36 Antiretroviral Therapy

Speaker: Roy Gulick, MD, MPH

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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

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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 disorder
  - Organ transplantation
  - Primary care
  - Misc non-HIV complications
  - Pregnancy

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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

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When To Start?

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Question #1

PREVIEW QUESTION

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

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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 2024 Gandhi JAMA 2025;333:609-628	Recommended				

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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)

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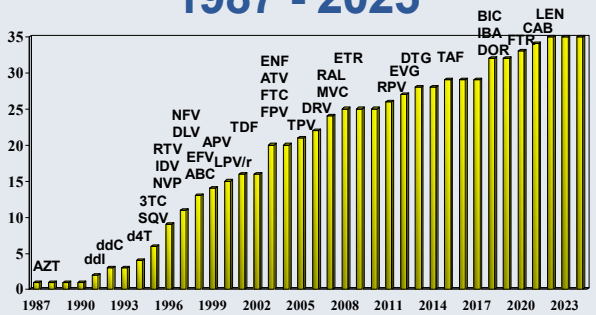
Antiretroviral Drug Approval: 1987 - 2025



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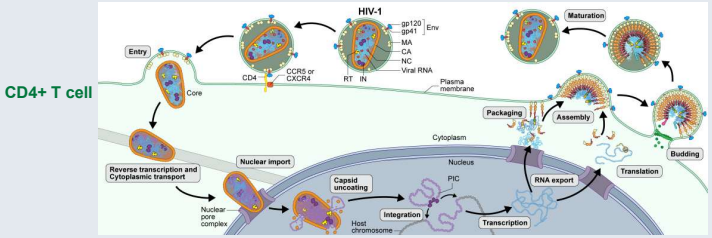
Life Cycle of HIV



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36 Antiretroviral Therapy

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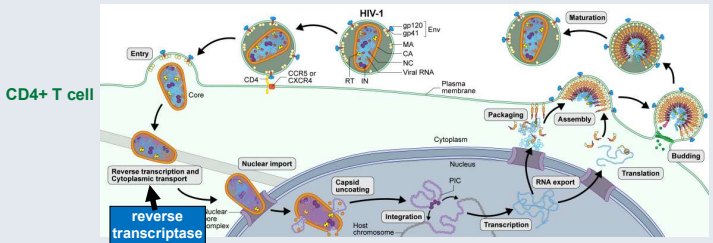
Life Cycle of HIV



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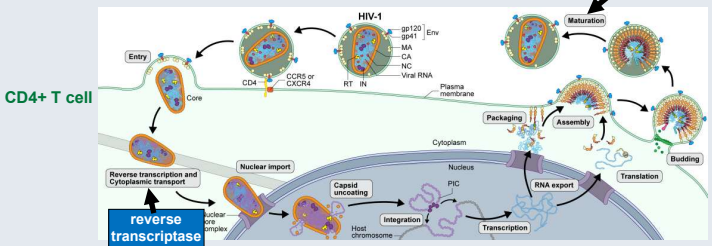
Life Cycle of HIV



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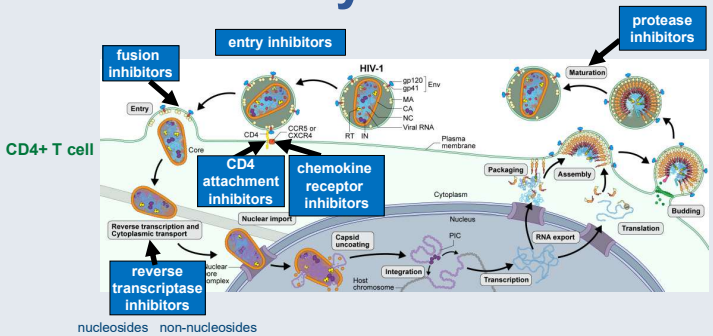
Life Cycle of HIV



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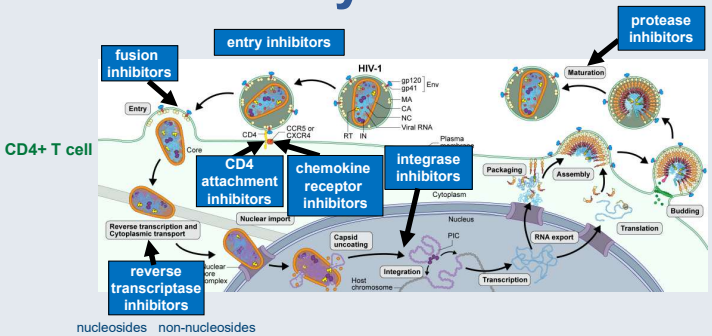
Life Cycle of HIV



