HIV, Hepatitis C, and Treatment
3/26/13

What Do HIV Medications Do?

George Beatty, MD, MPH

BIOGRAPHY:

Dr. Beatty is a clinician educator and has been on the faculty since 1998. He served as Director of the UCSF's HIV Clinical Trials Unit at San Francisco General Hospital from 2001 to 2007. He has worked extensively in the field in sub-Saharan Africa training healthcare providers and assisting HIV treatment programs in implementation of antiretroviral treatment programs, and the development of clinical algorithms and treatment regimens. He serves as a consultant to African Ministries of Health and U.S. non-governmental organizations. He has particular interest and experience in the management of patients with multi-drug resistant HIV and/or viral hepatitis in the developing world, and the use of remote and web-based training modalities for resource-limited countries. He collaborates with the UCSF Transplant Service on management of HIV infected recipients of solid-organ transplants and the use of novel therapies in this population. He collaborates with the UCSF Department of Psychiatry on investigations of interactions of antiretrovirals and alcohol and treatments for opiate addiction. He has also served as consultant to the California Department of Corrections.

Faster, Better and Shorter:
The Current Revolution in Hepatitis C Treatment

Annie Luetkemeyer, MD

BIOGRAPHY:

Dr. Luetkemeyer is an Assistant Professor of Medicine at UCSF and Attending Physician at the HIV/AIDS Clinic at San Francisco General Hospital. She is active nationally in designing and conducting clinical trials in Hepatitis C treatments both mono-infected and co-infected patients and has published numerous articles in the fields of HCV and HIV. She has an active clinical practice of HIV and HIV/HCV co-infected patients at San Francisco General Hospital and is an attending physician in the Co-Infection Clinic.
What Do HIV Medications Do?

Introduction to Antiretroviral Therapy

George Beatty, MD, MPH

Therapeutic Effects of ART

- Reduce mortality overall
- Reduce risk of opportunistic infections (OI) within CD4 strata
- Reduce risk of OI’s by increasing CD4 cell count
- Suppress viral replication in plasma
- Reduce, but not normalize, chronic inflammation and immune activation
- Ameliorate hypersensitivity and HIV-related autoimmune disorders
- Reverse some neurocognitive deficits and neurologic damage
- Reduce, but not eliminate, risk of AIDS-defining cancers
- Reduce, but not normalize, increased risk of non-AIDS defining cancer
- Improve fatigue, malaise and restore general sense of well-being
- Reduce risk of mother-to-child transmission
- Prevent HIV infection before (PrEP) and after (PEP) HIV exposure
- Reduce risk of sexual transmission

Adverse Effects of ART

- Nausea, vomiting, diarrhea
- Fatigue, malaise
- Headache
- Hypersensitivity reactions
- Dissociative neurologic symptoms, insomnia
- Hepatotoxicity
- Nephrotoxicity
- Bone demineralization
- Teratogenicity
- Drug interactions
- Insulin resistance
- Hyperlipidemia
- Increased cardiovascular risk
- Peripheral neuropathy

What HIV Medications DON’T Do

- Completely normalize mortality
- Completely reverse risk of malignancies
- Eliminate all risk of transmission
- Normalize levels of immune activation
- Eliminate excess cardiovascular mortality
- Eliminate rate of end-organ disease and mortality
- Normalize neurocognitive deficits
- Reduce size of latent reservoir of HIV
- Eradicate HIV infection

Natural history of viral load in an untreated patient
Viral load response to ARVs

2-phase decay

Expect at least 1 log decrease in first 4 weeks

Undetectable at 3-6 months

CD4 cell counts during the first 12 months on potent regimen

Preferred Regimens

DHHS and IAS-USA

<table>
<thead>
<tr>
<th>Cornerstone</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td>Efavirenz + tenofovir/emtricitabine</td>
</tr>
<tr>
<td></td>
<td>Efavirenz + abacavir/lamivudine</td>
</tr>
<tr>
<td>Boosted PI</td>
<td>Atazanavir/ritonavir + tenofovir/emtricitabine</td>
</tr>
<tr>
<td></td>
<td>Atazanavir/ritonavir + abacavir/lamivudine</td>
</tr>
<tr>
<td></td>
<td>Darunavir/ritonavir + tenofovir/emtricitabine</td>
</tr>
<tr>
<td>Integrase</td>
<td>Raltegravir + tenofovir/emtricitabine</td>
</tr>
</tbody>
</table>

