PCSS MAT TRAINING
PROVIDERS' CLINICAL SUPPORT SYSTEM
For Medication Assisted Treatment

Medical Considerations for Patients with Opioid Use Disorder

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Jeanette Tetrault, Disclosures

- No financial relationships to disclose.

The contents of this activity may include discussion of off label or investigative drug uses. The faculty is aware that is their responsibility to disclose this information.

Target Audience

- The overarching goal of PCSS-MAT is to make available the most effective medication-assisted treatments to serve patients in a variety of settings, including primary care, psychiatric care, and pain management settings.

Educational Objectives

- At the conclusion of this activity participants should be able to:
  - Recognize skin and soft tissue infections in people who inject drugs
  - Educate individuals about risk factors and risk groups for Hepatitis C and HIV
  - Describe prevention interventions for HCV and HIV including effective addiction treatment, behavioral risk reduction, and antiviral agents
  - Discuss how treatment regimens for both HCV and HIV are highly effective in patients with OUD and can be safely used with opioid agonist therapy

Case J.O.

- J. O. is a 26 year old man who has no PCP who presents to urgent care clinic with a red, warm indurated area on his L forearm.
- He has a history of opioid use disorder:
  - Started using oxycodone/acetaminophen intranasally up to 180 mg daily at age 18
  - Age 22 switched to heroin use intranasally daily and at age of 24 began using up to 5-10 bags of heroin IV daily.
- Other pertinent history:
  - Has multiple female sexual partners and rarely uses barrier protection.
  - Drinks 3-4 beers daily

What should we do now, in addition to discussion of treatment for OUD?

Skin and Soft Tissue Infections (SSTI) In People Who Inject Drugs (PWID)

- Most common cause of hospitalization for PWID
- Cutaneous and subcutaneous abscesses are the most common type of SSTI in PWID
- Commonly found in sites of frequent injection: antecubital fossae, groin, feet
- Treatment of cellulitis
  - General approach includes antibiotics directed toward staph and strep species
    - Special consideration for MRSA coverage
- Treatment of abscesses
  - Incision and drainage, often frequent, is required
  - Polymicrobial infections found in > 50% of cases and treatment should include coverage of anaerobes

Important Complications to Consider of SSTIs in PWID

- Bacteremia/sepsis
- Seeding of joints or heart valves
- Osteomyelitis
- Discitis
- Mycotic aneurysm
- Necrotizing fasciitis
- Paraspinal abscess

Important Treatment Considerations for J.O.

- If wound care/packing are needed:
  - Where does patient live?
  - Who lives with patient and can they do the packing?
- Tetanus-diphtheria-pertussis (Tdap) vaccine administration if not performed in last 10 years
- Given his lack of ongoing primary care:
  - Link to primary care and addiction treatment
  - What screening tests should be performed?
    - CBC, Chemistries, UA, liver enzymes, HCV ab, HIV ELISA, HbSab, HbSag, HbCab
    - Offer STD screening
    - Consider screening for latent tuberculosis infection

J.O. Screening Results

- CBC unremarkable, chemistries unremarkable, LFTs normal

- HCV Ab - reactive
- HIV ELISA-non-reactive
- HbSab-nonreactive
- HbCab-nonreactive
- HbSag-nonreactive

HCV: Epidemiology

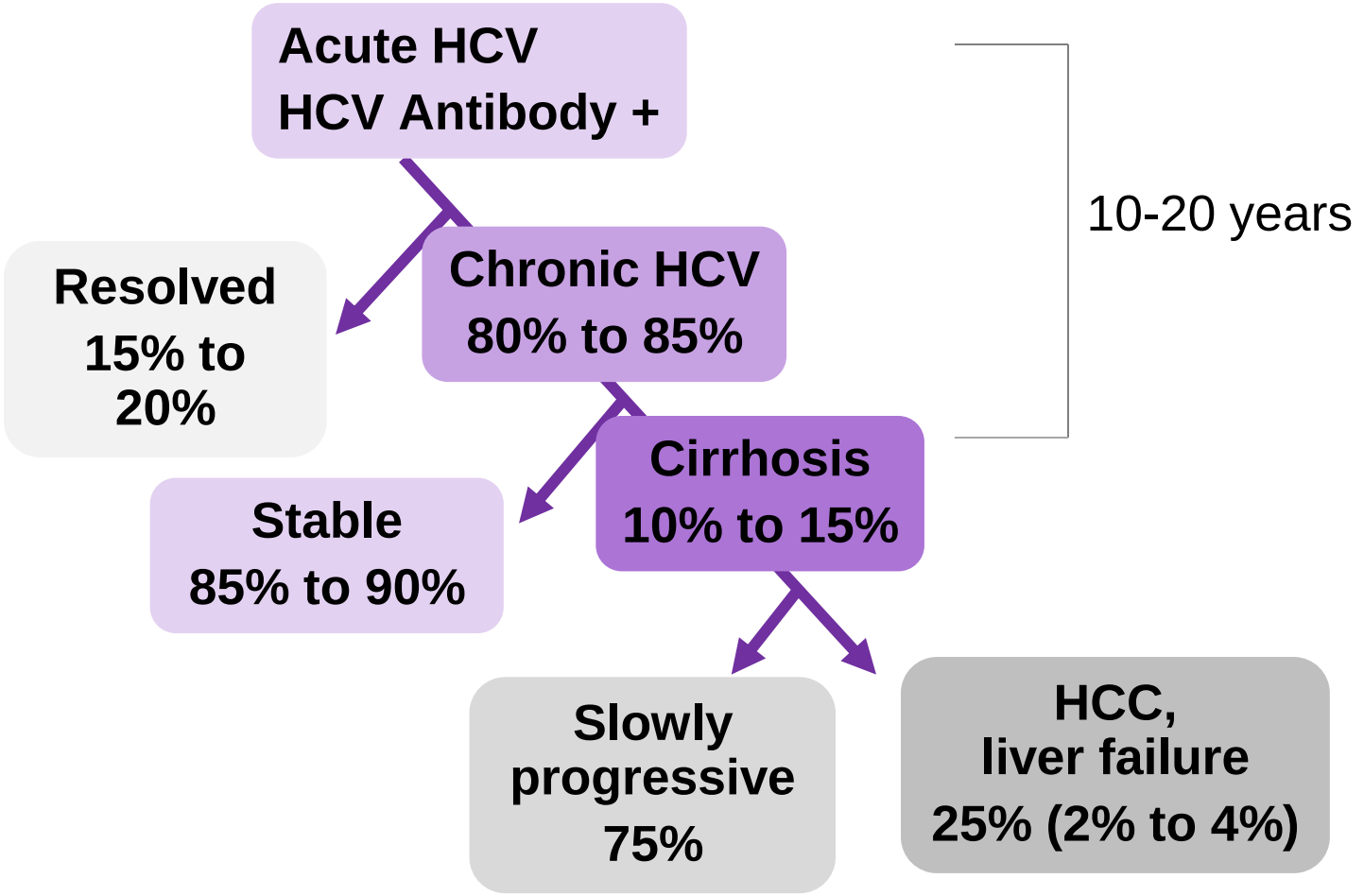
- 2.7 million in U.S.
- One third of PWID age 18-30 years
- >70% of PWID age 30+ years
- “Baby boomers” (1945-65) account for 75% of HCV
- Up to 75% of those infected with HCV are unaware
- Leading cause of cirrhosis, hepatocellular cancer, and reason for liver transplantation in the U.S.

