

46 – Antiretroviral Therapy

Speaker: Roy Gulick, MD



Antiretroviral Therapy (ART)

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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, dermat
- 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 switch?
 - What to switch 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 HIV+ man 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.

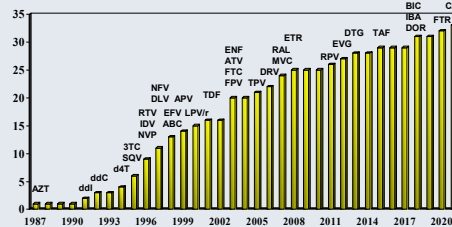
When to Start?: Chronic Infection

	AIDS/ symptoms	Asymptomatic			
		CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2021 <small>www.clinicalinfo.hiv.gov</small>		recommended			
IAS-USA 2020 <small>Saag JAMA 2020;324:1651-1669</small>		recommended			

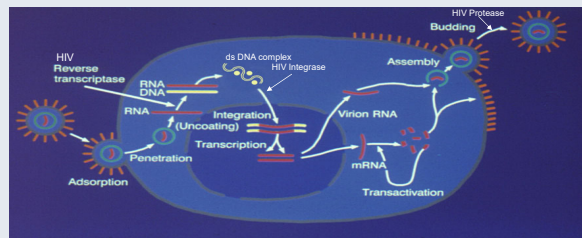
Goal of Antiretroviral Therapy

- 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)

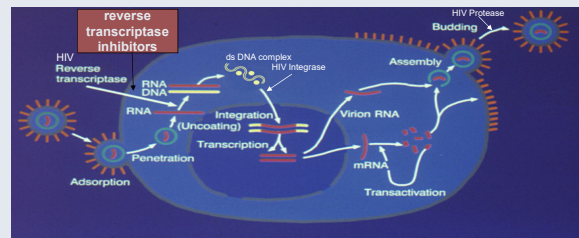
Antiretroviral Drug Approval: 1987 - 2021



Life Cycle of HIV

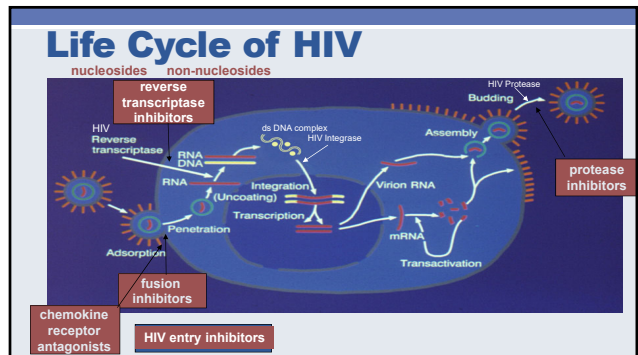
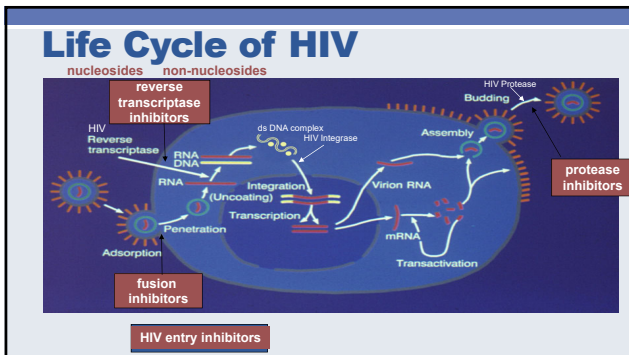
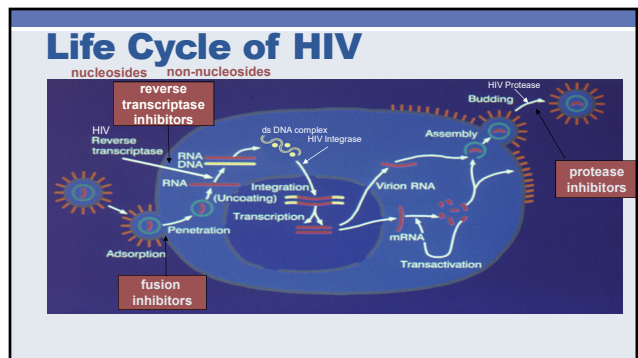
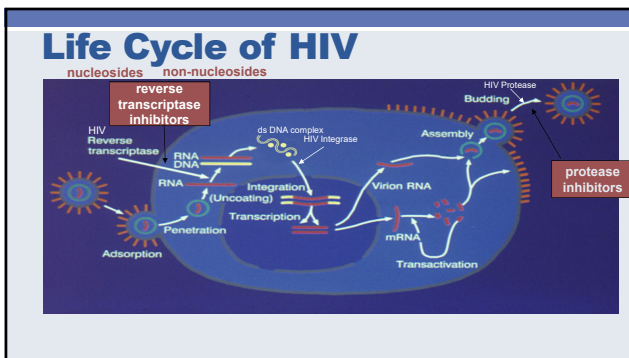
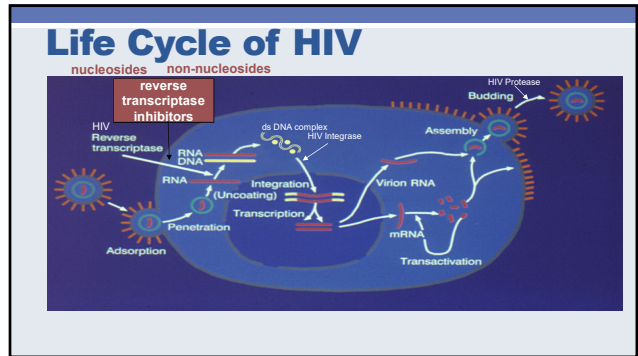
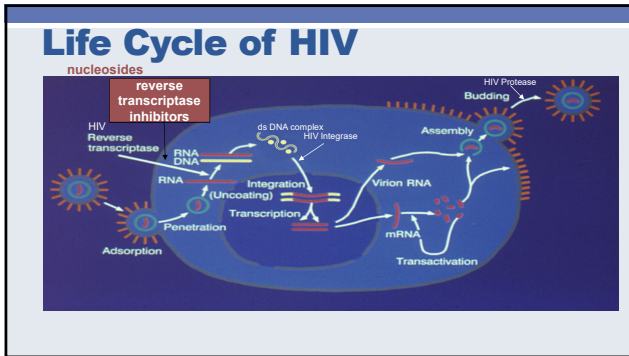


