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# Blood and Body Fluid Exposure (BBFE) Management: Key Updates and Panel Discussion

AOHP PNW 2019 Symposium
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- No disclosures

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# Learning objectives

(1) Identify current CDC recommendations regarding testing and follow-up for health care professionals potentially exposed to hepatitis C
(2) Discuss how the "Undetectable = Untransmittable (U=U)" health equity initiative may help inform clinical decision making regarding HIV post-exposure prophylaxis
(3) Compare various HIV and hepatitis C-related laboratory tests in order to determine the clinical utility and application of differing testing strategies
(4) Discuss the importance of recognizing and managing bilateral exposures

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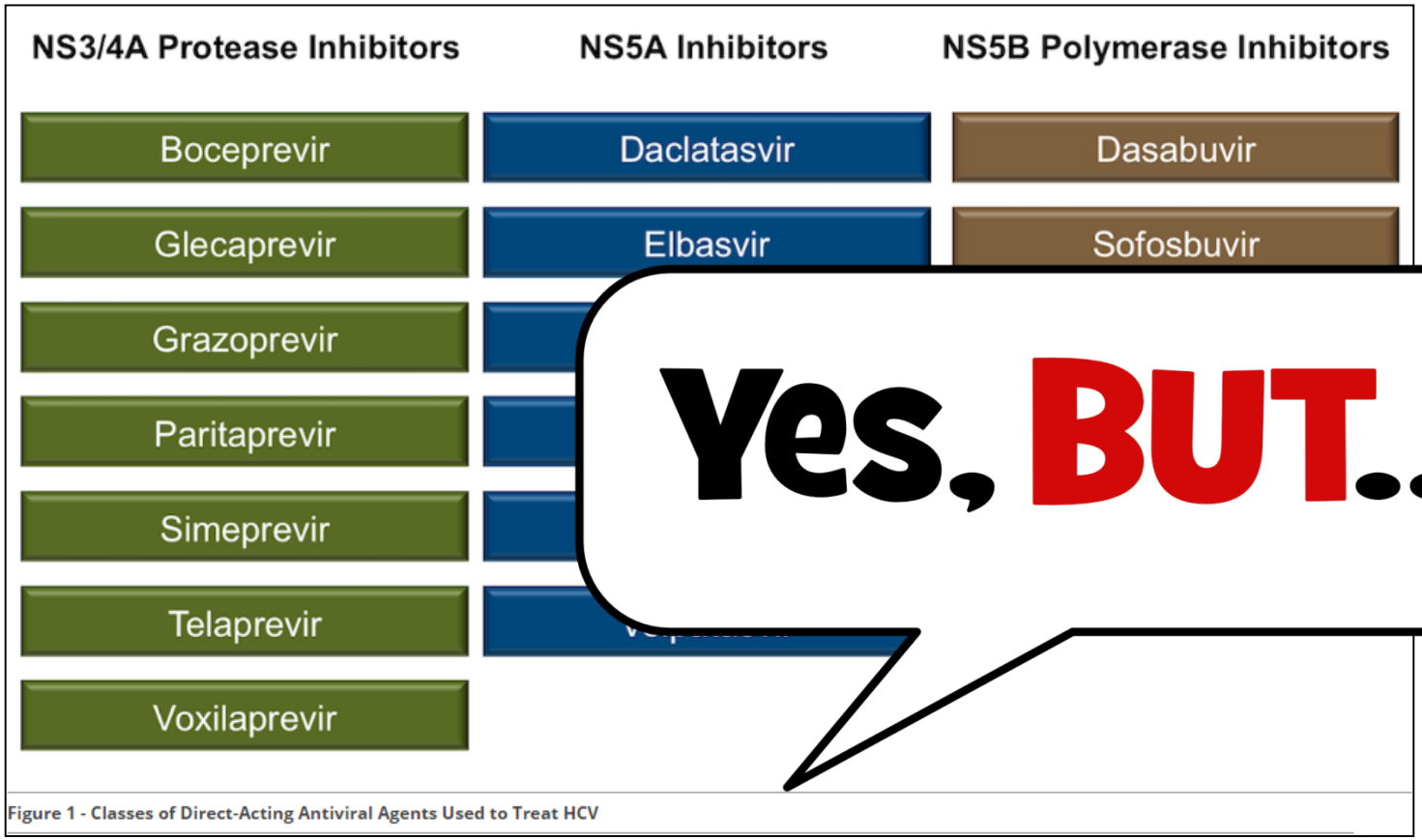
# Hepatitis C: a whole new world?




