Fundamentals of Antiretroviral Therapy

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Learning Objectives

After attending this presentation, learners will be able to:

• Articulate the mechanisms of action of antiretroviral therapy
• Describe viral dynamics and how viral replication drives HIV pathogenesis
• Explain how antiretroviral drug resistance occurs and how to prevent it

Financial Relationships With Commercial Entities

Dr. Saag has received research grants and support awarded to his institution from Gilead Sciences, Inc, and ViiV Healthcare. (Updated 11/21/19)
BACK TO BASICS

Viral load over time:

- Week 0: Initial viral load
- Week 1, 2, 3, 4: Decreasing viral load
- Week 5, 6, 7, 8, 9, 10: Further decrease
- Week 11: Viral load remains low

Half-life ($T_{1/2}$) = 1.1 days

Weeks

0 2 4 6 8 10 12

$T_{1/2} = 1.1$ days
ARS Question 1: How many HIV virions are produced a day in an HIV infected person?

A. 1
B. ~ 1000
C. 570,342
D. ~ 1 million
E. > 1 billion
ARS Question 2: At steady state, when an actively producing cell dies, it is replaced by how many newly infected cells?

A. One
B. Twenty-Five
C. One Hundred
D. One Thousand
E. It depends on the viral load
Viral Load

\[ T_{1/2} = 1.1 \text{ days} \]
ARS Questions 3: When should antiretroviral therapy be started? At a CD4 count of:

A. 200 cells/ul or less  
B. 200 – 350 cells/ul  
C. 350 – 500 cells/ul  
D. 500 – 750 cells/ul  
E. Any CD4 count
Co-morbid conditions common in HIV-infected adults
HIV-infected adults age 50-55 similar to uninfected adults > 65

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

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


Jain et al, CROI 2011
Inverse Probability Weighted Cox Regression
Multivariate Analysis

<table>
<thead>
<tr>
<th>Relative Hazard (RH)</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Deferral of HAART at 351-500</td>
<td>1.7</td>
<td>1.4, 2.1</td>
</tr>
<tr>
<td>Female Sex</td>
<td>1.1</td>
<td>0.9, 1.5</td>
</tr>
<tr>
<td>Older Age (per 10 years)</td>
<td>1.6</td>
<td>1.5, 1.8</td>
</tr>
<tr>
<td>Baseline CD4 count (per 100 cells/mm³)</td>
<td>0.9</td>
<td>0.7, 1.0</td>
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- 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% CI 1.4, 2.2; p < 0.001)
- 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 0.44, 95% CI 0.30-0.62; P<0.001)

Cost-Effectiveness of Early vs. Deferred ART

- Markov modeling approach
- Johns Hopkins HIV clinic database

<table>
<thead>
<tr>
<th>ART Initiation</th>
<th>Incremental Lifetime Costs</th>
<th>Incremental Discounted QALY* Gained</th>
<th>Cost Per Life-Year Gained</th>
<th>Cost Per QALY* Gained</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 &gt;350 vs 200-350</td>
<td>$19,074</td>
<td>0.75 (0.61)</td>
<td>$25,567</td>
<td>$31,226</td>
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- “Starting ART earlier … rather than later … is a cost-effective strategy (by the generally accepted benchmark in the US).”
Relative Time on Treatment...

HARM?

30 35 40 45 50 55 60 65 70
AGE (years)

CD4 650/ul
CD4 500/ul

5 years

40 years on Rx

35 years on Rx

5 years

Relative Time on Treatment...

CD4 650/ul
CD4 500/ul

5 years

40 years on Rx

35 years on Rx

5 years

Improved Clinical Outcomes With Rapid ART Initiation

- Universal recommendations for treating all HIV-infected persons
- Systematic review of 22 studies of rapid ART initiation (including 4 RCTs)

<table>
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<tr>
<th>Characteristic</th>
<th>RR (95% CI)</th>
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<tr>
<td>Art start within 90 days</td>
<td>1.35 (1.13-1.62)</td>
</tr>
<tr>
<td>Retained in care at 12 mos</td>
<td>1.11 (0.99-1.26)</td>
</tr>
<tr>
<td>Viral suppression at 12 mos</td>
<td>1.17 (1.07-1.27)</td>
</tr>
<tr>
<td>LTFU at 12 mos</td>
<td>0.86 (0.42-1.04)</td>
</tr>
<tr>
<td>Died by 12 mos</td>
<td>0.53 (0.28-1.00)</td>
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**Expedited ART-- Experience in Atlanta**

- Grady reduced barriers, with goal to begin ART within 72hrs
- Post-intervention days to ART = 22, Post-intervention days to ART = 4.

**Outcome**
- Pre-REACH (n=117)
- Post-REACH (n=99)
- aHR (95% CI)

<table>
<thead>
<tr>
<th>Attended 1st scheduled appointment</th>
<th>Pre-REACH (75)</th>
<th>Post-REACH (68)</th>
<th>aHR (95% CI)</th>
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<tbody>
<tr>
<td>Achieved viral suppression*</td>
<td>87 (74)</td>
<td>63 (66)</td>
<td>0.77 (0.59, 1.02)</td>
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*Adjusted for age, race, sex, and using ART before

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**Timeline of ARV Approvals**
- 1987: 1st NRTI Approved
- 1995: 1st PI
- 1996: 1st NNRTI
- 2003: 1st Fusion Inhibitor
- The Future: Capsid inhibitors, Gag inhibitors

**Site of Action of ARV Drugs**
- Enzyme Inhibitors
  - Protease Inhibitors
- Nucleoside RTI
  - Non-Nucleoside (NNRTI)
  - Host Cell

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New Orleans, LA, December 4-7, 2019, Ryan White HIV/AIDS Program CLINICAL CONFERENCE
What is Immunologic Failure?

Conclusions
- Understanding HIV viral life-cycle is critical to understanding basis of ARV therapy
- Viral replication is very dynamic (1-10 billion new viruses produced a day) and is the driving force of HIV pathogenesis
- 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

Question-and-Answer Period