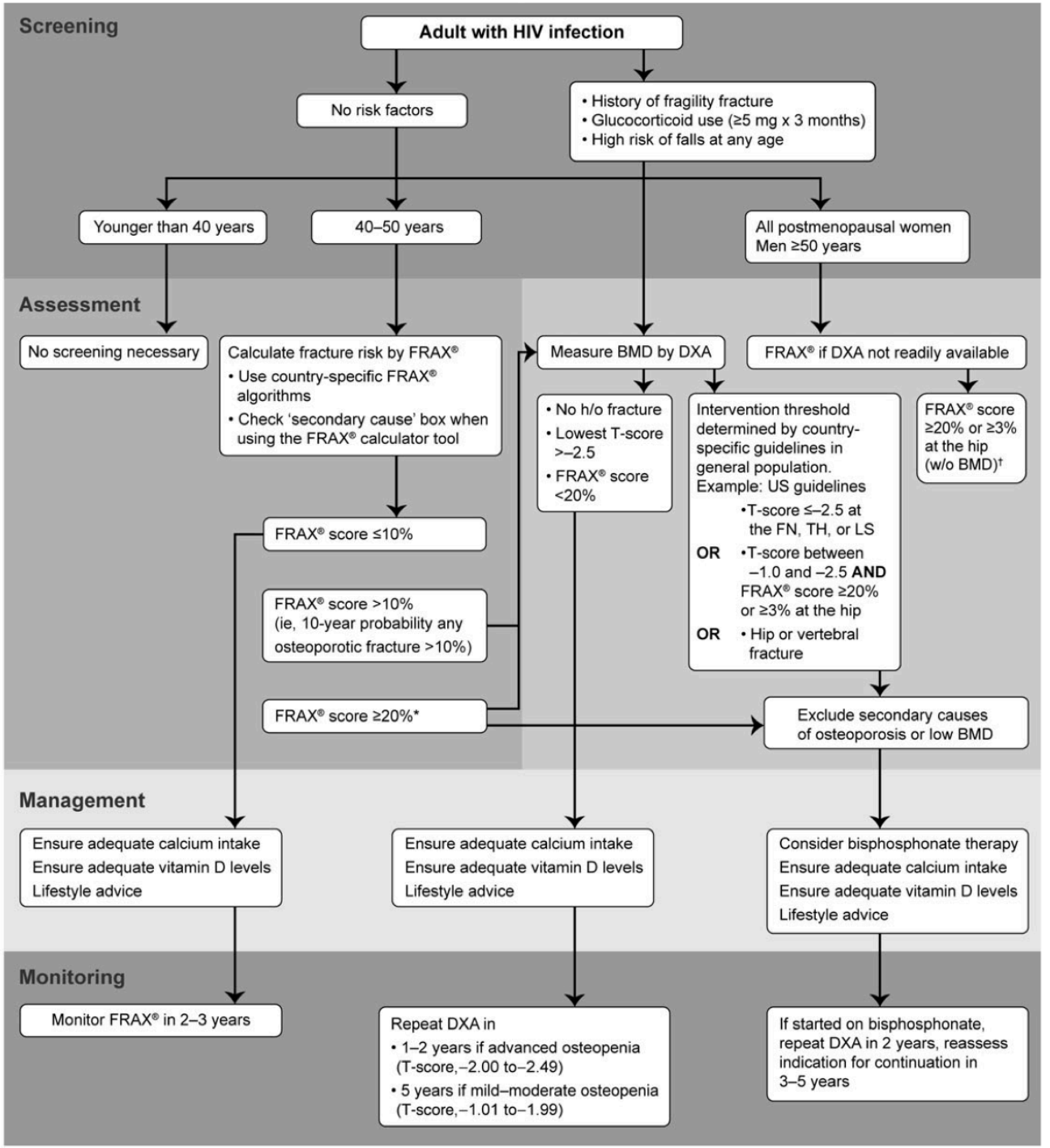
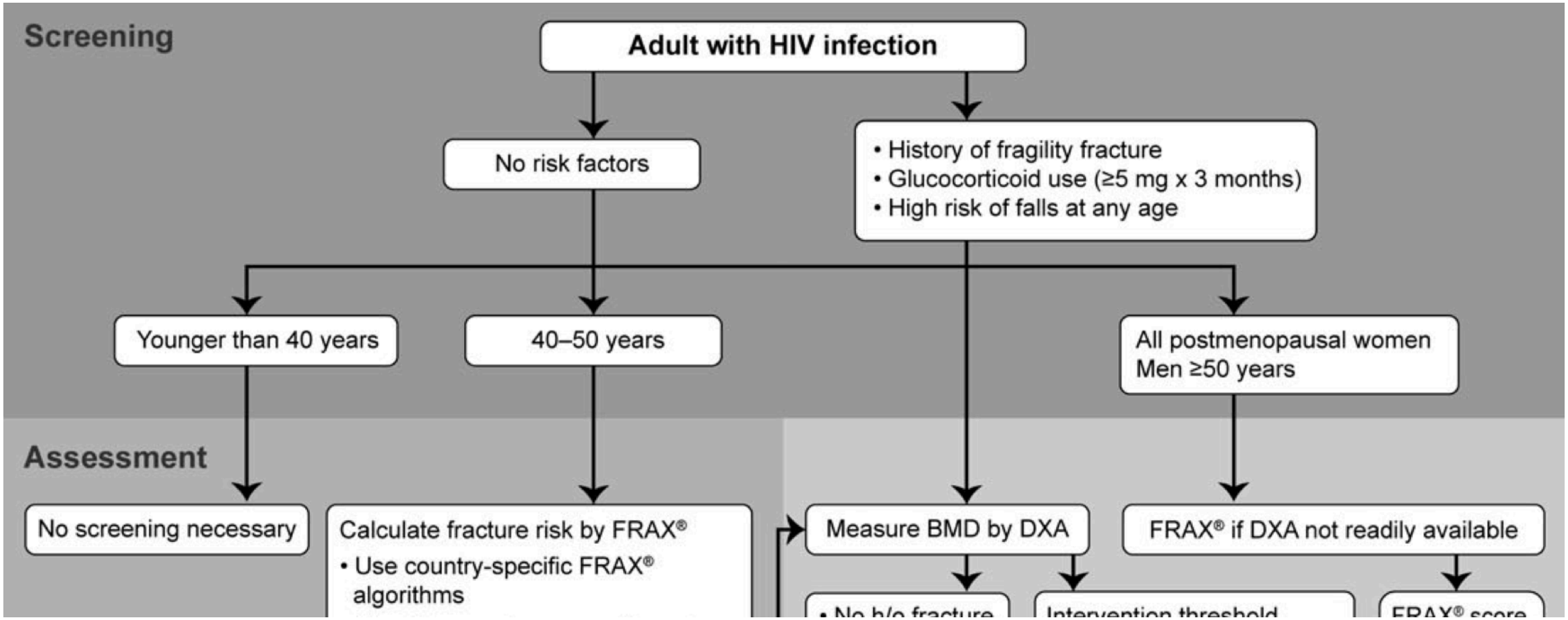


