HIV 101. Applications of Antiretroviral Therapy

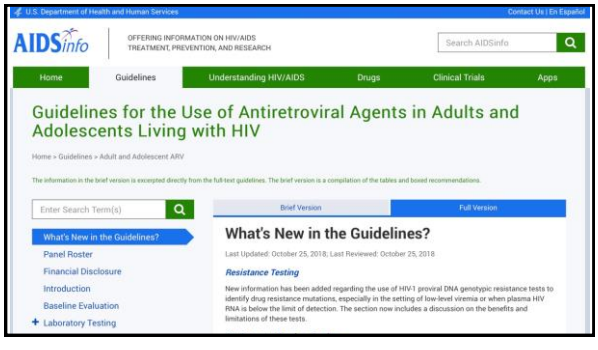
Michael S. Saag, MD
Professor of Medicine
Associate Dean for Global Health
Jim Straley Chair in AIDS Research
University of Alabama at Birmingham
Birmingham, Alabama

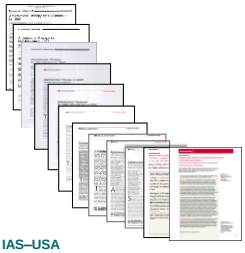
IAS–USA

Learning Objectives

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

- Are starting initial therapy
- Have persistently low-level viremia
- Are pregnant or considering pregnancy
- Are experiencing virologic failure / resistance





IAS–USA
Antiretroviral Guidelines
1996 – 2018

Initiate ART As Soon As Possible After HIV Diagnosis

- Rapid start (including same day as diagnosis) ART, unless that patient is not ready to commit to starting therapy
  - Structural barriers should be removed
- Samples for HIV-1 RNA level; CD4 cell count; HIV genotype for NRTI, NNRTI, and PI; HLA-B*5701 testing; laboratory tests to exclude active viral hepatitis; and chemistries should be drawn before beginning ART, but treatment may be started before results are available.
- NNRTIs (possible transmitted resistance) and abacavir (without HLA-B*5701 results) should not be used for rapid ART start
- ART should be started as soon as possible (but within 2 weeks) after diagnosis of most opportunistic diseases

Saag, Benson, Gandhi, et al, *JAMA*, 2018.

Question

What regimen should I use as initial therapy?

Case 1

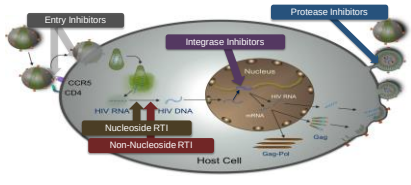
- 48yo man presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial:** HIV RNA 28,000 c/ml
  CD4 count 650 cells/ul
- Other labs are normal; HLA-B57 positive
- Genotype is Wild-type virus
- No prior medical history. Normal renal function
- Ok to start therapy if you think he should

ARS Question 1: At this point which regimen would you choose?

1. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
2. DTG / 3TC (fdc)
3. ABC/ 3TC / DTG (fdc)
4. TAF/ FTC (fdc) + DTG
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 10 of 152

