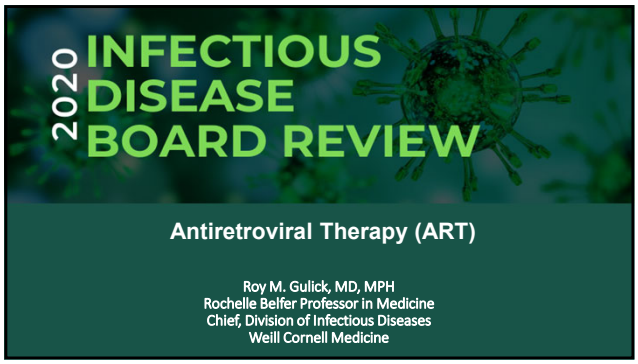
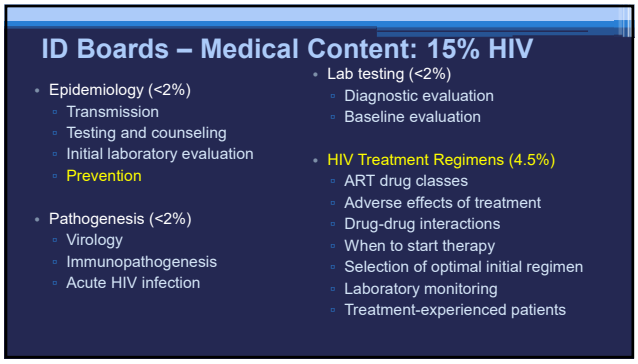
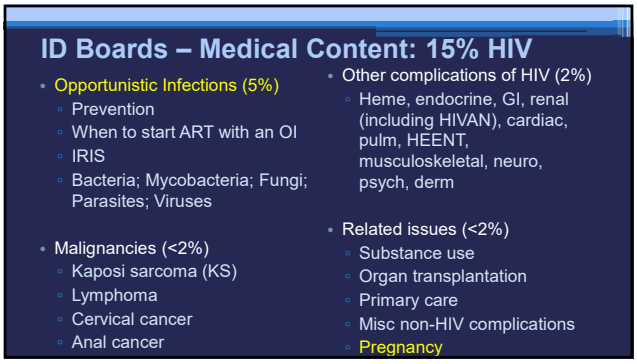
31 – Antiretroviral Therapies

Speaker: Roy Gulick, MD







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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-progresser 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.

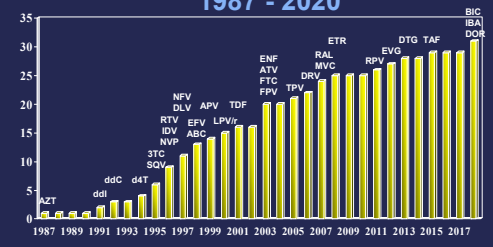
When to Start?: Chronic Infection

	AIDS/ symptoms	Asymptomatic			
		CD4 <200	CD4 200-350	CD4 350-500	CD4 >500
US DHHS 2019 www.aidsinfo.nih.gov	recommended				
IAS-USA 2018 JAMA 2018;320:379-396	recommended				

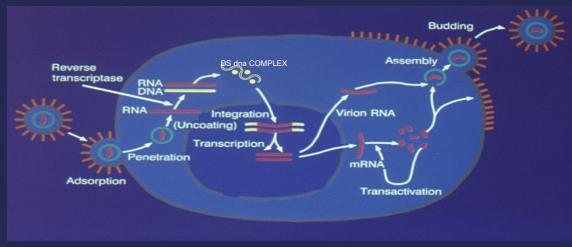
Goal of Antiretroviral Therapy

- 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 - 2020



Life Cycle of HIV



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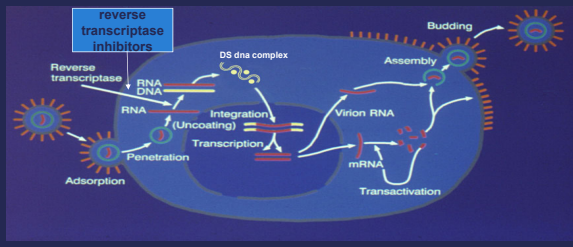