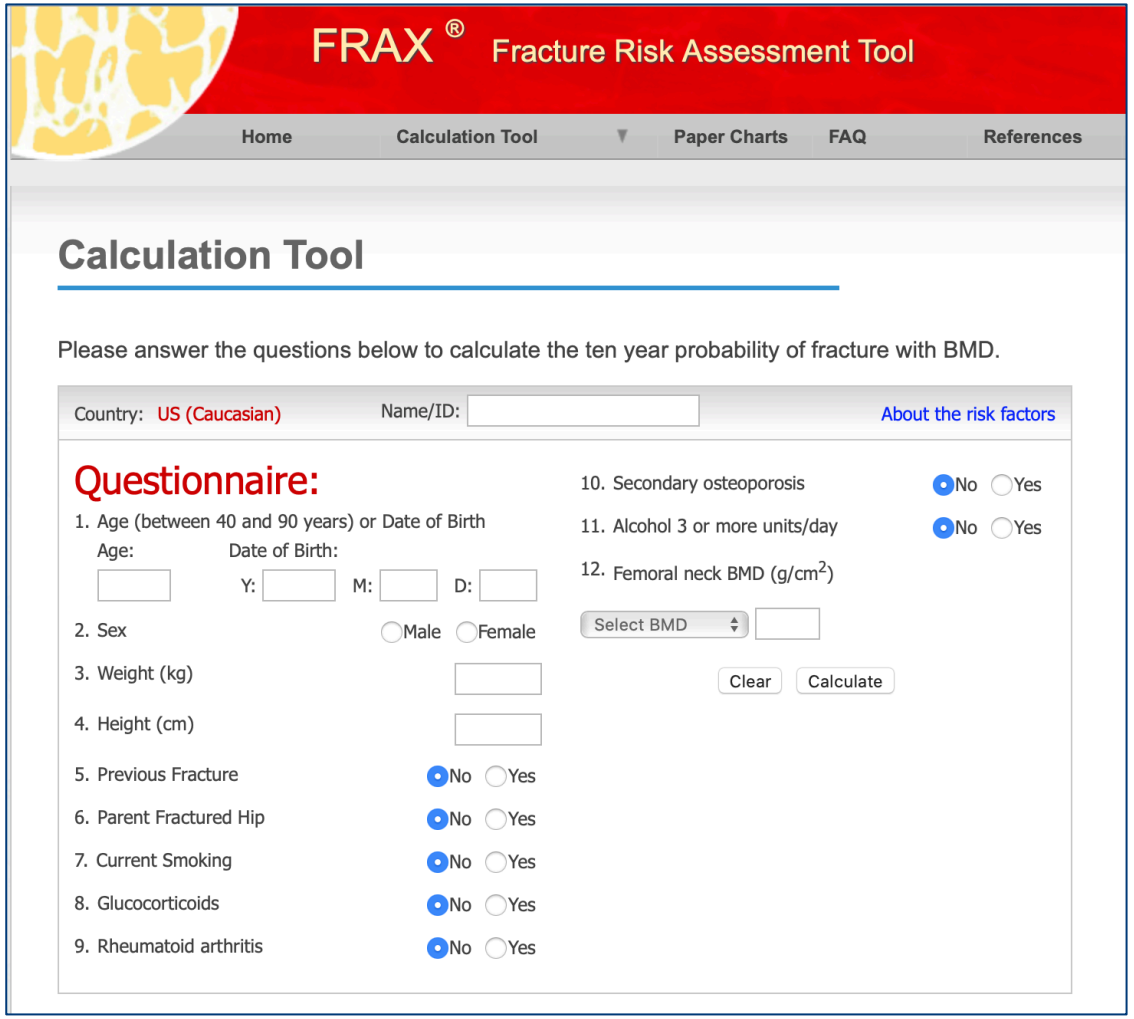
Brown TT, CID, 2015.

Screening for Osteoporosis in PWH



Brown TT, CID, 2015.

Fracture Risk Assessment Tool FRAX Score



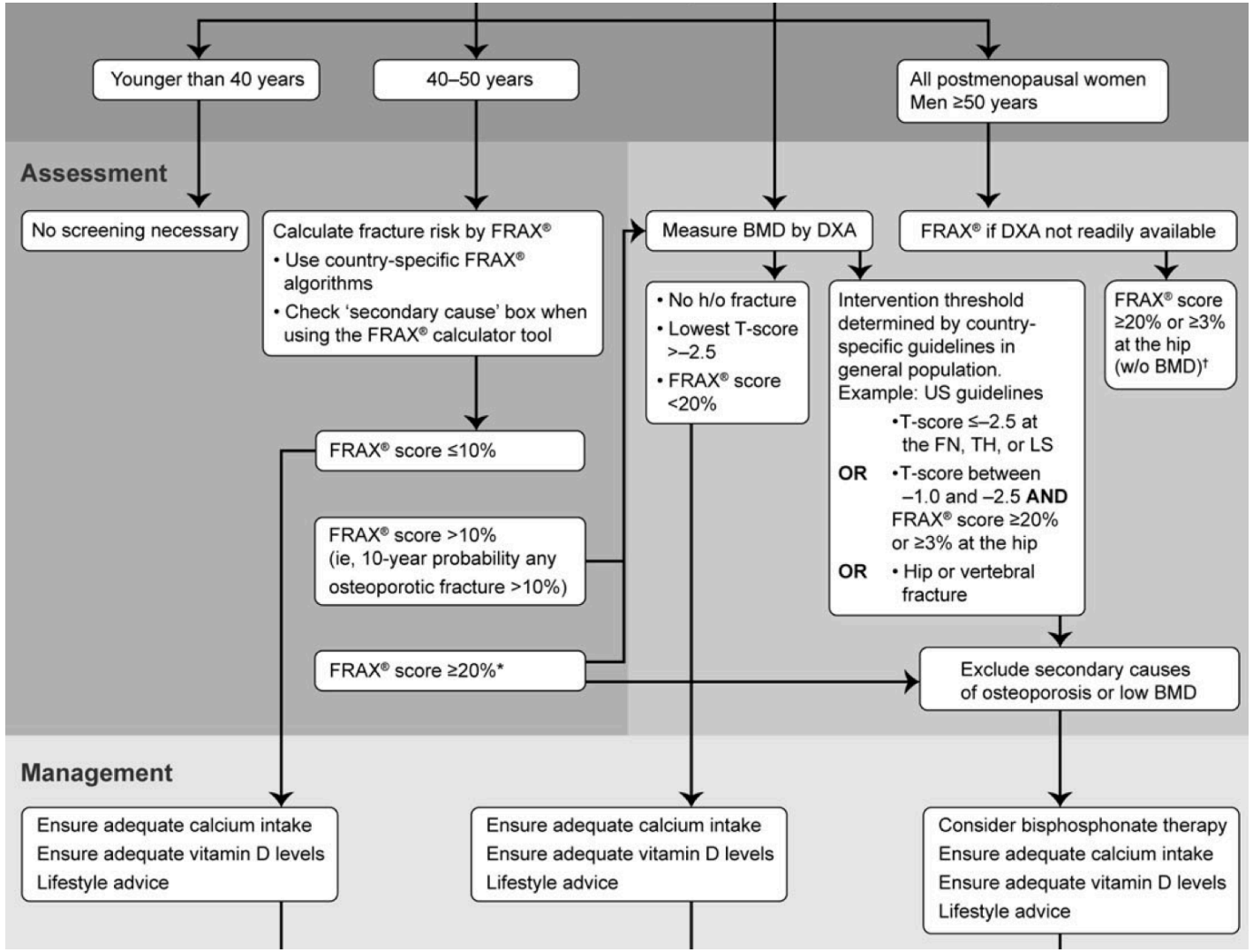
Use FRAX if age < 50, do not have access to DXA, or receive DXA result with osteopenia