HCV: Transmission Risk Factors and Risk Groups

- Risk factors:
  - Intravenous drug use
  - Intranasal drug use
  - Multiple sexual partners
  - HIV positive, HBV positive
  - Blood transfusion/organ transplant pre-1992

- Risk groups:
  - Children born to HCV+ mothers
  - Healthcare workers: occupational exposure
  - Patients on hemodialysis
  - Incarcerated persons

HCV: Natural History



NIH Management of Hepatitis C Consensus Conference Statement. June 10-12, 2002. Available at: http://consensus.nih.gov/2002/2002HepatitisC2002116html.

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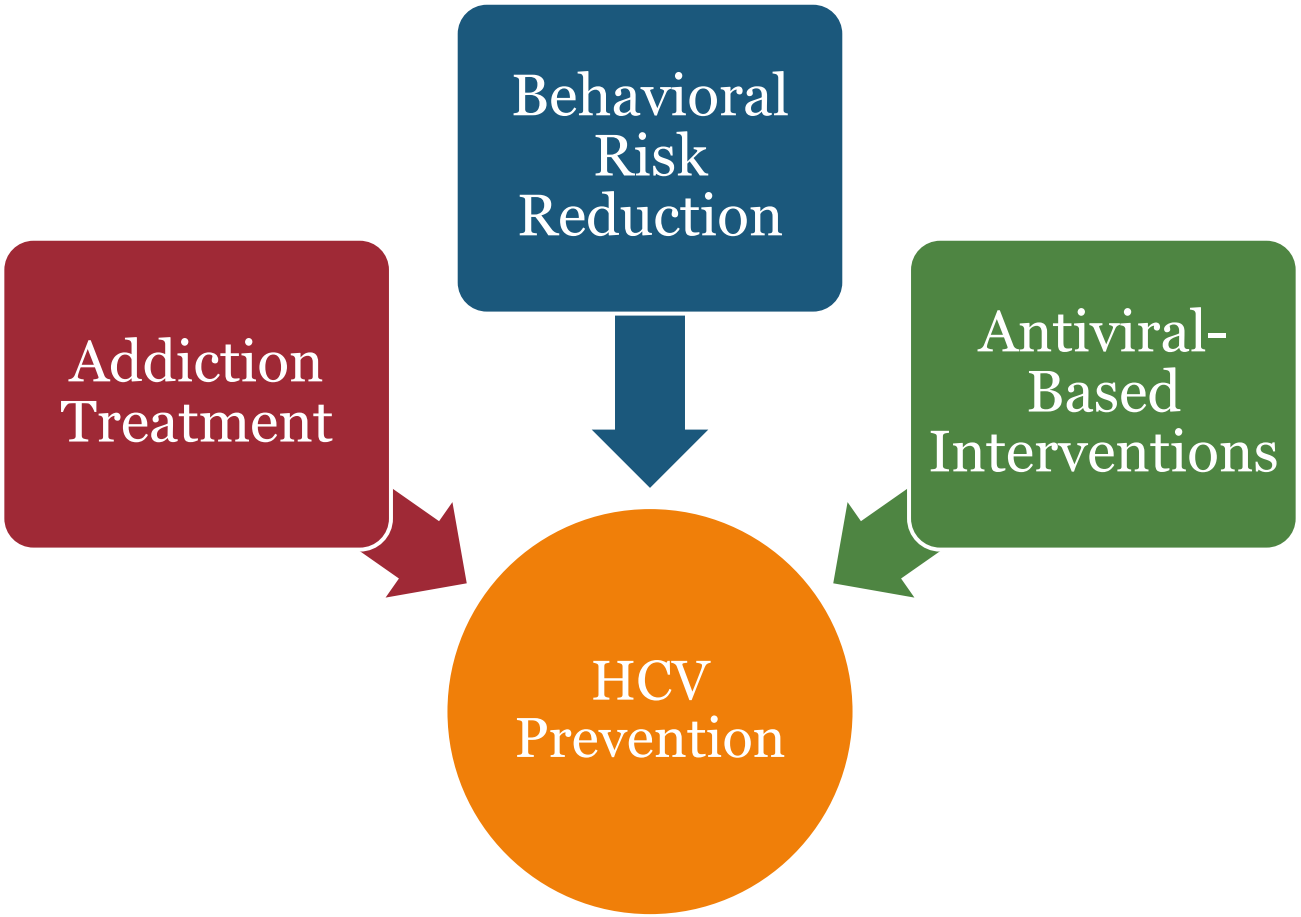
HCV Prevention Strategies



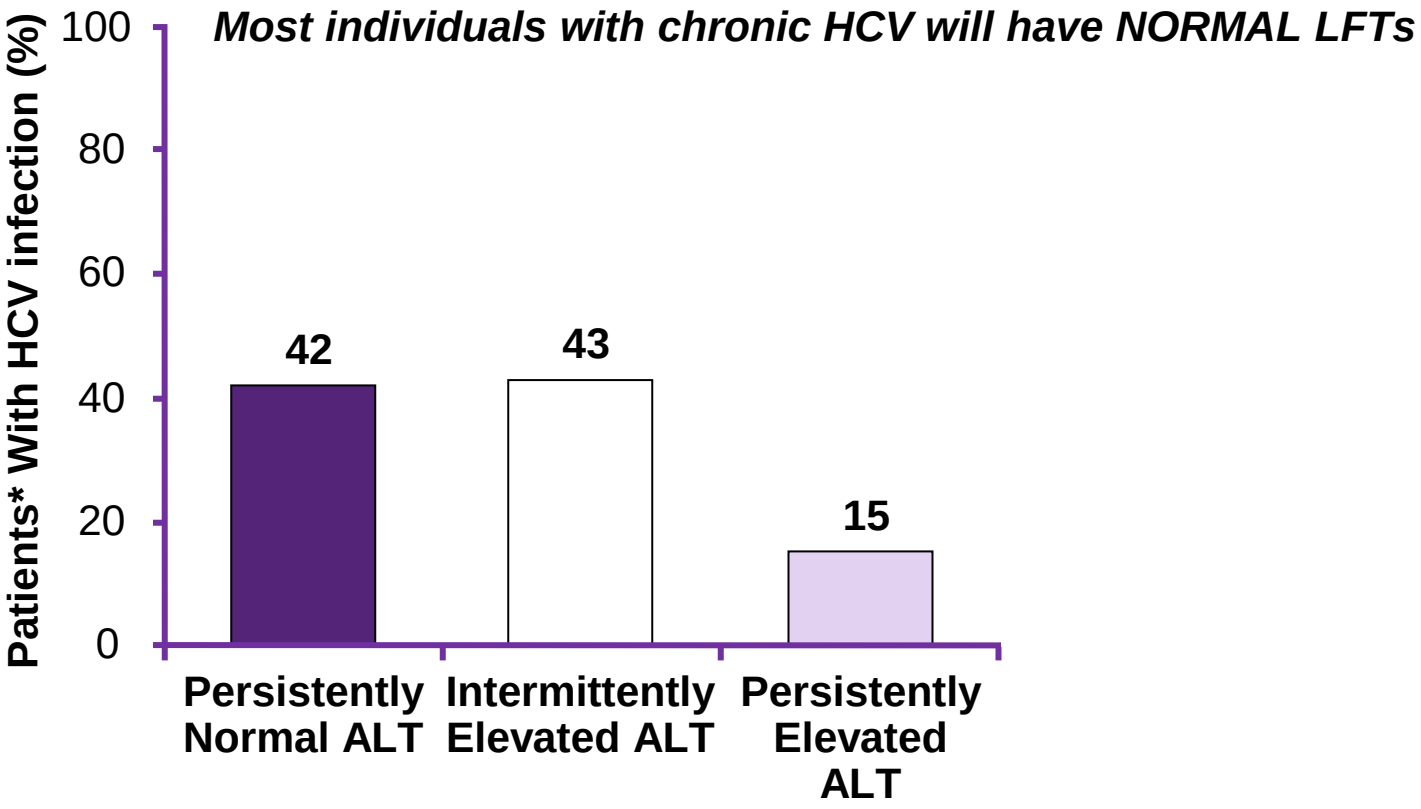
Adapted from: Coffin, PO et al. *Current HIV/AIDS reports*

