HIV 101: Evaluation and Treatment of People Newly Diagnosed with HIV

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2021 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

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(Updated 09/28/21)

Pretest Question #2

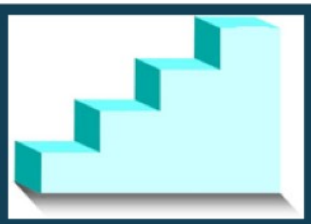
A woman in her 30s, who is in her 2nd trimester of pregnancy, is diagnosed with HIV. Which of the following antiretroviral medications should not be prescribed?

1. Dolutegravir
2. Raltegravir
3. Atazanavir/cobicistat
4. Darunavir/ritonavir
5. Atazanavir/ritonavir

Case

- 45 yo MSM is tested for HIV
- HIV 4th generation antigen/antibody and confirmatory tests are positive
- No previous HIV testing
- He asks you the following questions:
  - When should I start therapy for HIV?
  - What should I be treated with?
  - What are the options if I don't want to take a medicine every day?

Approach to a Person with HIV: 3 Steps



Step 1: History, examination, and lab tests

Step 2: Opportunistic infection prophylaxis (if indicated)

Step 3: Antiretroviral therapy: when and what to start

Step 1: History and Exam

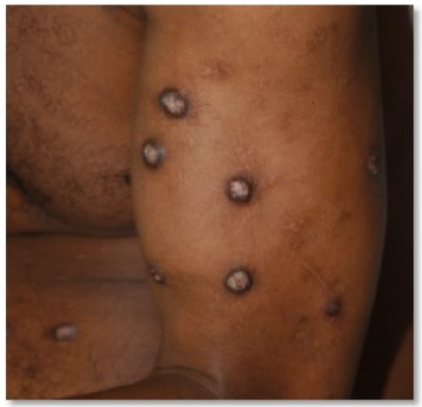
- Risk behaviors; approx. date of infection
- Exposures: tuberculosis, endemic fungi, sexually transmitted infection (STIs)
- Medications, including alternative meds
- Disclosure

Exam:

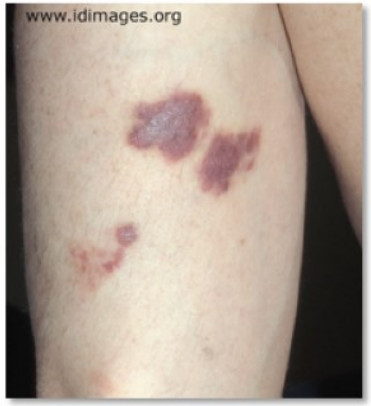
- Skin
- Fundoscopic exam → ophthalmologist if CD4 <50 (risk of cytomegalovirus retinitis)
- Oropharynx
- Lymph nodes → biopsy if dominant node, rapid enlargement
- Cervical pap; rectal exam for anal masses, cytology

Dermatologic & Oropharyngeal Findings

Prurigo nodularis

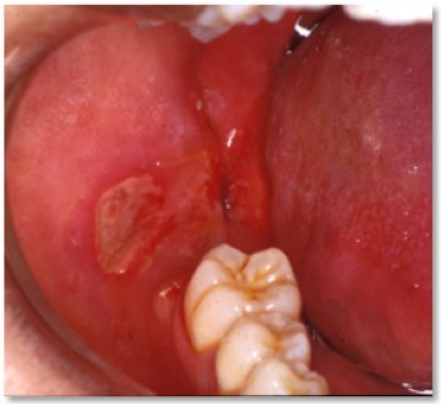


Kaposi Sarcoma

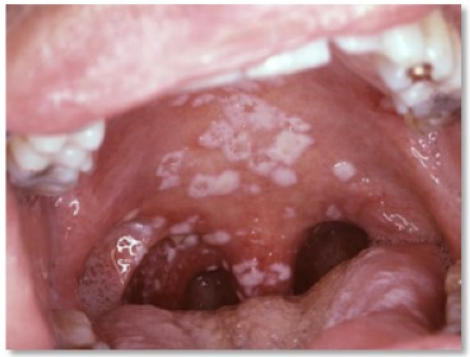


www.idimages.org

Aphthous ulcers



Oral candidiasis



Images courtesy of Drs. Anisa Mosam, Richard Johnson and Medscape

Lab Evaluation: Routine Tests

- Chemistries, BUN/Cr, liver enzymes
- CBC/diff
- Lipids and glucose (repeat fasting if abnormal)
- G6PD: blacks; males from Mediterranean, India, Southeast Asia
- Urinalysis (U/A)

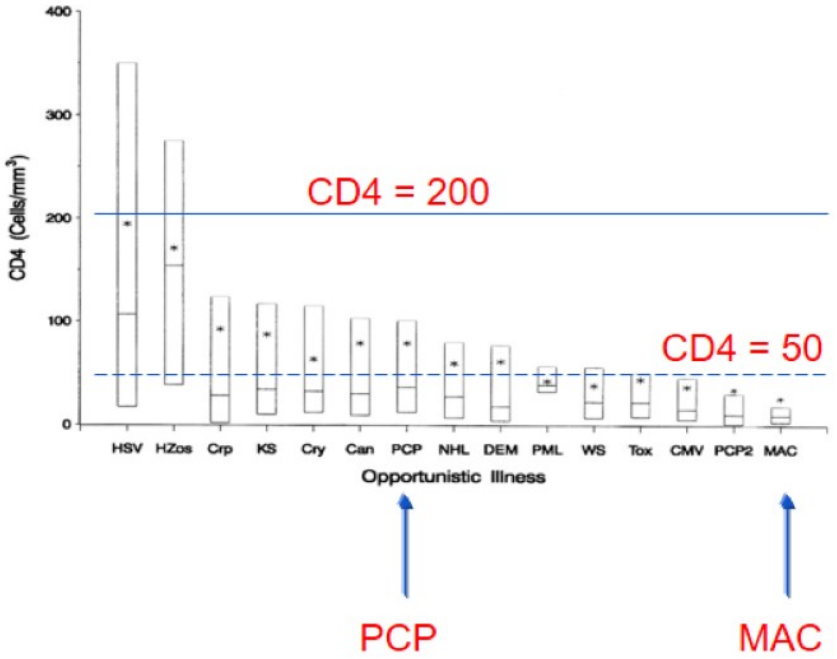
Labs: Screening for Infection

- Serologic testing for infections that can reactivate:
  - If CD4 count <100/uL: toxoplasma IgG, consider serum cryptococcal antigen
  - Varicella IgG if no history of chickenpox or shingles
  - Tuberculin skin test (TST) or IGRA (IGRA preferred if history of BCG vaccination)
    - TST >5 mm is positive in PWH
    - If negative and CD4 count is <200/uL, repeat TST or IGRA after immune reconstitution
- STI screening (syphilis, GC, chlamydia): annually; every 3-6 months if exposures; in MSM: urethral, rectal, oral
- Hepatitis serologies (A, B, C)
  - HCV antibody annually for at-risk MSM, people who inject drugs

