



Antiretroviral Therapy (ART)

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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

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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, dermat
- 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

When to Start?

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

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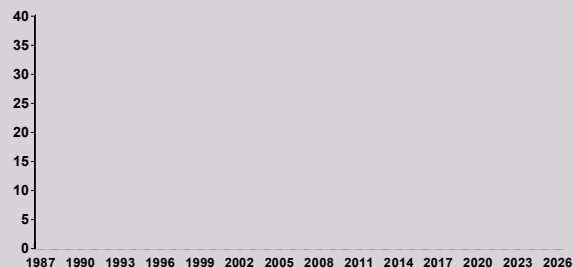
When to Start?: Chronic Infection

	AIDS/ symptoms	Asymptomatic			
		CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2025 www.clinicalinfo.hiv.gov		Recommended			
IAS-USA 2024 Gandhi JAMA 2025;333:609-628		Recommended			

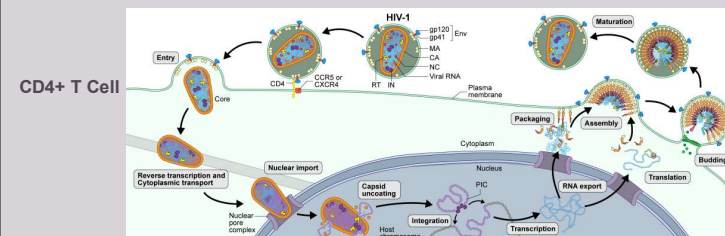
Goal of Antiretroviral Therapy

- 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 - 2026

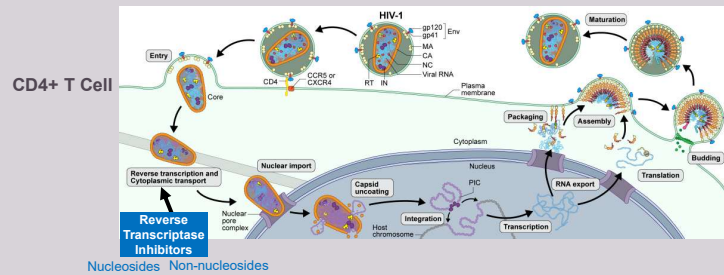


Life Cycle of HIV



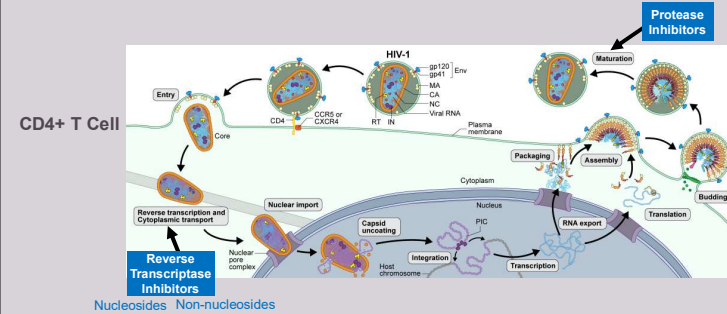
<https://scienceofhiv.org/wp/animations/>

Life Cycle of HIV



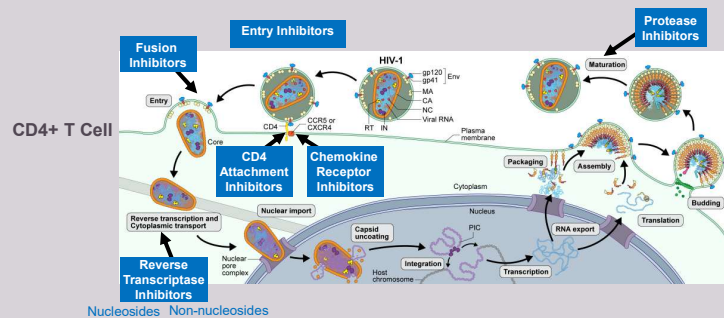
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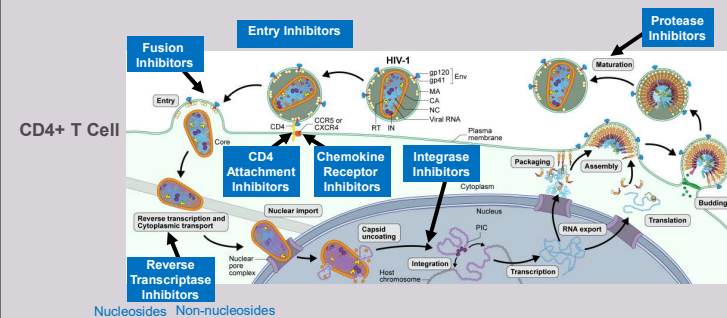
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Life Cycle of HIV