HIV: Antiretroviral Therapy



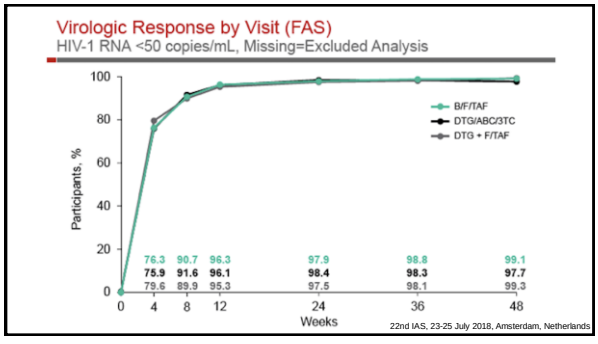
National HIV Curriculum

Recommended Initial Regimens: InSTI Plus 2 nRTIs

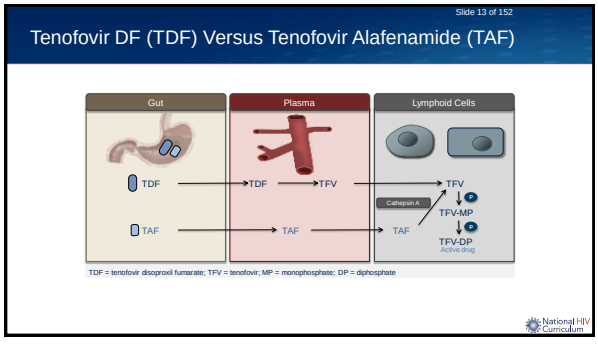
- Bictegravir/TAF/emtricitabine
- Dolutegravir/abacavir/lamivudine
- Dolutegravir plus TAF/emtricitabine
- (Raltegravir plus tenofovir / emtricitabine)*

*HHS Guidelines; AIDSinfo

Saag, Benson, Gandhi, et al, *JAMA*, 2018.



22nd IAS, 23-25 July 2018, Amsterdam, Netherlands



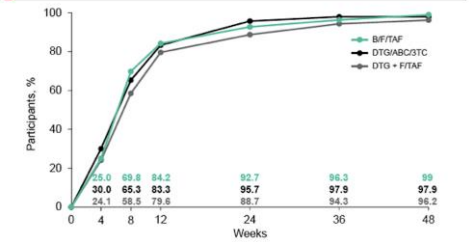
Case 2

- 48 yo man presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- **Initial: HIV RNA 760,000 c/ml**
  CD4 count 21 cells/ul
- Other labs are normal; HLA-B57 negative
- Genotype is Wild-type virus
- No prior past medical history. Normal renal function
- Ok to start therapy if you think he should

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

1. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
2. DTG / 3TC (fdc)
3. ABC/ 3TC / DTG (fdc)
4. TAF/ FTC (fdc) + DTG
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 …)

Virologic Efficacy:
HIV-1 RNA <50 copies/mL, Missing=Excluded Analysis
Baseline HIV-1 RNA >100,000 copies/mL



The 7-8 initial regimens we'll probably be using most

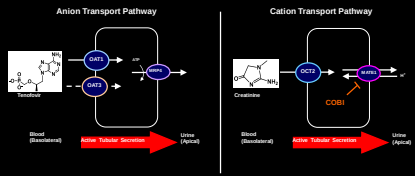
INSTI-based	▪ BIC/FTC/TAF ▪ DTG + FTC/TAF ▪ DTG/3TC/ABC ▪ DTG/3TC ▪ RAL + FTC/ TAF (once daily)
PI-based	▪ DRV/c + FTC/TAF
NNRTI-based	▪ RPV/FTC/TAF ▪ DOR /3TC / TDF

ARS Question 3:

Which ARV drug is most likely to cause a 0.1 mg/dl jump in serum creatinine 1 week after starting Rx?

1. Bictegravir
2. Tenofovir DF
3. Tenofovir AF
4. Atazanavir
5. Emtricitabine

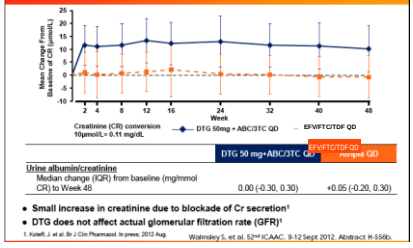
Tenofovir and COBI Interact with Distinct Renal Transport Pathways



- The active tubular secretion of tenofovir and the effect of COBI on creatinine are mediated by distinct transport pathways in renal proximal tubules

Ray A, et al. Antimicro Agents Chemo 2006;3297-3304
Lepist E, et al. ICAAC 2011; Chicago. #A1-1724

Renal Safety



- Small increase in creatinine due to blockade of Cr secretion[1]
- DTG does not affect actual glomerular filtration rate (GFR)[1]

1. Kotwil, J. et al. Br J Clin Pharmacol. In press; 2012 Aug.

Wolmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Recommended Initial Regimens: If an InSTI Is Not Available

- Darunavir/cobicistat/TAF (or TDF)/emtricitabine*
- Darunavir boosted with ritonavir plus TAF (or TDF)/emtricitabine
- Efavirenz/TDF/emtricitabine
- Elvitegravir/cobicistat/TAF (or TDF)/emtricitabine
- Raltegravir plus TAF (or TDF)/emtricitabine
- Rilpivirine/TAF (or TDF)/emtricitabine (if pretreatment HIV RNA level is <100,000 c/mL and CD4 cell count is >200/µL)
- Fixed-dose D/c/TAF/FTC tablet approved July 2018

Saag, Benson, Gandhi, et al, *JAMA*, 2018.