FRAX underestimates risk of osteoporosis in PWH[1]

If no BMD result, then for PWH, select #10 Secondary Osteoporosis; not helpful if you already have BMD

Image accessed at https://www.sheffield.ac.uk/FRAX/tool.aspx?country=9. 1 – Yang J, AIDS, 2018.

Interpreting FRAX Score



Brown TT, CID, 2015.

General Management for Bone Health

- Ensure adequate calcium intake
- Ensure vitamin D repletion
- Lifestyle modifications
  - Smoking cessation
  - Alcohol reduction
  - Weight-bearing exercise
- Evaluate for secondary causes of osteoporosis prior to starting treatment
  - Send calcium, vitamin D, PTH, free T in a cisgender man, TSH
  - Other rare causes can be worked up based on ROS
  - Address underlying issue, then repeat DXA in 6 months

Brown TT, CID, 2015.

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Optimize ART if possible

- If osteopenia or osteoporosis, avoid PIs and TDF if possible

- Switching from TDF to TAF leads to improvements in BMD
  - Over 48 weeks, can improve BMD by +1.5 to +2.3[1]
  - In a switch from TDF-containing regimen to TAF/FTC/c/EVG at 96 weeks[2]
    - BMD increased ~2.5%
    - Some individuals experienced BMD increases ≥ 5%
    - A reversion from osteoporosis occurred in approximately ¼ of patients

- In osteoporosis, OK to use TAF or can switch to a TFV-sparing regimen entirely

1-Pozniak, JAIDS, 2017. 2-Brown TT, CROI 2017 abstract #683.

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Treatment of Osteoporosis: Medication Overview

- Anti-Resorptives
  - Bisphosphonates
    - Alendronate
    - Zoledronic acid
  - Denosumab (monoclonal Ab)
  - SERMs
    - Raloxifene
  - Estrogen

- Anabolic
  - PTH/PTHrP analogues
    - Teriparatide
    - Abaloperatide
  - Sclerostin inhibitor
    - Romosozumab

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Treatment of Osteoporosis

- Who to Treat?
  - Those with a hip or vertebral fracture
  - Those with osteoporosis (BMD T-score < -2.5)
  - Those with osteopenia with FRAX score ≥ 20% or hip fracture ≥ 3%

- In HIV primary care, use bisphosphonates; for other agents, consult endocrine
  - Alendronate (weekly oral pill)
    - Oral bisphosphonates have poor bioavailability and adherence is difficult
  - Zoledronic acid (once yearly infusion)
    - Zoledronic acid can cause flu-like symptoms for first 1-2 days after infusion

Brown TT, CID, 2015.

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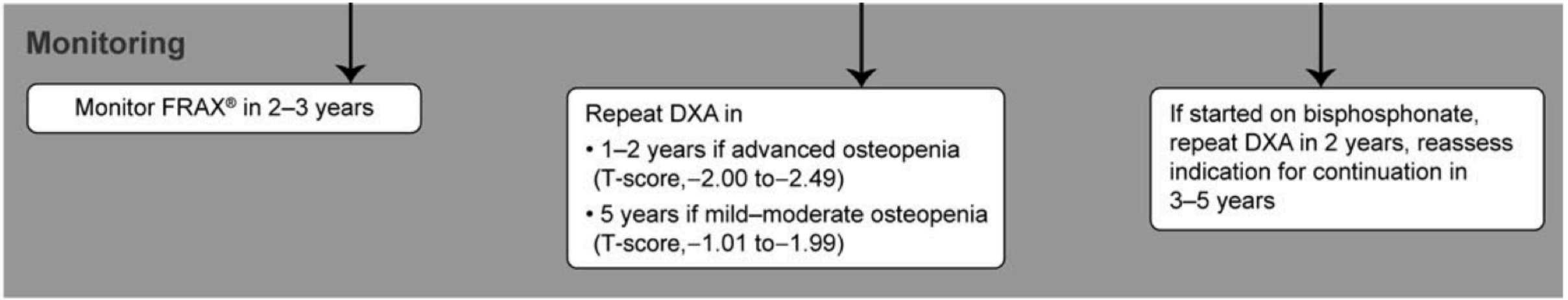
Monitoring



Brown TT, CID, 2015.

Monitoring

- Osteopenia
  - Repeat DXA yearly
- Osteoporosis
  - Treat for 3 years with zoledronic acid or 5 years with alendronate
  - Obtain a DXA scan to evaluate for possibility of a drug holiday
  - If meets criteria for drug holiday, continue Ca/Vit D and check DXA yearly

Table 2 Recommendations for Drug Holiday from Bisphosphonates

Patient Category	Recommendation
High-risk: T-score still ≤−2.5 at the hip, previous fracture of the hip or spine or ongoing high-dose glucocorticoid therapy.	Drug holiday not justified.
Moderate risk: Hip bone mineral density value is now >−2.5 (T-score), and no prior hip or spine fracture.	Consider drug holiday after 3-5 years of alendronate, risedronate, or zoledronic acid therapy. No information about ibandronate and drug holidays.
Low risk: Did not meet current treatment criteria at the time of treatment initiation.	Discontinue therapy

McClung, Am J Med, 2013.

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Osteoporosis in PWH: Key Points

1. There is a higher risk of osteoporosis in PWH, beyond just risk from ART (mostly TDF)
2. Screen for osteoporosis with DXA in PWH (men > 50 and postmenopausal women)
3. If DXA shows osteopenia, calculate a FRAX score, and recognize that FRAX underestimates risk in PWH
4. If DXA shows osteoporosis, treat with bisphosphonate for 3-5 years
5. TAF can be used in persons with osteoporosis
6. We need more data in PrEP use and osteoporosis

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Low Level Viremia

Case #2

A 60-year-old man with HIV (last CD4 478 cells/mm^3, HIV RNA 80 copies/mL) and multiple medical problems is seen for routine follow-up. He has been taking TAF/FTC + DTG + MVC + r/DRV BID since 2016.