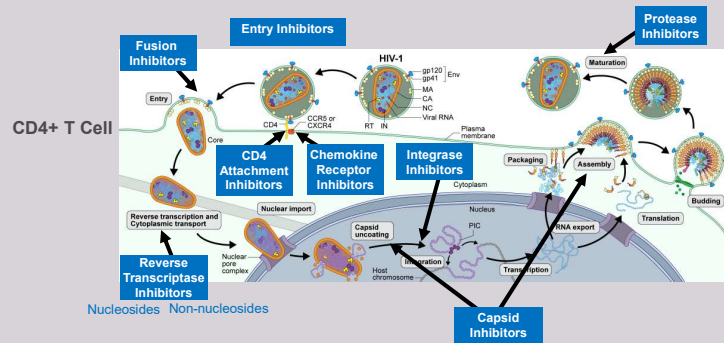
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Life Cycle of HIV



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

Life Cycle of HIV



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

Approved ART: 2026*

Nucleoside/tide RTIs (NRTIs)

- Zidovudine (ZDV, AZT)
- Lamivudine (3TC)
- Abacavir (ABC)
- Emtricitabine (FTC)
- Islatravir (ISL)
- 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, SQV, IDV, APV, FPV, + ENF (T-20) discontinued

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What to Start?

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?

- IM cabotegravir/rilpivirine
- Dolutegravir/rilpivirine
- Tenofovir alafenamide/emtricitabine/rilpivirine
- Dolutegravir/lamivudine
- Tenofovir alafenamide/emtricitabine + dolutegravir

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- B. Dolutegravir/rilpivirine
- C. Tenofovir alafenamide/emtricitabine/rilpivirine
- D. Dolutegravir/lamivudine
- E. **Tenofovir alafenamide/emtricitabine + dolutegravir***

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 (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 9/25/25 clinicalinfo.hiv.gov

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 9/25/25 clinicalinfo.hiv.gov

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 9/25/25 clinicalinfo.hiv.gov

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; ↑CV/MI
Zidovudine/lamivudine (ZDV/3TC)	No longer recommended	1 tab bid	GI, anemia, lipoatrophy	Toxicity

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Based on DHHS Guidelines 9/25/25

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)
Rilpivirine (RPV)	Alternative	qd	Not well absorbed with PPI	(TAF or TDF)/FTC/RPV (1 pill, once-daily <u>with a meal</u>); <u>NOT</u> 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

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Based on DHHS Guidelines 9/25/25

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

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Based on DHHS Guidelines 9/25/25

Choice of Integrase Inhibitors

Drug	DHHS GL	Dosing	Toxicities	Considerations
Bictegravir (BIC)	Recommended with TAF/FTC	1 coformulated pill	Few, ↑creat, wt gain	TAF/FTC/BIC (1 pill, qd); ↑ 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); ↑ barrier to resistance
Cabotegravir (CAB)	Recommended for Δ with viro suppression	IM with IM RPV	Few	All injectable regimen
Elvitegravir (EVG)	No longer recommended	1 coformulated pill	Mild GI	Drug interactions with cobicistat
Raltegravir (RAL)	No longer recommended	400 mg bid	Few	Twice-daily dosing; no co-formulations

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Based on DHHS Guidelines 9/25/25

Selected Drug Interactions 1

• Integrase inhibitors

- Divalent cations (aluminum, calcium, iron, magnesium)
 - Bind to integrase inhibitors – separate or give with full meal
- Metformin
 - Levels raised by bictegravir or dolutegravir
 - Titrate metformin dose
- Rifampin
 - Need to double dose dolutegravir (or raltegravir)
 - Bictegravir dosing controversial

