2020 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

Treating HIV in 2020 — Interactive Cases From the Clinic(ians)

Michael S. Saag, MD
Professor of Medicine
Associate Dean for Global Health
University of Alabama at Birmingham
Birmingham, Alabama

Financial Relationships With Commercial Entities

Dr Saag has received research grants and support awarded to his institution from Gilead Sciences, Inc and ViiV Healthcare. (Updated 08/08/20)

Slide 2 of 49

Learning Objectives

After attending this presentation, learners will be able to select antiretroviral therapy in patients who :

- Are starting initial therapy
- Are Elite Controllers
- Are debating between starting TDF or TAF
- Are pregnant
- Have persistent low-level viremia
- Have M184V at baseline
- Have a slow CD4 count response to Rx

Slide 3 of 49

Question

Seems like we are now starting ARV therapy for about everyone, what about starting therapy immediately at time of diagnosis?

Case 1

- 30 yo male was diagnosed with HIV infection 4 hours ago in the ER
- Asymptomatic
- **Initial:** No Viral Load, CD4, Resistance Data, or HLA-B57 neg
- Other labs are normal
  WBC 3800 / Lymphocytes 20%
- No prior medical history.
- Ok to start therapy if you think he should

ARS Question 1: When would you choose to start therapy?

1. Right now in the ED
2. Within 1 - 2 days (outpt Clinic)
3. In the next 2 weeks (outpt Clinic)
4. Within 2 – 4 weeks
5. Some other option

Question

What regimen should I use as initial therapy for this patient?

Slide 7 of 49

ARS Question 2: At this point which regimen would you choose?

1. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
2. ABC/ 3TC / DTG (fdc)
3. TAF/ FTC (fdc) + DTG
4. DTG + 3TC
5. TAF / FTC/ ELV / cobi (fdc)
6. TAF/ FTC / BIC (fdc)
7. TAF / FTC (fdc) + RAL (once daily)
8. TAF / FTC / RPV (fdc)
9. TAF/ FTC (fdc) + DRV/r (or cobi / fdc)
10. Some other option (e.g., DRV/r + DTG or …)

Slide 8 of 49

Question

What regimen should I use as initial therapy?

Slide 9 of 49

Case 2

- 48 yo male presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial:** HIV RNA 28,000 c/ml
  CD4 count 650 cells/ul
- Other labs are normal
- Genotype is Wild-type virus
- No prior medical history. Normal renal function
- Ok to start therapy if you think he should

Slide 10 of 49

ARS Question 3: At this point which regimen would you choose?

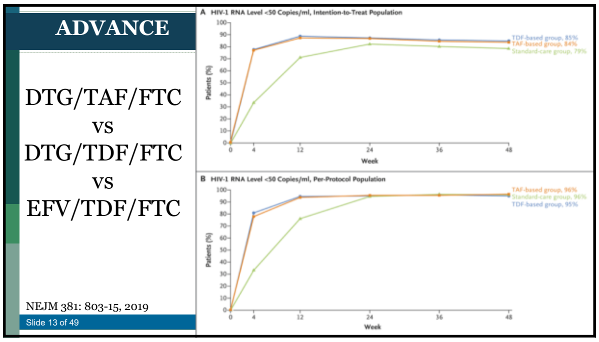
1. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
2. ABC/ 3TC / DTG (fdc)
3. TAF/ FTC (fdc) + DTG
4. TAF / FTC/ ELV / cobi (fdc)
5. TAF/ FTC / BIC (fdc)
6. 3TC/DTG (fdc)
7. TAF / FTC / RPV (fdc)
8. TAF/ FTC (fdc) + DRV/r (or cobi / fdc)
9. Some other option (e.g., DRV/r + DTG or …)

