37 – Antiretroviral Therapy

Speaker: Roy Gulick, MD

Antiretroviral Therapy (ART)

Roy M. Gulick, MD, MPH
Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medicine

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- **Disclosures of Financial Relationships with Relevant Commercial Interests**

  - None

ID Boards – Medical Content: 15% HIV

- Epidemiology (<2%)
  - Transmission
  - Testing and counseling
  - Initial laboratory evaluation
  - Prevention
- Pathogenesis (<2%)
  - Virology
  - Immunopathogenesis
  - Acute HIV infection
- Lab testing (<2%)
  - Diagnostic evaluation
  - Baseline evaluation
- HIV Treatment Regimens (4.5%)
  - ART drug classes
  - Adverse effects of treatment
  - Drug-drug interactions
  - When to start therapy
  - Selection of optimal initial regimen
  - Laboratory monitoring
  - Treatment-experienced patients

ID Boards – Medical Content: 15% HIV

- Opportunistic Infections (5%)
  - Prevention
  - When to start ART with an OI
  - IRIS
  - Bacteria; Mycobacteria; Fungi; Parasites; Viruses
- Malignancies (<2%)
  - Kaposi sarcoma (KS)
  - Lymphoma
  - Cervical cancer
  - Anal cancer
- Other complications of HIV (2%)
  - Heme, endocrine, GI, renal (including HIVAN), cardiac, pulmonary, HEENT, musculoskeletal, neuro, psych, derm
- Related issues (<2%)
  - Substance use
  - Organ transplantation
  - Primary care
  - Misc non-HIV complications
  - Pregnancy

Antiretroviral Therapy (ART)

- Questions
  - When to start?
  - What to start?
  - When to change?
  - What to change to?
- Treatment as Prevention
- HIV Drug Resistance / Case Scenarios
- ART for Special Populations

WHEN TO START?

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Question #1

A 43-year-old man with HIV has CD4 900-1200 and HIV RNA consistently <200 copies over the last 11 years. Do you recommend starting ART?

A. Yes, all current guidelines recommend starting.
B. No, he's a long-term non-progressor and doesn't need ART.
C. No, he should wait until his viral load level is confirmed >200 copies/ml.
D. No, he should wait until CD4 is confirmed <500 cells/uL.

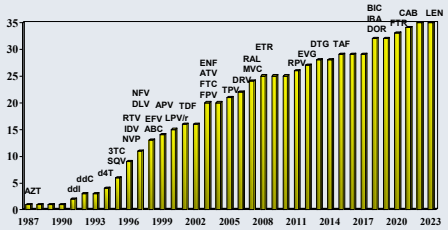
When to Start?: Chronic Infection

	AIDS/ symptoms	Asymptomatic			
		CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2024 www.clinicalinfo.hiv.gov	recommended				
IAS-USA 2023 Gandhi JAMA 2023;329:63-84	recommended				

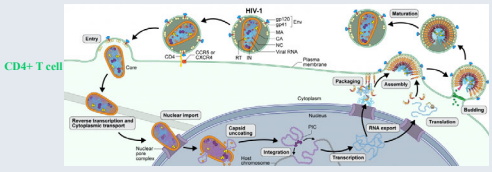
Goal of Antiretroviral Therapy

- To suppress HIV RNA (viral load level) as low as possible, for as long as possible
- To preserve or enhance immune function
- To delay clinical progression of HIV disease (and prolong healthy life)