Alternative Regimens

DHHS
IAS

Alterative Regimens

Cornerstone

DHHS
NNRTI

IAS

Boosted PI

Integrase Inhibitor

HIV Life Cycle
HIV Life Cycle

- Reverse transcription
- Integration
- gp120-CD4 binding
- Processing of viral proteins/RNA
- Co-receptor binding
- Fusion
- Viral assembly/maturation
- Protease inhibitors
- NRTIs
- NNRTIs
- Protease inhibitors

Prevalence of X4 increases with decreasing CD4

Chemokine coreceptor antagonists

HIV Life Cycle

- Co-receptor binding
- CCR5 antagonists
- gp120-CD4 binding
- Integration
- Reverse transcription
- Fusion
- Protease inhibitors

HIV attachment and fusion: Targets for inhibition

- CD4 binding
- Coreceptor binding
- Virus-cell fusion
- gp41
- gp120
- V3 loop
- Enfuvirtide
- CD4
- Coreceptor binding

CCR5/CXCR4

Maraviroc

Enfuvirtide

CD4+ T-cell targets

Fusion with viral entry

T20 peptides prevent conformational change and prevent the hairpin structure

Fusion is prevented and viral entry is blocked

Harrigan, et al. XV IAC, 2004
HIV Life Cycle

- gp120-CD4 binding
- Co-receptor binding
- Integration
- Reverse transcription
- Viral transcription
- Processing of viral proteins/RNA
- Integration inhibitors
- Protease inhibitors
- Fusion inhibitors
- CCR5 antagonists

4 Key Steps in Integration

- Assembly of a stable PIC after reverse transcription of viral DNA
- 3’-end processing
- Strand transfer
- Creation of intact double-stranded DNA
HIV Integrase Mechanism

**HIV Life Cycle**

1. **3'-endonucleolytic processing (3'-EP)**
2. **Strand Transfer (STF)**
   - a. Pre-integration Complex (PIC)
   - b. Targeting to Chromatin by LIGASE
   - c. Host DNA nicked and ligated to viral DNA
3. **Trimming of proviral DNA and gap-filling**
4. **Gap filling**
5. **Integrated Provirus**

**STARTMRK: Virologic and Immunologic Efficacy at Wk 48**

![Graph showing virologic and immunologic efficacy at Wk 48.]

- Patients with HIV RNA < 50 copies/mL (%)
- RAL: 86.1%
- EFV: 81.9%

**HIV Life Cycle**

- Co-receptor binding
- gp120-CD4 binding
- CCR5 antagonists
- Integration Inhibitors
- Reverse transcription
- Fusion inhibitors

**Virologic Control falls sharply with diminished adherence**

- Patients with HIV RNA < 400 copies/mL, %
- Paterson, et al. 6th Conference on Retroviruses and Opportunistic Infections; 1999; Chicago, IL. Abstract #

**Protease Inhibitor**

- A protease inhibitor binds directly to the active site of protease enzyme causing the enzyme to lack and prevents cleavage of virus subunits.
- A drug resistant mutation against a protease inhibitor is an amino acid change that decreases the binding affinity of the drug to the enzyme thus not impairing virus replication.

**Immunopedia.org**
How Quickly Resistance Can Occur Depends on the Viral Load

<table>
<thead>
<tr>
<th>Viral Load</th>
<th>Days Before Mutation Arises</th>
</tr>
</thead>
<tbody>
<tr>
<td>300,000</td>
<td>0.1</td>
</tr>
<tr>
<td>30,000</td>
<td>1</td>
</tr>
<tr>
<td>3,000</td>
<td>10</td>
</tr>
<tr>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>30</td>
<td>1,000</td>
</tr>
</tbody>
</table>

Adapted from Siliciano, 2002

Genetic barrier models

- Small change in IC50 per mutation
  - BUT
  - Low IQ

- High IQ
- Large change in IC50 per mutation
- AND
- High IQ

Antiretroviral Class Characteristics

<table>
<thead>
<tr>
<th>Class</th>
<th>Potency</th>
<th>Genetic Barrier</th>
<th>Toxicity</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTI</td>
<td>Moderate</td>
<td>Variable</td>
<td>Low</td>
<td>Good</td>
</tr>
<tr>
<td>NNRTI</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Good</td>
</tr>
<tr>
<td>PI</td>
<td>High</td>
<td>High</td>
<td>Moderate</td>
<td>Fair</td>
</tr>
<tr>
<td>Fusion</td>
<td>High</td>
<td>Very low</td>
<td>Low</td>
<td>Poor</td>
</tr>
<tr>
<td>CCR5</td>
<td>High</td>
<td>Moderate</td>
<td>Low</td>
<td>Good</td>
</tr>
<tr>
<td>INSTI</td>
<td>High</td>
<td>Low (now)</td>
<td>Low</td>
<td>Excellent</td>
</tr>
</tbody>
</table>