Question

What regimen should be used as initial therapy when an M184V mutation is present?

Case 3

- 30 yo woman presents with newly diagnosed HIV infection
- Asymptomatic
- **Initial:** HIV RNA 128,000 c/ml
  CD4 count 350 cells/ul
- Other labs are normal; HLA-B57 neg
- Genotype shows **M184V and K103N mutation**
- No prior medical history. No children. Does not plan to become pregnant.
- Ok to start therapy if you think she should

ARS Question 4: At this point which regimen would you choose?

1. TDF / 3TC / low dose (400mg) EFV (fdc; generic)
2. DTG / 3TC (fdc)
3. ABC/ 3TC / DTG (fdc)
4. TAF/ FTC (fdc) + DTG
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 …)

Recommendations for Switching for Virologic Failure

- Virologic failure should be confirmed and, if resistance is identified, a prompt switch to another active regimen
- Dolutegravir, plus 2 NRTIs (with at least 1 active by genotype) after initial treatment failure with an NNRTI
- A boosted PI plus 2 NRTIs (with at least 1 active NRTI) for initial treatment failure of an InSTI-containing regimen
- Dolutegravir plus at least 1 fully active other agent may be effective in the setting of raltegravir or elvitegravir resistance. Dolutegravir should be dosed **twice daily** in this setting

Saag, Benson, Gandhi, et al. JAMA. 2018.

Laboratory Monitoring

IAS–USA Recommendations 2018

IAS–USA

Recommended Laboratory Monitoring

- Pre-ART: CD4 cell count, plasma HIV-1 RNA, HAV, HBV, and HCV serologies, serum chemistries, estimated CrCl rate, complete blood cell count, urine glucose and protein, STI screening, fasting lipids
- Genotypic testing for RT and Pro mutations for all patients
- HLA-B*5701 and CCR5 tropism testing results must be confirmed prior to initiating therapy with abacavir or maraviroc, respectively.

Saag, Benson, Gandhi, et al, *JAMA*, 2018.

Recommended Laboratory Assessments and Monitoring Across the HIV Care Continuum

Test	At HIV Diagnosis	During ART	At Virologic Failure
HIV RNA level	✔	Within the first 6 weeks of starting ART or a new ART regimen, then every 3 mo until <50 copies/mL for 1 y, then every 6 mo	✔
CD4 cell count	✔	Every 6 mo until >250/μL for 1 y then stop as long as virus is suppressed	✔
HIV RT-pro genotype	✔		✔
HIV integrase genotype			If failing ART regimen included an InSTI
Viral tropism			Each time before the start of ART that includes maraviroc
HLA-B*5701	✔ (before initiating abacavir; just once)	✔ (if considering abacavir and not determined previously)	
Safety testing	✔	✔	✔
Co-infection (STIs, tuberculosis, hepatitis, Pap test)	✔	✔	
Health maintenance	✔	✔	

Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society–USA Panel. JAMA. 2018;320(4):379-396. doi:10.1001/jama.2018.8431

Recommended Laboratory Monitoring (Cont.)

- Once HIV RNA level is <50 c/mL, monitor **every 3 months until virus is suppressed for at least a year**. Then, monitoring can be reduced to **every 6 months** if the patient maintains adherence
- CD4 cell counts every 6 months until counts >250/μL for at least 1 year with concomitant viral suppression; **Then no longer monitor CD4 counts unless virologic suppression is lost**
- Age- and risk-appropriate screening for STIs at various anatomical sites, anal or cervical dysplasia, TB, general health, and medication toxicity is recommended
- Once a viral load is >50 c/mL, repeat test within 4 weeks and reassess for adherence and tolerability
- Measurement of viral load at 4 to 6 weeks after starting a new ART regimen is recommended

Saag, Benson, Gandhi, et al, *JAMA*, 2018.

