HIV 101: Initiation of Antiretroviral Therapy and Primary Care for People With HIV

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Financial Relationships With Ineligible Companies* (Formerly Described as Commercial Interests by the ACCME)

Speakers
Dr Saag has received research grants and support awarded to his institution from Gilead Sciences, Inc and ViiV Healthcare, and serves as a consultant to TFF Pharmaceuticals and American Gene Technologies. (Updated 9/28/22)

Dr Thompson serves as chair of the independent data monitoring committee for Excision BioTherapeutics, and her institution has received research grants from Cepheid, Frontier Biotechnologies, Gilead Sciences, Inc, GlaxoSmithKline, Merck Sharp and Dohme, and ViiV Healthcare. (Updated 9/28/22)

Planner/Reviewer
Planner/Reviewer 1 has no relevant financial relationships with ineligible companies to disclose. (09/28/22)
Planner/Reviewer 2 has no relevant financial relationships with ineligible companies to disclose. (09/28/22)

The IAS–USA has identified and resolved ahead of time any possible conflicts of interest that may influence this CME activity with regard to exposition or conclusion. All relevant financial relationships with ineligible companies have been mitigated among the planners (eg, COW Board) and the presenter.

*The ACCME defines ineligible companies (formerly described as commercial companies) as those whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Slide 2

Conference Funding

This conference is funded by Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services (HHS) under grant number U1OHA28686 (AIDS Education and Training Center National Coordinating Resource Center) awarded François-Xavier Bagnoud Center from the Rutgers University School of Nursing with a sub award to International Antiviral Society–USA (IAS–USA) to sponsor this CME activity.

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ACCME ACCREDITED

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- 2.00 CME credits
- 2.00 ABIM MOC points
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- 2.00 Hours of pharmacotherapy credit
- 2.00 Pharmacy contact hours (0.200 CEUs)

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2022 Ryan White HIV/AIDS Program CLINICAL CONFERENCE

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Navigating This Activity

Poll Questions
- A separate window will show the poll question
- Choose your response for the poll
- Responses will be displayed after the poll closes

How to Submit Questions
- Submit questions using the Q&A button
- We apologize in advance if we are not able to address all questions in the time allotted

Chat is Open
- Use Chat to start discussion with other attendees
- **Do not submit questions to Chat as presenter and moderator will only monitor questions submitted to Q&A**

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HIV 101: Fundamentals of Antiretroviral Therapy

Michael S. Saag, MD

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Birmingham, AL, USA

Poll Question #1

What is the setting of your current work?

1. Clinical research
2. Clinical/sessional work
3. Commercial company (eg, pharmaceutical)
4. Community-based health center/clinic
5. Government
6. Hospital based
7. In fellowship or other training
8. Laboratory research
9. Managed care organization
10. Other

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Learning Objectives

Upon completion of this webinar, learners will be able to:

- Basic mechanisms of antiretroviral therapy
- Antiretroviral regimens based on patient parameters

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Pretest Question #1

A 32 year old is started on his first ARV regimen. Within 1 week, his serum creatinine increased from 1.0 to 1.15 mg/dl. Which of the following drugs is most likely responsible for the 0.15 mg/dl increase in serum creatinine?

1. Tenofovir DF (TDF)
2. Tenofovir AF (TAF)
3. Abacavir
4. Bictegravir
5. Emtricitibine

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Pretest Question #2

A 23 year old woman has been told she is 3 weeks pregnant. An HIV test is positive and her HIV RNA level is 12,000 c/ml, CD4 count 456 cells/μL. She has no underlying medical conditions and no concomitant medications. Which of the following regimens is the best option for ARV treatment?

1. TAF/ FTC / Bictegravir
2. TAF / FTC / Dolutegravir
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4. TDF / FTC / Atazanavir / cobisistat
5. TAF / FTC / Elvitegravir / cobisistat

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Approach to a Person with HIV: 3 Steps

Step 1: History, Examination and Lab Tests

Step 2: Opportunistic infection prophylaxis (if indicated)

Step 3: Antiretroviral therapy: when and what to start

Slide courtesy of Dr. Raj Gandhi

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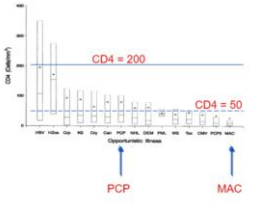
Lab Evaluation: HIV-specific Tests

- **CD4 cell count:**
  - Best predictor of risk of opportunistic infection or cancer
  - Used to decide when to start opportunistic infection prophylaxis
- **HIV RNA** ("viral load")
  - Most important predictor of response to therapy: should decline to undetectable within few months of starting treatment



Moore, Ann Intern Med 124:633.