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines Thompson MA et al, CID, 2020

Lab Evaluation: HIV-specific Tests

- **CD4 cell count:**
  - Best predictor of risk of opportunistic infection or cancer
  - Used to decide when to start opportunistic infection prophylaxis
- **HIV RNA** ("viral load")
  - Most important predictor of response to therapy: should decline to undetectable within few months of starting treatment



Moore, Ann Intern Med 124:633.

HIV Resistance Testing

Patient	Resistance Test
Newly Diagnosed or Treatment Naive	**Genotype – mutations in viral genes** (Reverse transcriptase and protease)
Virologic Failure to 1st or 2nd Lines of Therapy	**Genotype** (Integrase genotype if integrase inhibitor is failing)
Suspected Complex Resistance	**Phenotype and Genotype**

Interpretation:

- **www.iasusa.org/content/hiv-drug-resistance-mutations**
- **Stanford HIV Drug Resistance: http://hivdb.stanford.edu/**

Approach to the Person with HIV: 3 Steps

Step 1: History, Examination and Lab Tests

Step 2: Opportunistic infection (OI) prophylaxis (if indicated)

Step 3: Antiretroviral therapy

Case - Continued

- 45 yo MSM with newly diagnosed HIV
- PMH: gastroesophageal reflux disease (GERD), allergic rhinitis, hypertension, smoking, elevated lipids
- Medications: omeprazole, fluticasone
- Cr 1.5 (estimated GFR = 48)
- CD4 count 550, HIV RNA 650,000 copies/mL
- HIV genotype: no resistance mutations
- HBsAg negative

Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America

- Pneumocystis pneumonia (PCP) prophylaxis (trim/sulfa DS daily) if:
  - CD4 count <200 (CD4 percentage <14)
  - History of thrush
- *Mycobacterium avium* complex prophylaxis no longer routinely recommended

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/whats-new-guidelines

Saag M et al, JAMA 2020

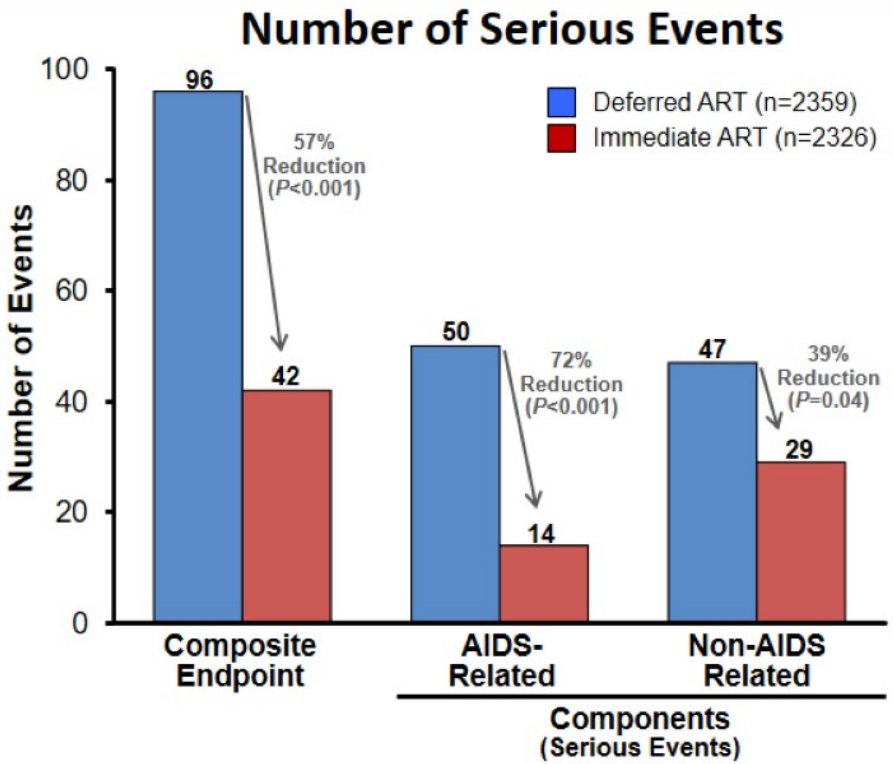
Approach to the Person with HIV: 3 Steps

- Step 1: History, Examination and Lab Tests
- Step 2: Opportunistic infection prophylaxis (if indicated)
- Step 3: Antiretroviral therapy: when and what to start

"When should I start treatment?"