Recommended Laboratory Monitoring (Cont.)

- Repeating assay within 4 weeks if HIV RNA level remains above the limit of quantification by 24 weeks after starting new treatment or if rebound above 50 c/mL occurs
- Tropism testing at the time of virologic failure of a CCR5 inhibitor

Saag, Benson, Gandhi, et al, *JAMA*, 2018.

Question

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

*(or a patient considering pregnancy)

Case 4

- 30 yo woman 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

ARS Question 5: At this point which regimen would you choose?

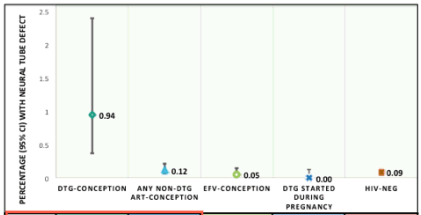
1. TDF / FTC / EFV (fdc)
2. ABC/ 3TC / DTG (fdc)
3. TAF / FTC/ ELV / cobi (fdc)
4. TDF / FTC / RPV (fdc)
5. TAF/ 3TC (fdc) / DTG (fdc)
6. TDF/ FTC (fdc) / DRV/r (or cobi / fdc)
7. TAF/ FTC / ATV/r (or cobi / fdc)
8. TDF / FTC / ATV/r (or cobi / fdc)
9. Some other option

Dolutegravir in pregnancy: Background

- No fetal toxicity or teratogenicity in animal studies described in manufacturer's submission for regulatory approval[1]
- High placental transfer of DTG relative to other ARVs in an ex vivo study[2]
- "*Unexpected placental transfer of DTG with fetal accumulation and then slow neonatal clearance*"[3]
- ***18 May 2018: Report of Neural tube defects in 4/426 (0.9%) babies born to women taking DTG in Botswana…compared to 14/11,173 (0.1%) non-DTG[4]***

DOI: 10.1056/NEJMc1807653 ; 24 July 2018

NTD Prevalence Difference by Exposure



NTDs/ Exposures	4/426	14/11,300	3/5,787	0/2,812	61/66,057
% with NTD (95% CI)	0.94% (0.37%, 2.4%)	0.12% (0.07%, 0.21%)	0.05% (0.02%, 0.15%)	0.00% (0.00%, 0.13%)	0.09% (0.07%, 0.12%)
Prevalence Difference (95% CI)	ref	-0.82% (-0.24%, -2.3%)	-0.89% (-0.31%, -2.3%)	-0.94% (-0.35%, -2.4%)	-0.85% (-0.27%, -2.3%)

Question

Should I change a regimen when low level detectable virus is present?

Case 5

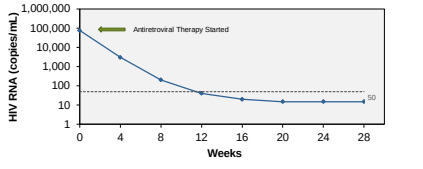
- 55 yo man referred to you for evaluation
- Diagnosed 18 years ago with HIV infection
- **Initial:** HIV RNA 936,000c/ml
  CD4 count 70 cells/ul
- **Current:** HIV RNA 85 c/ml (prior value 62 c/ml)
  CD4 count 525 cells/ul
- Started on NEL/D4T/3TC; subsequently treated with
  - LOP-r / TDF/FTC,
  -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

ARS Question 6: Should you change ARV therapy now?

1. Yes
2. No
3. Not sure

Virologic Responses on Antiretroviral Therapy

Virologic Suppression



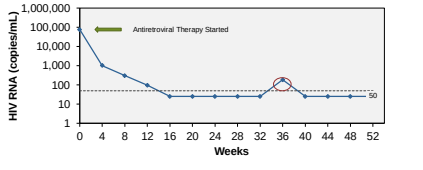
A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).