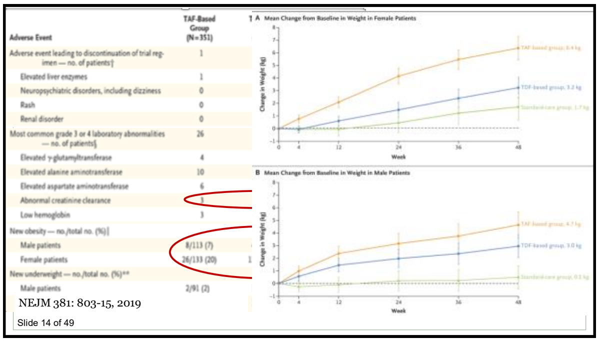
Slide 11 of 49

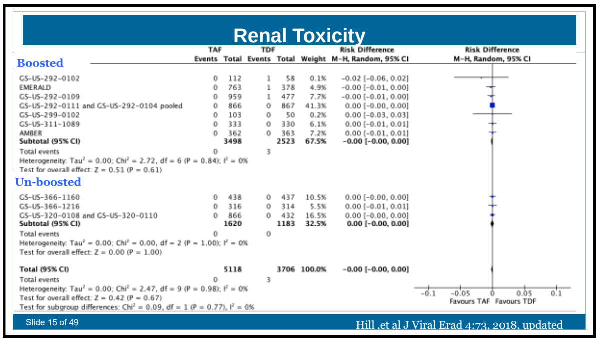
ARS Question 4: Would you use TAF or TDF with an InSTI?

1. TAF
2. TDF
3. Either

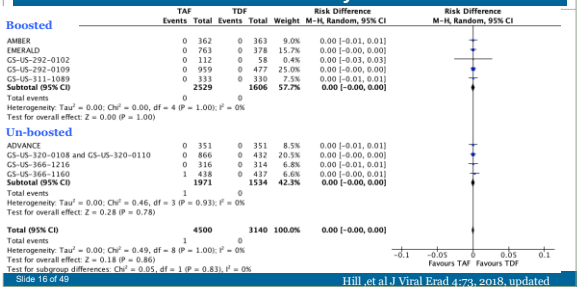
Slide 12 of 49


ADVANCE
DTG/TAF/FTC
vs
DTG/TDF/FTC
vs
EFV/TDF/FTC
NEJM 381: 803-15, 2019
Slide 13 of 49
A HIV-1 RNA Level <50 Copies/ml, Intention-to-Treat Population
Patients (%)
Week
TDF-based group, 85%
TAF-based group, 84%
Standard-care group, 79%
B HIV-1 RNA Level <50 Copies/ml, Per-Protocol Population
TAF-based group, 96%
Standard-care group, 96%
TDF-based group, 95%


Adverse Event
TAF-Based Group (N=351)
Adverse event leading to discontinuation of trial regimen — no. of patients† 1
Elevated liver enzymes 1
Neuropsychiatric disorders, including dizziness 0
Rash 0
Renal disorder 0
Most common grade 3 or 4 laboratory abnormalities — no. of patients§ 26
Elevated γ-glutamyltransferase 4
Elevated alanine aminotransferase 10
Elevated aspartate aminotransferase 6
Abnormal creatinine clearance 3
Low hemoglobin 3
New obesity — no./total no. (%)
Male patients 8/113 (7)
Female patients 26/133 (20)
New underweight — no./total no. (%)**
Male patients 2/91 (2)
NEJM 381: 803-15, 2019
Slide 14 of 49
A Mean Change from Baseline in Weight in Female Patients
B Mean Change from Baseline in Weight in Male Patients
Change in Weight (kg)
Week