HIV Therapy Recommended Regardless of CD4: START

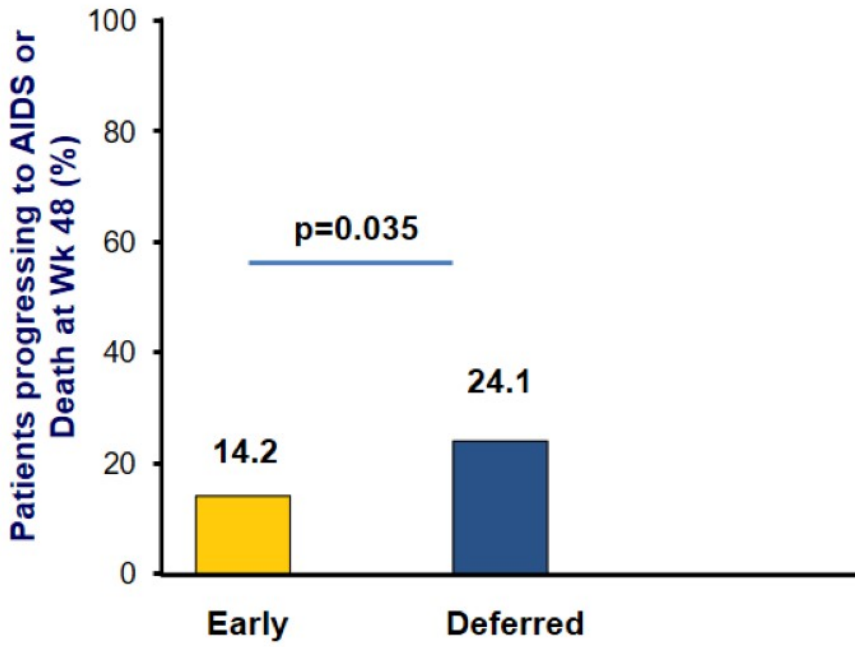
- Adults with HIV and CD4 >500
- Randomized to immediate or deferred ART (CD4 <350)
- TB, KS, lymphoma — most common AIDS-related events — all less frequent in immediate-ART group
- Cancer rates (combining AIDS/non-AIDS) lower in immediate-ART group



Lundgren J, et al. 8th IAS Conference. Vancouver, 2015. Abstract MOSY0301.
The INSIGHT START Study Group. *N Engl J Med.* 2015;July 20. Lifson A et al, CROI 2016, #475; Borges et al, CROI 2016, #160

When to Start ART in Patients with Acute OI: ACTG 5164

- 282 HIV pts with acute OI
- ~2/3 PCP. TB excluded
- Randomized to:
  - Early ART: ~2 wks after OI therapy
  - Deferred ART: ~6 wks after OI therapy
- Rate of AIDS progression/death lower in "early" ART group



Zolopa A et al, PLoS One. 2009

When to Start ART in Patient with OI

OI	When to start
Cryptosporidiosis, microsporidiosis, PML	As part of initial therapy of OI
PCP, MAC, Toxoplasma, most other OIs	Within 2 weeks
Tuberculosis	If CD4 <50: within 2 wk If CD4 >50: within 8-12 wks (TB meningitis: close monitoring/consultation)
Cryptococcal meningitis	4-5 wks after anti-fungal Rx

When patient presents with OI or low CD4 count, ART should be started in hospital or soon after discharge

Zanoni and Gandhi, Inf Dis Clin N Am, 2014;
Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents, 2021;

"How should I be treated?"

Case – What to Start?

- 45 yo M with HIV
- GERD, allergic rhinitis, HTN, smoking, elevated lipids
- Medications: fluticasone, omeprazole
- Cr 1.5, estimated GFR 48
- CD4 cell count 550. HIV RNA 650,000
- HBsAg negative

Which regimen would you start?

1. Dolutegravir/abacavir/3TC
2. Dolutegravir + TAF/FTC
3. Bictegravir/TAF/FTC
4. Doravirine/TDF/3TC
5. Darunavir/cobi/TAF/FTC
6. Dolutegravir/3TC

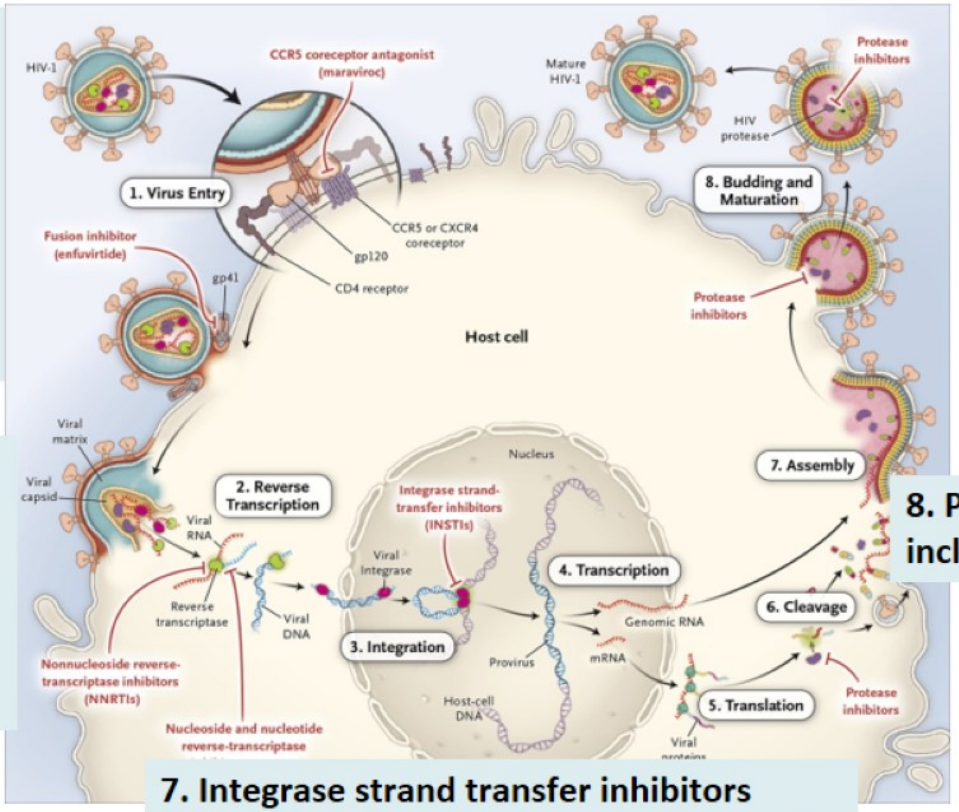
Sites of Action of Major Classes of Current Antiretroviral Medications

Entry inhibitors:

1. Fusion Inhibitor
2. CCR5 Antagonist
3. CD4 post-attachment inhibitor, Ibalizumab
4. gp120 attachment inhibitor, Fostemsavir

Reverse Transcriptase Inh. (RTI)

5. Nucleoside RTI (NRTIs), including tenofovir DF and AF, abacavir
6. Non-nucleoside RTI (NNRTIs)



8. Protease inhibitors (PI), including darunavir

7. Integrase strand transfer inhibitors (INSTI), including dolutegravir, bictegravir

Gandhi M, Gandhi RT. NEJM, 2014.