Antiretroviral Drug Approval: 1987 - 2024

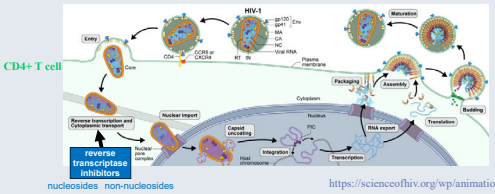


Life Cycle of HIV



https://scienceofhiv.org/wp/animations/

Life Cycle of HIV



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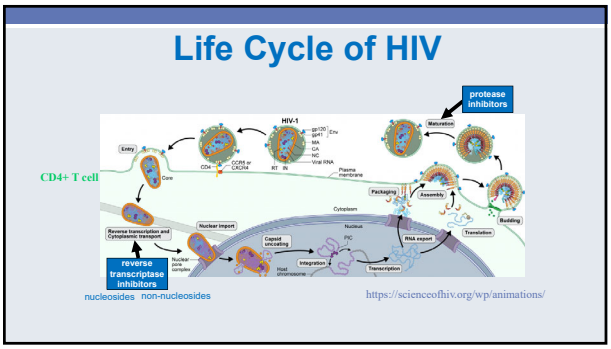

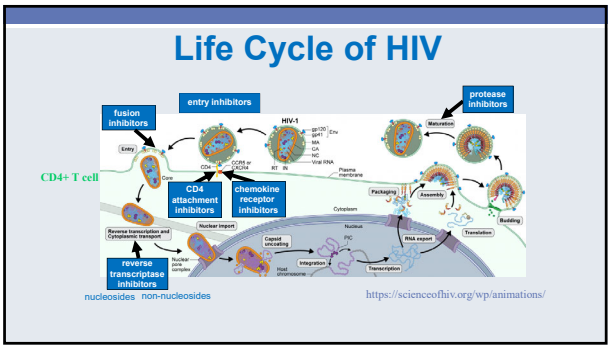

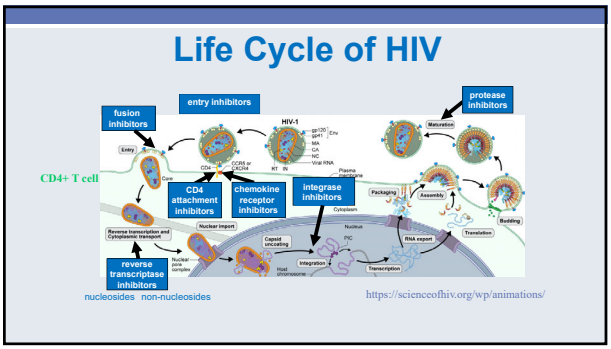

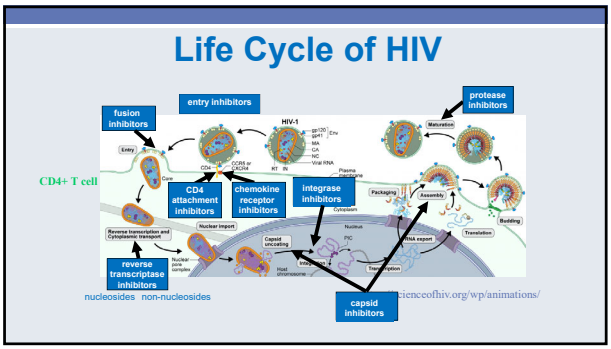

Approved ART: 2024*

nucleoside/tide RTIs (NRTIs)
- zidovudine (ZDV, AZT)
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TAF, TDF)

NNRTIs
- nevirapine (NVP)
- efavirenz (EFV)
- etravirine (ETR)
- rilpivirine (RPV)
- doravirine (DOR)

protease inhibitors (PIs)
- saquinavir (SQV)
- ritonavir (RTV)
- indinavir (IDV)
- nelfinavir (NFV)
- lopinavir/r (LPV/r)
- atazanavir (ATV)
- tipranavir (TPV)
- darunavir (DRV)

integrase inhibitors (IIs)
- raltegravir (RAL)
- elvitegravir (EVG)
- dolutegravir (DTG)
- bictegravir (BIC)
- cabotegravir (CAB)

entry inhibitors (EIs)
- enfuvirtide (T-20, fusion inhibitor)
- maraviroc (MVC, CCR5 antagonist)
- ibalizumab (IBA, CD4 post-attachment inhibitor)
- fostemsavir (FTR, CD4 attachment inhibitor)

capsid inhibitors (CIs)
- lenacapavir (LEN)

*ddI, ddC, d4T, DLV, APV, and FPV discontinued from market

WHAT TO START?