HCV: Screening and Testing

- HCV antibody testing by immunoassay
  - Rapid testing and self-collection kits available
  - Recombinant immunoassay (RIBA) no longer available US

- If positive→
  - HCV Viral load qualitative or
  - HCV Viral load quantitative + HCV genotype

Liver Function Tests in HCV



*Patients with ≥ 4 serum ALT level measurements during 25 months of follow-up (n = 1042).

Inglesby TV, et al. *Hepatology*. 1999;29:590-596.

Pre-Treatment Management

- Further work-up
  - HCV Viral load quantitative with genotype testing
  - CBC, BMP, LFTs, TSH, INR, urine HCG for women of childbearing age
  - HIV, Hepatitis A and Hepatitis B screening and vaccination as appropriate
  - Assessment of degree of liver fibrosis
    - Non-invasive testing (serologic or US transient elastography) or bx
    - If evidence of cirrhosis, screen for varices and HCC
- Review addiction treatment plan
  - Reduce alcohol and other drug use and promote abstinence through treatment
- Prevention messaging:
  - HIV prevention - Limit hepatotoxins, including EtOH
  - HCV transmission prevention - Harm reduction

When and Whom to Initiate Therapy

Goal of treatment

Reduce all-cause mortality and liver-related health adverse consequences by the achievement of virologic cure as evidenced by an SVR.

Recommendations for when and in whom to initiate treatment

Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions.

Immediate treatment is assigned the highest priority for those patients with advanced fibrosis, those with compensated cirrhosis, liver transplant recipients, and patients with severe extrahepatic hepatitis C.

Immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications are given high priority.

When and Whom to Initiate Therapy

Recommendations for pretreatment assessment

An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended.

Recommendation for repeat liver disease assessment

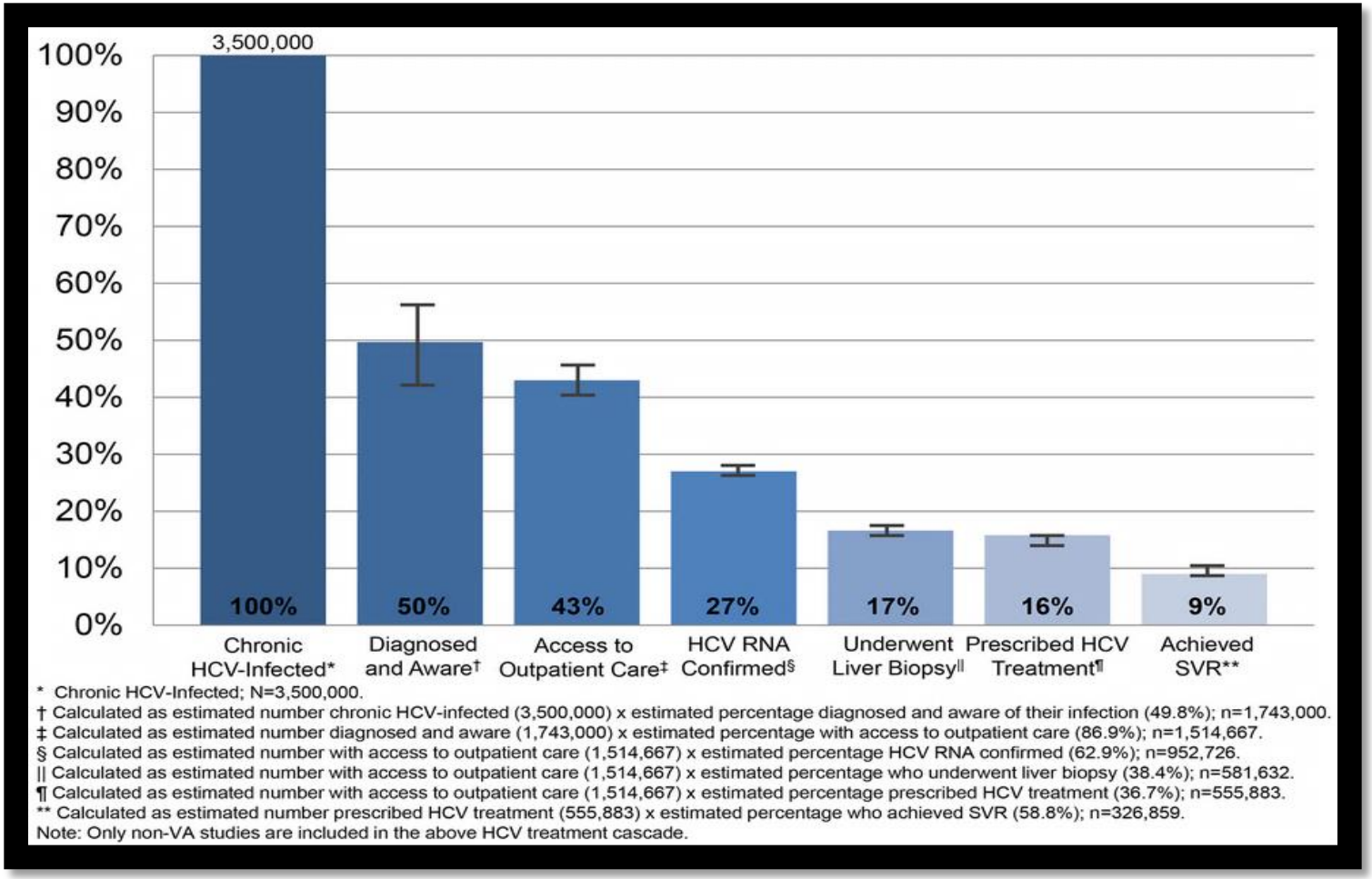
Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.

