Management of Co-occurring Conditions

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Outline

- Mental health disorders
- Substance abuse/dependence
- Sexually transmitted diseases
- Hepatitis C
Commonly Seen Psychiatric Disorders in PLWHIV (Persons Living with HIV/AIDS)

- Mood Disorders – Depression is most common (clinical or situational?)
- Adjustment Disorders
- Anxiety Disorders
- Substance Use Disorder
Co-occurring Disorders

- Individuals are said to have COD if they have a Psychiatric Disorder as well as a Substance Use Disorder (SUD)

- It can be difficult to establish which came first. Why?
Where do You Start?

- Both disorders must be treated, however it may be more efficacious to treat one before the other.

- Providers must be aware of the complexities of treating co-occurring disorders and MUST rely on their MH or Addictions Tx counterparts to effectively treat (Like MH providers, Addictions Tx providers must carry certification (state at minimum).

- Acknowledgement of patient’s rights and belief in his/her ability to change.

- Cultural competency a must-Examples?
No Wrong Door

- No Wrong Door philosophy is *vital*. What does this mean, not just for our patients but for us as providers?

- (Willingness to work with COD, awareness of resources, awareness of scope of practice – ASAM requires majority of SUD treatment providers be cross-trained)
PSYCHIATRIC ILLNESS IN HIV/AIDS

- HIV Associated Dementia (HAD)
- Delirium
- Psychotic Disorders
- Mood Disorders
- Anxiety Disorders
- Substance Abuse and Dependence
HIV ASSOCIATED DEMENTIA

- 15-20% of AIDS patients
- Combination of motor, cognitive and mood/personality changes
- Insidious onset, CD4 count < 200 cells/ul
- CSF Beta-2-microglobulin > 3.8 mg/dL, HIV-1 RNA >10,000/ml
DELIRIUM

- Disturbance of consciousness with attention problems
- Change in cognition or development of a perceptual disturbance
- Acute onset with fluctuating course
- Underlying etiology
  - fever/infection, trauma, metabolic, meds/drugs, other cause(s)
DELIRIUM

- Common in later stages of disease, 30-60% of patients
- Often confused with dementia and depression
- Associated with poor outcomes - mortality, long term care, longer hospitalization
- Treatment of choice is haloperidol unless etiology is alcohol/benzodiazepine withdrawal
PSYCHOTIC DISORDERS

- Substance induced during intoxication or withdrawal
- Medical illness induced
  - must be distinguished from delirium
  - late stage HIV associated dementia
MOOD DISORDERS

- Bipolar disorder - 8% of outpatients

- Major depressive episode
  - 6-10% current and 20-35% lifetime
  - similar to other medically ill populations

- Substance induced mood disorder

- Medical illness induced
  - must distinguish from dementia, hypoactive or hyperactive delirium
ANXIETY DISORDERS

- 2 to 38% of patients depending on stage of illness
- Panic disorder
- Adjustment disorder
- Substance induced due to intoxication or withdrawal
- Medical illness induced, e.g. untreated pain
SUICIDE ASSESSMENT

- Gender: M > F
- Age: 15-25 years and > 45 years
- Ethnicity: Caucasian (Black, Hispanic, Native American)
Suicidality Assessment

- Suicide plans, means and intent
- Delusions and command hallucinations
- Impulsivity or impaired judgment of cognition
- History of suicidal or homicidal behavior
SUICIDE ASSESSMENT

- Family history
  - suicide, early parental loss, mood disorder, chaos
- Psychiatric illness
  - auditory hallucinations, mood disorder, substance use, prior attempts
- Medical illness
  - acute v chronic, terminal, pain, medications
SUICIDE ASSESSMENT

- Behavioral factors
  - Changes in behavior
  - Messages saying goodbye
  - Social isolation

- Lethality
  - Access to means
  - Method of attempt
  - Possibility of rescue
  - Thorough plan
  - Prior attempts
SUICIDE ASSESSMENT

- HIV/AIDS Risk Factors
  - Stage of disease
  - Number of AIDS related losses
  - Social isolation
  - Disease progression/fear of progression
  - Uncontrolled pain
  - Experience with HIV-related suicide
SUICIDE INTERVENTIONS

- Medication/hospitalization
- Address contributing factors
- Encourage expression of feelings/thoughts
- Promote sense of self control
- Build alternative coping strategies
- Educate patient and family
- Develop a crisis plan
TREATMENT

- Psychotherapy
  - supportive, interpersonal, cognitive-behavioral, group, psychoeducational
  - ongoing risk of crises
  - countertransference issues
    - homophobia, sex, substance use, existential beliefs, rescue fantasies, identification, therapeutic nihilism, guilt, fear of contagion
TREATMENT

- Pharmacotherapy
  - Antidepressants
    - SSRIs          Paroxetine, Sertraline, Fluoxetine
    - TCAs           Nortriptyline, Desipramine
    - Other          Nefazodone, Venlafaxine, Mirtazapine
  - Stimulants
    - Methylphenidate
    - Dextroamphetamine
  - Testosterone
TREATMENT