ART 2021: >30 options

Nucleoside/nucleotide RTIs
- Zidovudine, AZT
- Abacavir, ABC
- Lamivudine, 3TC
- Didanosine, ddI
- Stavudine, d4T
- Tenofovir DF, TDF
- Emtricitabine, FTC
- AZT/3TC
- AZT/3TC/ABC
- ABC/3TC
- TDF/FTC
- TAF/FTC
- TDF/3TC

Integrase inhibitors
- Raltegravir, RAL
- Elvitegravir, EVG
- Dolutegravir, DTG
- Bictegravir, BIC

Non-nucleoside RTIs
- Nevirapine, NVP
- Efavirenz, EFV
- Etravirine, ETR
- Rilpivirine, RPV
- Doravirine, DOR

Protease inhibitors:
- Indinavir, IDV
- Saquinavir, SQV
- Nelfinavir, NFV
- Amprenavir, APV
- Atazanavir, ATV
- Fosamprenavir, FPV
- Lopinavir/ritonavir
- Tipranavir
- Darunavir
- Darunavir/cobicistat
- Atazanavir/cobicistat

Injectable ART

Cabotegravir/Rilpivirine

CCR5 receptor blocker
- Maraviroc

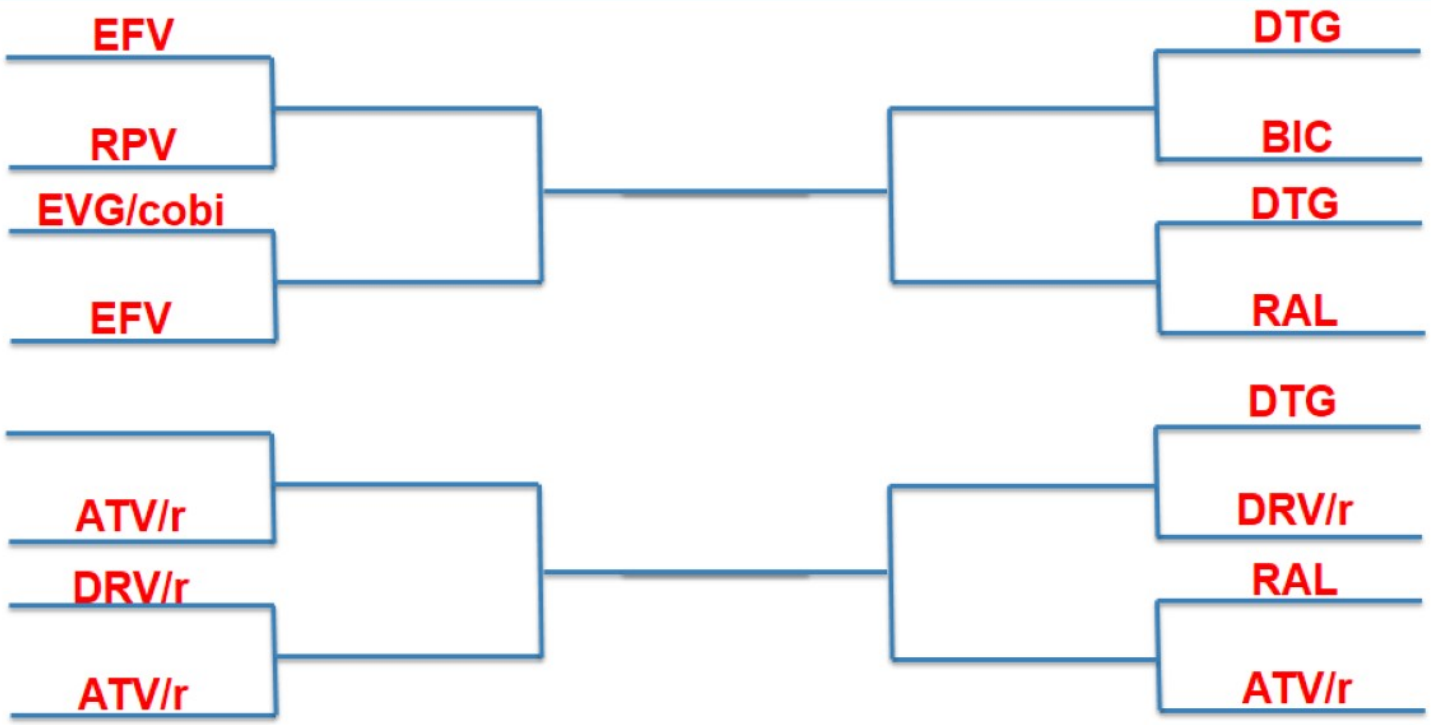
Fusion inhibitors
- Enfuvirtide, ENF, T20

Attachment inhibitors
- Ibalizumab
- Fostemsavir

Single pill combinations
- EFV/FTC/TDF
- EFV/3TC/TDF
- RPV/FTC/TDF
- EVG/cobi/FTC/TDF
- DTG/ABC/3TC
- EVG/cobi/FTC/TAF
- Rilpivirine/FTC/TAF
- BIC/FTC/TAF
- EFV 400/3TC/TDF
- DOR/TDF/3TC

Red – combination agents

Choosing An Initial Regimen



Initial Therapy for PWH: What Do the Guidelines Say?