Source: 2016 DHHS Antiretroviral Therapy Guidelines. AIDS Info.

National HIV Curriculum

Virologic Responses on Antiretroviral Therapy

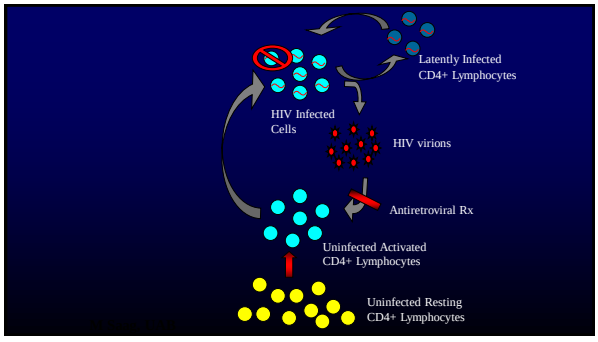
Virologic Blip



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



Question

How should I counsel a patient with undetectable HIV RNA about sexual transmission risk?

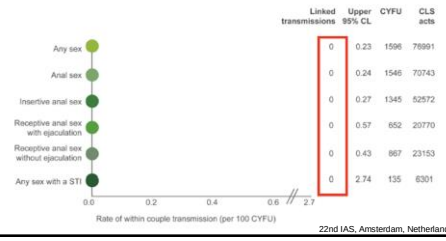
Case 9

- 48 yo man presents with newly diagnosed HIV infection
- Asymptomatic except for weight loss / fatigue
- **Initial: HIV RNA 160,000 c/ml**
  CD4 count 221 cells/ul
- Other labs are normal; Started on ARV Rx
- Returns for a 3 month follow up visit
- **HIV RNA < 20 c/ml; CD4 390 cells/ul**

ARS Question 7: Assuming he remains undetectable, you tell him that his risk of transmitting HIV to a seroneg partner via sex is:

1. Zero risk (under these circumstances)
2. Virtually zero risk (no one knows for sure)
3. Very low risk
4. Possible
5. It depends on which ARV regimen he's on
6. C'mon Saag, I don't like this question!

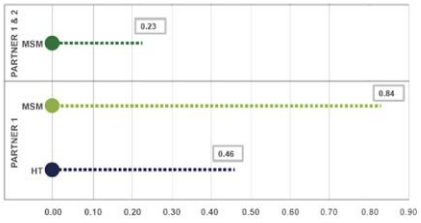
Rate of HIV transmission according to sexual behaviour reported by the negative partner



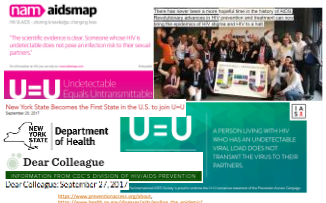
22nd IAS, Amsterdam, Netherlands, July 23-27, 2018

Upper 95% CI around estimated rate of zero HIV transmissions: PARTNER 1 compared to PARTNER 1&2

22nd IAS, Amsterdam, Netherlands, July 23-27, 2018



U=U: Undetectable=Untransmittable



https://www.preventionaccess.org/blog/,
https://www.health.ny.gov/diseases/aids/ending_the_epidemic/,
https://www.cdc.gov/hiv/library/spotlight/dear20170327.html

Recommendations for HIV Prevention

- HIV-seropositive and -negative individuals should be reminded that **condoms are required to prevent acquisition of non-HIV STIs**
- Quarterly screening for asymptomatic STIs for all populations with high rates of bacterial STIs and incomplete condom use
- PrEP for populations whose annual **HIV incidence is at least 2%**
- Daily TDF/emtricitabine for men and women and transgender individuals at risk of sexual exposure and people who inject drugs
- 1-week lead-in time with daily dosing for rectal, penile, and vaginal exposures, with daily TDF/emtricitabine to ensure adequate tissue levels are achieved

Saag, Benson, Gandhi, et al, *JAMA*, 2018.

Question-and-Answer