- Pharmacotherapy
  - Antipsychotics
    - typical haloperidol
    - atypical risperidone, olanzapine
  - Antianxiety agents
    - benzodiazepines
  - Mood stabilizers
    - lithium, valproic acid, carbamazepine
MEDICATION INTERACTIONS

- Multiple medications
- Multiple medical illnesses
- Renal or hepatic disease
- Elderly
- Individual differences in liver metabolism
- Specific liver metabolism inhibitors
CHOOSING MEDICATIONS

- Adverse effects
- Interactions with other medications/drugs
- Metabolism via liver
- Elimination via liver or kidney or both
- Time to expected *onset* of action
- Expected *duration* of action
- “Less is better”
Substance Abuse

- recurrent use in setting of failure at work, home or school
- use in physically hazardous settings
- recurrent legal problems
- recurrent social or interpersonal problems
Substance Dependence

- tolerance/withdrawal
- larger amounts/longer period of time
- unable to cut down or control use
- time spent obtaining drug or recovering from it
- love, work or play compromised
- use in setting of physical/psychological problems
Use the CAGE to Assess for Alcohol Abuse/Dependence

- Have you ever tried to cut back on your drinking?
- Have you ever been angry or annoyed because someone said something about your drinking?
- Have you ever felt guilty about your drinking?
- Have you ever needed an eye-opener?
Use ADEPT RAFFT for to Assess for Alcohol or Drug Abuse/Dependence with Adults and Teens

- Do you use alcohol or drugs as a way to relax, feel better about yourself or fit in?
- Do you ever drink or use drugs while you are alone?
- Do you or any of your closest friends drink or use drugs?
- Do you have a close family member who has an alcohol or drug problem?
- Have you ever been in trouble because of drinking or drugs?
Time

- Often substance abusers fail to recognize symptoms of disease and seek Rx only when they become acutely ill or emergent, thus prolonging the transmission period to uninfected partners.

- HIV or Hep C may be asymptomatic for many years (HIV-10 years), (Hep C- 20 years) so many partners may be infected.

- “Processing time” (denial, etc.)
Developing Treatment Plans for Patients with Significant COD

- Concentrate on setting limits – why?
- Consider the use of behavioral contracts
- Make all staff aware of the contract – why?
- Use a healthcare network/team to provide care
- Focus on long term goals, not immediate rewards
- Educate staff!

Sellers, M. 2010
Consider Possibility of PTSD
(Not just HIV but also SUD)

- Alterations in affect regulation (blocking)
- Alterations in consciousness (numbing)
- Alterations in self-perception (dirty)
- Alterations in relations with others (isolation)
- Alterations in systems of meaning (church)
- Proposed in DSM V alterations in perception of perpetrator
Relapse

- Relapse is common and must not be considered a failure (~90% in 1st 4 years w/ ETOH; 60% in first 4 weeks-all substances)

- Relapse may be preventable in an “ideal world”, but sadly, for our patients, it is likely inevitable

- Community support groups (AA, NA) remain the most effective, focused and economical method of relapse prevention

- Relapse is rarely a sudden event; it is a sequence that, with proper intervention and willingness on the part of the individual may (but not always) be averted
Relapse (cont’d.)

- “Stinking thinking”
- HALT - Hunger, Anger, Loneliness, Tired (but can also be joy, wealth, etc. i.e. many emotional “Danger Zones”)
- Social Danger Zones
- Specific Personal Danger Zones
<table>
<thead>
<tr>
<th>LEVELS OF CARE</th>
<th>I. OUTPT</th>
<th>II. INTENSIVE OUTPT</th>
<th>III. MED MON INPT</th>
<th>IV. MED MGD INPT</th>
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<tbody>
<tr>
<td>CRITERIA</td>
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<td></td>
<td></td>
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<tr>
<td>Withdrawal</td>
<td>no risk</td>
<td>minimal</td>
<td>some risk</td>
<td>severe risk</td>
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<tr>
<td>Medical Complications</td>
<td>no risk</td>
<td>manageable</td>
<td>medical monitoring required</td>
<td>24-hr acute med. care required</td>
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<tr>
<td>Psych/Behav Complications</td>
<td>no risk</td>
<td>mild severity</td>
<td>moderate</td>
<td>24-hr psych. &amp; addiction Tx required</td>
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<tr>
<td>Readiness For Change</td>
<td>cooperative</td>
<td>cooperative but requires structure</td>
<td>high resist., needs 24-hr motivating</td>
<td></td>
</tr>
<tr>
<td>Relapse Potential</td>
<td>maintains abstinence</td>
<td>more symptoms, needs close monitoring</td>
<td>unable to control use in outpt care</td>
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<tr>
<td>Recovery Environment</td>
<td>supportive</td>
<td>less support, w/ structure can cope</td>
<td>danger to recovery, logistical incapacity for outpt</td>
<td></td>
</tr>
</tbody>
</table>

The ASAM Patient Placement Criteria (PPC): Design, Validation, and Technology Transfer, DR Gastfriend MD, E Sharon PsyD, R Lefebvre PhD, SS Kang MD
Essential Elements of Programs Meeting ASAM Criteria

- MD and PhD level staff skilled in Dx and referral
- A majority of staff are cross-trained to deal with SA and MH disorders
- Psycho-educational components of Tx address both SA and MH disorders
- A psychiatrist is available on site in acute settings and through coordination in all other settings
- Medication management is integrated into the Tx plan
- Counselors and nursing staff are trained to monitor and promote compliance with pharmaco-therapies
- In programs that work with severely mentally ill persons, intensive CM and assertive community Tx services are available
Motivational Interviewing

- A directive, patient/client centered counseling style for eliciting behavior change by helping them explore and resolve ambivalence.