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Question #2

PREVIEW QUESTION

You have been monitoring a 36-year-old man with HIV, CD4 ~350, VL 636,000 who is now ready to start ART, but wants the "simplest regimen possible." Which of these regimens do you recommend?

A. IM cabotegravir/rilpivirine
B. dolutegravir/rilpivirine
C. tenofovir alafenamide/emtricitabine/rilpivirine
D. dolutegravir/lamivudine
E. tenofovir alafenamide/emtricitabine/bictegravir

First ART Regimen: Individual Factors

- antiretroviral activity (VL, CD4, clinical responses)
- durability of responses
- baseline drug resistance
- tolerability
  - acute side effects
  - chronic side effects
- convenience (number of pills, dosing interval, food/fasting requirements)
- preserving future treatment options
- stage of HIV disease, concomitant illnesses and medications (drug-drug interactions)
- access and cost

Recommended Regimens (for most people) (1-2 NRTI + integrase inhibitor)

- Integrase inhibitor-based
  - **bictegravir**/tenofovir alafenamide (TAF)/emtricitabine
  - **dolutegravir**/abacavir/lamivudine (if HLA-B*5701 negative)
  - **dolutegravir** + tenofovir (TAF or TDF) + (emtricitabine or lamivudine)
  - **dolutegravir**/lamivudine (except HIV RNA >500,000 cps/ml, HBV surface antigen +, or no resistance results)

U.S. DHHS Guidelines 2/27/24 clinicalinfo.hiv.gov

Alternative Regimens (Certain Situations) (1)

- Integrase inhibitor-based (INSTI + 2 NRTI)
  - **elvitegravir**/cobicistat/tenofovir (TAF or TDF)/emtricitabine
  - **raltegravir** + tenofovir (TAF or TDF) + (lamivudine or emtricitabine)
- Protease inhibitor-based (Boosted PI + 2 NRTI)
  - In general, boosted darunavir preferred over boosted atazanavir
  - **darunavir**/(ritonavir or cobicistat) + tenofovir (TDF or TAF) + (lamivudine or emtricitabine)
  - **darunavir**/(ritonavir or cobicistat) + abacavir*/lamivudine
  - **atazanavir**/(ritonavir or cobicistat) + tenofovir (TDF or TAF) + (lamivudine or emtricitabine)

U.S. DHHS Guidelines 2/27/24 www.clinicalinfo.hiv.gov

Alternative Regimens (Certain Situations) (2)

- NNRTI-based (NNRTI + 2 NRTI)
  - **doravirine**/TDF/lamivudine or **doravirine** + TAF/emtricitabine
  - **efavirenz** + tenofovir (TAF or TDF) + (emtricitabine or lamivudine)
    - efavirenz 600 + TDF + (emtricitabine or lamivudine)
    - efavirenz 600 + TAF/emtricitabine
    - efavirenz 400/TDF/lamivudine
  - **rilpivirine** + tenofovir (TAF or TDF)/emtricitabine (if VL <100,000 cps/ml and CD4 >200)

U.S. DHHS Guidelines 2/27/24 www.clinicalinfo.hiv.gov

Alternative Regimens (Certain Situations) (3)

- Options when ABC, TAF, and TDF cannot be used
  - **dolutegravir** + lamivudine (except HIV RNA >500,000 cps/ml, HBV surface antigen +, or no resistance results)
  - **darunavir**/ritonavir + lamivudine
  - **darunavir**/ritonavir + raltegravir BID (if HIV RNA <100,000 cps/ml and CD4 >200)