HCV Treatment and Active Illicit Substance Use

- Barriers to HCV treatment include:
  - Ability to adhere to medication
  - Comorbid psychiatric conditions
  - Risk of reinfection (0-5 cases/100 person years in IFN era)
  - Insurance coverage considerations

- AASLD guidelines suggest that *HCV treatment should not be withheld from those who actively use illicit substances or are enrolled in a substance use treatment program*

HCV Treatment Cascade



* Chronic HCV-Infected; N=3,500,000.
† Calculated as estimated number chronic HCV-infected (3,500,000) x estimated percentage diagnosed and aware of their infection (49.8%); n=1,743,000.
‡ Calculated as estimated number diagnosed and aware (1,743,000) x estimated percentage with access to outpatient care (86.9%); n=1,514,667.
§ Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage HCV RNA confirmed (62.9%); n=952,726.
‖ Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage who underwent liver biopsy (38.4%); n=581,632.
¶ Calculated as estimated number with access to outpatient care (1,514,667) x estimated percentage prescribed HCV treatment (36.7%); n=555,883.
** Calculated as estimated number prescribed HCV treatment (555,883) x estimated percentage who achieved SVR (58.8%); n=326,859.
Note: Only non-VA studies are included in the above HCV treatment cascade.

Yehia BR, et al. 2014. PLoS ONE

Evolution of HCV Treatment

- Prior to 2013, pegylated IFN + ribavirin standard of care for HCV treatment
  - Long duration of therapy (24-72 weeks)
  - Likelihood of SVR (50-70%) not favorable
  - Extensive side effect profile-→ high rates of treatment discontinuation

- 2013, introduction of protease inhibitors (telaprevir, boceprevir)
  - Decrease treatment duration
  - Improved efficacy (80-90%)
  - Still required an IFN backbone
  - Extensive side effect profile

- 2014, introduction of polymerase inhibitor
  - Drastically reduced treatment duration (8-24 weeks)
  - Efficacy 90-98%
  - ALL ORAL—NO IFN
  - Reduced side effect profile
  - Downside→ high cost

HCV Treatment Regimen Considerations

- Genotype (1, 2, 3, 4, 5 and 6)
- The presence or absence of cirrhosis
- Comorbidities
- Contraindications
- Medication interactions
- The presence or absence of baseline NS5A resistance-associated variants (RAVs) for certain treatments

HCV Treatment Regimens

- NS3/4A (Protease Inhibitors)
- Simeprevir
- Paritaprevir
- Grazoprevir
- Voxilaprevir

- NS5A Inhibitors
- Ledipasvir
- Ombitasvir
- Daclatasvir
- Elbasvir
- Velpatasvir

- NS5B Inhibitors (RNA Polymerase Inhibitors)
- Sofosbuvir
- Dasabuvir

GT	Medication	Duration	SVR	Side Effects	Interactions
1	Fixed dose ledipasvir/ sofosbuvir	8-12 weeks	>90%	Headache Nausea Fatigue	PPIs/H2 blockers Rosuvastatin Digoxin Oxcarbazepine Modafanil Some HIV/TB medications
2	Fixed dose sofosbuvir/ velpatasvir	12 weeks	99%	Headache Nausea Fatigue	Amiodarone PPI/H2 Blockers Atorvastatin/rosuvasatin +others
3	Fixed dose sofosbuvir/ velpatasvir	12 weeks	97%	Headache Nausea Fatigue	Amiodarone PPI/H2 Blockers Atorvastatin/rosuvasatin +others
4	Fixed dose sofosbuvir/ velpatasvir	12 weeks	60%	Headache Nausea Fatigue	Amiodarone PPI/H2 Blockers Atorvastatin/rosuvasatin +others

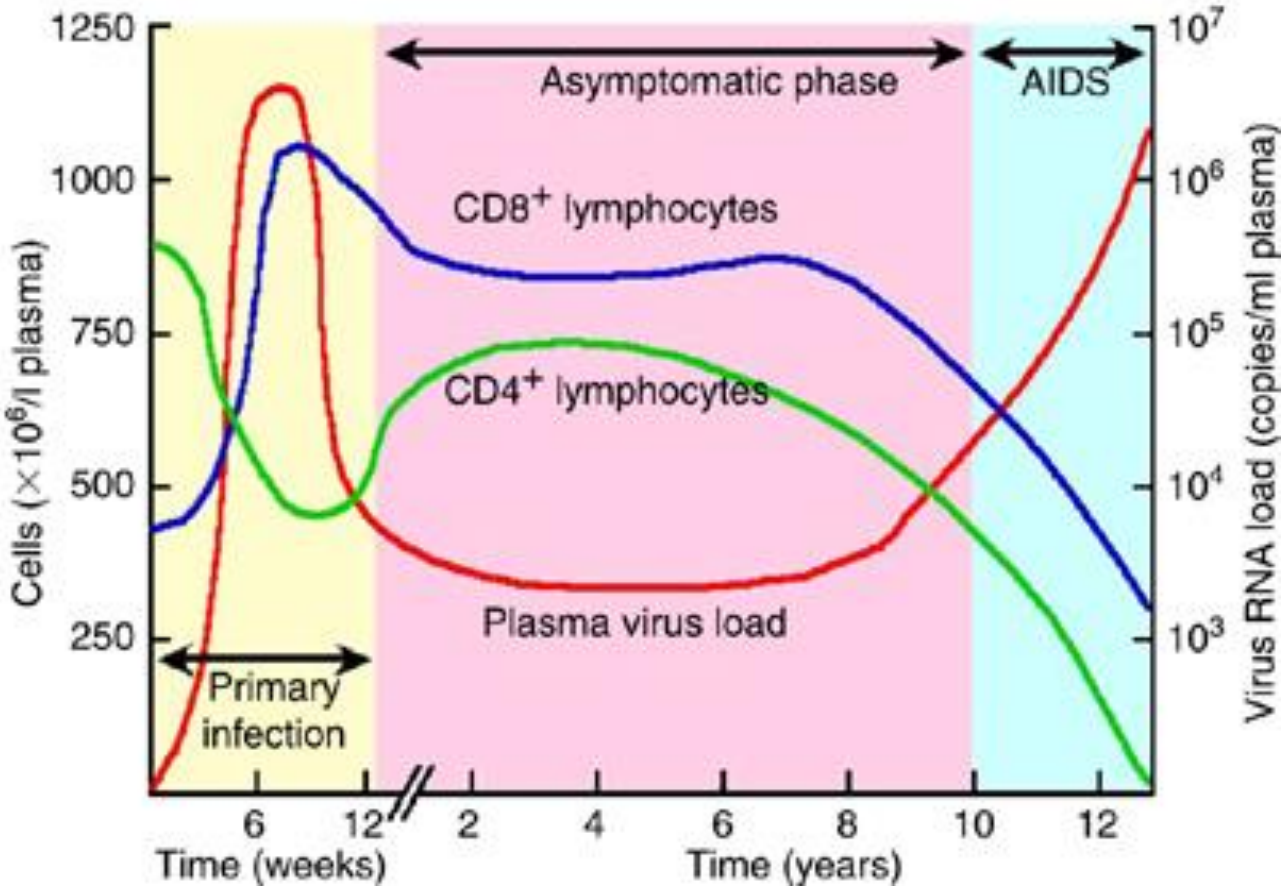
J.O. Continued

- J.O. is found to have 3 million copies/mL of HCV virus genotype 1a
- Liver fibrosis testing reveals approximately F1 fibrosis
- Initiated on ledipasvir/sofosbuvir one pill once a day for 8 weeks initiated onsite at his methadone clinic
- Cleared virus at the end of treatment
- 3 month after end of treatment, viral load remains undetectable = SVR

J.O. Continued

- He successfully completes HCV treatment.
- After three years of consistent engagement in treatment for his opioid use disorder, he is lost to follow-up.
- When he returns to care to reinitiate treatment, he reports that he is injecting 5 bags of heroin daily. He denies any needle sharing, but reports unprotected sex with multiple female partners.
- He is found on routine screening to have established HIV infection. His HCV-ab remains positive but quantitative viral load testing is negative.