- Most Recent Genotype
  - NRTI: M184V, M41L, T215Y
  - NNRTI: K103N, Y181C, H221Y
  - PI: I84V
  - INSTI: none

M184V – resistance to ABC, 3TC, and FTC
M41L, T215Y (TAMs) – resistance to ABC and Tenofovir
K103N – resistance to EFV and NVP
Y181C – resistance to EFV, NVP, ETR, and RPV
H221Y – some resistance to all NNRTIs
I84V – low-level resistance to DRV

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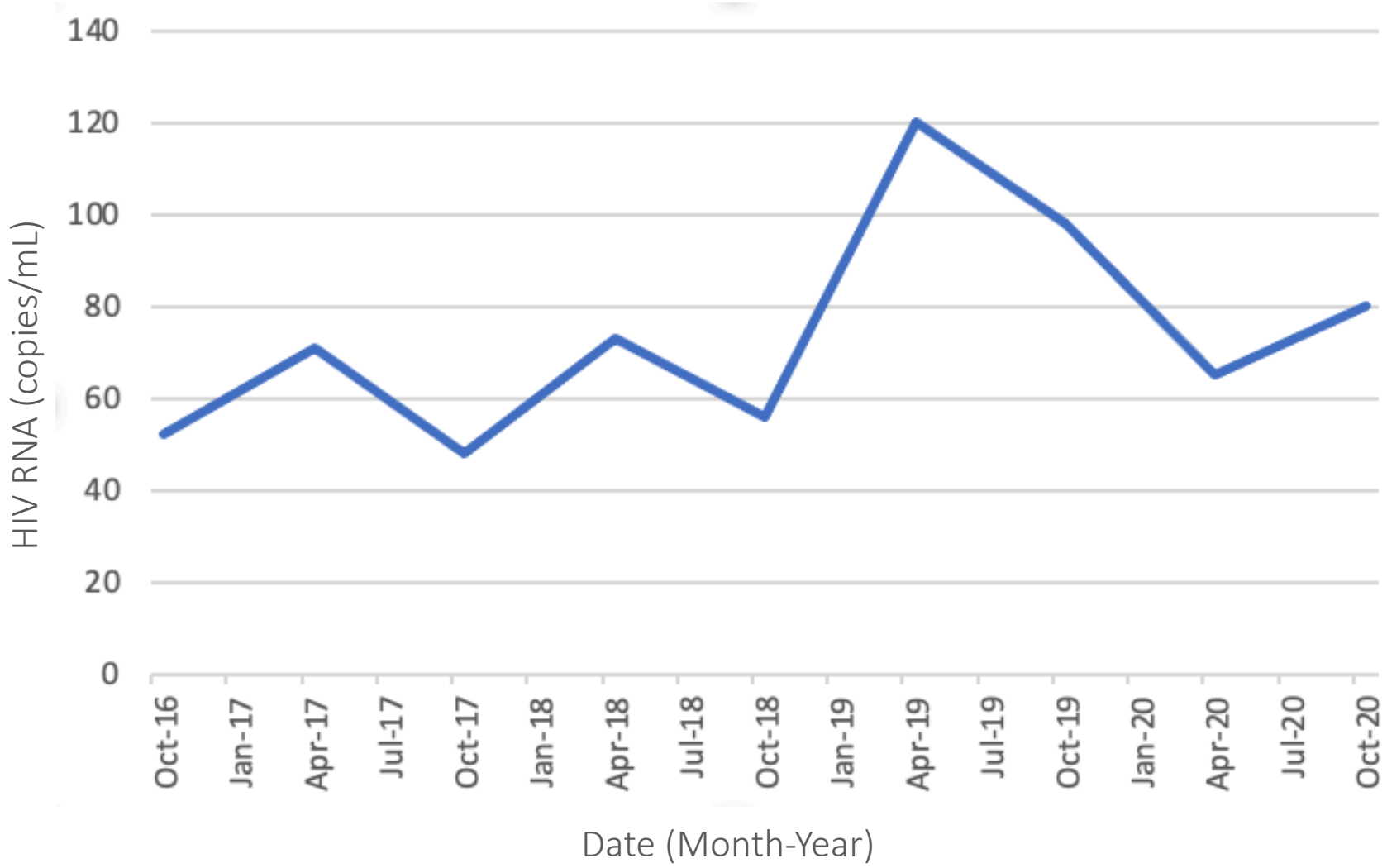
Case #2: HIV RNA Levels



Adherence ROS

Missed Doses	When was the last time you missed a dose? In the past week/month, how many doses did you miss?
Logistics	What is your system for taking pills/how do you take your ART? Do you take it with food? Do you take all the pills together?
DDI	Beyond your medication list, what OTC meds do you take? Do you take any vitamins or supplements?
Existential	How do you feel about your ART? What issues or annoyances do you have with your ART?

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What would you do with his ART in the setting of his low-level viremia?

A. Continue current regimen (TAF/FTC + DTG + MVC + r/DRV BID)

B. Add fostemsavir

C. Double the dolutegravir dose

D. Add doravirine

Terms Related to Virologic Response

Incomplete Virologic Response	Failure to suppress HIV RNA to undetectable after 24 weeks of an ARV regimen
Virologic Blip	After achieving virologic suppression, a single detectable HIV RNA level (usually < 200 copies/mL), followed by a return to suppression
Virologic Rebound	Confirmed HIV RNA level ≥ 200 copies/mL after achieving virologic suppression on ART
Low-Level Viremia	Persistent HIV RNA levels above the level of detection for the assay but often < 200 copies/mL (i.e. usually 50-199 copies/mL)

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Low Level Viremia

- Possible etiologies include suboptimal adherence, drug interactions, drug-food interactions, early virologic failure, or none of the above

- Low-level viremia (LLV) is rare
  - In a cohort of 1485 PWH from Taiwan switched to DTG or BIC, between 2016 and 2021, incidence ranged from 1.2-1.7%[1]

- Persistent low-level viremia in the setting of excellent adherence to a potent ARV regimen is felt by many to be due to replication incompetent HIV being released from a latent reservoir

1-Chen GJ, Int J Antimicrob Agents, 2022.

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Data on Low Level Viremia is Mostly Conflicting

- Some data show an association between LLV and overall mortality; others do not[1]
  - LLV was associated with increased mortality (aHR 2.2, CI 1.3-3.8)[2]

- Most studies have shown a low risk of virologic resistance in persons with persistently detectable HIV RNA levels < 200 copies/mL
  - LLV was associated with virologic failure (aHR 1.83, CI 1.1-3.04)[3]
  - In Taiwan cohort, there was no increased risk of virologic failure in those with LLV while on DTG or BIC[4]

- Adding drugs does not work[5]

1-Ryscavage P, AAC, 2014. 2-Elvstam O, CID, 2020. 3-Fleming J, AIDS, 2019. 4-Chen GJ, Int J Antimicrob Agents, 2022. 5-Gandhi RT, PLOS Medicine, 2010.