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Choice of NRTIs

Combination	DHHS GL	Dosing	Toxicities	Considerations
tenofovir (TAF or TDF)/ **emtricitabine** (FTC)	recommended	1 tab qd	renal, bone (with TDF); ↓ toxicity with TAF	1-pill, once-daily formulations available
abacavir/ lamivudine (ABC/3TC)	recommended (with dolutegravir only) / alternative	1 tab qd	HSR (5-8%) (do HLA-B*5701 test)	ABC/3TC/DTG available; less effective with VL >100K; ??↑MI
zidovudine/ lamivudine (ZDV/3TC)	not recommended	1 tab bid	GI, anemia, lipoatrophy	toxicity

Based on DHHS Guidelines 2/27/24

Choice of NNRTIs

Drug	DHHS GL	Dose	Toxicities	Considerations
doravirine (DOR)	alternative	qd	↓ CNS toxicity than EFV; ↓ lipids	TDF/FTC/DOR (1 pill, once-daily)
efavirenz (EFV)	alternative	qd (600 or 400 mg)	CNS toxicity (50%), rash (10%), suicidality (rare)	TDF/FTC/EFV (1 pill, once-daily)
rilpivirine (RPV)	alternative	qd	not well absorbed with PPI	(TAF or TDF)/FTC/RPV (1 pill, once-daily with a meal); NOT for HIV RNA >100K or CD4 <200
nevirapine (NVP)	not recommended	qd or bid	hepatotoxicity, hypersensitivity	toxicity

Based on DHHS Guidelines 2/27/24

Choice of PIs

Drug	DHHS GL	Dose	Toxicities	Considerations
darunavir /(ritonavir or cobicistat) (DRV/r or c)	alternative; in general, preferred over ATV	qd (if no prior PI resistance) or bid	skin rash (rare);	active against PI-resistant viral strains
atazanavir /(ritonavir or cobicistat) (ATV/r or c)	alternative	qd	↑ indirect bilirubin, GI	avoid PPI; kidney stones (uncommon)
lopinavir/ ritonavir (LPV/r)	not recommended	bid or qd	diarrhea, ↑lipids	co-formulated

Based on DHHS Guidelines 2/27/24

Choice of Integrase Inhibitors

Drug	DHHS GL	Dosing	Toxicities	Considerations
bictegravir (BIC)	recommended with TAF/FTC	1 coform-ulated pill	few, ↑creat, wt gain	TAF/FTC/BIC (1 pill, qd); ↑ barrier to resistance
dolutegravir (DTG)	recommended with (TAF or TDF)/(FTC or 3TC) or ABC/3TC	50 mg qd (bid with II resistance)	few, ↑creat, CNS, wt gain	ABC/3TC/DTG (1 pill, qd); ↑ barrier to resistance
elvitegravir (EVG)	alternative with (TAF or TDF) /FTC/cobicistat	1 coform-ulated pill	mild GI	(TAF or TDF)/FTC/ EVG/cobicistat (1 pill, qd); drug interactions
raltegravir (RAL)	alternative with (TAF or TDF)/FTC	400 mg bid; 600 mg X 2 qd	few	twice-daily dosing; no co-formulations

Based on DHHS Guidelines 2/27/24

Selected Drug Interactions (1)

- Cytochrome P450 3A4 effects
- Most NNRTI (EFV, ETR, NVP, RPV – NOT DOR) are inducers
  - In general, ↓ levels of other metabolized drugs
- Concern with: rifampin/(rifabutin), ketoconazole/itraconazole, anticonvulsants, simvastatin/lovastatin, midazolam/triazolam, ergotamines
- HIV protease inhibitors
- maraviroc
- Some HCV drugs

Selected Drug Interactions (2)

- Cytochrome P450 3A4 effects
- PIs are inhibitors; ritonavir is the most potent inhibitor ever described; cobicistat is a potent inhibitor
  - In general, ↑ levels of other metabolized drugs
- Concern with: rifampin – cannot be used/(rifabutin), ketoconazole/itraconazole, anticonvulsants, simvastatin/lovastatin, midazolam/triazolam, ergotamines, St. John's Wort
- HIV NNRTI
- maraviroc
- HCV drugs