- Begins with the supposition that patients/clients come to the process with a basic capacity for actualization of a positive self and are responsible for creating change.

- Therapist’s role: create conditions shown to enhance likelihood that a patient/client will engage in efforts to change behavior.

Source: Rollnick & Miller, 1995
The Four Parts of Motivational Interviewing

- **Express empathy** - reflective listening clarifies and enhances the patient’s/client’s thinking, helps build a working alliance and supports patient’s exploration of his/her ambivalence about change
  
  - Empathetic therapist style has been shown to be a predictor of decreased patient resistance  

What Empathy Is

- According to *Miller and Rollnick, 1991*, empathy is a specifiable and learnable skill for understanding another’s meaning through the use of reflective listening, i.e. letting them know you’re on the same page by “reflecting back” what they’ve said.

  - Communicates respect for and acceptance of patients and their feelings.
  - Encourages a nonjudgmental, collaborative relationship.
  - Allows you to be supportive.
  - Listens rather than tells.
  - Sincerely complements rather than put down.
  - Gently persuades, keeping the understanding that the decisions about change are the patient’s.
  - Is NOT identifying with the patient.
  - Accepts that ambivalence is normal.
  - Example: “I don’t know why my wife is making such a big deal about this. I don’t have a drinking problem” - Your wife has some issues with how much you drink.
What Empathy is *Not*

- Ordering, directing or *even giving advice* (if I were you, I would think about or maybe you should think about)
- Trying to persuade with logic, arguing or lecturing
- Warning or threatening
- Moralizing, preaching or telling patients their “duty”
- Judging, criticizing or blaming
- *Agreeing, approving or praising inappropriately*- These can shut down further communication
- Shaming, labeling
- Interpreting, analyzing, supplying answers
- Reassuring, sympathizing or consoling
- Questioning or probing
- Withdrawing, or using humor to distract
The Four Parts of Motivational Interviewing (con’t)

- **Develop discrepancy**
  - Develop awareness of discrepancy between where patient/client is and where he/she wants to be

- **Roll with resistance**
  - Just as empathetic style as been shown to reduce resistance, confrontational style has been shown to not only increase likelihood of resistance but also to be predictive of increased drinking at the end of a 12 month follow up.

Source: Miller and Rollnick, 1991
The Four Parts of Motivational Interviewing (con’t)

- **Support self-efficacy**
  - Remember that the patient/client is responsible for choosing and implementing change
  - Develop awareness of supports
  - Talking about how they would go about changing and what it might look like makes patients more likely to view those changes as realistic options

Considerations When Referring Clients into Tx Programs

- Access to medical care & follow up
- How will their medications be supplied?
- If referring out of state, what is that state’s ADAP status?
- Possible loss of Medicaid
Gorski’s Developmental Model of Recovery

1) **Transition:** Recognizes problems but tries to surmount them by controlling substance use

2) **Stabilization:** Individual decides to refrain from substance use completely and improves over an extended period of time (6-18 mos.)

3) **Early recovery:** Individual becomes comfortable with abstinence

Source: Gorski, 1989
Gorski’s Developmental Model of Recovery

4) **Middle Recovery:** Individual repairs past damages caused to others by AOD use and develops balanced lifestyle

5) **Late Recovery:** Individual overcomes barriers to healthy life that stem from childhood experiences

6) **Maintenance:** Individual recognizes need for continued growth and balanced life

Source: Gorski, 1989
Additional Resources

- www.daodas.state.sc.us
- www.nida.nih.gov
- www.samhsa.gov
- http://sbirt.samhsa.gov/
Overview

- Importance of diagnosis and treatment of STDs
- 2010 Treatment Guidelines
  - Clinician’s role in STD prevention
  - Highlights of key recommendations
  - Important changes from 2006 guidelines
Why Diagnose and Treat STDs?

- > 19 million STDs occur in the US annually
- Health consequences of untreated STDs
  - Women’s reproductive health
    - Untreated CT or GC may lead to PID
    - Leading infectious cause of infertility in the US
  - Infant mortality/morbidity
    - Neonatal HIV, HSV and congenital syphilis
  - HIV transmission
- Health care cost
  - $16.4 billion (2009)*

*Estimate incorporates minor corrections in the Persp Sex Rep Hlth 2009
Populations at Greatest Risk for STDs

- **Youth**
  - ~50% of STDs occur in 15-24 years old

- **Racial/ethnic minorities**
  - STDs among highest of all racial/ethnic health disparities
  - AA 71% GC, 48% CT, 52% syphilis
  - Over last 5 years syphilis cases increased more than 150% among young African American men.