HIV: Natural History



Munier 2007 *Immunology and Cell Biology*

HIV: Screening 2006 CDC Guidelines

ONE TIME SCREENING	REPEAT SCREENING AT LEAST ANNUALLY
Age 13-64 years old, unless documented prevalence <0.1%	People with injection drug use and their sex partners
Patients initiating tuberculosis treatment	Persons who exchange sex for money or drugs
Patients seeking treatment for a sexually transmitted infection	Sexual partners of HIV-infected persons
Opt-out approach	Men who have sex with men
	Heterosexual individuals who themselves/or partner >1 sex partner since last HIV test

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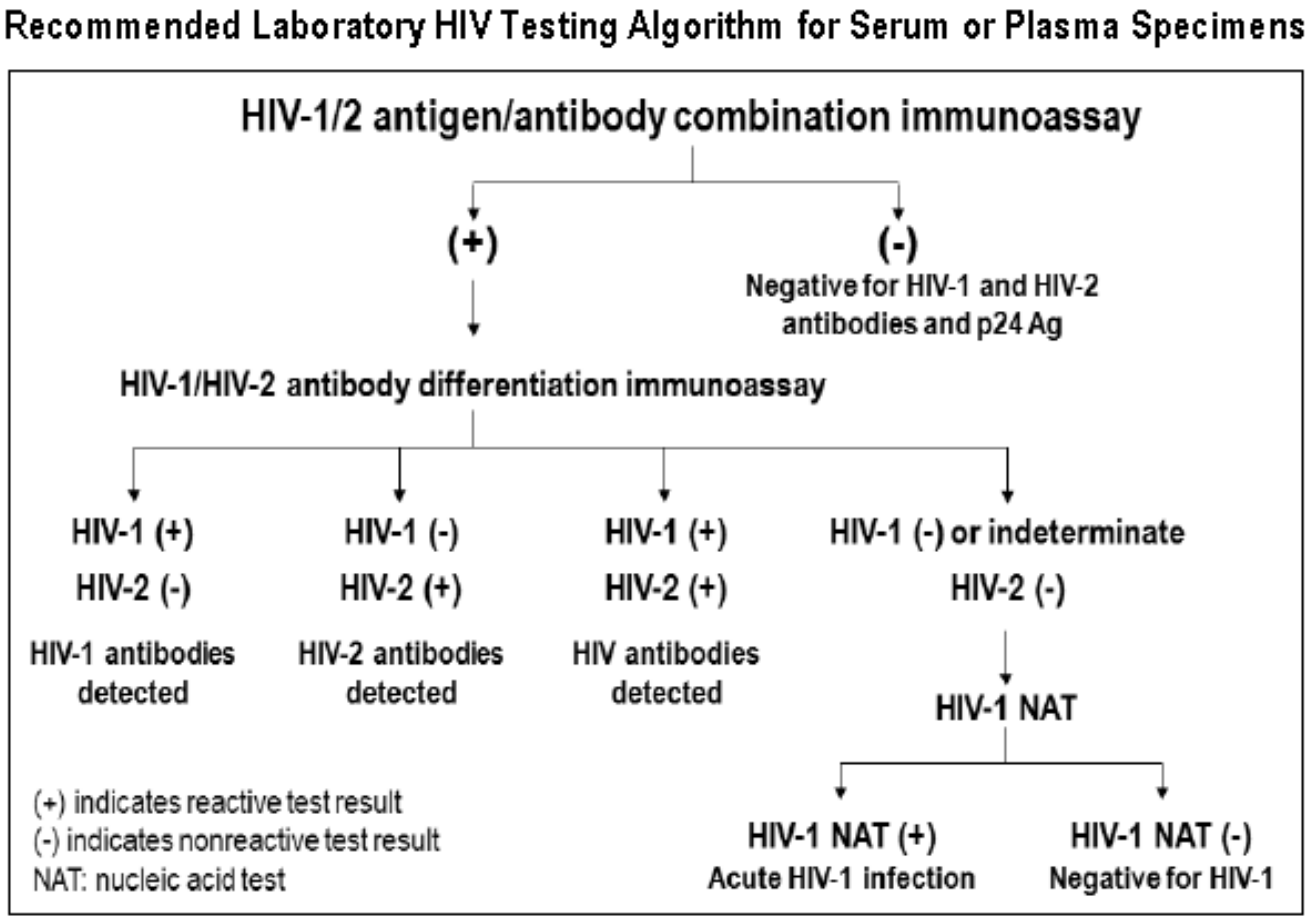
Branson BM et al MMWR 2006