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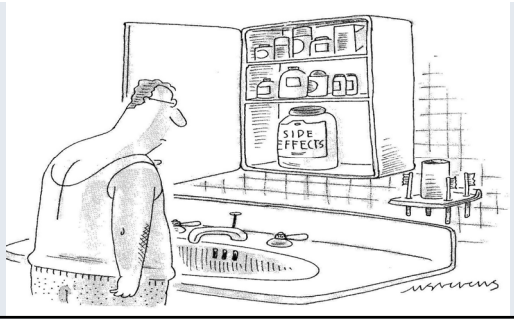
ART: What NOT to use as Initial therapy

- Monotherapy
- Nucleosides (NRTI)
  - 3 or 4 all-NRTI combination regimens
  - older drugs (e.g. zidovudine, didanosine)
- Non-nucleosides (NNRTI)
  - older drugs (e.g. nevirapine)
  - etravirine
- Protease Inhibitors (PI)
  - unboosted PIs
  - older drugs (fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir [except as a booster], saquinavir tipranavir)
- Entry inhibitors (EI)
- Some 2-drug regimens
  - IM CAB/RPV or DTG/RPV

Based on DHHS Guidelines 2/27/24



ART: Side Effects (1)

- **Life threatening**
  - hepatitis (NNRTIs, PIs)
    - nevirapine – women with CD4 >250; men with CD4 >400;
  - hypersensitivity reaction (HSR) (abacavir, nevirapine, etravirine)
    - abacavir HSR greatly reduced by HLA-B*5701 screening
    - stop nevirapine or etravirine for rash with constitutional symptoms
  - Stevens-Johnson syndrome (nevirapine, etravirine)
  - teratogenicity
    - efavirenz = pregnancy category D
    - dolutegravir during conception/very early pregnancy
      → neural tube defects – RARE, not significantly ↑ vs. other ART

ART Side Effects (2)

- **Acute/early**
  - gastrointestinal (zidovudine, TDF, PIs, ?all ART)
  - anemia, neutropenia (zidovudine)
  - bone mineral density ↓ (TDF)
  - central nervous system (efavirenz, integrase inhibitors[?])
  - fatigue (zidovudine)
  - indirect hyperbilirubinemia (atazanavir, indinavir)
  - injection site reactions (enfuvirtide)
  - rash (NNRTIs)

ART Side Effects (3)

- **Chronic/longer term**
  - cardiovascular (abacavir??, PIs except atazanavir)
  - kidney stones (indinavir > atazanavir)
  - metabolic – glucose, lactate, lipids (older PIs)
  - morphologic –
    - fat loss – lipoatrophy (stavudine, zidovudine)
    - fat gain – lipohypertrophy (older PIs)
  - proximal renal tubular dysfunction (TDF)
  - weight gain (bictegravir, dolutegravir, TAF)

WHEN TO CHANGE?

ART Change

- Reasons: adverse events, drug-drug or drug-food interactions, pill burden, pregnancy, cost, simplification
- Fundamental principle: maintain virologic suppression
- Review ART history, prior ART-associated toxicities, cumulative drug resistance testing results
- Within-class or between-class Δ usually works if no resistance
- Specific regimens:
  - DTG/3TC; DTG/RPV; Boosted PI (ATV, DRV) + [3TC or FTC]; Boosted PI + II (e.g. DRV/r + DTG); IM CAB + RPV
  - Not recommended: monotherapy, boosted ATV + RAL, MVC-based
- Consideration: concomitant HBV infection

DHHS Guidelines 2/27/24

Why Does Treatment Fail Patients?

- ADHERENCE
- Baseline resistance or cross-resistance
- Prior use of antiretroviral therapy
- Less potent antiretroviral regimens
- Drug levels and drug interactions
- Tissue reservoir penetration
- Provider inexperience
- Other, unknown reasons

Question #3

PREVIEW QUESTION

28-year-old man with HIV on TDF/emtricitabine + atazanavir/ritonavir for 2 years with HIV RNA <50 cps/ml and CD4 200s→300s presents for routine follow-up; labs reveal HIV RNA 68 cps/ml and CD4 352.