- **MSM**
  - Accounted for 62% of syphilis cases in 2009
  - High rates of HIV co-infection
STD Prevention: Clinician Role (1)

- Talk to patients about pre-exposure vaccination
- Provide referral for prevention/risk reduction counseling
- Talk to patients about testing
- Assess patients’ risk and test accordingly
STD Prevention: Clinician Role (2)

- Diagnose and treat infected patients
- Provide or refer for partner management/services
- Report STDs and HIV in accordance with state and local statutory requirements
- Keep STD/HIV report confidential
STD Screening: Follow up visits

- Periodic retesting for all sexually active patients
- Annually for all
- More frequent (3-6 months) depending on risk:
  - Multiple or anonymous partners
  - UAI or UVI with partners
  - Sex or needle sharing with partners with above risks
  - “Life changes” associated with increased risk
Case 1

- 44 year old female who routinely donates blood every 3-4 months. Last donation in 12/09 w/o report.
- Donated again in 2/6/10 with report of positive TPPA.
- Referred to health department. No history of ever having or being treated for syphilis. No sex in past 10 years.
- Benign physical examination and stat RPR non-reactive that day.
Case 1 (continued)

- Health department RPR returned negative, TPPA positive.
- What is her diagnosis?
- Next clinical / laboratory step?
- Should she be treated? With what?
Syphilis

- Definitive diagnosis for early syphilis
  - darkfield microscopy; PCR
  - No commercially available Treponema pallidum detection tests
- Nontreponemal/treponemal serologic testing
  - Reverse serologic screening
- Management principles for HIV+ similar
  - Frequent clinical/serologic monitoring
- Neurosyphilis can occur at any stage
Syphilis EIA/CLIA

- Some labs are moving to a new testing algorithm: screening EIA followed by confirmatory RPR if the EIA is positive

  MMWR. 2008;57(32):872

- Treponemal test FDA cleared for clinical use

- Both IgG and IgM test are available
  - No clinical value of IgM in adult early syphilis diagnosis

- Highly automated, occupational advantage (no pipette), less costly, no prozone
Consequences of Automated EIA Syphilis Screening

- Many more EIA test positive / RPR test negative cases are being identified.
  - False positive in low prevalence population
- Treponemal tests remain positive for life in 85% of treated syphilis cases so many more of these individuals also are being identified.
Diagnostics: The Positive EIA & Negative RPR Dilemma

- The possibilities for a positive EIA & negative RPR test include:
  - Adequately treated past syphilis
  - Untreated syphilis of long-standing duration
  - Early syphilis [unlikely but possible]
  - False-positive treponemal test [if the pre-test probability for syphilis is low, up to 50% of positive treponemal tests may be FALSE positives]
Addressing a Positive EIA & Negative RPR

- Approach to the patient with a positive treponemal test but a negative reagin test.
  - Take a careful history
  - If there is no history of treatment or if in doubt, treat for late latent syphilis.
  - Counseling – infectivity is very low but partners should be tested.
  - Repeat testing using a different treponemal test
  - If second treponemal test is also positive, treat for stage-appropriate infection
Pharyngeal & Rectal Gonorrhea

- Studies suggest that up to 65% of cases of GC and 50% of cases of CT in MSM would be missed if genital only testing is performed
  - *Sex Transm Dis.* 2008;35(10):845  

- Omitted rectal screening of MSM resulted in substantial missed cases in SF STD clinic

- Pharynx may be a major reservoir for GC; role of CT unclear and testing not recommended
NAATs Extragenital Sites

- NAATs perform better than culture (rectal/pharynx)
- Commercial laboratories validate NAATs
- Most infections asymptomatic
- Self-collected vaginal swab preferred specimen in women
- Urine preferred specimen in men
## NAAT Laboratory Ordering and Billing Codes

<table>
<thead>
<tr>
<th>Company-Specific Ordering Codes for Combined GC/CT Nucleic Acid Amplified Tests (NAATs)</th>
<th>Company-Specific Ordering Codes for CT test only</th>
</tr>
</thead>
<tbody>
<tr>
<td>LabCorp*</td>
<td>Quest*</td>
</tr>
<tr>
<td>Rectal</td>
<td>188672</td>
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<tr>
<td>Pharyngeal</td>
<td>188698</td>
</tr>
</tbody>
</table>

NAATs are offered at (or from) any location in the country with these two codes.

For information on specimen collection and transportation, clinicians should contact the local reference laboratory representative.