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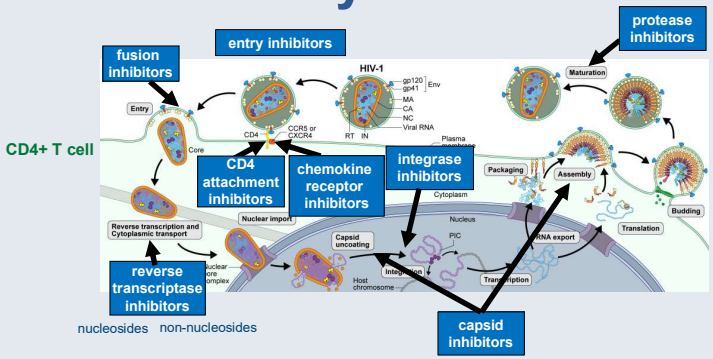
Life Cycle of HIV



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

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Approved ART: 2025*

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)
- Ritonavir (RTV)
- 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)
- 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, SQV, IDV, FPV, ENF (T-20) discontinued from U.S. market

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What To Start?

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Question #2

You have been monitoring a 36-year-old man with HIV, CD4 ~350, VL 636,000 who is now ready to start ART, and wants “a simple-to-take” regimen.

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 + dolutegravir

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E. **Tenofovir alafenamide/emtricitabine + dolutegravir**

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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

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

- Integrase inhibitor-based
  - **Bictegravir**/tenofovir alafenamide (TAF)/emtricitabine (FTC)
  - **Dolutegravir** + tenofovir (TAF or TDF) + (FTC or lamivudine [3TC])
  - **Dolutegravir**/lamivudine (except HIV RNA >500,000 cps/ml, HBV surface antigen +, or no resistance results)
- With a history of cabotegravir as PrEP: do integrase genotype
  - **Darunavir**/(cobicistat or ritonavir) + (TAF or TDF) + (FTC or 3TC)

U.S. DHHS Guidelines 9/12/24 clinicalinfo.hiv.gov

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Alternative Regimens (Certain Situations) (1)

- Integrase inhibitor-based (INSTI + 2 NRTI)
  - **Dolutegravir**/abacavir*/lamivudine
- Protease inhibitor-based (Boosted PI + 2 NRTI)
  - **Darunavir**/(cobicistat or ritonavir) + tenofovir (TDF or TAF) + (lamivudine or emtricitabine)
  - **Darunavir**/(cobicistat or ritonavir) + abacavir*/lamivudine

*Test for HLA-B*5701, do not use if positive

U.S. DHHS Guidelines 9/12/24 www.clinicalinfo.hiv.gov

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Alternative Regimens (Certain Situations) (2)

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

U.S. DHHS Guidelines 9/12/24 www.clinicalinfo.hiv.gov

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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)	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)	No longer recommended	1 tab bid	GI, anemia, lipoatrophy	Toxicity

Based on DHHS Guidelines 9/12/24

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Choice of NRTIs

Drug	DHHS GL	Dose	Toxicities	Considerations
Doravirine (DOR)	Alternative	qd	↓ CNS toxicity than EFV; ↓ lipids	TDF/FTC/DOR (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
Efavirenz (EFV)	No longer recommended	qd (600 or 400 mg)	CNS toxicity (50%), rash (10%), suicidality (rare)	TDF/FTC/EFV (1 pill, once-daily)
Nevirapine (NVP)	No longer recommended	qd or bid	Hepatotoxicity, hypersensitivity	Toxicity

Based on DHHS Guidelines 9/12/24

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Choice of PIs

Drug	DHHS GL	Dose	Toxicities	Considerations
Darunavir /(Cobicistat or Ritonavir) (DRV/C or R)	Alternative; preferred if integrase inhibitor exposure	qd (if no prior PI resistance) or bid	Skin rash (rare);	Active against PI-resistant viral strains
Atazanavir /(Cobicistat or Ritonavir) (ATV/C or R)	No longer recommended	qd	↑ indirect bilirubin, GI	Avoid PPI; kidney stones (uncommon); low Barrier to resistance
Lopinavir/ Ritonavir (LPV/R)	No longer recommended	bid or qd	diarrhea, ↑lipids	Co-formulated

Based on DHHS Guidelines 9/12/24

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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); binds divalent cations; ↑ barrier to resistance
Dolutegravir (DTG)	Recommended with (TAF or TDF)/(FTC or 3TC); alternative with ABC/3TC	50 mg qd (bid with II resistance)	Few, ↑creat, CNS, wt gain	ABC/3TC/DTG (1 pill, qd); binds divalent cations; ↑ barrier to resistance
Elvitegravir (EVG)	No longer recommended	1 coform-ulated pill	Mild GI	Drug interactions with cobicistat
Raltegravir (RAL)	No longer recommended	400 mg bid	Few	Twice-daily dosing; no co-formulations