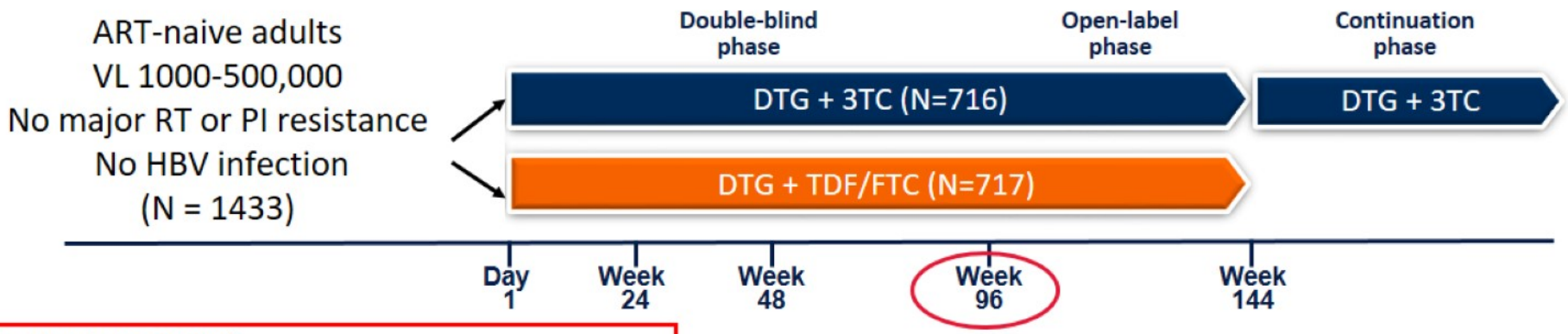
Dept. Health & Human Services (DHHS)	IAS-USA
▪ Bictegravir/FTC/TAF ▪ Dolutegravir/3TC/abacavir *if HLA-B*5701 and HBs Ag negative* ▪ Dolutegravir +(FTC or 3TC) + (TAF or TDF) ▪ Dolutegravir/3TC*	▪ Bictegravir/FTC/TAF ▪ Dolutegravir + FTC/(TAF or TDF) ▪ Dolutegravir + 3TC/TDF ▪ Dolutegravir/3TC*

*Except for individuals with baseline HIV-1 RNA >500,000 copies/mL, with HBV, or for whom results of HIV genotypic resistance testing or HBV testing are not yet available. Limited data in people with CD4 cell count <200

DHHS Guidelines. June 2021. Saag M et al JAMA. 2020; 324:1651.

GEMINI-1 and -2: DTG + 3TC vs DTG + TDF/FTC in Treatment Naïve People with HIV

- International, double-blind phase 3 studies

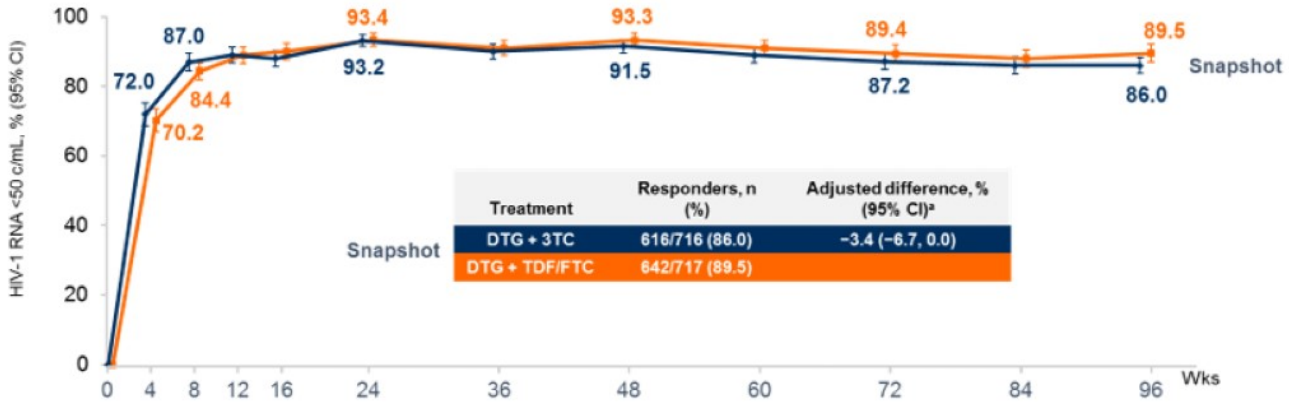


Who was in GEMINI?
- Male: 85%.
- Age: 32-33 years.
- Black: 12%.
- HIV RNA level: Mean: 4.4 $\log_{10}$ c/mL; >100K: 20%.
- CD4 count: Mean: 462; ≤200 8%.

Cahn. Lancet. 2019;393:143. Cahn. JAIDS. 2020;83:310. Cahn. HIV Glasgow 2020. Abstr P018

DTG + 3TC Non-inferior to DTG + TDF/FTC

Snapshot VL <50 at Week 96



	Treatment	Responders, n (%)	Adjusted difference, % (95% CI)[a]
Snapshot	DTG + 3TC	616/716 (86.0)	−3.4 (−6.7, 0.0)
	DTG + TDF/FTC	642/717 (89.5)	

- No treatment emergent resistance (INSTI or NRTI) in either arm

In subset with CD4 count <200 (n=118), virologic suppression rate numerically lower in 2-drug group, but not related to virologic failure

Cahn. Lancet. 2019;393:143. Cahn. JAIDS. 2020;83:310. Cahn. HIV Glasgow 2020. Abstr P018