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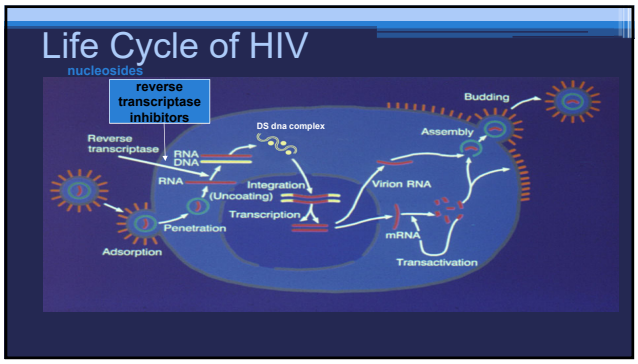

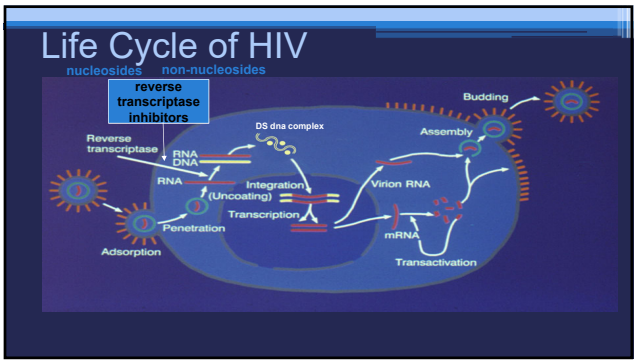

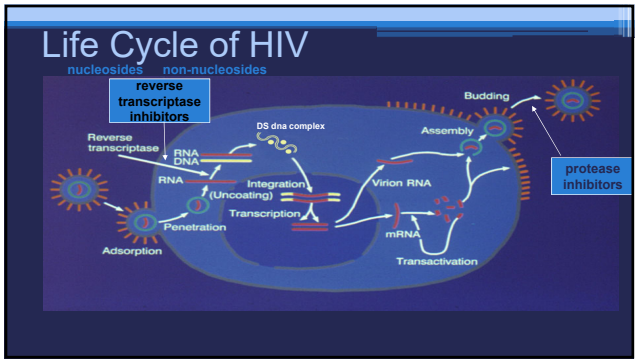

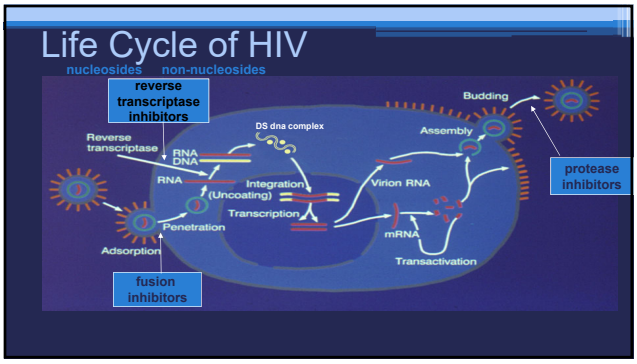

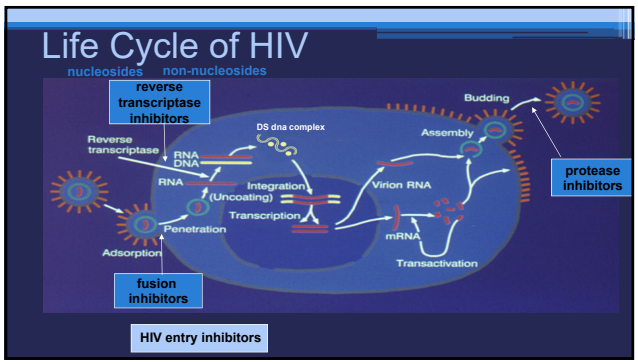

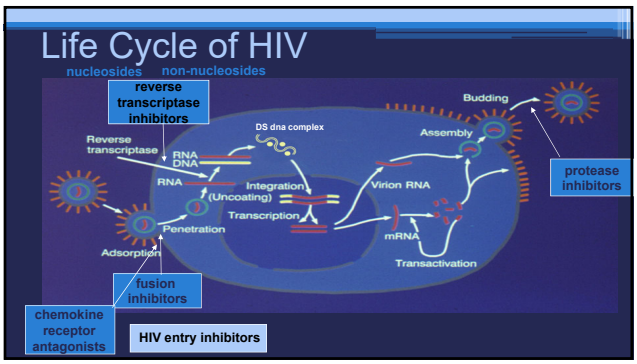

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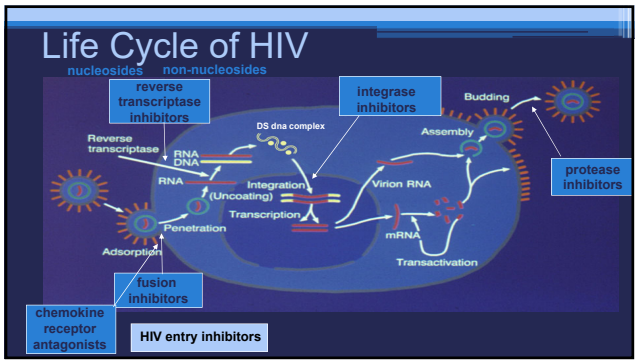

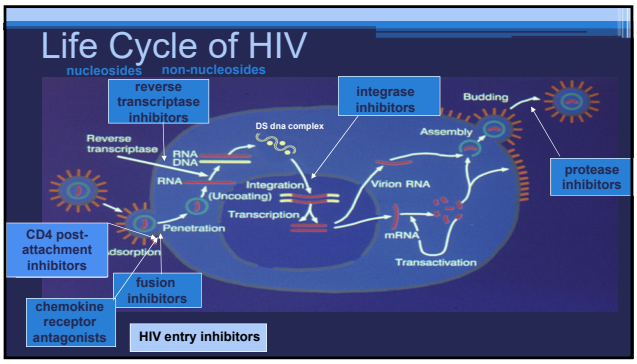

Approved ART: 2020

nucleoside/tide RTIs (NRTIs)
- zidovudine (ZDV, AZT)
- didanosine (ddI)**
- stavudine (d4T)**
- lamivudine (3TC)
- abacavir (ABC)
- emtricitabine (FTC)
- tenofovir (TAF, TDF)

NNRTIs
- nevirapine (NVP)
- delavirdine (DLV)**
- 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)
- fosamprenavir (FPV)
- tipranavir (TPV)
- darunavir (DRV)

*ddC and APV withdrawn from market
**withdrawal from market planned

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

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

What to start?

Question #2

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?

A. zidovudine/lamivudine + darunavir (boosted)
B. tenofovir/emtricitabine/rilpivirine
C. abacavir/lamivudine + efavirenz
D. lamivudine/dolutegravir
E. tenofovir/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

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

- Integrase inhibitor-based
  - bictegravir/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)
  - raltegravir + tenofovir (TAF or TDF) + (emtricitabine or lamivudine)

U.S. DHHS Guidelines 12/18/19 www.aidsinfo.nih.gov

Alternative Regimens (Certain Situations) (1)