## CPT Billing Codes

<table>
<thead>
<tr>
<th>CPT Billing Codes</th>
<th>Code</th>
</tr>
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<tbody>
<tr>
<td>CT detection by NAAT</td>
<td>87491</td>
</tr>
<tr>
<td>GC detection by NAAT</td>
<td>87591</td>
</tr>
</tbody>
</table>
STD Screening in MSM

- HBsAg to detect current infection
- Hepatitis A and B vaccination if non-immune
- Hepatitis C virus sexual transmission (HIV+ MSM)
  - HCV serology at initial visit
  - HCV RNA with unexplained ALT rise
  - Routine HCV testing with high risk sexual behavior and ulcerative STDs
  - Prevention (condoms) at sites of penetration
Urethritis

- Bacterial STDs: GC (5-20%), CT (15-40%)

- Nongonococcal Urethritis (NGU)
  - *Mycoplasma genitalium* 5-25%
  - *Ureaplasma* 0-20%; data inconsistent, biovars differ
  - *Trichomonas vaginalis* 5-20% (age, geography)
  - HSV 15-30%; urethritis in primary infection
  - Adenovirus, enteric, candidiasis and anaerobes
Mycoplasma genitalium

- Association with acute or persistent NGU
- Conflicting/insufficient evidence: cervicitis, PID, infertility, ectopic pregnancy, adverse birth outcomes
- Azithromycin superior to doxycycline for MG urethritis
- Moxifloxacin for persistent NGU
NGU Treatment

- Current drug regimen is adequate
  - Azithromycin or doxycycline

- Cost consideration and lack of public health impact data for MG insufficient to demote doxycycline to alternative regimen

- Recurrence
  - Re-exposure from untreated partners
  - *T. vaginalis* and *M. genitalium*
  - *U. Ureaplasma* may account for some failures
Cervicitis

- CT/GC NAATs-vaginal, cervical, urine
- No new antimicrobial treatment trials
- Research needed on the etiology of persistent cervicitis including the potential role of *Mycoplasma genitalium*
Cervicitis Treatment

- Presumptive vs awaiting results
- Treat for CT (<25 y.o.; new or multiple partners; unprotected sex) and GC (if prevalence >5%)
- Trichomoniasis and BV should also be treated if detected
Chlamydia

- Primary focus of screening efforts to detect and prevent complications in women
- Selective male screening (adolescent clinics, corrections, national job training program, < 30 yrs, STD, military)
- Retest women/men 3 mo post treatment
  - CT testing in third trimester (reinfection)
## Gonorrhea

- **Screen sexually active women at increased risk (USPSTF)**
  - <25 years
  - Previous GC or other STDs
  - Commercial sex work
  - New or multiple partners
  - Inconsistent condom use
  - Drug use

- **No screening in men or women at low risk of infection (USPSTF)**

- **Retest women/men 3 mo after treatment**
Gonorrhea Treatment Efficacy

- **Anogenital**
  - Ceftriaxone
    - 125 mg = 98.9%
    - 250 mg = 99.2%
    - Geographic distribution *in vitro* decreased susceptibility, ceftriaxone failures, enhanced pharyngeal efficacy, consistent guidance at all anatomic sites

- **Oropharyngeal**
  - Ceftriaxone
    - 125 mg = 94.1%
    - 250 mg = 98.9%
  - Oral cephalosporins limited (poor penetration)
  - Azithromycin 2 gm = 95%
  - + oral exposure- regimen with enhanced pharyngeal efficacy
Anogenital GC Treatment

• **Recommended**
  – Ceftriaxone **250 mg** IM (preferred)
    • PLUS azithromycin 1 gm or doxycycline 100 mg bid x 7
  – Cefixime 400 mg PO (if ceftriaxone is not an option)
    • PLUS azithromycin 1 gm or doxycycline 100 mg bid x 7

• **Alternatives**
  – Cefpodoxime 400 mg or cefuroxime axetil 1 g
  – Azithromycin 2 g (penicillin allergy)
Oropharyngeal GC Treatment

- **Recommended**
  - Ceftriaxone **250 mg** IM

- **Alternatives**
  - Azithromycin 2 g (penicillin allergy)
Dual Treatment of Gonorrhea is now Standard of Care

- Is *Neisseria gonorrhoeae* Initiating a Future Era of Untreatable Gonorrhea?: Detailed Characterization of the First Strain with High-Level Resistance to Ceftriaxone†
  - ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2011, p. 3538–3545

- CDC now recommends dual therapy for gonorrhea with a cephalosporin (ceftriaxone 250 mg) plus either azithromycin or doxycycline
Lymphogranuloma Venereum (LGV)
Chlamydia: Serological Classification

- A, B, Ba, C (Trachoma)
- D-K (Genitourinary and ocular infections)
- L1-L3 (Lymphogranuloma venereum)
Clinical Manifestation

- **Heterosexuals**
  - Tender inguinal and/or femoral lymphadenopathy that is typically unilateral
  - A self-limited genital ulcer or papule sometimes occurs at the site of inoculation
  - Lesion may disappear by the time the patient seeks treatment

- **MSM and women with rectal exposure**
  - Protocolitis (mucoid/hemorrhagic rectal discharge, anal pain, constipation, fever, and/or tenemus
  - May lead to chronic, colorectal fistulas and strictures
  - Secondary bacterial infections
  - Co-infection with other STD
Resurgence of LGV in N. America & Western Europe

Histology: Mucosal ulcers, cryptitis, crypt abscesses and granulomas
Lymphogranuloma venereum (LGV)

- Proctitis presentation (HIV+ MSM)
- Diagnosis
  - Genital or lymph node aspirates-culture, DFA, nucleic acid detection (CLIA validation)
  - Genotyping required for determining LGV strains
  - Serology not validated for proctitis presentation
- Empiric treatment for appropriate clinical syndrome
  - Doxycycline 100 mg PO bid x 21 d
  - Azithromycin 1 g PO q wk x 3 wks (limited data)
Proctitis