*Hepatitis C Online- https://www.hepatitisc.uw.edu/go/treatment-infection/treatment-genotype-3/core-concept/all*

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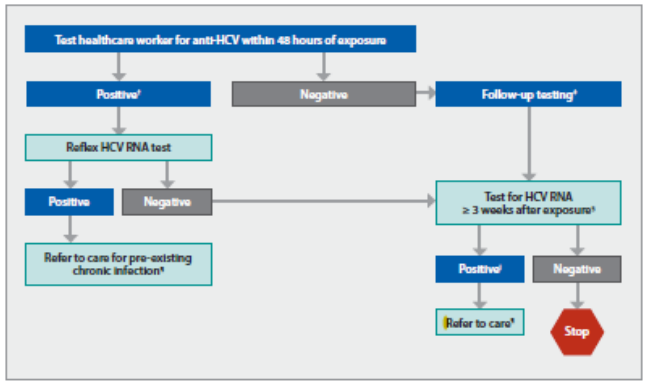
# There's a *different* whole new world! (…at least, since 2016)

## Information for Healthcare Personnel Potentially Exposed to Hepatitis C Virus (HCV)

### Recommended Testing and Follow-up

Exposure to viral hepatitis has long been recognized as an occupational risk for healthcare personnel, with recommendations previously established for the management of occupational exposures to hepatitis C virus (HCV). This notice, which is based on current laboratory guidance[1], updates the 2001 HCV testing algorithm for healthcare personnel[2]. Postexposure prophylaxis (PEP) of hepatitis C is not recommended, as outlined in the 2001 MMWR on management of healthcare personnel who have occupational exposure to blood and other body fluids[2].

Test the source for HCV RNA*. If the source is HCV RNA positive, or if HCV infection status unknown, follow the algorithm below. After a needlestick or sharps exposure to HCV-positive blood, the risk of HCV infection is approximately 1.8%[2]. If the healthcare worker does become infected, follow AASLD/IDSA guidelines (www.hcvguidelines.org) for management and treatment of hepatitis C.




*If it is not possible to test source for HCV RNA, then test for antibodies to HCV (anti-HCV) and screen HCW exposed to anti-HCV positive source. Note that persons with acute infection may test HCV RNA positive but anti-HCV negative.

†In a nationally representative population sample with low (1%) HCV infection prevalence, 22% of anti-HCV positive results were determined to be false-positive. An additional 10% had indeterminate results in a confirmatory assay; most were likely to be false-positive. Among the subset of persons testing anti-HCV screening reactive and subsequently HCV RNA negative, 50% of the anti-HCV tests were false-positive.[3]

‡Anti-HCV testing at >= 6 months with reflex to HCV RNA test, if positive, could also be done.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Continued on next page

§A single negative HCV RNA test using currently available FDA-approved tests in the US (all with lower limit of detection <100 IU/mL in serum)[4] is considered sufficient to rule out chronic HCV infection when screening an HCV antibody-positive individual with no known ongoing risk of exposure. HCV RNA becomes detectable within 3 weeks after exposure even when the antibody is still undetectable. Persons who develop symptoms of acute HCV infection such as jaundice may be tested earlier than 3 weeks, but if negative would require re-testing at ≥ 3 weeks. Spontaneous clearance of acute infection may occur up to six months after exposure, therefore persons testing HCV RNA positive < 6 months after exposure should be tested again at ≥ 6 months to determine infection status.

¶All patients with current HCV infection as evidenced by a positive HCV RNA test result should be evaluated by a practitioner with expertise in assessment of liver disease severity and HCV treatment. Guidance for hepatitis C treatment may be found at www.hcvguidelines.org and is changing rapidly with the advent of new therapies.

**Spontaneous clearance of infection may occur up to six months after exposure; persons testing HCV RNA positive < 6 months after exposure should be tested again at ≥ 6 months after exposure to determine infection status.

**References**


1. CDC. Testing for HCV Infection: An Update of Guidance for Clinicians and Laboratorians. MMWR 2013; 62(18): 362-5.
2. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. MMWR 2001; 50 (RR11): 1-42.
3. Moorman A, Drobeniuc J, Kamili S. Prevalence of false-positive hepatitis C antibody results, National Health and Nutrition Examination Study (NHANES) 2007-2012. J Clin Virol 2017; 89: 1-4.
4. FDA Executive Summary, Prepared for the March 21-22, 2018 meeting on the Reclassification of HIV and HCV Diagnostic Devices Joint Panel Meeting of the Blood Products Advisory Committee and the Microbiology Devices Panel of the Medical Devices Advisory Committee. Table 3: FDA Approved HCV RNA Tests for the Detection of HCV RNA in HCV Antibody Positive Individuals; Table 4: FDA Approved HCV RNA Tests for the Quantitation of HCV in Anti-HCV Positive Individuals. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/UCM598744.pdf Accessed April 27, 2018.