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Guideline Recommendations Regarding Low Level Viremia

DHHS Guidelines

The Adult and Adolescent ARV Guidelines recommend persons with low-level viremia continue the same antiretroviral regimen but undergo monitoring with HIV RNA levels every 3 months.[1]

IAS-USA Guidelines

Patients with intermittent or persistent low-level viremia between 50 - 200 copies/mL should be assessed for treatment adherence, tolerability, and toxicity; however, changing ART regimens is not recommended unless ART toxicity or intolerability are identified (evidence rating: BIII).[2]

1-DHHS ART Guidelines. 2-Saag MS, JAMA, 2020.

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Undetectable = Untransmittable (U=U)

- Concept that an individual with an undetectable HIV VL cannot transmit HIV infection to their sexual partners

STUDY	FINDINGS
HPTN-052	96% reduction in infections among heterosexual couples when the HIV+ partner started ART[1]
PARTNER-1	Of 58K condomless sex acts in 888 serodiscordant couples (40% MSM, HIV+ partner with UD VL), no new HIV infections phylogenetically linked[2]
PARTNER-2	972 serodiscordant MSM who are coupled had 76K condomless sex acts, no HIV infections phylogenetically linked[3]

1-Cohen NEJM 2016, 2-Rodger JAMA 2016, 3-Rodger Lancet 2019

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Low Level Viremia: Key Points

1. Low-level viremia is defined as persistent HIV RNA levels above the level of detection for the assay but below 200 copies/mL.
2. Assess adherence, ask exactly how the patient takes medications, and asess drug interactions, food requirements, and absorption.
3. LLV may or may not increase risk of virologic failure and/or mortality.
4. If on an ART regimen with a low barrier to resistance, update ART. Otherwise, changing or intensifying ART is not recommended.

Dr. Paul Sax writes, “regardless, the absolute risk [of failure] is still quite low, especially if adherence is good. And [patients] do not appear to be slowly developing resistance to their regimens.”[1]

1-Sax P, NEJM Journal Watch, 2017.

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ART and Weight Gain

Case #3

- 58-year-old man with well-controlled HIV (last CD4 586/28%, HIV RNA undetectable) on TDF/FTC + DTG is switched to Biktarvy (BIC/TAF/FTC) to minimize long term potential toxicity from TDF.

- Six months later, he has gained 15 pounds. He experiences food insecurity, is as active as he was previously, and has not changed how much or how often he eats.

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Which one of the following combinations has been associated with the most weight gain in PWH?

A. Dolutegravir in combination with TAF/FTC

B. Dolutegravir in combination with TDF/FTC

C. Elvitegravir in combination with TAF/FTC

D. Elvitegravir in combination with TDF/FTC

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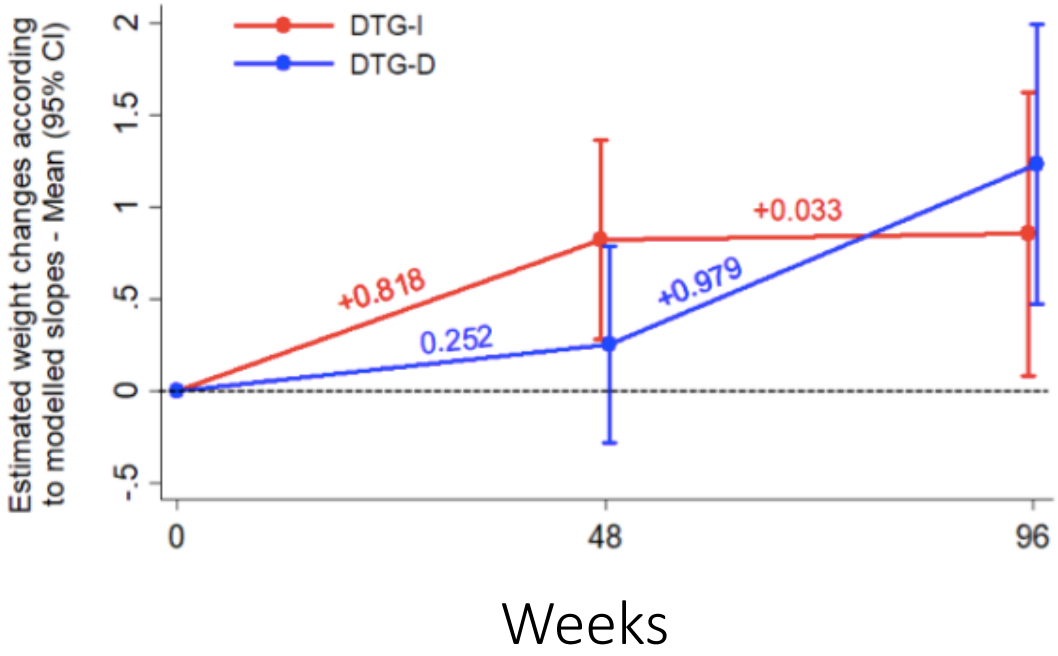
Data Pre-CROI 2019

1. ACTG 5257 Cohort: Weight gain RAL > rPI in treatment naïve[1]
2. SCOLTA Cohort: No difference b/t INSTIs and r/DRV or RPV if failing PI[2]
3. Vanderbilt Cohort: More weight gain with INSTIs than r/PI or Atripla[3]
4. NEAT-022 Analysis: In high CVD risk, switch from r/PI to DTG associated with small but statistically significant weight gain[4]

NEAT-022 Analysis Results



1-Bhagwat, CROI 2017 #695. 2-Taramasso, OFID 2017. 3-Norwood, JAIDS 2017. 4-Waters, HIV Drug Therapy 2018 #102.

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ART and Weight Gain: A Chronology

- CROI 2019 – An association between INSTIs & weight gain is reported, perhaps more so with DTG[1-4]

1-Lake, CROI 2019 #669. 2-Bourgi, CROI 2019 #670. 3-McComsey, CROI 2019 #671. 4-Kerchberger, CROI 2019 #672.

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Data from CROI 2019

Abstract	Study Type	Size	Population	Findings
Lake 669[1]	Retrospective	972	A5001 & A5322	Weight gain accelerated after switch to INSTI
Bourgi 670[2]	Retrospective	24K	NA-ACCORD	More weight gain with INSTI start than with NNRTI start; most with DTG
McComsey 670[3]	Retrospective	3468	TRIO Health Network	INSTI switch not associated with ≥ 3% annualized weight gain
Kerchberger 671[4]	Retrospective	1118	WIHS (WLH)	INSTI switch associated with increases in weight and BMI

1-Lake, CROI 2019 #669. 2-Bourgi, CROI 2019 #670. 3-McComsey, CROI 2019 #671. 4-Kerchberger, CROI 2019 #672.