- HSV/LGV presumptive treatment - painful perianal or mucosal ulceration
- Consider LGV treatment in MSM with anorectal Chlamydia and either proctitis (anoscope) with >10 wbc/s/high-power field or HIV +
Hepatitis C Virus
Hepatitis C Virus Infection

**Identification of Patients**

- Found to have elevated serum ALT during
  - Routine physical examination
  - Routine blood testing after starting certain medications
- Test positive for anti-HCV during
  - Volunteer blood donation
  - Health or life insurance applications
- Physician
  - Inquires about previous risk behaviors
Role of Frontline Providers in HCV Diagnosis Counseling

- Counsel patients who test positive for HCV infection
  - Prevention of transmission to others
  - Reduce/eliminate alcohol intake
    - Assist with linkage to alcohol/drug addiction treatment if needed
  - Weight management in patients who are overweight
  - HAV vaccination (if no preexisting antibodies) and, if risk factors are present, HBV vaccination (if no preexisting antibodies)

Claudia needs to see her family physician. She wants to be tested for HCV. What test do you recommend?
Diagnostic Tests for HCV

- Anti-HCV
- RIBA (supplemental assay)
- Qualitative PCR
- Quantitative PCR
- Genotyping assays
Viral Hepatitis

Role of Diagnostic Testing

- Identify patients with viral hepatitis infection
  - Previous exposure to hepatitis virus
  - Active infection
  - Inactive infection
  - Resolved infection
- Assess response to therapy
  - Prior to onset of treatment
  - During and following treatment
## Hepatitis C Virus Diagnostic Testing

<table>
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<tr>
<th>Specifications</th>
<th>Serologic</th>
<th>Virologic</th>
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<tbody>
<tr>
<td>Mode of detection</td>
<td>Antibodies</td>
<td>Virus</td>
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<tr>
<td>Sensitivity</td>
<td>&gt; 95%</td>
<td>&gt; 98%</td>
</tr>
<tr>
<td>Specificity</td>
<td>Variable</td>
<td>&gt; 98%</td>
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<tr>
<td>Detection postexposure</td>
<td>2-6 months</td>
<td>2-6 weeks</td>
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<tr>
<td>Use</td>
<td>Screening</td>
<td>Confirmation</td>
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</table>
HCV Antibody Testing

Limitations

- False positives
  - Autoimmune disorders
  - Spontaneous resolution of viral infection

- False negatives
  - Chronically immune suppressed
  - Transplant recipients
  - Chronic renal failure on dialysis
  - HIV positive
Testing for Hepatitis C Virus

*Recombinant Immunoblot Assay*

- Supplemental assay
- Detects circulating antibodies to 4 HCV proteins
- Antigen-antibody reaction
- More specific than anti-HCV enzyme immunoassay
- False positive reaction can still occur
- Largely replaced by HCV RNA testing

Illustration by Mitchell L. Shiffman, MD.
Testing for Hepatitis C Virus

*Indications for HCV RNA*

- Confirm HCV infection
  - Persistently normal serum ALT
  - No risk factors
  - HCV antibody positive
  - Antinuclear antibodies
  - Prior to initiating therapy

- Assess effectiveness of treatment
  - Predict likelihood of response before and during therapy
  - Confirm response after therapy completed
## Testing for Hepatitis C Virus

**Virologic Assays**

<table>
<thead>
<tr>
<th>PCR</th>
<th>TMA</th>
<th>b-DNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymerase chain reaction</td>
<td>Transcription mediated amplification</td>
<td>Branched chain DNA</td>
</tr>
<tr>
<td>Amplifies target</td>
<td>Amplifies target</td>
<td>Amplifies probe</td>
</tr>
<tr>
<td>Qualitative</td>
<td>Qualitative</td>
<td>Quantitative</td>
</tr>
</tbody>
</table>
## Diagnostic Evaluation of HCV Infection

<table>
<thead>
<tr>
<th>Step in Diagnosis</th>
<th>EIA</th>
<th>RIBA</th>
<th>Qualitative PCR</th>
<th>RNA Quantitation</th>
<th>Genotyping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Screening</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Confirmation of HCV Ab tests</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Predicting Rx Response</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Viral response during Rx</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Viral response after Rx</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Determining Rx Length</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
HCV Screening Algorithm

EIA for Anti-HCV

- Negative (non-reactive) → STOP
- Positive (repeat reactive) OR

- RIBA for Anti-HCV
  - Negative → Additional Laboratory Tests (e.g. PCR, ALT)
    - Negative PCR, Normal ALT → STOP
    - Positive PCR, Abnormal ALT
  - Indeterminate

- RT-PCR for HCV RNA
  - Negative
  - Positive

Medical Evaluation

Source: MMWR 1998;47 (No. RR 19)
Diagnosis of Viral Hepatitis in the Primary Care Setting: Patients Who Have Risk Factors

- A single normal ALT level does not rule out chronic viral hepatitis
- ALT levels may be intermittently normal in a significant number of patients who have chronic hepatitis C
## Management of Chronic HCV