NRTI: Nucleos(t)ide reverse transcriptase inhibitor
NNRTI: Non-nucleoside reverse transcriptase inhibitor
PI: Protease inhibitor
CCR5: Chemokine co-receptor antagonist
INSTI: Integrase strand transfer inhibitor

Developing Resistance

Developing Resistance
Developing Resistance

Example of Slow, Stepwise Appearance of Mutations in Subjects With Virologic Rebound

Summary

- ART restores health and longevity in infected persons
- ART does not normalize all morbidity and mortality of HIV
- ART reduces transmission and risk of infection in exposed individuals
- ART has some short and long term toxicity
- Efficacy is limited by drug resistance
- ART has yet to reduce the latent reservoir or eradicate infection
Faster, Better and Shorter: The Current Revolution in Hepatitis C Treatment

Annie Luetkemeyer, MD
UCSF Mini-Medical School
HIV/AIDS Division
San Francisco General Hospital

Disclosures
I have received research grant support to UCCSF related to HCV from the following
• Bristol Myers Squibb
• Gilead
• Pfizer

Goals of this activity
• Changing paradigms in HCV treatment with availability of new HCV drugs: FDA approved and in clinical trials
• What to do NOW for HCV-coinfected patients?
• Who should be treated, who can wait?

Hepatitis C in the US
• Estimated 4-5 million people infected
• 80% of those infected don’t know it
• 75% of infections in Baby boomers (born 1945-1965)
• One of leading causes of liver transplantation in US
• HCV-related mortality rising and by 2007, superceded HIV as cause of death in US (15,000/yr)

The old standard:
Interferon + Ribavirin

<table>
<thead>
<tr>
<th>Genotype 1</th>
<th>Genotype 2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>12 months</td>
<td>6 months</td>
</tr>
<tr>
<td>Cure rate</td>
<td></td>
</tr>
<tr>
<td>40-50%</td>
<td>80%</td>
</tr>
</tbody>
</table>

• Side effects: substantial
• Contraindications: decompensated liver disease, severe depression

HCV Paradigm is changing

<table>
<thead>
<tr>
<th>OLD PARADIGM</th>
<th>NEW PARADIGM</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV only affects the liver</td>
<td></td>
</tr>
<tr>
<td>Advanced fibrosis required to increase mortality</td>
<td></td>
</tr>
<tr>
<td>IFN-based treatment: long, poorly tolerated and low cure rates</td>
<td></td>
</tr>
<tr>
<td>HCV Treatment is the exception</td>
<td></td>
</tr>
</tbody>
</table>
Glossary

- **DAA**: Direct Acting Agent. Anti-HCV medications that target specific aspects of HCV viral replication
- **PEG**: Pegylated interferon
- **RBV**: Ribavirin
- **PR**: PEG + ribavirin
- **Genotype**: Strains of HCV that affect treatment response (1-6)
  - Genotypes 1 & 4 harder to cure than 2 & 3
- **IL28b**: human gene that contributes to response to IFN-based treatment
  - Response from best to worst: CC > CT > TT

Glossary (2)

- **SVR**: Sustained virologic response (HCV viral load undetectable off of treatment) SVR_{12} and SVR_{24} considered cures
- **Null response**: Failure to attain at least 2 log_{10} drop in HCV after 12 weeks of treatment
- **Response Guided Therapy**: Shortening therapy based on good early virologic response (1st 12 weeks)

Overview of HCV Directly Acting Agents (DAAs)

**Protease inhibitors (NS3A)**
- **Examples**: Boceprevir, Telaprevir
- **Many others**

**NS5A inhibitors**
- **Examples**: BMS 790052 ("Daclatasvir")
- **Gilead 5885**

HCV Lifecycle

![HCV Lifecycle Diagram](image-url)
Interferon Sparing Regimens

Snapshot of the current state of drug development

IFN may still have a role to play...
12 weeks of 3 DRUGS: IFN/RBV+Polymerase inhibitor