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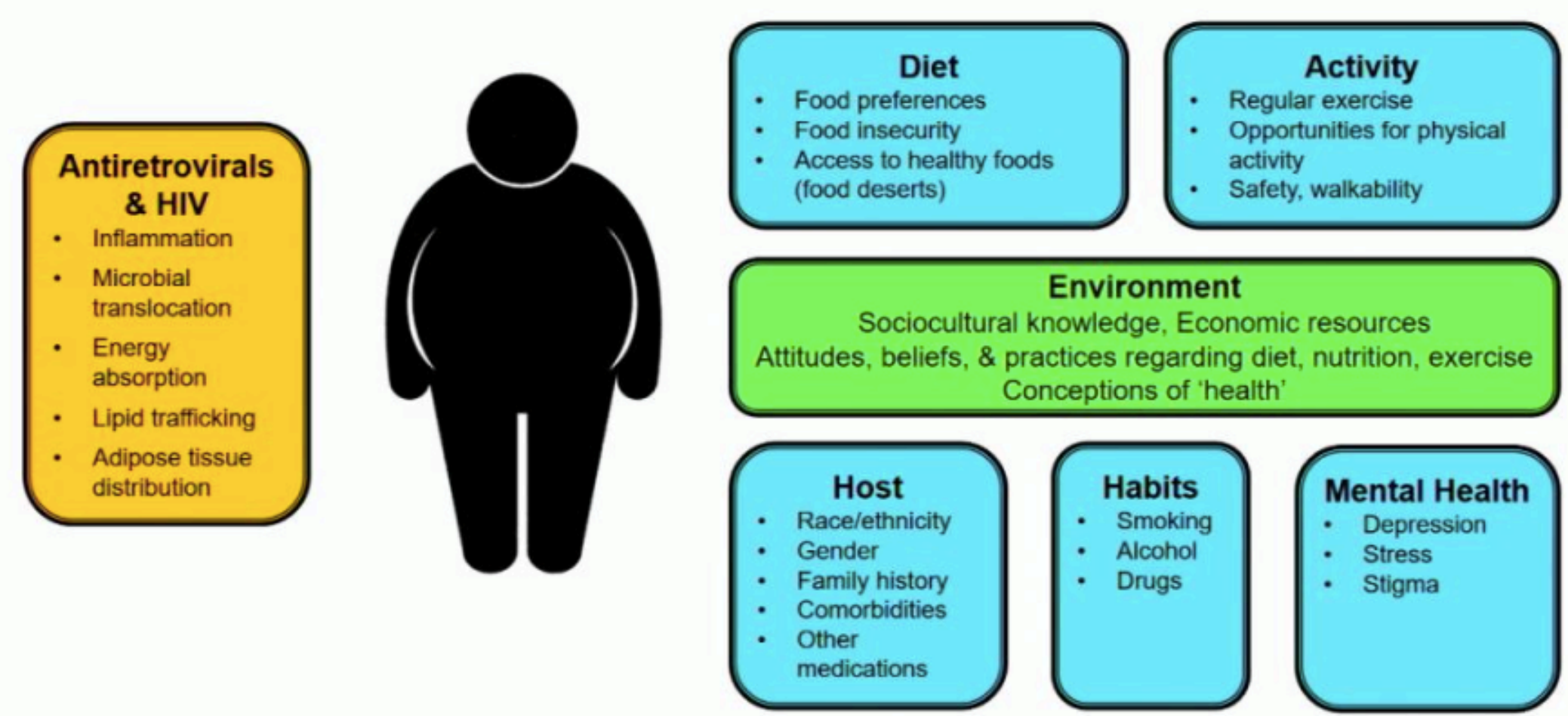
Weight gain is multifactorial



Koethe, CROI 2019 #158.

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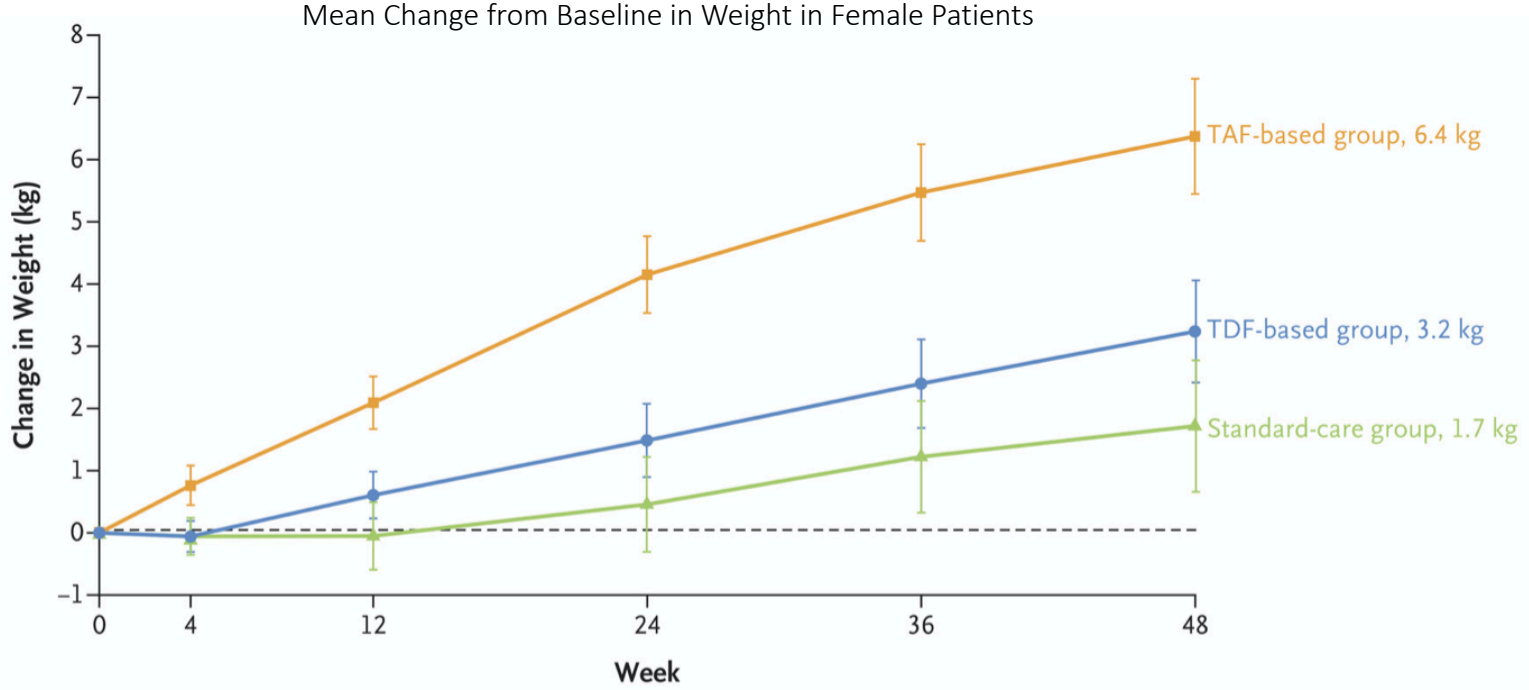
Mean Change from Baseline in Weight in Female Patients



1-Lake, CROI 2019 #669. 2-Bourgi, CROI 2019 #670. 3-McComsey, CROI 2019 #671. 4-Kerchberger, CROI 2019 #672. 5-Venter WDF et al. NEJM. 2019.