Renal Toxicity
Boosted
TAF Events Total | TDF Events Total | Weight | Risk Difference M-H, Random, 95% CI
GS-US-292-0102 0 112 1 58 0.1% -0.02 [-0.06, 0.02]
EMERALD 0 763 1 378 4.9% -0.00 [-0.01, 0.00]
GS-US-292-0109 0 959 1 477 7.7% -0.00 [-0.01, 0.00]
GS-US-292-0111 and GS-US-292-0104 pooled 0 866 0 867 41.3% 0.00 [-0.00, 0.00]
GS-US-299-0102 0 103 0 50 0.2% 0.00 [-0.03, 0.03]
GS-US-311-1089 0 333 0 330 6.1% 0.00 [-0.01, 0.01]
AMBER 0 362 0 363 7.2% 0.00 [-0.01, 0.01]
Subtotal (95% CI) 3498 2523 67.5% -0.00 [-0.00, 0.00]
Total events 0 3
Heterogeneity: Tau² = 0.00; Chi² = 2.72, df = 6 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
Un-boosted
GS-US-366-1160 0 438 0 437 10.5% 0.00 [-0.00, 0.00]
GS-US-366-1216 0 316 0 314 5.5% 0.00 [-0.01, 0.01]
GS-US-320-0108 and GS-US-320-0110 0 866 0 432 16.5% 0.00 [-0.00, 0.00]
Subtotal (95% CI) 1620 1183 32.5% 0.00 [-0.00, 0.00]
Total events 0 0
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 2 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Total (95% CI) 5118 3706 100.0% -0.00 [-0.00, 0.00]
Total events 0 3
Heterogeneity: Tau² = 0.00; Chi² = 2.47, df = 9 (P = 0.98); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%
-0.1 -0.05 0 0.05 0.1
Favours TAF Favours TDF
Slide 15 of 49
Hill ,et al J Viral Erad 4:73, 2018, updated

Bone Toxicity



Hill ,et al J Viral Erad 4:73, 2018, updated

Question

Does InSTI therapy cause weight gain?

Case 3

- 47 yo female starts on BIC/FTC/TAF 12 months ago from her original ARV regimen (TDF/FTC/DRV/r)
- Diagnosed 4 years ago
- **Initial:** HIV RNA 28,000 c/ml (Wildtype virus)
  CD4 count 450 cells/ul
- **Current:** HIV RNA <20 c/mL / CD4+ count 930 /uL
- Since starting her current regimen her weight has increased from **145 lbs to 171 lbs**

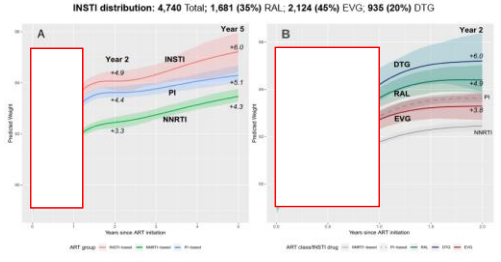
ARS Question 5: At this point you would

1. **Keep her on her current Rx** (TAF/FTC/BIC)
   Or Switch her to:
2. TDF/ FTC (fdc) / DRV/r
3. TAF/ FTC / DRV/c (fdc)
4. TDF / FTC / RPV (fdc)
5. DTG / RLP (fdc)
6. TAF / FTC / ATV/c
7. Some other option

Slide 19 of 49

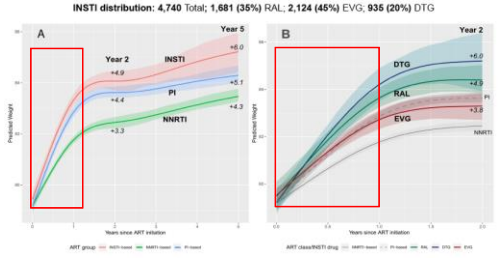
Change in Weight Overtime – NA-ACCORD

Bourgi et al CROI 2019

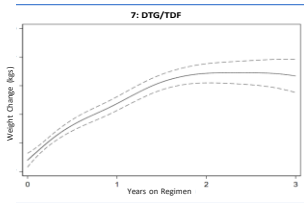


Change in Weight Overtime – NA-ACCORD

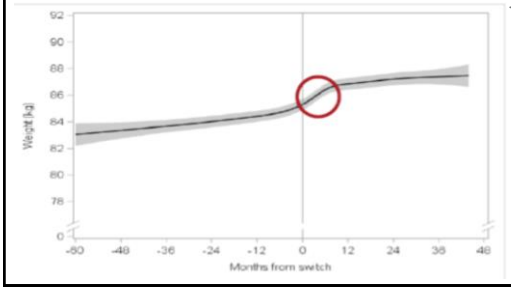
Bourgi et al CROI 2019



GAM PLOT: CHANGE IN WEIGHT IN KG OVER TIME



WEIGHT GAIN AFTER SWITCH FROM TDF TO TAF



OPERA C COHORT

IAS 2020

Question

What regimen should I use as initial therapy in a pregnant patient?