What do you recommend?

A. Obtain genotype.
B. Obtain genotype and phenotype.
C. Repeat HIV RNA at next visit.
D. Change regimen to TAF/emtricitabine/bictegravir to improve adherence

When to change therapy?

Virologic failure

- VL undetectable – drug resistance unlikely
- VL <200 cps/ml (low-level viremia) – risk of resistance believed to be relatively low
- VL persistently >200 cps/ml – drug resistance often associated (particularly >500 cps/ml)
- Caution with change to newer VL assays and blips

Immunologic failure

- Associated factors:
  - CD4 <200 at ART initiation
  - older age
  - co-infections
  - meds
  - persistent immune activation
  - loss of regenerative potential
  - other reasons
- No consensus on definition or treatment

DHHS Guidelines 2/27/24

WHAT TO CHANGE TO?

What to change to?: U.S. DHHS Guidelines

- Review goal of therapy:
  - Maximal virologic suppression (HIV RNA below detection)
- Review ART history
- Assess adherence, tolerability, and PK
- Perform resistance testing while on drugs (or within 4 weeks of d/c of ART)
- Identify susceptible drugs/drug classes (e.g. fostemsavir, lenacapavir)
- Do not add a single active drug to a failing regimen
- Goal:

  Design a regimen with 2 fully active drugs (one with a high barrier to resistance: boosted darunavir, dolutegravir, [bictegravir]), or if no high-barrier drug available, 3 fully active drugs

DHHS Guidelines 2/27/24

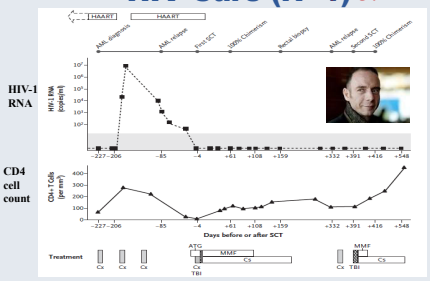
TREATMENT = PREVENTION

Treatment = Prevention

- Pregnant women with HIV — *Fowler NEJM 2016;375:1726*
  - 3-drug ART ↓ transmission risk to child to 0.5%
- Men and women with HIV — *Cohen NEJM 2016;375:830*
  - Suppressive ART ↓ transmission to sexual partners by 93%
- HIV- post-exposure prophylaxis (PEP) — *CDC Guidelines*
  - 3-drug integrase inhibitor-based ART recommended for 4 weeks (e.g. TDF/FTC + DTG)
- At-risk men and women without HIV
  Molina NEJM 2015, McCormack Lancet 2016, Landovitz NEJM 2021, Delany-Moretlwe Lancet 2022; Choopanya Lancet 2013
  - PrEP ↓ HIV acquisition by sex >75-85% (TDF/FTC ♂♀; TAF/FTC ♂ only; IM CAB ♂♀)
  - PrEP ↓ HIV acquisition by injection drug use ~50% (TDF/FTC)

CURE

HIV Cure (N=1) 5!



Cure #2
London
Gupta, et al
Nature 2019;568: 244-248

Cure #3
NYC
Hsu, et al
Cell 2023;186:1115-1126

Cure #4
Dusseldorf
Jensen, et al
Nat Med 2023;29:583-587

Cure #5
City of Hope
Dickter, et al
NEJM 2024;39;669-671

Hutter NEJM 2009;360:692

ART Controversies: Conclusions

- **When to start?** Any viral load or CD4 count and "when the patient is ready."
- **What to start?** Excellent options; integrase inhibitor-based regimens for most people.
- **When to change?** Evaluate virologic response; try to prevent emergence of resistance.
- **What to change to?** Use treatment history and drug resistance testing to design new regimen with 2 active drugs (1 with ↑ barrier to resistance) or 3 active drugs.
- **Treatment = Prevention** Treat HIV, offer PEP and PrEP

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rgulick@med.cornell.edu