Better Response in IL28b CC vs. non-CC

M11-652: Three Oral DAA’s + RBV
Genotype 1

AI444-014: 2 Oral Agents +/- RBV
Genotypes 1,2,3

KEY:
SOF = GS7977 [polymerase inhibitor]
DCV = Daclatasvir [NS5A inhibitor]
DCC = DCV + SOF
### Electron: Polymerase Inhibitor + RBV +/- IFN

**Genotypes 2 & 3**

**Electron: Genotype 2/3 Cohorts**

<table>
<thead>
<tr>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 10</td>
<td>SOF + PEG + RBV</td>
<td>SOF + RBV</td>
<td>100% SVR</td>
</tr>
<tr>
<td>n = 10</td>
<td>SOF + PEG + RBV</td>
<td>SOF + RBV</td>
<td>100% SVR</td>
</tr>
<tr>
<td>n = 11</td>
<td>SOF + RBV</td>
<td>SOF + RBV</td>
<td>100% SVR</td>
</tr>
<tr>
<td>n = 10</td>
<td>SOF</td>
<td>SOF</td>
<td>60% SVR</td>
</tr>
</tbody>
</table>

**KEY**
- SOF: Sofosbuvir (formerly GS-7977)
- 100% SVR when given with IFN

**Electron: Polymerase Inhibitor + RBV**

**Genotypes 2 & 3**

**Electron: Genotype 2/3 Cohorts**

<table>
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<td>n = 11</td>
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</tr>
<tr>
<td>n = 10</td>
<td>SOF</td>
<td>SOF</td>
<td>60% SVR</td>
</tr>
</tbody>
</table>

**Polymerase Inhibitor + RBV: Genotype 1**

**12 weeks treatment**

**Patients with HCV RNA <LOD> over Time, n/N (%)**

<table>
<thead>
<tr>
<th></th>
<th>Treatment-naive (n = 25)</th>
<th>Null responder (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>3/25 (12)</td>
<td>1/10 (40)</td>
</tr>
<tr>
<td>Week 2</td>
<td>17/25 (68)</td>
<td>7/10 (70)</td>
</tr>
<tr>
<td>Week 4</td>
<td>25/25 (100)</td>
<td>10/10 (100)</td>
</tr>
<tr>
<td>EOT</td>
<td>25/25 (100)</td>
<td>10/10 (100)</td>
</tr>
<tr>
<td>SR/R4</td>
<td>22/25 (88)</td>
<td>1/10 (10)</td>
</tr>
<tr>
<td>SR/R2</td>
<td>21/25 (84)</td>
<td>1/10 (10)</td>
</tr>
</tbody>
</table>

**100% SVR**
- Treatment-naive
- Null responder

**84% SVR**
- 10% SVR

**Interferon Sparing Regimens: When?**

- Still active clinical trial development
- Anticipate FDA filing for Sofosbuvir for genotype 2/3 in 2013, genotype 1’s 2014
- HIV-HCV studies lag behind HCV monoinfected studies
  - Drug-drug interactions with ART
  - Unclear if response rates will be worse in HIV-HCV coinfection

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**IFN-sparing regimen: Hope**

- All oral, interferon-sparing treatment with cure rates > 90% will be a reality
  - 12 weeks in genotypes 2,3
  - 12-24 weeks in genotype 1
- Ribavirin may still be part of some of these regimens
- Better response in genotypes 2/3, as well as genotype 1b>1a
- IL28b genotype may still predict response- need more regimen specific data
Timing of HCV treatment
• All oral, IFN sparing therapy on the horizon but at least a year away, likely longer

Current Treatment Options for Genotype 1

### Telaprevir (HCV protease inhibitor) + PEG/RBV

<table>
<thead>
<tr>
<th>Treatment Naive, No HIV infection</th>
<th>Treatment Naive, HIV-HCV coinfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>% SVR</td>
</tr>
<tr>
<td>TP = 69</td>
<td>75</td>
</tr>
<tr>
<td>TVR = 44</td>
<td>45</td>
</tr>
<tr>
<td>TP2PR = 26</td>
<td>24</td>
</tr>
<tr>
<td>TVR2PR = 35</td>
<td>31</td>
</tr>
<tr>
<td>SOC = 31</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Naive, HIV-HCV coinfected</th>
</tr>
</thead>
<tbody>
<tr>
<td>% SVR</td>
</tr>
<tr>
<td>TP = 64</td>
</tr>
<tr>
<td>TVR = 45</td>
</tr>
</tbody>
</table>