Slide 14

HIV Resistance Testing

Patient	Resistance Test
Newly Diagnosed or Treatment Naive	Genotype – mutations in viral genes (Reverse transcriptase and protease)
Virologic Failure to 1st or 2nd Lines of Therapy	Genotype (Integrase genotype if failing integrase inhibitor)
Suspected Complex Resistance	Phenotype and Genotype

Interpretation:

- **www.iasusa.org/content/hiv-drug-resistance-mutations**
- **Stanford HIV Drug Resistance: http://hivdb.stanford.edu/**

Slide courtesy of Dr. Raj Gandhi

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Common Rules of Antiretroviral Therapy

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BACK TO BASICS

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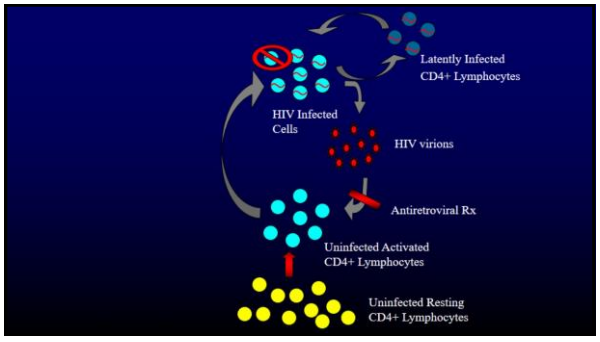

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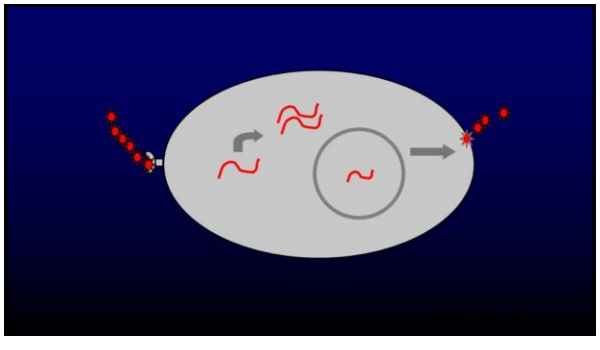

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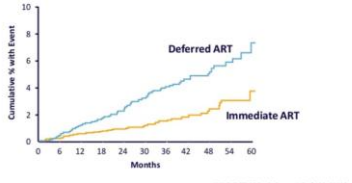
Inverse Probability Weighted Cox Regression Multivariate Analysis

*Stratified by Cohort and Year	Relative Hazard (RH)*	95% Confidence Interval	P-value
Deferral of HAART at 351-500	1.7	1.4, 2.1	<0.001
Female Sex	1.1	0.9, 1.5	0.290
Older Age (per 10 years)	1.6	1.5, 1.8	<0.001
Baseline CD4 count (per 100 cells/mm^3)	0.9	0.7, 1.0	0.083

- Results were similar when restricting the analysis to the 77% of participants with baseline HIV RNA data
- Adjusted RH for deferral vs. immediate treatment was also 1.7 95% C.I. 1.4, 2.2; p <0.0001
- HIV RNA was not an independent predictor of mortality

START: 57% Reduced Risk of Serious Events or Death With Immediate ART

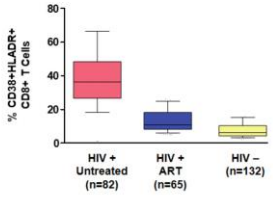
- Serious AIDS or non-AIDS event or death: 4.1% vs. 1.8% in deferred vs. immediate ART (HR 0.43; 95% CI 0.30-0.62; *P*<0.001)



INSIGHT START Study Group. N Engl J Med 2015

Slide 24

T cell "activation" is lower in treated than untreated adults, but consistently higher than "normal"

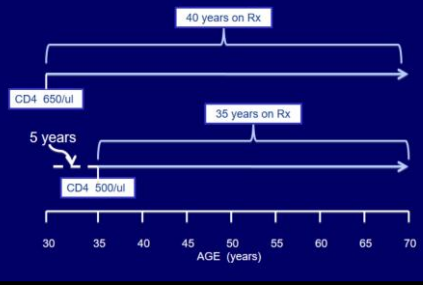


Slide 25

Hunt et al JID 2003, PLoS ONE 2011 and unpublished

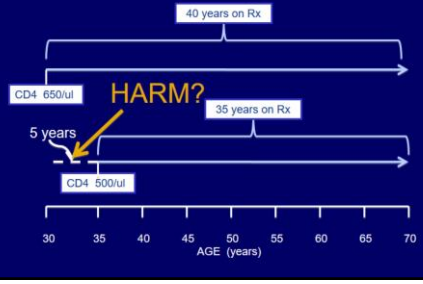
Relative Time on Treatment…

Slide 26



Relative Time on Treatment…

Slide 27



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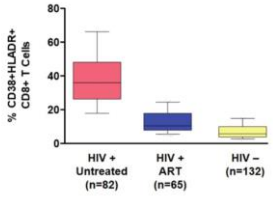
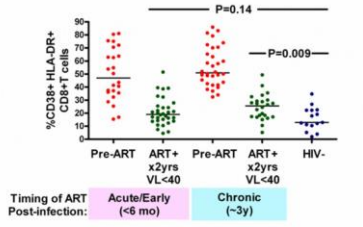