Life Cycle of HIV



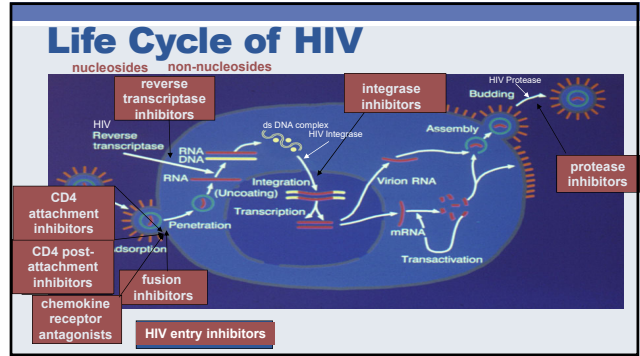
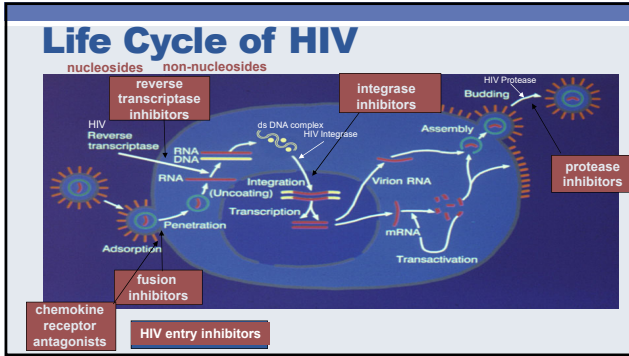
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Approved ART: 2021*

nucleoside/tide RTIs (NRTIs)	protease inhibitors (PIs)	entry inhibitors (EIs)
<ul style="list-style-type: none"> zidovudine (ZDV, AZT) lamivudine (3TC) abacavir (ABC) emtricitabine (FTC) tenofovir (TAF, TDF) 	<ul style="list-style-type: none"> saquinavir (SQV) ritonavir (RTV) indinavir (IDV) nefinavir (NFV) lopinavir/r (LPV/r) atazanavir (ATV) fosamprenavir (FPV) tipranavir (TPV) darunavir (DRV) 	<ul style="list-style-type: none"> enfuvirtide (T-20, fusion inhib.) maraviroc (MVC, CCR5 antagonist) ibalizumab (IBA, CD4 post-attachment inhib.) fostemsavir (FTR, CD4 attachment inhib.)
<p>NNRTIs</p> <ul style="list-style-type: none"> nevirapine (NVP) efavirenz (EFV) etravirine (ETR) rilpivirine (RPV) doravirine (DOR) 	<ul style="list-style-type: none"> integrase inhibitors (IIs) raltegravir (RAL) elvitegravir (EVG) dolutegravir (DTG) bictegravir (BIC) cabotegravir (CAB) 	

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

WHAT TO START?