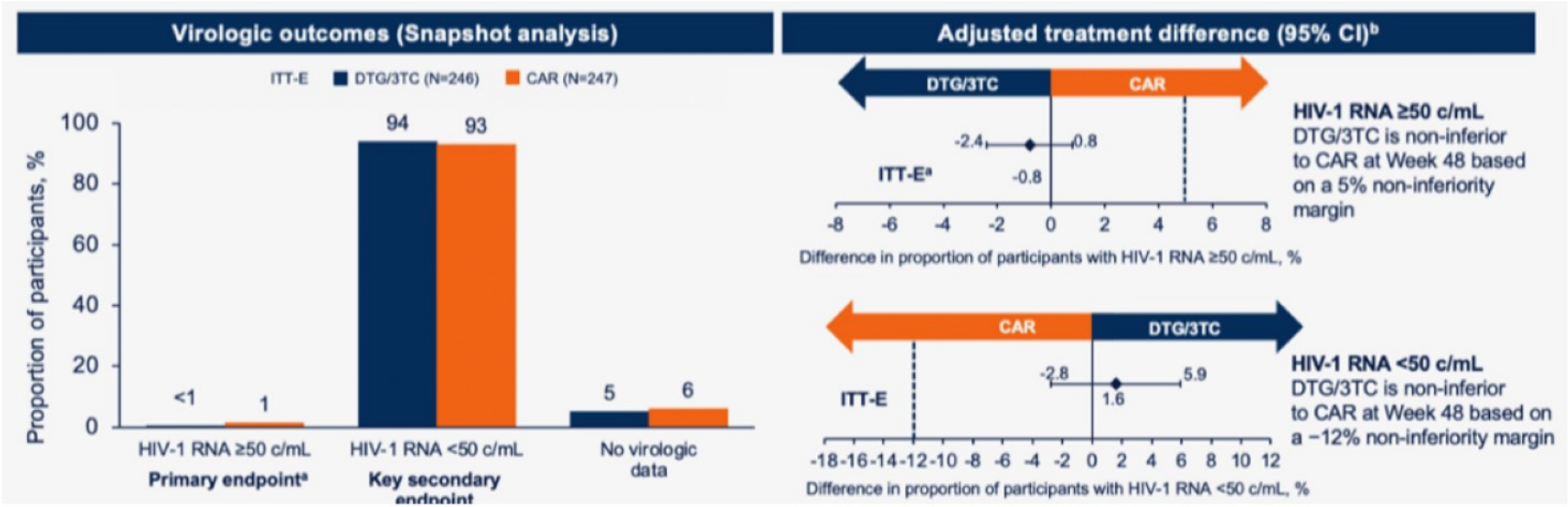
SALSA: DTG/3TC for Maintenance Therapy

- SALSA: efficacy of switching to DTG/3TC compared with continuing any current 3- or 4-drug ART regimen

CAR: current antiretroviral therapy

Llibre J et al, IAS 2021, Abstract OALB0303

SALSA: DTG/3TC Non-Inferior to Continuing 3- or 4-Drug Therapy



- No participant had confirmed virologic withdrawal; no participant had resistance
- Switching to DTG/3TC also supported by results of TANGO trial

Llibre J et al, IAS 2021, Abstract OALB0303; Wang. IAS 2021. Abstr OAB0301

My take on 2-drug therapy with DTG/3TC

- DTG/3TC is a reasonable option, particularly for people who match GEMINI population (HIV RNA <500,000, CD4 cell count >200)
  - Avoid: HBV coinfection; pregnancy/women trying to conceive
- When initiating ART immediately after diagnosis, often starting with 3-drug therapy with plans to "step-down" to DTG/3TC in the future (supported by results of TANGO and SALSA studies)
- No longer using ABC in people on first-line therapy

REGIMEN	PROS	CONS
TDF/FTC + DTG	• TDF associated with lower lipids (tenofovir lowers lipids), less weight gain than TAF • May be used with rifampin (give DTG twice daily)	• Greater nephrotoxicity than ABC and TAF (avoid if CrCl <60) • Larger decline in bone mineral density than with ABC or TAF (avoid if osteopenia/osteoporosis) • DTG increases metformin levels
TAF/FTC + DTG	• TAF: more favorable effects on renal and bone markers than TDF	• Two pills per day • TAF: greater weight gain than TDF • TAF: higher lipids than TDF (tenofovir lowers lipids) • DTG increases metformin levels
TAF/FTC/BIC	• Single pill combination	• TAF: greater weight gain than TDF • TAF: higher lipids than TDF (tenofovir lowers lipids) • Bictegravir not recommended during pregnancy • Bictegravir should not be given with rifampin
DTG/3TC	• Similar virologic efficacy as 3-drug therapy • Fewer medications	• Must confirm virus not resistant to 3TC • Only if VL <500,000, not HBV infected • Less data when CD4 cell count <200

What to Start in Pregnancy: DHHS Guidelines Feb 10, 2021

Two NRTIs

Abacavir/3TC

or

TDF/FTC or TDF/3TC

TAF/FTC – alternative NRTI

Plus

Integrase inhibitor:

Raltegravir (twice daily) or

Dolutegravir (*Preferred ARV throughout pregnancy and for those who are trying to conceive*)

or

Protease inhibitor:

Darunavir/ritonavir (twice daily) or

Atazanavir/ritonavir

Bictegravir (insufficient data)
Elvitegravir/cobi (PK concerns)
DRV/cobi (PK concerns)
ATV/cobi (PK concerns)
DOR (insufficient data)
2-drug regimens not recommended

Tsepamo: Decreasing Rate of Neural Tube Defects (NTDs) in Women with HIV who Conceive While on DTG

- 2018: unplanned analysis found increase in NTD prevalence among infants born to Botswanan women who conceived on DTG (DTG vs non-DTG: 0.94% vs. 0.12%)
- As more data have accrued, NTD prevalence with DTG has decreased; not significantly different from non-DTG ART at conception

	Conception			HIV Negative
	DTG	Non-DTG	EFV	
Total NTDs per exposures, n/N	9/5860	22/22,475	8/13,217	97/144,967
NTD prevalence, % (95% CI)	0.15 (0.08-0.29)	0.10 (0.06-0.15)	0.06 (0.03-0.12)	0.07 (0.05-0.08)
Prevalence diff. for DTG at conception, % (95% CI)	Ref	0.06 (-0.03 to 0.20)	0.09 (-0 to 0.23)	0.09 (0.01-0.23)

1. Zash. NEJM. 2018; 379:979. 2. Zash. IAS 2021. Abstr. PE02B52.

IMPAACT 2010: DTG + FTC/TAF vs DTG + FTC/TDF vs EFV/FTC/TDF for First-line ART During Pregnancy

- Randomized trial in women (mostly in Africa) initiating ART during pregnancy (14-28 wk of gestation)
- Results through delivery:
  - Virologic efficacy of DTG-based ART superior to that of EFV/FTC/TDF (98% vs 91%, *P* = .0052)
  - Adverse pregnancy outcomes significantly less frequent with DTG + FTC/TAF (24%) vs DTG + FTC/TDF (33%) or EFV/FTC/TDF (33%)
  - Neonatal death significantly less frequent with DTG + FTC/TAF vs EFV/FTC/TDF (1% vs 5%; *P* = .019) and with DTG + FTC/TDF vs EFV/FTC/TDF (2% vs 5%; *P* = .05)