Slide 24 of 49

Case 4

- 30 yo female presents with newly diagnosed HIV infection
- Asymptomatic, 2.5 months pregnant
- **Initial:** HIV RNA 28,000 c/ml
  CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype is Wild-type virus
- No prior medical history. First pregnancy
- Ok to start therapy if you think she should

Slide 25 of 49

ARS Question 6: At this point which regimen would you choose?

1. TDF / FTC / EFV (fdc)
2. ABC/ 3TC / DTG (fdc)
3. TAF / FTC/ ELV / cobi (fdc)
4. TDF / FTC / RPV (fdc)
5. TAF/ 3TC (fdc) / DTG (fdc)
6. TDF/ FTC (fdc) / DRV/r (or cobi / fdc)
7. TAF/ FTC / ATV/r (or cobi / fdc)
8. TDF / FTC / ATV/r (or cobi / fdc)
9. Some other option

Slide 26 of 49

Prospective Antiretroviral Pregnancy Registry (APR): Integrase Inhibitors (InSTI) and Neural Tube Defects (NTD)

Albano J et al. CROI 2019 Seattle, WA Abs. 747

- 1,193 live births with InSTI exposure at any time in pregnancy; 604 periconceptional exposure, including 174 DTG, 186 EVG, 244 RAL.
- 2 CNS defect cases were reported with InSTI exposure at any time (both DTG, one 1st trimester, one 2nd/3rd trimester).
- There were **no NTD** among **prospective cases** for any InSTI drug.

	Earliest Trimester of Exposure – Prospective Cases		
	Periconception	1st Trimester	2nd/3rd Trimester
	Defects/live birth	Defect/live birth	Defects/live birth
Exposure to any INSTI	16/604 (2.6%)	4/135 (3.0%)	17/452 (3.8%)
Dolutegravir	6/174 (3.4%)	2/55 (3.6%)	4/137 (2.9%)
Elvitegravir	5/186 (2.7%)	0/27 (0%)	0/57 (0%)
Raltegravir	5/244 (2.0%)	4/68 (5.9%)	13/290 (4.5%)

Can be more than one organ system for a defect

No Neural Tube Defects

CNS: 2: 1 (lissencephaly – neural migration disorder) with periconception DTG; 1 (ventriculomegaly) with 2nd/3rd trimester DTG exposure.

Face, ear, face, neck: 2
Cleft lip/palate: 2
Respiratory: 1
Cardiac/circulatory: 11
Lower GI: 1
Renal: 4
Musculoskeletal: 8
Chromosome abnl: 2
Other organ systems: 1
Specified syndromes 1

From JR Anderson, MD at New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE, IAS--USA.

More Rapid VL Decline with Dolutegravir than Efavirenz

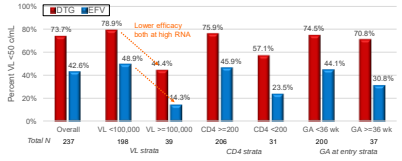
DolPHIN 2

Khoo S et al. CROI 2019 Seattle, WA Abs 40LB

- Primary outcome
  - Time on medication before delivery, median 55 days

Delivery	Dolutegravir	Efavirenz	aRR DTG vs EFV*	P value
VL <50	73.8% (90/122)	42.6% (49/115)	1.66 (1.2, 2.1)	<0.0001
VL <1000	92.6% (113/122)	82.6% (95/115)	1.11 (1.0, 1.2)	0.0513

*Adjusted for age, country, VL (<> 100,000), CD4 (<>200), GA at start ART



From JR Anderson, MD at New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE, IAS–USA.

Recommendations of Perinatal Guidelines Panel: DTG (November 2019)

- **DTG is a preferred INSTI for ART-naïve women irrespective of trimester**
  - For pregnant women receiving DTG and present to care in 1st trimester, counsel about risks/benefits of continuing DTG vs switch to alternative regimen. In most cases, continuation of DTG is recommended (**AIII**)
    - NTDs may have already occurred
    - Additional risk of NTD may be small, depending on current GA
    - Background risk of NTD (0.06% in US)
    - Changes in ART, even in 1st trimester, may increase risk of viral rebound
- DTG +TDF/FTC is recommended with acute HIV in pregnancy
- DTG is an alternative agent for women trying to conceive

From JR Anderson, MD at New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE, IAS–USA.