Based on DHHS Guidelines 9/12/24

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Selected Drug Interactions (1)

- Cytochrome P450 3A4 effects
- Most NNRTI (EFV, ETR, NVP – 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

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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., efavirenz, nevirapine)
  - Etravirine
- Protease Inhibitors (PI)
  - Older drugs (atazanavir, lopinavir, nelfinavir, ritonavir [except as a booster], tipranavir)
- Integrase inhibitors (INSTI)
  - Elvitegravir or raltegravir
- Entry inhibitors (EI)
- Some 2-drug regimens
  - IM CAB/RPV or DTG/RPV

Based on DHHS Guidelines 9/12/24

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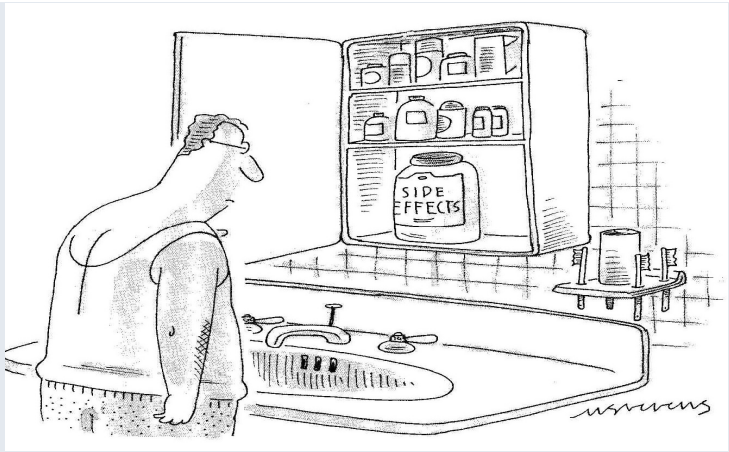

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ART: Side Effects (1)

- **Life threatening**
  - Hepatitis (NNRTIs, PIs)
  - 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

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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)
  - Rash (NNRTIs)

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ART: Side Effects (3)

- **Chronic/longer term**
  - Cardiovascular (abacavir, PIs except atazanavir)
  - Kidney stones (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 (?) (TAF, bictegravir, dolutegravir)

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When to Change?

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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

Based on DHHS Guidelines 9/12/24

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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

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Question #3

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

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Question #3

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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

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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

Based on DHHS Guidelines 9/12/24

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What To Change To?

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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, bictegravir, dolutegravir), or if no high-barrier drug available, 3 fully active drugs

DHHS Guidelines 9/12/24

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Treatment = Prevention

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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) *Tanner CDC Guidelines MMWR 2025;74:1*
  - 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)

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Cure

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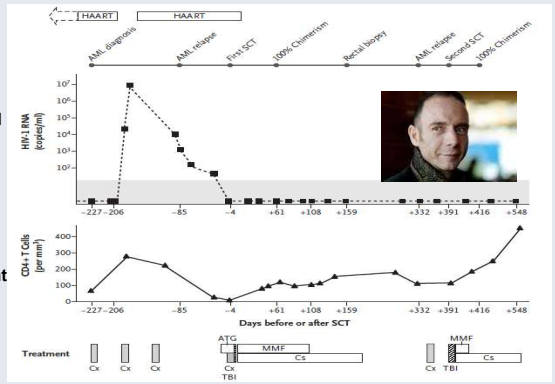
HIV Cure (N=~~1~~ 9!



Hutter NEJM 2009;360:692

Cure #2 *first Latino
London
Gupta, Nature 2019;568:244-248
Cure #3 *first woman
NYC
Hsu, Cell 2023;186:1115-1126
Cure #4
Dusseldorf
Jensen, Nat Med 2023;29:583-587
Cure #5
City of Hope
Dickter, NEJM 2024;390:669-671
Cure #6 *wild-type donor
Geneva
Saez-Cirion, Nat Med 2024;30:3544-3554
Cure #7 *first Δ32 hetero donor
Berlin
Gaebler, et al IAS 2024
Cure #8 *HIV rebound
Chicago
Rubinstein CROI 2025 #531
Cure #9
Oslo
Troseid CROI 2025 #532

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ART: 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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Acknowledgements

- **Cornell HIV Clinical Trials Unit (CCTU)**
- Division of Infectious Diseases
- Weill Cornell Medicine
- AIDS Clinical Trials Group
- HIV Prevention Trials Network
- Division of AIDS/NIAID/NIH
- The patient volunteers!

rgulick@med.cornell.edu

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