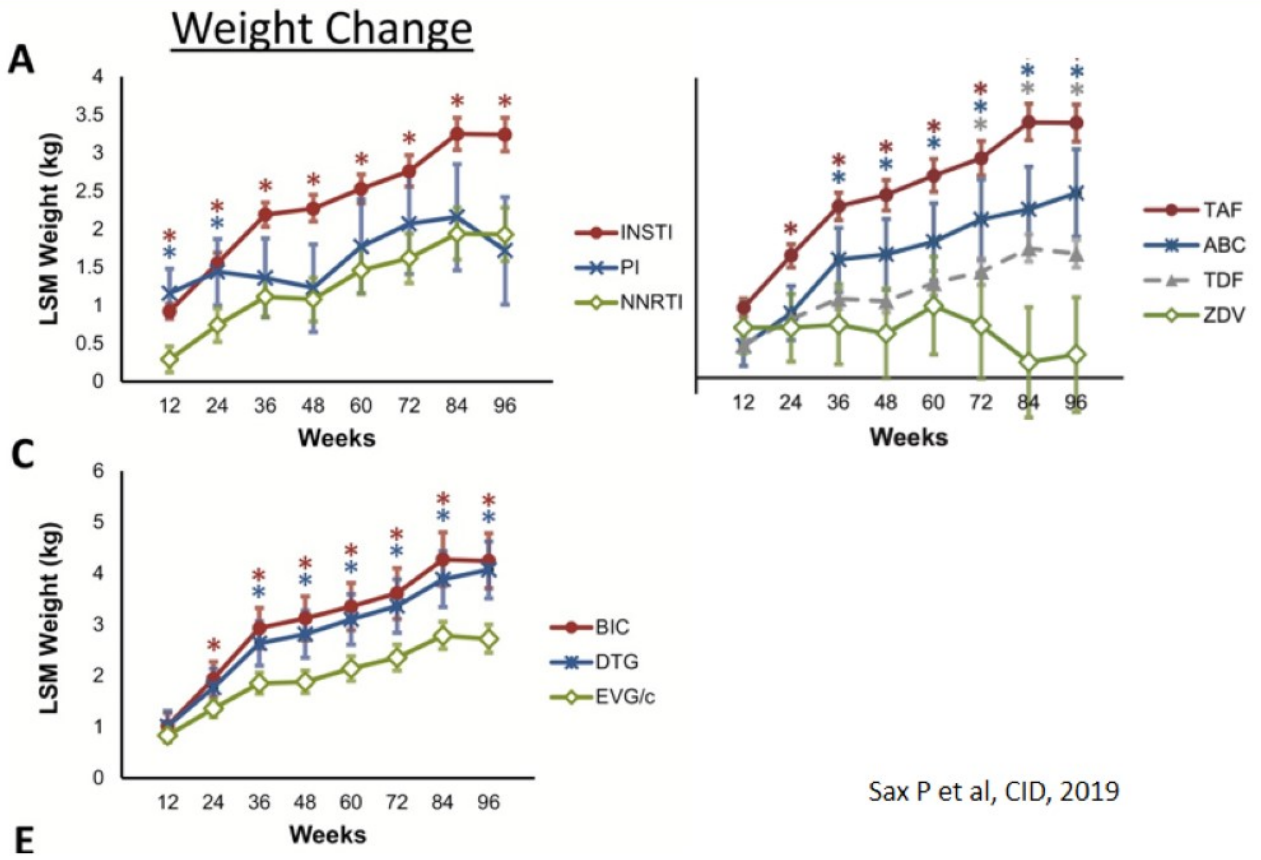
Lockman. Lancet. 2021;397:1276.

Are integrase inhibitors perfect for everyone with HIV?

- Drug interactions:
  - Polyvalent cations
  - Dolutegravir increases metformin levels
- Side effects – weight gain

Weight Gain after Initiation of ART

- Industry-sponsored randomized trials of people initiating ART (n=5680)
- 96-wk median wt gain: 2 kg
- Risk factors for wt gain >10% (12.8% of participants)
  - Low CD4, high HIV RNA
  - Female sex, black race
  - BIC = DTG > EVG/c
  - TAF > ABC, TDF > AZT



Sax P et al, CID, 2019

Does changing ART ameliorate weight gain?

Open Forum Infectious Diseases

NOVEL ID CASES (INVITED)

Case Report: Reversal of Integrase Inhibitor– and Tenofovir Alafenamide–Related Weight Gain After Switching Back to Efavirenz/Emtricitabine/Tenofovir DF

F. Will Pohlman,[1] Kara S. McGee,[2,3] and Mehri S. McKellar[2]

ACTG A5391 (Do-IT study): Doravirine for Persons with Excessive Weight Gain on Integrase Inhibitors and TAF

	Week 0	Week 48
Overweight/obese (BMI ≥27.5 kg/m^2) persons on RAL, DTG, or BIC + TAF/FTC (or TAF/3TC) with unintentional >10% weight gain over prior 1-3 years	Arm 1: Switch to DOR+TAF/FTC (or TAF/3TC)	
	Arm 2: Switch to DOR+TDF/FTC (or TDF/3TC)	
	Arm 3: Continuation of INSTI+TAF/FTC (or TAF/3TC)	

Other Treatment Options When You Don't Think an Integrase Inhibitor is Optimal

- Rilpivirine/FTC/TDF or Rilpivirine/FTC/TAF
  - Food requirement (about 400 calorie meal)
  - Do not use with proton-pump inhibitor; stagger dosing if on H2 blocker
- Doravirine/3TC/TDF or Doravirine + FTC/TAF
- Darunavir/cobi/FTC/TAF
  - Drug interactions with CYP3A4 metabolized medications, like inhaled fluticasone, certain statins