### Tests Utilized

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Response to Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST/ALT</td>
<td>ALT</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>HCV RNA</td>
</tr>
<tr>
<td>Albumin</td>
<td>HCV genotype</td>
</tr>
<tr>
<td>Pro-time (INR)</td>
<td>Liver histology</td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
</tr>
<tr>
<td>Liver histology</td>
<td></td>
</tr>
</tbody>
</table>

**LFTs**
Liver Biopsy

- May be guided by CT or ultrasound
- Provides information regarding
  - Degree of inflammation
  - Disease severity
  - Tissue damage
  - Presence/absence of cirrhosis
- Helps determine
  - Degree of disease progression
  - Cause of liver disease
  - Need for treatment
Histologic Staging

Stage 0
No Fibrosis
No fibrosis

Stage 1
Portal Fibrosis
Portal fibrosis

Stage 2
Few septa
Few septae

Stage 3
Numerous septa
Numerous septae

Stage 4
Cirrhosis
Cirrhosis
### Management of Chronic HCV

**Is Liver Biopsy Necessary?**

<table>
<thead>
<tr>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Patient wants treatment even if no fibrosis</td>
<td>- Patient would only accept treatment if advanced fibrosis</td>
</tr>
<tr>
<td>- Patient does not want treatment or treatment contraindicated even if advanced fibrosis</td>
<td>- Labs or radiographic studies suggest cirrhosis may be present</td>
</tr>
<tr>
<td>- Labs and radiographic studies do not suggest cirrhosis</td>
<td>- Patient fails to achieve SVR and no recent biopsy available</td>
</tr>
<tr>
<td>- Patient achieves SVR</td>
<td></td>
</tr>
</tbody>
</table>
Assessment of Liver Histology

Noninvasive Serum Tests

Risk of Cirrhosis and Liver Cancer in Women with HCV

- Lower risk when compared to men
- Decreased risk of scarring in the liver (fibrosis)
- Higher estrogen states are “protective’ eg. during pregnancy, OCP or HRT
- Risk increases after menopause
Hepatitis C Screening and Diagnosis Summary

- Suspect disease on the basis of risk factors, not symptoms
- Positive anti-HCV result indicates current infection until refuted
- Measurement of HCV RNA may be required to establish diagnosis in selected cases
Treatment
Goals of HCV Therapy

- **Primary:** HCV RNA below limits of detection at end of treatment

- **Secondary:**
  - Inhibition of disease progression
  - Reduction of incidence of hepatocellular carcinoma
  - Reduction in need for liver transplant
HCV Therapy Options

- **Before 2011**
  - PegIFN/RBV constituted standard of care for patients infected with all major HCV genotypes
    - Genotypes 1 and 4: 48 wks of therapy
    - Genotypes 2 and 3: 24 wks of therapy

- **2011**
  - Patients with genotype 1 HCV have new options with the FDA approval of 2 protease inhibitors: telaprevir and boceprevir
    - Each agent used in combination with pegIFN/RBV
  - Patients with genotype 2, 3, or 4 HCV continue to receive pegIFN/RBV
### 1st Gen. HCV-NS3 Protease Inhibitors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Telaprevir</th>
<th>Boceprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype activity</td>
<td>HCV-1 (-2)</td>
<td>HCV-1 (-2)</td>
</tr>
<tr>
<td>Peginterferon alfa formulation</td>
<td>2a &gt;&gt; 2b</td>
<td>2b &gt;&gt; 2a</td>
</tr>
<tr>
<td>PI dosing requirements</td>
<td>TID (with food) (BID data limited)</td>
<td>TID (with food)</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>CYP 3A4, P-gp</td>
<td>CYP 3A4, P-gp</td>
</tr>
<tr>
<td>PEG-IFN alfa / RBV lead-in phase</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Duration of PI triple therapy</td>
<td>(8-)12 wks + 12/36 wks PR</td>
<td>LI + 44 wks or 24 wks ± 20 wks PR</td>
</tr>
<tr>
<td>Tx-naive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tx-experienced</td>
<td>± LI + 12 wks + 36 wks PR</td>
<td>LI + 44 wks or 32 wks ± 12 wks PR</td>
</tr>
<tr>
<td>Qualification for shortened therapy (response guided)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tx-naive</td>
<td>eRVR (HCV-RNA negativity at wk 4 + 12)</td>
<td>eRVR (HCV-RNA negativity at wk 8 - 24)</td>
</tr>
<tr>
<td>Tx-experienced</td>
<td>-</td>
<td>eRVR (HCV-RNA negativity at wk 8 + 12)</td>
</tr>
</tbody>
</table>
Pretreatment Counseling
Considerations Related to Boceprevir & Telaprevir (GT 1)

- New discussion topics
  - Potential for shorter duration of therapy if patient has early response
    - Treatment duration with telaprevir vs boceprevir
    - For boceprevir: role of lead-in treatment with pegIFN/RBV
    - Options if patient has RVR
  - Increased costs
Pretreatment Counseling
Considerations Related to Boceprevir & Telaprevir (GT 1)