Question #2 **PREVIEW QUESTION**

You have been monitoring a 36 year old HIV+ man with 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?

- raltegravir + darunavir (boosted)
- tenofovir alafenamide/emtricitabine/rilpivirine
- abacavir/lamivudine + efavirenz
- lamivudine/dolutegravir
- 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

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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 6/3/21 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 6/3/21 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)

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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)

U.S. DHHS Guidelines 6/3/21 www.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)	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, lipotrophy	toxicity

DHHS Guidelines 6/3/21

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 <u>with a meal</u>); NOT for HIV RNA >100K or CD4 <200
nevirapine (NVP)	not recommended	qd or bid	hepatotoxicity, hypersensitivity	toxicity

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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

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Choice of Integrase Inhibitors (II)				
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) or ABC/3TC	50 mg qd (bid with II resistance)	few, ↑ creat, CNS, neural tube defects (rare), wt gain	ABC/3TC/DTG (1 pill, qd); ↑ barrier to resistance
elvitegravir (EVG)	alternative with (TAF or TDF) /FTC/cobicistat	1 coformulated 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

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- ### 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

- ### ART: What **NOT** to use as Initial therapy
- **Nucleosides (NRTI)**
 - 3 or 4 all-NRTI combination regimens
 - older drugs (e.g. zidovudine)
 - **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)** all
 - **Some 2-drug regimens**
 - CAB + RPV or DTG + RPV
- Based on DHHS Guidelines 6/3/21



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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 with HLA-B*5701 screening
 - stop nevirapine or etravirine for rash + constitutional symptoms
- Stevens-Johnson syndrome (nevirapine, etravirine)
- teratogenicity*
 - efavirenz = pregnancy category D
 - dolutegravir during conception/very early pregnancy
 - neural tube defects – RARE

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 – lipodystrophy (stavudine, zidovudine)
 - fat gain – lipohypertrophy (older PIs)
- peripheral neuropathy (stavudine, zalcitabine, didanosine)
- proximal renal tubular dysfunction (TDF)
- weight gain (bictegravir, dolutegravir, TAF)

ART Switch

- **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+RPV; DTG+3TC; Boosted PI (ATV, DRV, LPV) + [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

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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

Question #3



PREVIEW QUESTION

28 year old HIV+ man 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 98 cps/ml and CD4 352.

What do you recommend?

- Obtain genotype.
- Obtain genotype and phenotype.
- Repeat HIV RNA at next visit.
- 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

DHHS Guidelines 6/3/21

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
- Consider newer agents (expanded access or clinical trials)
- Goal:
 - Design a regimen with 2 fully active agents (one with a high barrier to resistance: boosted darunavir, dolutegravir, [bictegravir])

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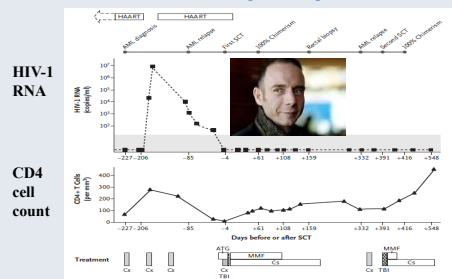
TREATMENT = PREVENTION

Treatment = Prevention

- HIV+ pregnant women *Fowler NEJM 2016;375:1726*
 - 3-drug ART ↓ transmission risk to child to 0.5%
- HIV+ men and women *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
- At-risk HIV- men and women *Molina NEJM 2015, McCormack Lancet 2016; Choopanya Lancet 2013*
 - PrEP ↓ HIV acquisition by sex >75-85% (TDF ♂ + ♀; TAF ♂ only)
 - PrEP ↓ HIV acquisition by injection drug use ~50%

CURE

HIV Cure (N=2)



Cure #2
Gupta
Nature
2019;568:
244-248.

Hutter NEJM 2009;360:692

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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; individualization is key.
- **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).
- **Treatment = Prevention** Treat HIV+, offer PEP and PrEP

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- HIV Prevention Trials Network
- Division of AIDS/NIAID/NIH
- The patient volunteers!



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