Question

Seems like we are now starting ARV therapy for about everyone, what about starting therapy for an **Elite Controller**?

Slide 30 of 49

Case 5

- 30 yo male was diagnosed with HIV infection 7 years ago
- Asymptomatic
- **Initial:** HIV RNA < 50 c/ml (HIV DNA positive)
  CD4 count 870 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype determined from DNA is wild-type
- No prior medical history.
- Ok to start therapy if you think he should

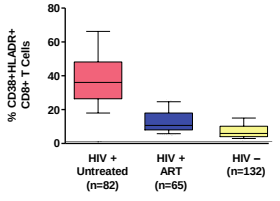
Slide 31 of 49

ARS Question 7: Would you choose to start therapy at this time?

1. Yes
2. No
3. Maybe

Slide 32 of 49

T cell "activation" is lower in treated than untreated adults, but consistently higher than "normal"



Slide 33 of 49

Hunt et al JID 2003, PLoS ONE 2011 and unpublished

Question

What do I do with a patient who has persistently detectable viremia?

Slide 34 of 49

Case 6

- 55 yo male referred to you for evaluation
- Diagnosed 18 years ago with HIV infection
- **Initial:** HIV RNA 936,000c/ml
  CD4 count 70 cells/ul
- **Current: HIV RNA 85 c/ml (prior value 62 c/ml)**
  CD4 count 525 cells/ul
- Started on NEL/D4T/3TC; subsequently treated with
  - LOP-r / TDF/FTC,
  - EFV/ FTC/ TDF (fdc).
  - Now **DTG / DRV/c / 3TC**
- No historical resistance tests are available

Slide 35 of 49

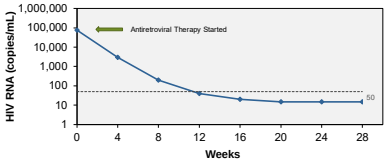
ARS Question 8: Should you change ARV therapy now?

1. Yes
2. No
3. Not sure

Slide 36 of 49

Virologic Responses on Antiretroviral Therapy

Virologic Suppression



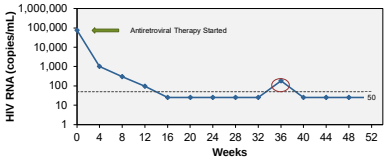
A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).

Source: 2016 DHHS Antiretroviral Therapy Guidelines. AIDS Info.

National HIV Curriculum

Virologic Responses on Antiretroviral Therapy

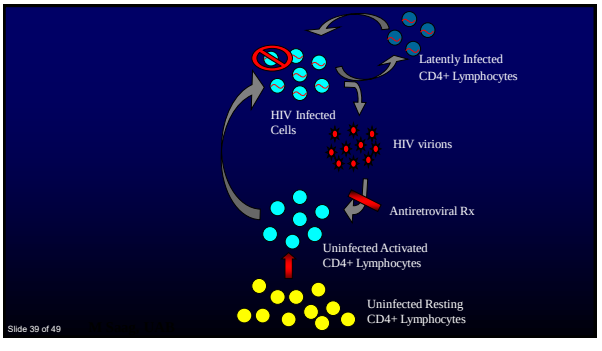
Virologic Blip



After virologic suppression, an isolated detectable HIV RNA level followed by return to virologic suppression.

Source: 2016 DHHS Antiretroviral Therapy Guidelines. AIDS Info.