Slide 29

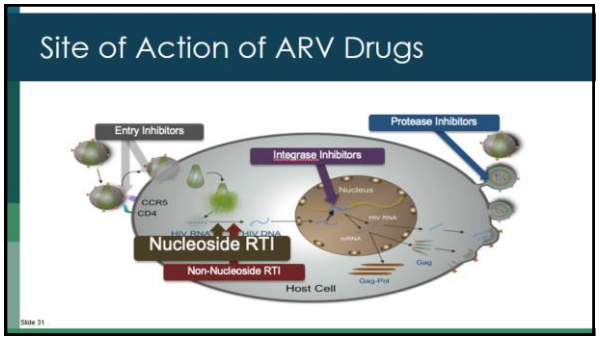
Hunt et al JID 2003, PLoS ONE 2011 and unpublished

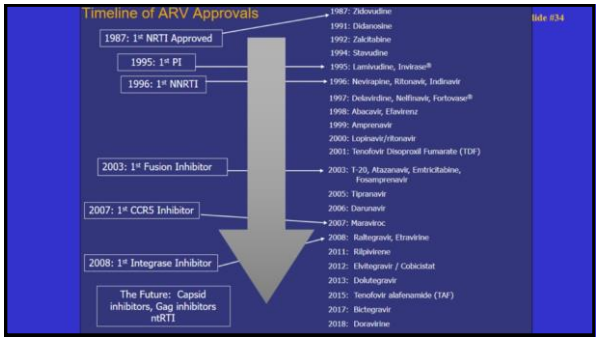
Early ART Also Appears to Reduce Residual T Cell Activation during ART

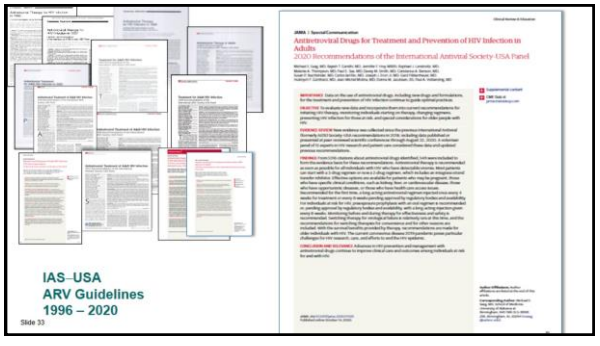


Slide 30

Jain et al, CROI 2011


Site of Action of ARV Drugs
Entry Inhibitors
Protease Inhibitors
Integrase Inhibitors
CCR5
CD4
Nucleus
HIV RNA
HIV RNA
HIV DNA
mRNA
Nucleoside RTI
Non-Nucleoside RTI
Gag
Gag-Pol
Host Cell
Slide 31


Timeline of ARV Approvals
lide 834
1987: 1st NRTI Approved
1995: 1st PI
1996: 1st NNRTI
2003: 1st Fusion Inhibitor
2007: 1st CCR5 Inhibitor
2008: 1st Integrase Inhibitor
The Future: Capsid inhibitors, Gag inhibitors ntRTI
1987: Zidovudine
1991: Didanosine
1992: Zalcitabine
1994: Stavudine
1995: Lamivudine, Invirase®
1996: Nevirapine, Ritonavir, Indinavir
1997: Delavirdine, Nelfinavir, Fortovase®
1998: Abacavir, Efavirenz
1999: Amprenavir
2000: Lopinavir/ritonavir
2001: Tenofovir Disoproxil Fumarate (TDF)
2003: T-20, Atazanavir, Emtricitabine, Fosamprenavir
2005: Tipranavir
2006: Darunavir
2007: Maraviroc
2008: Raltegravir, Etravirine
2011: Rilpivirene
2012: Elvitegravir / Cobicistat
2013: Dolutegravir
2015: Tenofovir alafenamide (TAF)
2017: Bictegravir
2018: Doravirine


IAS–USA
ARV Guidelines
1996 – 2020
Slide 33
Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults
2020 Recommendations of the International Antiviral Society–USA Panel

Key Recommendations for When to Start Antiretroviral Therapy

- Initiate as soon as possible after diagnosis, including immediately (rapid or same-day start) if the patient is ready
- Remove any structural barriers that delay ART
- In setting of starting OI treatment, begin ART within 2 weeks for most OIs
- *Exceptions are:*
  - Tuberculosis: within 2-8 weeks
    - Within 2-weeks for those with < 50 CD4 cells/μL*
    - Within 2-8 weeks for those with higher CD4 cells counts
  - Cryptococcal meningitis: 2- 4 weeks
- For individuals with cancer, immediate ART initiation with close attention to drug-drug interactions and monitoring for early ART adverse events