HIV: Screening Algorithm

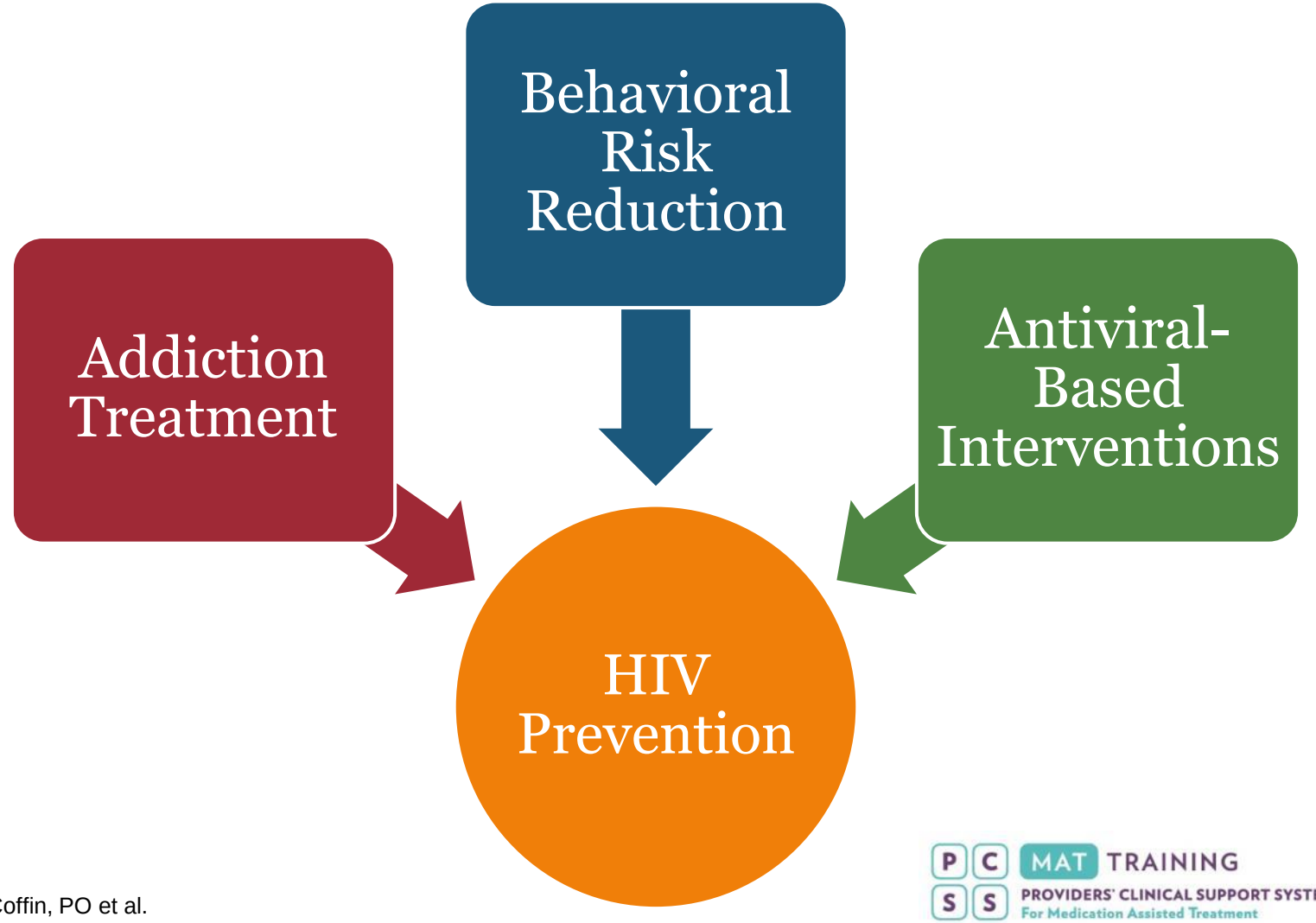


New Strategies:

- No longer rely on Western Blot testing
- 4th generation tests have improved sensitivity and specificity
- But still may miss infection if within 10 days of acquisition

http://stacks.cdc.gov/view/cdc/23447

HCV and HIV Prevention Strategies

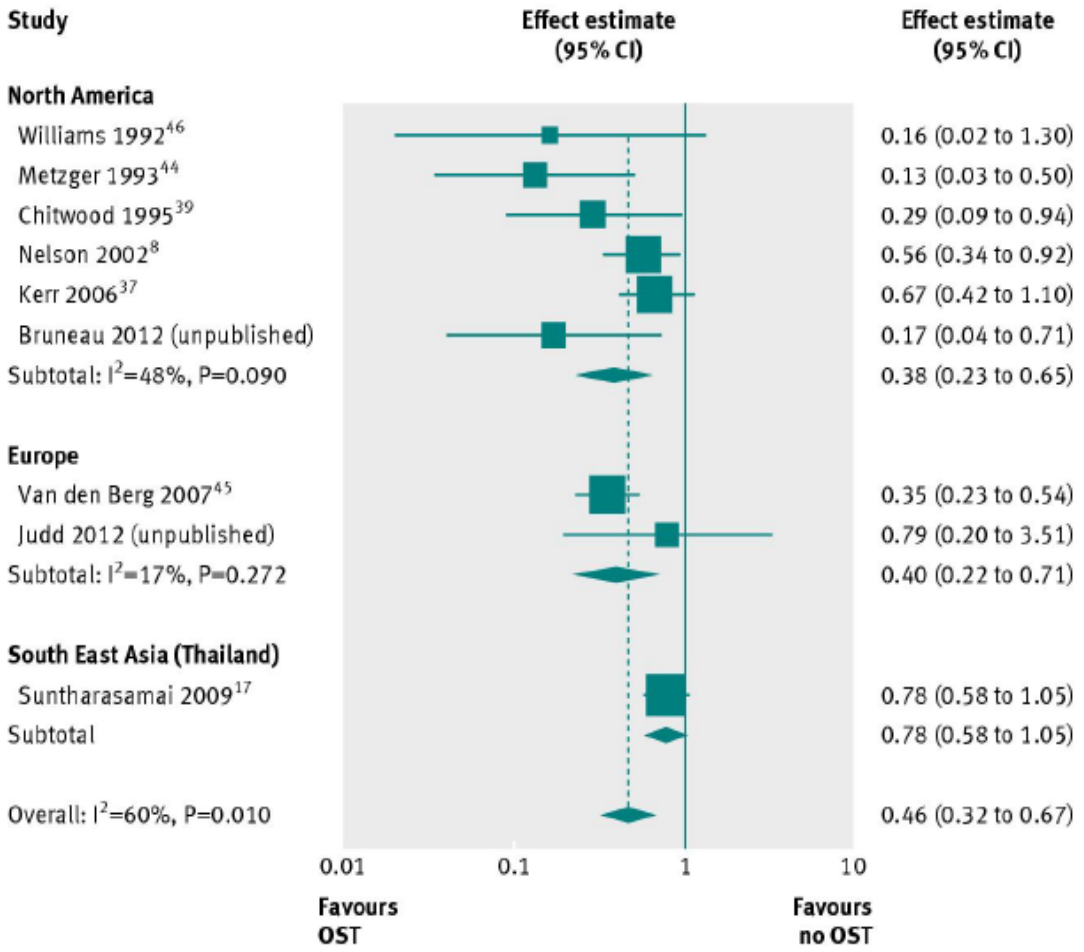


Adapted from Coffin, PO et al.
Current HIV/AIDS reports.

Opioid Agonist Therapy Decreases HIV Incidence

Systematic Review:

- 9 studies
- 23,608 person years
- Methadone only
- Overall effect: 54% reduction in HIV incidence