National HIV Curriculum



All-cause mortality

Elvstam, et al

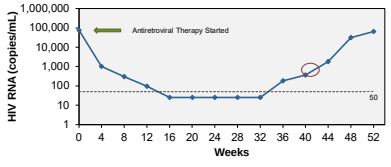
	Unadjusted model n=6,956	Fully adjusted model* n=4,541
LLV 50-999 copies/mL	1.7 (1.2-2.4)	2.2 (1.3-3.6)
High-level viremia	2.5 (2.0-3.1)	7.8 (3.8-15.7)
LLV 50-199 copies/mL	2.3 (1.5-3.3)	2.2 (1.3-3.8)
LLV 200-999 copies/mL	1.2 (0.69-2.0)	2.1 (0.95-4.7)
High-level viremia	2.5 (2.0-3.1)	7.7 (3.7-15.9)

Slide 40 of 49 CROI 2020 OL-13

Slide 41 of 152

Virologic Responses on Antiretroviral Therapy

Virologic Failure



Slide 41 of 49

Source: 2016 DHHS Antiretroviral Therapy Guidelines. AIDS Info.

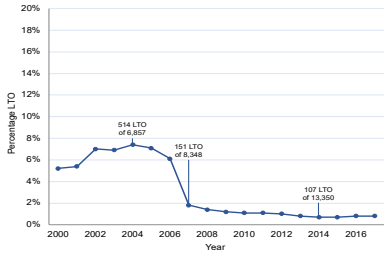
National HIV Curriculum

Question

How do I manage a heavily experienced patient who is experiencing virologic failure ?

Slide 42 of 49

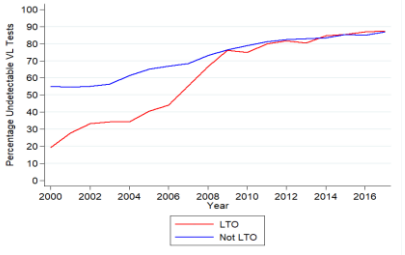
Prevalence of Patients with Limited Treatment Options



Slide 43 of 49

Crane et al, IAS 2019

Virologic Success in Those with or without LTO



Slide 44 of 49

Crane et al, IAS 2019

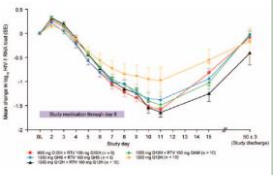
Discussion

- Confirm the virologic failure
- Explore all prior regimens and resistance tests
- Identify 2 fully active drugs (if possible)
  - Use Dolutegravir (50 mg) twice daily
  - Some form of Tenofovir (as long as no K65R)
  - Boosted darunavir
  - 3TC or FTC (despite resistance)
    - Ibalizumab
    - **Fostemsavir**

Slide 45 of 49

Fostemsavir (FTR): Oral HIV Attachment Inhibitor

- Prodrug of **temsavir (TMR)**
- Inhibits CD4 binding by **binding to gp120**
- PK suggests daily dosing without boosting
- Phase 1 dose-escalation over 8 days
  - 5 doses (4 with RTV)
  - up to 1.5 log cps/ml ↓
  - ↓ **baseline susceptibility in 12% of pts due to envelope polymorphism**



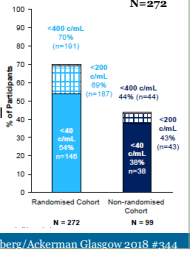
Slide 46 of 49

Nettles JID 2012;206:1002

Fostemsavir (FTR): BRIGHTE (Phase 3)

Heavily rx-experienced (1-2 remaining ART classes)
NOT screened for susceptibility

- Randomized to FTR 600 mg bid or placebo
  - Those with no remaining ART classes non-randomized)
    - **Day 8 (primary endpoint):**
      - mean HIV RNA Δ: -0.2 log (placebo) vs. -0.8 cps/ml (FTR) (p<0.0001)
    - **Then, optimized background ART**
      - wk 48: VL <40: 54% (randomized) vs. 38% (non-randomized)
- Approved July 2020



Slide 47 of 49

Aberg/Ackerman Glasgow 2018 #344

Conclusions

- ARV therapy should be initiated with an InSTI-based regimen (unless otherwise indicated), as close to time of Dx as possible
- Do not change Rx in setting of low-level viremia
- Do not change Rx in setting of low CD4 count response
- DTG is drug of choice in (most) pregnant women (GIVE FOLATE)
- Weight gain is associated with initiation of ARV Rx, with more weight gain observed in InSTI- and TAF-containing regimens
- Use two active drugs (if possible) in treating Virologic Failure

Slide 48 of 49

2020 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

Question-and-Answer Session