Expert opinion

Monitoring after Starting ART

- HIV RNA monthly until undetectable; then every 3-6 months
  - Expect HIV RNA to be undetectable within few months of starting ART; best indicator that treatment is working
- Chemistries, BUN/Cr, liver enzymes: week 2 to 8; then every 3-6 mo.
- CBC/diff: every 3-6 mo.
- Glucose and lipids: before starting ART; if normal, every 12 mo. (repeat fasting if abnormal)
- U/A annually (on TDF: every 6 months)
  - Consider urine protein/Cr; urine albumin/Cr
- CD4 cell count every 3 to 6 months during first 1 to 2 years of ART; when HIV RNA suppressed and CD4 cell count >250-300, can space out to every 12 months; optional when CD4 cell count >500

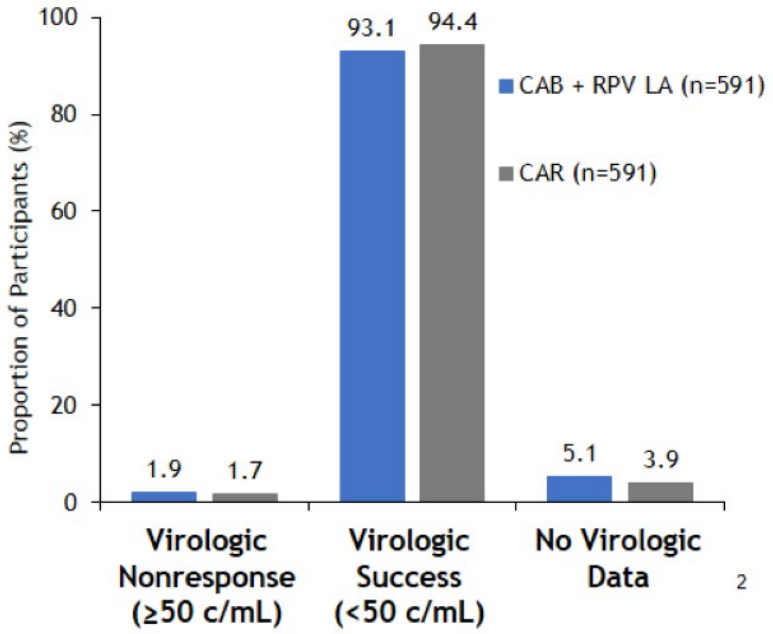
What are the options if I don't want to take a medicine every day?

Long-Acting ART

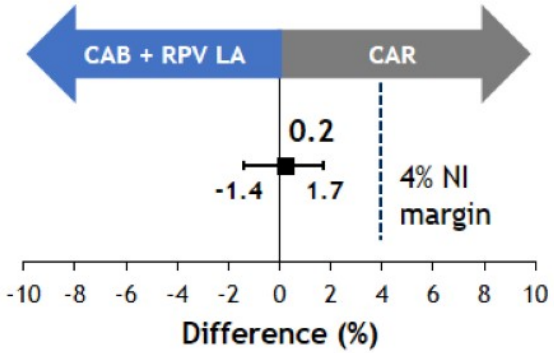
- Injectable Cabotegravir (CAB), an INSTI, and rilpivirine (RPV), an NNRTI
- Long-acting formulations; half-lives of months
- Phase 3 studies
  - FLAIR: Treatment naïve people with HIV; suppress with oral ART; then switch to monthly IM LA CAB/RPV or continue oral ART
  - ATLAS: Suppressed people with HIV; switch to monthly IM LA CAB/RPV or continue oral ART

Monthly LA Cabotegravir/Rilpivirine in PWH with Suppressed HIV RNA: ATLAS/FLAIR Week 48 Pooled Results

Virologic outcomes



Adjusted treatment difference (95% CI)*



Primary Endpoint:

LA noninferior to CAR (HIV-1 RNA ≥50 c/mL) at Week 48

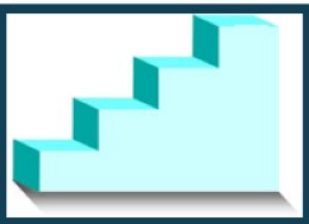
--- INDICATIONS AND USAGE----------

CAB/RPV … is indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

Note: LA CAB + RPV not active against HBV

Swindells S et al, NEJM 2020; Orkin C et al, NEJM, 2020; Overton E, IAS 2019 MOPEB257. DHHS Guidelines. June 2021.

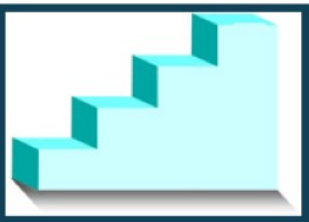
Approach to a Person with HIV



<u>Step 1</u>: History, Examination, Labs

- 45 yo M with HIV
- GERD, allergic rhinitis, hypertension, smoker
- Meds: omeprazole, fluticasone (interact with several commonly used regimens)
- CD4 cell count 550, HIV RNA 650,000
- HIV Genotype: no resistance mutations

Approach to a Person with HIV



Step 2: OI Prophylaxis

- CD4 count 550: OI prophylaxis not indicated

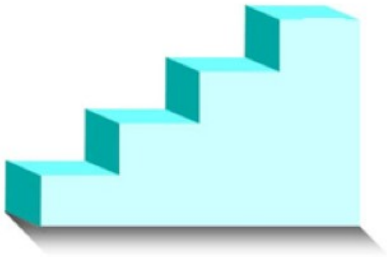
Step 3: ART – individualizing therapy

- On fluticasone: don't use PI or cobi-containing Rx
- Estimated GFR 48: avoid TDF; TAF OK
- HIV RNA >500,000: avoid DTG/3TC

Case – Bringing it all back home

- Initiated Bictegravir/FTC/TAF
- Monitor HIV RNA monthly until undetectable then every 3 – 6 months (space out once patient has durable suppression)
- Monitor safety labs (kidney function, liver enzymes; CBC) – space out once patient is stable
- Counseled him about U = U (undetectable = untransmissible)

Thank you for your attention!



Posttest Question #2

A woman in her 30s, who is in her 2nd trimester of pregnancy, is diagnosed with HIV. Which of the following antiretroviral medications should not be prescribed?

1. Dolutegravir
2. Raltegravir
3. Atazanavir/cobicistat
4. Darunavir/ritonavir
5. Atazanavir/ritonavir

Question-and-Answer Session

2021 Ryan White HIV/AIDS Program CLINICAL CONFERENCE