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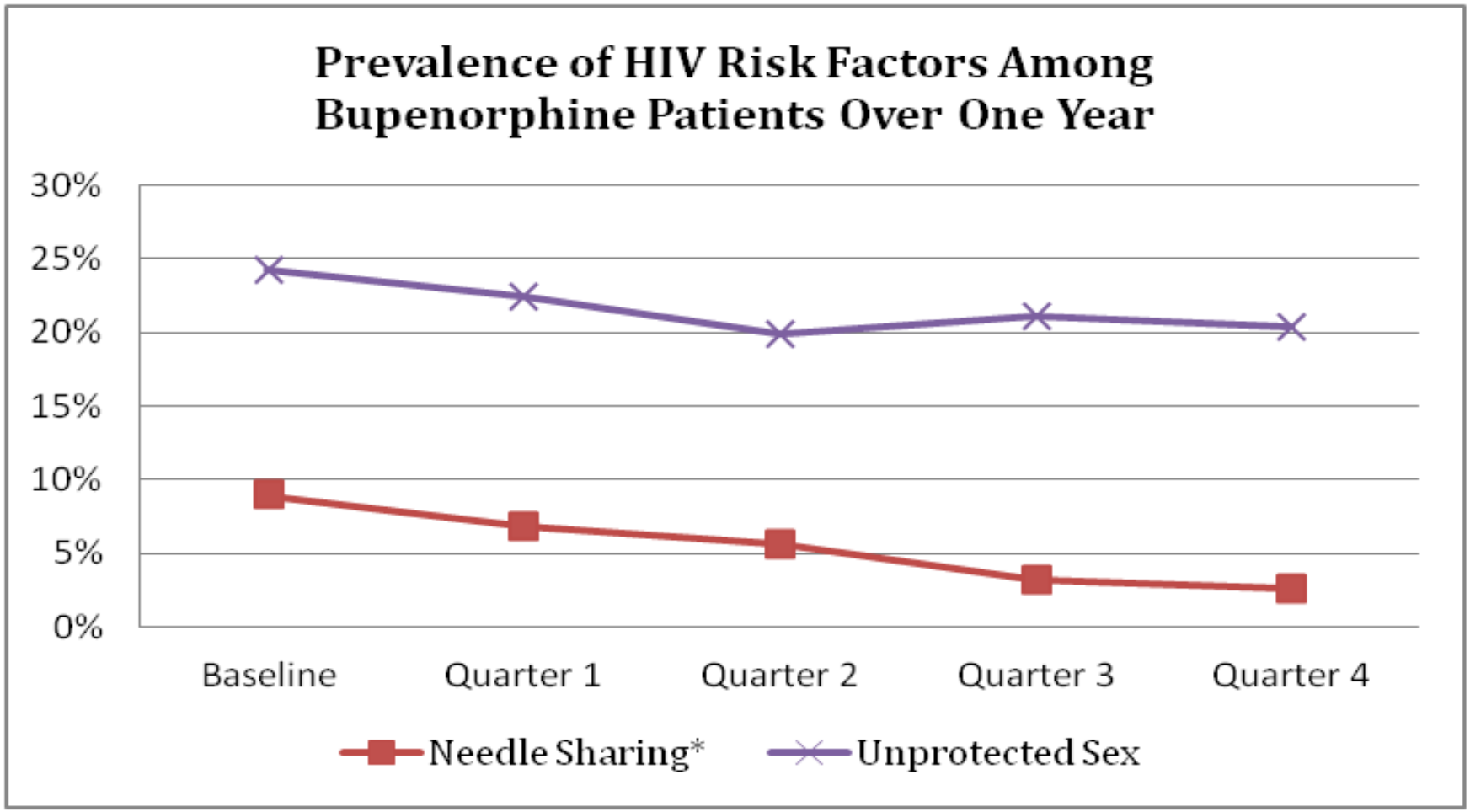
Gowing et al. *BMJ* 2012

HIV Risk Behaviors Over Time Among Patients on Buprenorphine Treatment



* p<0.05

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Behavioral Risk Reduction for HIV Prevention

- Needle and Syringe Programs
  - "Sufficient evidence to support effectiveness in reducing injection-related behavior"
  - "Tentative evidence to support effectiveness in preventing transmission of HIV"

- Some evidence of other Interventions:
  - Pharmacies, vending machines, supervised drug consumption/injecting facilities
  - Counseling and educational interventions

MacArthur et al. *Int Journ Drug Policy* 2014

Antiviral-based Interventions: Pre-Exposure Prophylaxis for HIV

- Combination of two antiviral medications taken once daily:
  - Emtricitabine/Tenofovir (Truvada)
    - No reported drug-drug interactions with methadone, buprenorphine and naltrexone
- FDA-approved July 2012 for HIV prevention, CDC guidelines 2014
- Indications for MSM, high risk sexual contact. PWID
- Bangkok Tenofovir Study, HIV-negative people with injection drug use (n=2,413):
  - HIV incidence decreased by 49%
  - Risk behaviors also decreased

http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf; Choopanya 2013 *Lancet*

Pre-Exposure Prophylaxis for HIV

Summary of Guidance for PrEP Use			
	Men Who Have Sex With Men	**Heterosexual Women and Men**	**Injection Drug Users**
Detecting substantial risk of acquiring HIV infection:	• Sexual partner with HIV • Recent bacterial STD • High number of sex partners • History of inconsistent or no condom use • Commercial sex work	• Sexual partner with HIV • Recent bacterial STD • High number of sex partners • History of inconsistent or no condom use • Commercial sex work • Lives in high-prevalence area or network	• HIV-positive injecting partner • Sharing injection equipment • Recent drug treatment (but currently injecting)
Clinically eligible:	• Documented negative HIV test before prescribing PrEP • No signs/symptoms of acute HIV infection • Normal renal function, no contraindicated medications • Documented hepatitis B virus infection and vaccination status		
Prescription	Daily, continuing, oral doeses of TDF/FTC (Truvada), ≤90 day supply		
Other services:	• Follow-up visits at least every 3 months to provide: • HIV test, medication adherence counseling, behavioral risk reduction support, side effect assessment, STD symptom assessment • At 3 months and every 6 months after, assess renal function • Every 6 months test for bacterial STDs		
	• Do oral/rectal STD testing	• Assess pregnancy intent • Pregnancy test every 3 months	• Access to clean needles/ syringes and drug treatment services

Source: US Public Health Service. Preexposure prophylaxis for the prevention of HIV infection in the United States —2014: a clinical practice guideline.

J.O. Continued

- When should HIV care be initiated?
- What are the treatment options for the newly diagnosed patient?
- What are important consideration regarding HIV care among patients with opioid use disorders?

HIV: Considerations for the Newly Diagnosed Patient

Adapted from the DHHS HIV/AIDS Treatment Guidelines	
Goals of Treatment	• Reduce HIV-associated morbidity and prolong duration and quality of survival • Restore and preserve immunologic function • Maximally and durably suppress plasma HIV viral load • Prevent HIV transmission
When to Initiate Treatment	• Recommended for ALL HIV-infected patients regardless of CD4 cell count • Patients starting ART should be willing and able to commit to treatment and understand risks and benefits and importance of adherence; may be deferred on case-by-case basis
Baseline Evaluation	• HIV antibody testing, CD4 T cell count, HIV RNA viral load • Complete blood count, chemistry, transaminase levels, UA • Hepatitis A, B and C serologies • Fasting blood glucose and lipids • HIV genotype at treatment entry regardless of whether starting treatment • Sexually transmitted infections & opportunistic infections screening

HIV: Recommended Treatment for ART- Naïve Patients

Recommended Agents and Considerations: Consult Guidelines for Details	
Integrase Strand Transfer Inhibitor-Based Regimen	
• Dolutegravir/abacavir/lamivudine	ONLY if HLA-B*5701 negative
• Dolutegravir + tenofovir/emtrictiabine	
• Elvitegravir/cobicstat/tenofovir/emtricitabine	ONLY if CrCl > 70 ml/min pre-ART
• Raltegravir + tenofovir/emtricitabine	
Protease Inhibitor-Based Regimen	
• Darunavir/ritonavir + tenofovir/emtricitabine	