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Recommended Initial ART for Most People With HIV

- Bictegravir/tenofovir alafenamide/emtricitabine
- Dolutegravir plus TAF/FTC or TDF/FTC or TAF/3TC
- Dolutegravir/lamivudine with caveats*

*Not recommended for:
1) rapid start (before results of hepatitis B and HIV genotypic testing are available)
2) patients with chronic hepatitis B
3) patients with HIV RNA level >500,000 copies/mL, or perhaps with CD4 cell count <200/μL
4) patients being treated for an active opportunistic infection
Monitor for adherence and virological response closely.

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Other Recommended Initial ART Regimens

- Darunavir/cobicistat/TAF/FTC or + TDF/3TC
- Dolutegravir/abacavir/3TC
- Doravirine/TDF/3TC or + TAF/FTC or + TDF/3TC
- Efavirenz (400 mg or 600 mg) + TDF/3TC or + TDF/FTC
- Raltegravir + TAF/FTC or + TDF/FTC or + TDF/3TC
- Rilpivirine/TAF/FTC or /TDF/3TC

* See advantages and disadvantages in the article

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Recommendations for Starting ARV in the Setting of OIs

- Active TB; on rifamycin
  - Dolutegravir 50 mg bid
  - Efavirenz 600 mg qd
  - Raltegravir 800 mg bid

  } plus 2 nRTIs
- Bictegravir with rifampin is not recommended
- Boosted PIs:
  - Only if an InSTI or efavirenz is not available
  - If possible, rifabutin not rifampin should be used with PIs

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Recommended Initial ART During Pregnancy

- Atazanavir/ritonavir
- Darunavir/ritonavir
- **Dolutegravir**
- Efavirenz
- Raltegravir
- Rilpivirine

} **plus TXF/XTC**

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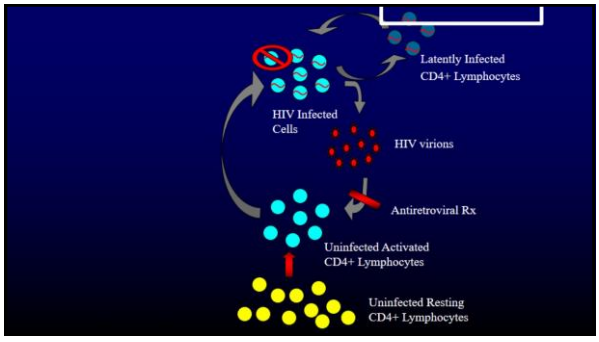

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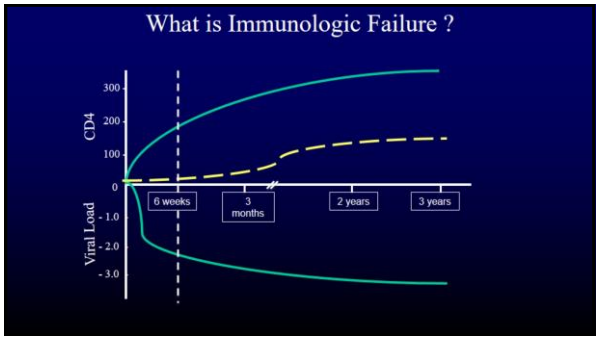

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Conclusions

- Understanding HIV viral life-cycle is critical to understanding basis of ARV therapy
- ARV therapy interrupts HIV replication ~ completely, halting the most of the damage done by HIV
- ARV therapy protects uninfected cells from becoming infected and has no effect on cells already infected
- All ARV drugs target specific sites within the viral life-cycle
- Initiate ARV Rx with an InSTI and 2 nucleosides (occasionally 1 or with an NNRTI)
- Timing of initiation may be delayed with certain OIs

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Posttest Question #1

A 32 year old is started on his first ARV regimen. Within 1 week, his serum creatinine increased from 1.0 to 1.15 mg/dl. Which of the following drugs is most likely responsible for the 0.15 mg/dl increase in serum creatinine?

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Posttest Question #2

A 23 year old woman has been told she is 3 weeks pregnant. An HIV test is positive and her HIV RNA level is 12,000 c/ml, CD4 count 456 cells/μL. She has no underlying medical conditions and no concomitant medications. Which of the following regimens is the best option for ARV treatment?

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Changes/Queries

- Slides 1-7: Added introduction slides for Dr Saag to go over
- Slide 9: Added poll test questions
- Slide 10: Added learning objectives
- Slides 11-12, 45-46: Added pre/posttest questions, minor text edits