- Integrase inhibitor-based (INSTI + 2 NRTI)
  - elvitegravir/cobicistat/tenofovir (TAF or TDF)/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)
  - atazanavir/(ritonavir or cobicistat) + tenofovir (TDF or TAF) + (lamivudine or emtricitabine)
  - darunavir/(ritonavir or cobicistat) + abacavir*/lamivudine

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

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Alternative Regimens (Certain Situations) (3)

- Consider 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 + raltegravir BID (if HIV RNA <100,000 cps/ml and CD4 >200)
  - darunavir/ritonavir + lamivudine

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Choice of NRTIs

Combination	DHHS	Dosing	Toxicities	Considerations
tenofovir (TAF or TDF)/ emtricitabine	recommended	1 tab qd	renal, bone (with TDF); ↓ tox with TAF	1-pill, once-daily formulations available
abacavir/ lamivudine	recommended (with dolutegravir only) / alternative	1 tab qd	HSR (5-8%) (do HLA-B*5701 test)	ABC/3TC/DTG available; ?less effective; ??↑MI
zidovudine/ lamivudine	no longer recommended	1 tab bid	GI, anemia, lipoatrophy	toxicity

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Choice of NNRTIs

Drug	DHHS	Dose	Toxicities	Considerations
doravirine	alternative	qd	↓ CNS toxicity than EFV; ↓ lipid abnor.	TDF/FTC/DOR (1 pill, once-daily)
efavirenz	alternative	qd (600 or 400 mg)	CNS toxicity (50%), rash (10%), suicidality (rare)	TDF/FTC/EFV (1 pill, once-daily)
rilpivirine	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	no longer recommend	qd or bid	hepatotoxicity, hypersensitivity	toxicity