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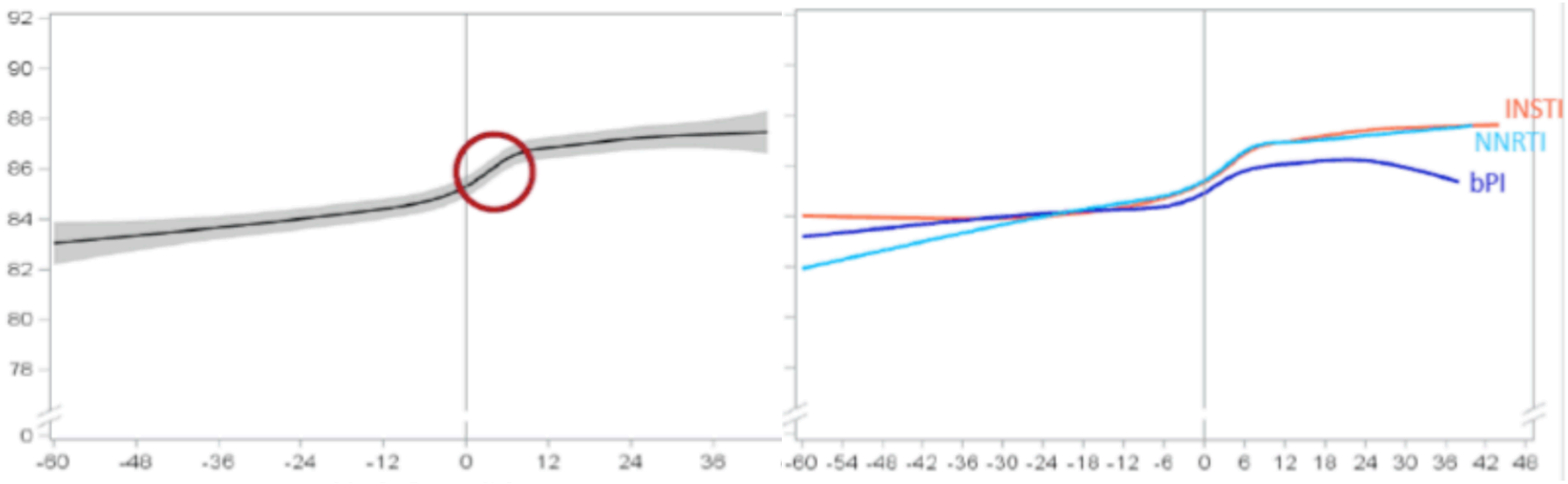
Weight Gain in OPERA Cohort Occurred In the First 9 Months

- Longitudinal cohort of ~ 115,00 PWH in the US
- Current analysis examined weight gain in virologically suppressed PWH on a 3-drug TDF-containing regimen & what happens to weight when switched from TDF to TAF containing regimen



Months from Switch

Months from Switch

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- ID Week 2020 – A cohort study finds switch from TDF to TAF associated with more weight gain than switch from ABC to TAF[7]

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- ID Week 2020 – A cohort study finds switch from TDF to TAF associated with more weight gain than switch from ABC to TAF[7]
- IAS 2021 – TANGO 144-week review of metabolic outcomes showed weight gain with both regimens[8]

1-Lake, CROI 2019 #669. 2-Bourgi, CROI 2019 #670. 3-McComsey, CROI 2019 #671. 4-Kerchberger, CROI 2019 #672. 5-Venter WDF et al. NEJM. 2019. 6-Mallon, AIDS 2020 # OAB0604. 7-McComsey GA, ID Week 2020. 8-van Wyk, IAS 2021 #PEB164

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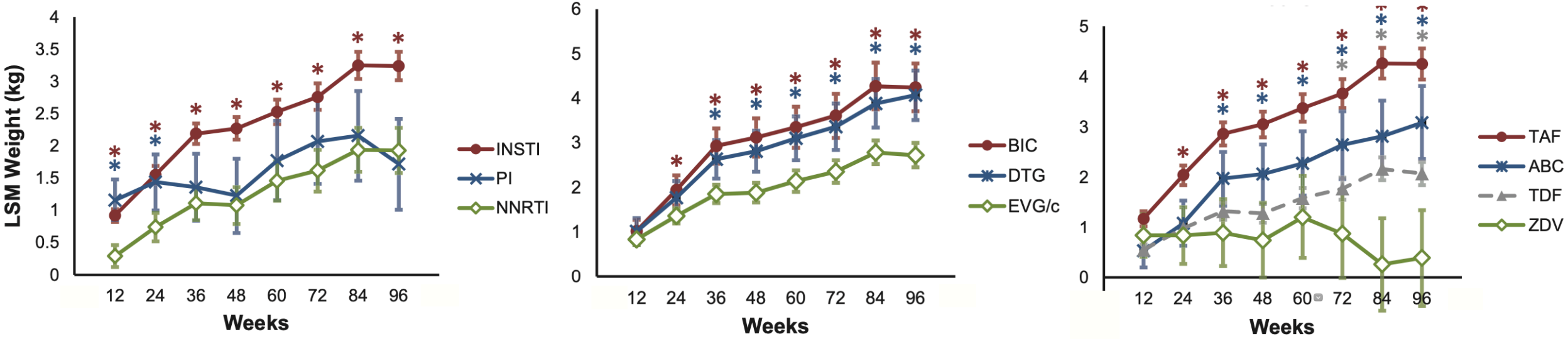
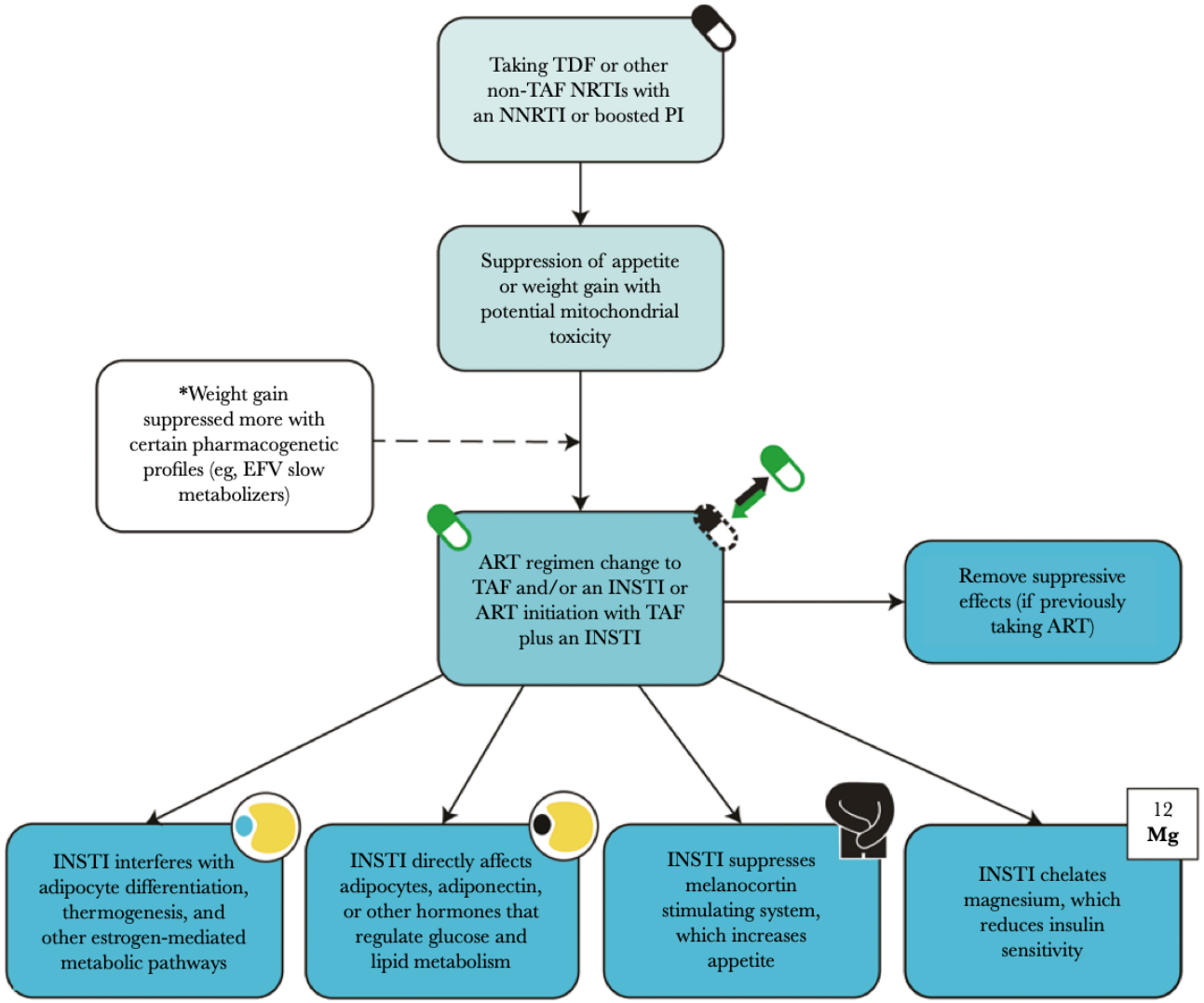
Weight Change from a Pooled Analysis of 8 ART Start Trials