- New discussion topics
  - Anticipated adverse events and management
    - Hematologic events with boceprevir, particularly anemia
    - Rash, pruritus, anemia, anorectal disorders, elevated uric acid, and elevated bilirubin with telaprevir
  - Importance of and potential challenges with adherence
    - Pill burden and dosing frequency
    - Potential for viral drug resistance
  - Need for liver biopsy?
  - Drug-drug interactions (drug substitution therapy)
  - Frequency of office visits and on-treatment monitoring
Certain side effects are more common in women

- Depression
  - Women 2X more likely than men in general population
  - Antidepressants can be used to manage these symptoms
- Sexual issues
  - Overall dryness – skin, eyes, mouth.
  - Vagina – manage with lubricating gels
- Anemia
  - Can cause fatigue, weakness and SOB
  - Symptoms can occur earlier and more severe than in men
Pregnancy and Treatment

- Antiviral therapy prior to pregnancy results in delayed time to conception
- Treatment cannot be taken during pregnancy or when breastfeeding
- Ribavirin is teratogenic. Necessary to wait 6-months after last dose before trying to conceive
Predicting Response to Treatment
Predictors of Response: The Old and the New

**Old**
- genotype 2/3
- absence of fibrosis
- low viral load
- younger age
- female gender
- lower weight

**New**
- genotype 2/3
- lack of steatosis
- adherence
- early viral response
- ribavirin dosage
- ethnicity
- 4-week viral clearance
- IL28B genotype

A Polymorphism on Chromosome 19 Predicts Sustained Virologic Response

Chromosome 19 graphic courtesy of Oak Ridge National Laboratory. Available at: 
IL28B: A New Predictor of Sustained Virologic Response

- The IL28 gene encodes for interleukin 28 also known as IFN-λ3
- IFN-λ3 is typically induced by viral infections and demonstrates antiviral activity in vitro similar to IFN-α, although less potent

IL28B-Associated Single Nucleotide Polymorphism (SNP)

- DNA is comprised of four types of nucleotides chained together, forming chromosomes:
  - adenine (A) guanine (G) cytosine (C) thymine (T)
- Humans chromosomes are paired together, providing two copies of our genetic information.
- The presence of the C/C genotype has been shown to be positively correlated with HCV clearance and treatment success.
Rate of SVR and rs12979860 C-allele frequency in diverse ethnic groups

Role of PEG/RBV lead-in phase

- Virologic value of LI phase is questionable
  - SPRINT-1: higher SVR rates with lead-in (but small number of patients)
  - REALIZE: Lead-in phase did not affect breakthrough, relapse and SVR rates
- Lead-in may be clinically useful if physician is willing to take decisions at week 4
  - only PEG/RBV, no PI in excellent initial virologic responders (RVR)
  - stop therapy in patients with poor initial virologic response (< 1 log) to avoid treatment failure and selection of resistant variants
- Lead-in for assessment of adherence (?)
SPRINT-2: SVR to Boceprevir According to Race

- Phase III: genotype 1, treatment naive

![Graph showing SVR (%) for Nonblack and Black races.]

ADVANCE: SVR to Telaprevir According to Race and Ethnicity

- Phase III: genotype 1, treatment naive

![Bar chart showing SVR (%) for different races and ethnicities: White, Black, Latino, Non-Latino.](chart)

SVR (%)

Race/Ethnicity

- White: 75, 70, 46
- Black: 62, 58, 25
- Latino: 74, 66, 39
- Non-Latino: 75, 69, 44

REALIZE: SVR Rates to Telaprevir by *IL28B* Genotype and Previous Response

- Phase III: genotype 1, failed previous pegIFN/RBV

Anticipated Impact of BOC and TVR on Number of Patients Seeking Care

- Likely to increase number of patients with genotype 1 infection seeking treatment
  - How will this affect the number of patients actually receiving treatment?

- Outcomes in treatment-experienced patients differ based on type of previous treatment failure
  - Relapsers > partial responders > null responders

- Cost will be an important factor

- Education of providers needed

Summary

- Primary care providers play key role in identifying risk factors and screening for HCV
- Many factors need to be addressed when preparing patients for therapy
  - Approval of protease inhibitors for genotype 1 infection adds to the complexity of pretreatment counseling
- Several baseline factors affect the outcome of antiviral treatment of chronic hepatitis C; the most important are:
  - Viral genotype, baseline HCV RNA, race, *IL28B* genotype
- No baseline predictor has sufficient negative predictive value to deny treatment
- Baseline predictors appear to be less important for triple therapy
S.C. Hepatitis C Coalition
SC DHEC Hepatitis Consultant
   - Linda Brown, MPH
Pharmaceutical Companies
Physician Referral List
SC Hepatitis C Coalition

Mick Carnett, CDP, CRPS, D.Div., Executive Director

- Informational & support services to providers & patients
- Brochures/literature
- Presentations
- Annual Statewide Hepatitis C Summit
- Statewide Physicians Referral List
- ETV program, HCC videos, PSAs
Surveillance/Reporting

- Hepatitis C is reportable to the health department within 7 days.

- Acute and chronic HCV cases are reported by health department to CDC via CHESS.
Thank You!

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