### Boceprevir (HCV protease inhibitor) + PEG/RBV

<table>
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<th>Treatment Naive, No HIV infection</th>
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<tbody>
<tr>
<td>Overall</td>
<td>% SVR</td>
</tr>
<tr>
<td>TP = 64</td>
<td>66</td>
</tr>
<tr>
<td>TVR = 38</td>
<td>45</td>
</tr>
<tr>
<td>TP2PR = 26</td>
<td>24</td>
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<tr>
<td>TVR2PR = 35</td>
<td>31</td>
</tr>
<tr>
<td>SOC = 31</td>
<td>44</td>
</tr>
</tbody>
</table>

### Genotype 1 considerations

**Treatment Naives:** 60-75% SVR with 48 weeks of PEG/IFN + HCV protease inhibitor
- Shortened “response guided therapy” possible in about 50%

**Treatment experienced:** Important to know prior response to interferon as well as how well tolerated
- Relapsers did just as well as treatment naives
- Consider for partial responders = 50% SVR
- Would expect low SVR in null responders - strongly consider waiting (or clinical trial)
Genotype 1: Recommendations for treating now with IFN-based regimen

- Evidence of advanced fibrosis by imaging or biopsy
- Prior treatment with IFN-based regimen with relapse or prior partial response and willing to retreat
- No evidence of fibrosis but motivated to take IFN-based regimen and no contraindications to PEG:
  - Severe psychiatric disease
  - Life expectancy < 5 years
  - Prior decompensated hepatic disease (ascites, bleeding varices, encephalopathy)

Current Treatment Options for HCV Non-Genotype 1

Non-Genotype 1

- **No** current DAA 3rd agent to add on to PEG/RBV for non-genotype 1
  - Telaprevir/Boceprevir only for use in genotype 1
- **Genotype 2/3**: SVR rate with PEG/RBV x 48 weeks: 80%
  - Consider PEG/RBV for motivated patients and those with evidence of advanced fibrosis
- **Genotype 4**: Similar SVR with PEG/RBV to genotype 1: 40-50%
  - Given worse response with PEG/RBV alone, consider waiting until DAAs available with Geno 4 activity to add on to IFN/RBV

If patient is waiting to treat HCV...

- Review reduction in HCV transmission risk to others
  - Safe injection practices
  - Safer Sex
  - Household precautions
- For patients with cirrhosis
  - HCC screening with yearly imaging
  - EGD to evaluate for varices
  - Discussion of liver transplantation and current barriers (smoking, substance use, etc.)

HCV Clinical trials

<table>
<thead>
<tr>
<th>STRENGTHS</th>
<th>LIMITATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to new DAA agents prior to FDA approval</td>
<td></td>
</tr>
<tr>
<td>Access to treatment shortening strategies</td>
<td></td>
</tr>
<tr>
<td>Access to IFN-sparing treatment</td>
<td></td>
</tr>
<tr>
<td>Medications usually provided free of charge</td>
<td></td>
</tr>
</tbody>
</table>

Summary

- Incredibly exciting time for HCV treatment
- Challenging to keep up with rapid pace of drug development
- Interferon-sparing regimens are coming but unlikely to be a reality at least 1 year, likely longer for HIV-HCV
Acknowledgements

• Brad Hare
• Diane Havlir
• Val Robb
• Our Wonderful HCV coinfection Clinic staff
• Anna Smith and Jay Dwyer

References

• Rice et al “New Insights into HCV Replication: Potential Antiviral Targets” Topics in HIV Med 2011:19(3);117
• Ghany M “Update on Treatment of Genotype 1 Chronic HCV” Hepatology 2011: 54(4) 1433 (AASLD Guidelines)

Resources

• Clinical trial resource: www.clinicaltrials.gov
• Liverpool HCV Drug Interaction database http://www.hep-druginteractions.org/
• SFGH HCV treatment website: http://www.sfaetc.ucsf.edu/programs/sf_hepatitis_c_a_primary_care_initiative/
• Patient Education Resources: http://www.hcvadvocate.org/

Resources (2)

• AASLD 2011 Treatment guidelines
• EASL treatment guidelines
• www.natap.org
• Clinical Care Options CCO : http://www.clinicaloptions.com/Hepatitis.aspx