DHHS HIV/AIDS Guidelines 2015

Potential OUD/HIV Medication Interactions

Medication	Metabolism	Main ART Considerations
Methadone	• Delays gastric emptying • Metabolized by CYP 450 isoenzymes 2B6, 3A4, 2D6	• Efavirenz, nevirapine and all PIs, especially lopinavir/ritonavir decrease methadone levels → opioid withdrawal typically 7 days after co-administration; may need increased methadone dose • Atazanavir levels may be increased → monitor for toxicity
Buprenorphine	• Metabolized by CYP 3A4	• Concern for interaction with atazanavir and decreased levels, do not administer with ritonavir • Monitor for sedation if ritonavir + atazanavir as atazanavir may increase buprenorphine levels • Atazanavir/cobicistat and darunavir/cobicstat effects unknown
Naltrexone	• Not metabolized by CYP450 enzymes	• No significant interactions expected or observed

Suboptimal Care for People with IDU along HIV Treatment Cascade

- Approximately 14,500 with injection drug use unaware of their HIV status
  - Testing is not routine in opioid treatment programs and decreasing: 2005 to 2011: 93% → 64%
- Less likely to initiate antiretroviral therapy and quality care
- Less likely to achieve viral suppression
- Less likely to be retained in care

http://www.cdc.gov/hiv/pdf/2011_Monitoring_HIV_Indicators_HSSR_FINAL.pdf D'Aunno *Health Ser Research* 2014; Hanna DA 2013 *CID*; Korthuis PT 2012 *JAIDS*; Horberg MA 2013 *AIDS Pt Care STDS*; Rebeiro P 2013 *JAIDS*

A Potential Solution: Integrated Addiction and HIV Care

- At 12 months, nearly 50% engaged in addiction treatment
- Among those retained in treatment, past 30-day illicit opioid use decreased from 84% to 42%
- Among those retained in care, buprenorphine was associated with increased likelihood of initiating and remaining on ART and HIV viral suppression
- Demonstrated feasibility of delivering integrated care as an effective treatment strategy

http://journals.lww.com/jaids/toc/2011/03011

Considerations for HCV/HIV Co-Infected Patients

- Significant drug-drug interactions may occur between treatments used for HIV and HCV, therefore, patients should be cared for in collaboration with an HIV practitioner.

- HIV/HCV-co-infected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications

Summary

- PWID are at high risk for SSTI which may result in serious complications
- People living with opioid use disorders are at increased risk for HCV and HIV due to needle sharing and sexual risk behaviors
- Comprehensive prevention interventions for HCV and HIV include effective addiction treatment, behavioral risk reduction, and antiviral agents (pre-exposure prophylaxis for HIV, “PrEP”)
- Routine screening is essential for timely diagnosis
- Treatment regimens for both HCV and HIV are highly effective in this population and can be safely used with opioid agonist therapy

References

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PCSS-MAT Mentoring Program

- PCSS-MAT Mentor Program is designed to offer general information to clinicians about evidence-based clinical practices in prescribing medications for opioid addiction.
- PCSS-MAT mentors are a national network of providers with expertise in **addictions, pain, evidence-based treatment including medication-assisted treatment**.
- 3-tiered approach allows every mentor/mentee relationship to be unique and catered to the specific needs of the mentee.
- No cost.

For more information visit:

pcssmat.org/mentoring

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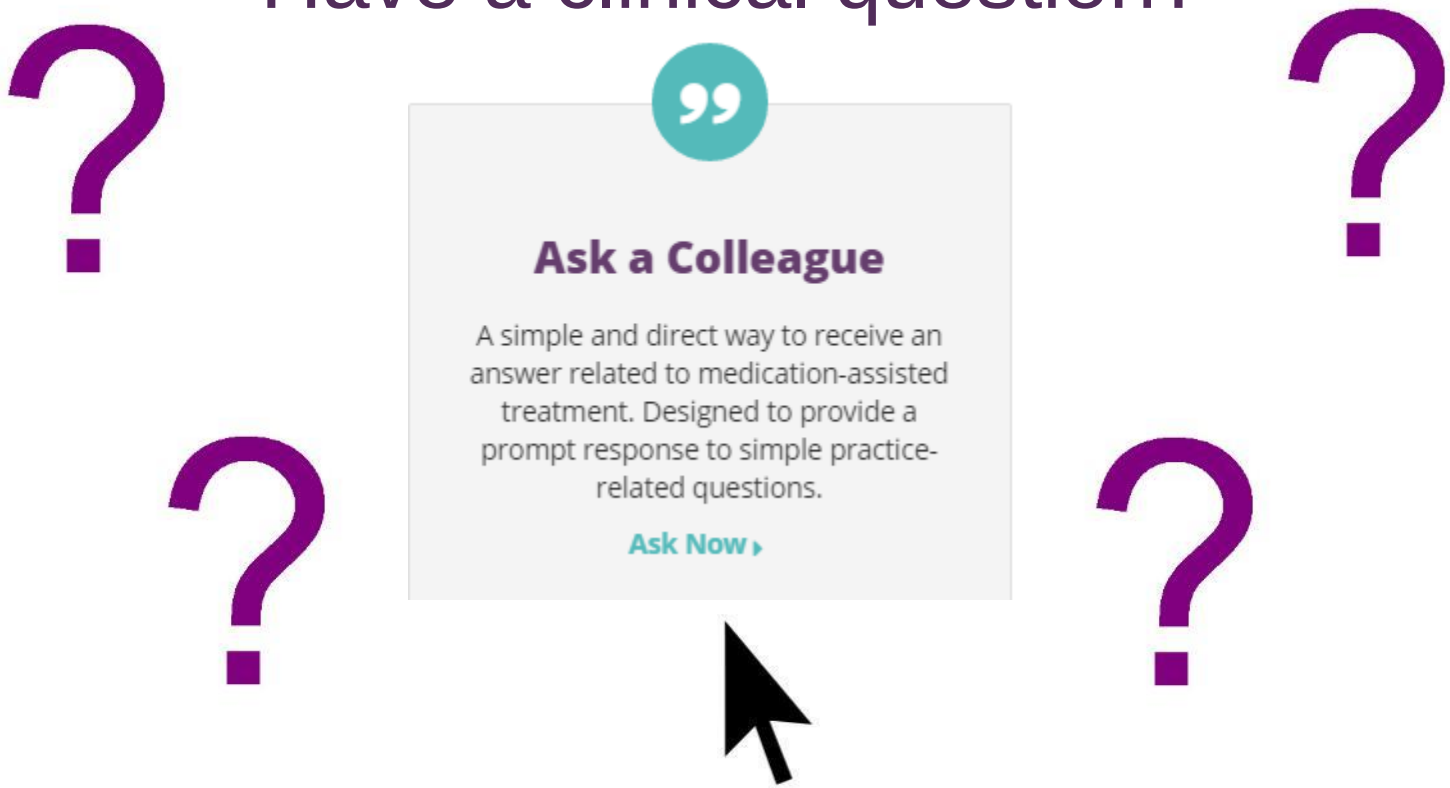
PCSS Discussion Forum

Have a clinical question?



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For more information: www.pcssmat.org

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