Sax PE, CID, 2021.

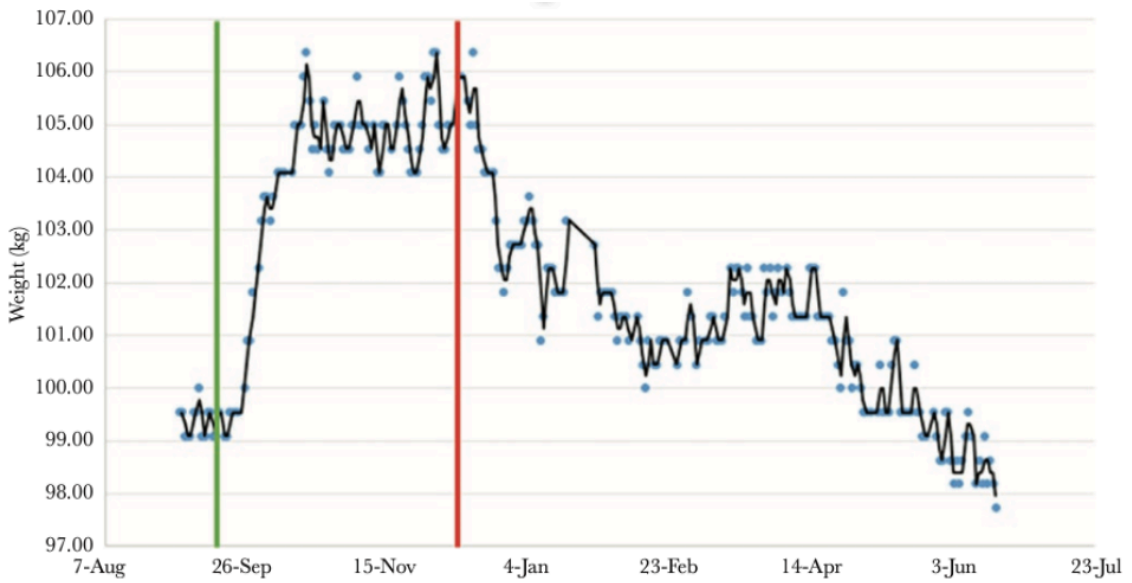
Proposed Mechanisms for TAF- and INSTI-Related Weight Gain



Wood BR, OFID, 2021.

PrEP and Weight Gain

- DISCOVER (CROI 2019): TAF/FTC associated with weight gain as compared to TDF/FTC, mean 1.2 kg difference in bodyweight change between groups at week 48
- DISCOVER OLE (CROI 2020): Median change in body weight at 48 weeks in TDF/FTC was 0.0 kg and at 96 weeks +0.5kg whereas in TAF/FTC arm was +1.0kg and +1.7kg, respectively
- OFID Case Report (2020): A 61-year-old cisgender man with HLD, HTN, and obesity, who has previously had significant and intentional weight loss with diet and exercise, switched to TAF/FTC 21 months after using TDF/FTC to reduce long-term toxicity



Weight after switch to F/TAF (green) and back to F/TDF (red)

Hare, CROI 2019 #104. Ogbuagu, CROI 2020 #92. Selvaraj, OFID 2020.

What to do about this?

- Lifestyle modifications
- Do IT Study (ACTG 5391): For those on INSTI + TAF with > 10% weight gain in 1-3 years after starting the regimen, RCT with switch to DOR-based regimen with TDF or TAF vs continuing current therapy
- DHHS Guidelines[1]
  - "…ARV-associated weight gain should be a factor to consider when initiating or changing ART, particularly in Black women….[because women in general and Black women in particular experience greater weight gain with ART over time than men (AI)]."
  - "To date, it remains unclear whether switching to a non-INSTI-based regimen results in the reversal of weight gain."

1-DHHS Guidelines, accessed September 2022.

MWAETC

ART and Weight Gain: Key Points

1. INSTIs are associated with weight gain, especially DTG and BIC
2. TAF is associated with weight gain
3. The combination of TAF + DTG may lead to the most weight gain
4. More information is needed on mechanisms and recommendations on how to manage weight gain

MWAETC

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