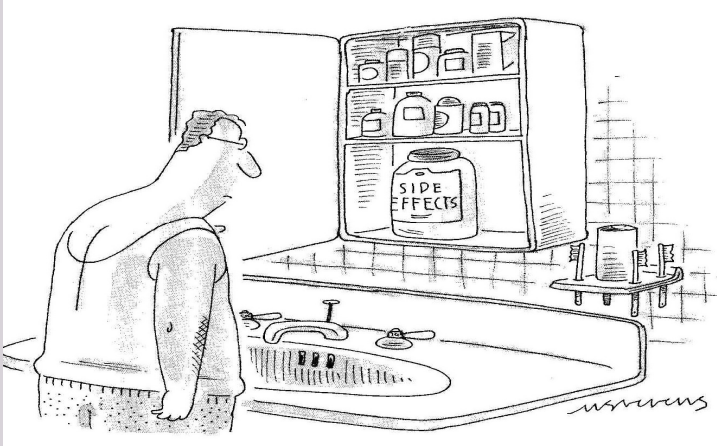
Selected Drug Interactions 2

- Cytochrome P450 3A4 effects
- Most **NNRTI** (EFV, ETR, NVP – NOT DOR) are **inducers**
 - In general, ↓ **levels of other metabolized drugs**
- All **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: rifamycins, ketoconazole/itraconazole, anticonvulsants, simvastatin/lovastatin, midazolam/triazolam, ergotamines, St. John's Wort, some HCV drugs

ART: What NOT to Use as Initial therapy

- **Monotherapy**
- **Nucleosides (NRTI)**
 - 3 or 4 all-NRTI combination regimens
 - Older drugs (e.g. zidovudine)
- **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 (or ISL/DOR)

Based on DHHS Guidelines 9/25/25



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 but used
 - 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)
- Rash (NNRTIs)

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)

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; DRV/r or /c + [3TC or FTC] or DTG; IM CAB + RPV; (ISL/DOR)
- Consideration: concomitant HBV infection

Based on DHHS Guidelines 9/25/25

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

- 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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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 9/25/25

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

Based on DHHS Guidelines 9/25/25

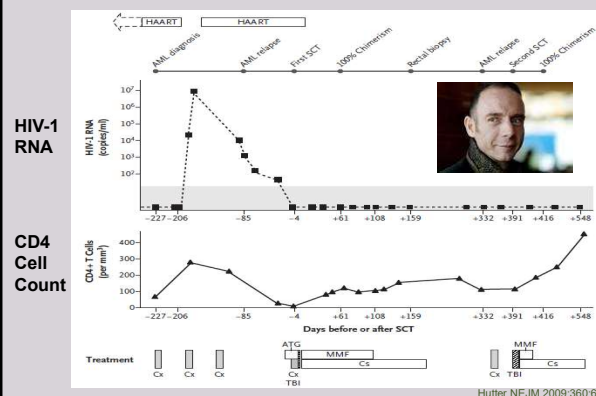
Treatment = Prevention

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) Tanner CDC Guidelines MMWR 2025;74:1
 - 3-drug integrase inhibitor-based ART recommended for 4 weeks (e.g., TAF/FTC/BIC or TDF/FTC + DTG) Molina NEJM 2015; McCormack Lancet 2016; Landovitz NEJM 2021; Delany-Moretlwe Lancet 2022; Bekker NEJM 2024; Kelley NEJM 2025; Choopanya Lancet 2013
- At-risk men and women without HIV (PrEP)
 - ↓ HIV acquisition by sex >75-100% (TDF/FTC; TAF/FTC; IM CAB; SQ LEN)
 - ↓ HIV acquisition by injection drug use ~50% (TDF/FTC)

Cure

HIV Cure (N=1) 10+!



Cure #2 *first Latino
 London
 Gupta, Nature 2019;568:244
Cure #3 *first woman
 NYC
 Hsu, Cell 2023;186:1115
Cure #4
 Dusseldorf
 Jensen, Nat Med 2023;29:583
Cure #5
 City of Hope
 Dickter, NEJM 2024;390:669
Cure #6 *wild-type donor
 Geneva
 Saez-Cirion, Nat Med 2024;30:3544
Cure #7 *first Δ32 hetero donor
 Berlin
 Gaebler, Nature 2026;650:701
Cure #8 *HIV rebound
 Chicago
 Rubinstein CROI 2025 #531
Cure #9
 Oslo
 Myhre Nat Micro 2026;11:1374

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Hutter NEJM 2009;360:692

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

Acknowledgements

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

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