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Choice of PIs

Drug	DHHS	Dose	Toxicities	Considerations
darunavir /(ritonavir or cobicistat)	alternative; in general, prefer-red over ATV	qd (if no prior PI resistance) or bid	skin rash (rare);	activity against PI-resistant viral strains
atazanavir /(ritonavir or cobicistat)	alternative	qd	↑ indirect bilirubin, GI	avoid PPI; kidney stones (uncommon)
lopinavir/ ritonavir	other	bid or qd	diarrhea, ↑lipids	co-formulated

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Choice of Integrase Inhibitors (II)

Drug	DHHS	Dosing	Toxicities	Considerations
bictegravir	recommended with TAF/FTC	1 coform-ulated pill	few, ↑creat, wt gain(?)	TAF/FTC/BIC (1 pill, qd) ↑ barrier to resistance
dolutegravir	recommended with (TAF or TDF)/(FTC or 3TC) or ABC/3TC	50 mg qd (bid with II resistance)	few, ↑creat, CNS, neural tube defects, wt gain	ABC/3TC/DTG (1 pill, qd) ↑ barrier to resistance
elvitegravir	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	recommended with (TAF or TDF)/FTC	400 mg bid; 600 mg X 2 qd	few	twice-daily dosing; no co-formulation

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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 an 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 (didanosine, stavudine, zidovudine)
- Non-nucleosides (NNRTI)
  - older drugs (delavirdine, nevirapine)
  - etravirine in initial regimens
- Protease Inhibitors (PI)
  - unboosted PIs
  - older drugs (fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir [except as booster], saquinavir tipranavir)
- Entry inhibitors (EI)
  - enfuvirtide, maraviroc, ibalizumab

Based on DHHS Guidelines 12/18/19

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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
  - lactic acidosis (older nucleoside analogues: didanosine, stavudine)
  - pancreatitis (older nucleoside analogues: didanosine, stavudine)
  - Stevens-Johnson syndrome (nevirapine, etravirine)
  - teratogenicity (efavirenz = pregnancy category D; dolutegravir during conception/very early pregnancy → neural tube defects)

ART Side Effects (2)

- **Acute/early**
  - gastrointestinal (zidovudine, didanosine, 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, stavudine)
  - morphologic –
    - fat loss – lipoatrophy (stavudine, zidovudine)
    - fat gain – lipohypertrophy (older PIs)
  - peripheral neuropathy (stavudine, didanosine)
  - proximal renal tubular dysfunction (TDF)
  - weight gain (bictegravir, dolutegravir)

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)
  - 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

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 102 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 abacavir/lamivudine/dolutegravir to improve adherence.

When to change therapy?

Virologic failure

- VL undetectable – drug resistance unlikely
- VL <200 cps/ml – controversial; one large retrospective analysis found no increased risk of failure
- 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

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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
- Consider newer agents (expanded access or clinical trials)
- Goal:
  Design a regimen with 2 (preferably 3) fully active agents

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Treatment = Prevention

Treatment = Prevention

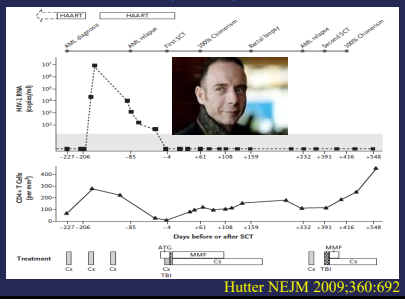
- HIV+ pregnant women
  - 3-drug ART decreases transmission risk to child to 0.5%
    Fowler NEJM 2016
- HIV+ men and women
  - Suppressive ART decreases transmission to sexual partners by 93% *Cohen NEJM 2016;375:830*
- HIV- men and women
  - 2-drug ART (PrEP) decreases HIV acquisition by sex ~99%
    Baeten NEJM 2012, Molina NEJM 2015, McCormack Lancet 2016
- HIV- post-exposure prophylaxis (PEP)
  - 3-drug integrase-inhibitor based ART recommended for 4 weeks *CDC Guidelines*

Cure

HIV Cure (N=2)

HIV-1 RNA

CD4 cell count



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

Hutter NEJM 2009;360:692

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