April 2018

www.cdc.gov/hepatitis

https://www.cdc.gov/hepatitis/pdfs/testing-followup-exposed-hc-personnel.pdf

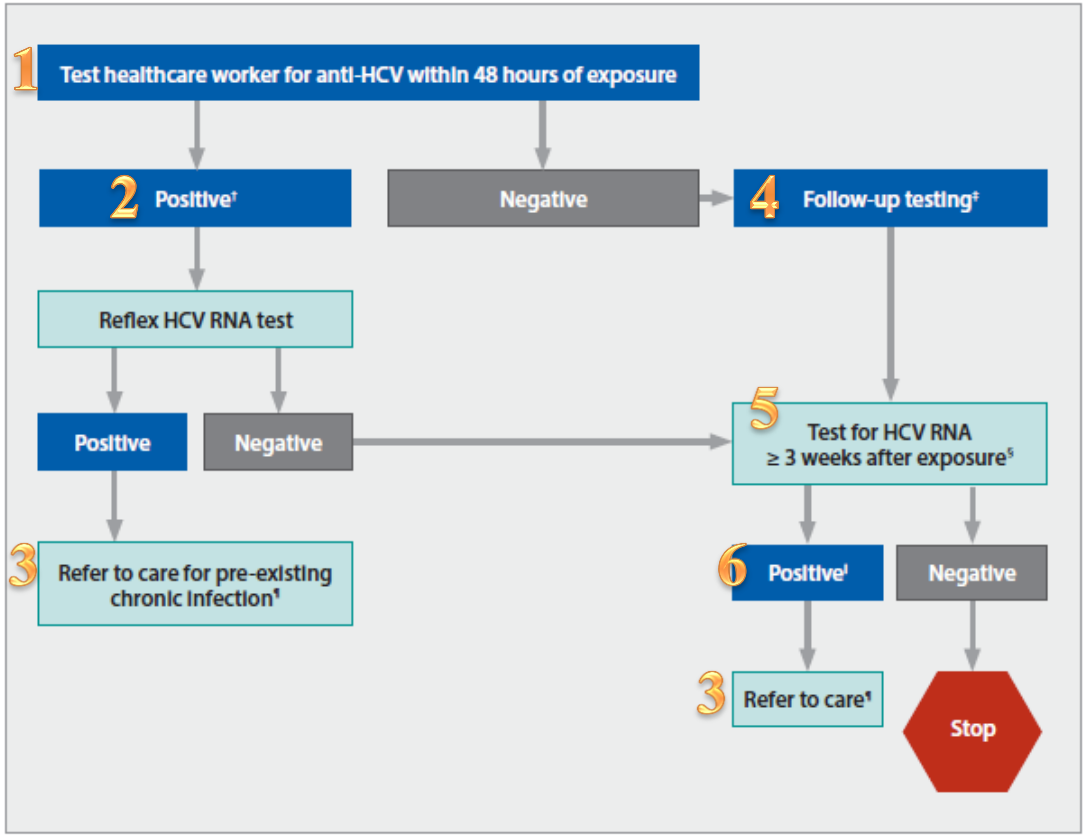
***( ■ = text updated in April 2018, 2-pg document previously posted by CDC 2016)***

# Information for Healthcare Personnel Potentially Exposed to Hepatitis C Virus (HCV)

## Recommended Testing and Follow-up

Exposure to viral hepatitis has long been recognized as an occupational risk for healthcare personnel, with recommendations previously established for the management of occupational exposures to hepatitis C virus (HCV). This notice, which is based on current laboratory guidance[1], updates the 2001 HCV testing algorithm for healthcare personnel[2].

Test the source for HCV RNA*. If the source is HCV RNA positive, or if HCV infection status unknown, follow the algorithm below:




1. If SP testing with HCV RNA isn't possible, use HCV antibody ("anti-HCV"). Screen EPs exposed to anti-HCV positive SPs. Persons with acute HCV may be anti-HCV negative but HCV RNA positive.
2. In a study of a low HCV prevalence (1%) population sample, 22% of anti-HCV positive results were determined to be "**false positives**". Another 10% had indeterminate results on confirmatory testing.
3. Spontaneous clearance of HCV may occur up to 6 months post-exposure; EPs who test HCV RNA positive < 6 months post-exposure should be tested again at/after 6 months to determine infection status.
4. Instead of testing an EP with HCV RNA 3+ weeks post-exposure, anti-HCV testing at/after 6 months with reflex to HCV RNA test (if positive) could also be done.
5. A single negative HCV RNA (using currently available FDA-approved tests) is sufficient to r/o chronic HCV when screening an anti-HCV positive person with *no known ongoing risk of exposure*. HCV RNA becomes detectable w/in 3 weeks post-exposure even when Ab remains undetectable. If someone develops signs/ symptoms, it's ok to test before 3 weeks. However, if this early HCV RNA is negative, EPs should still be re-tested at/after 3 weeks.
6. Pts with current HCV infection (+ HCV RNA) should be evaluated by a provider with expertise in liver disease/HCV treatment.

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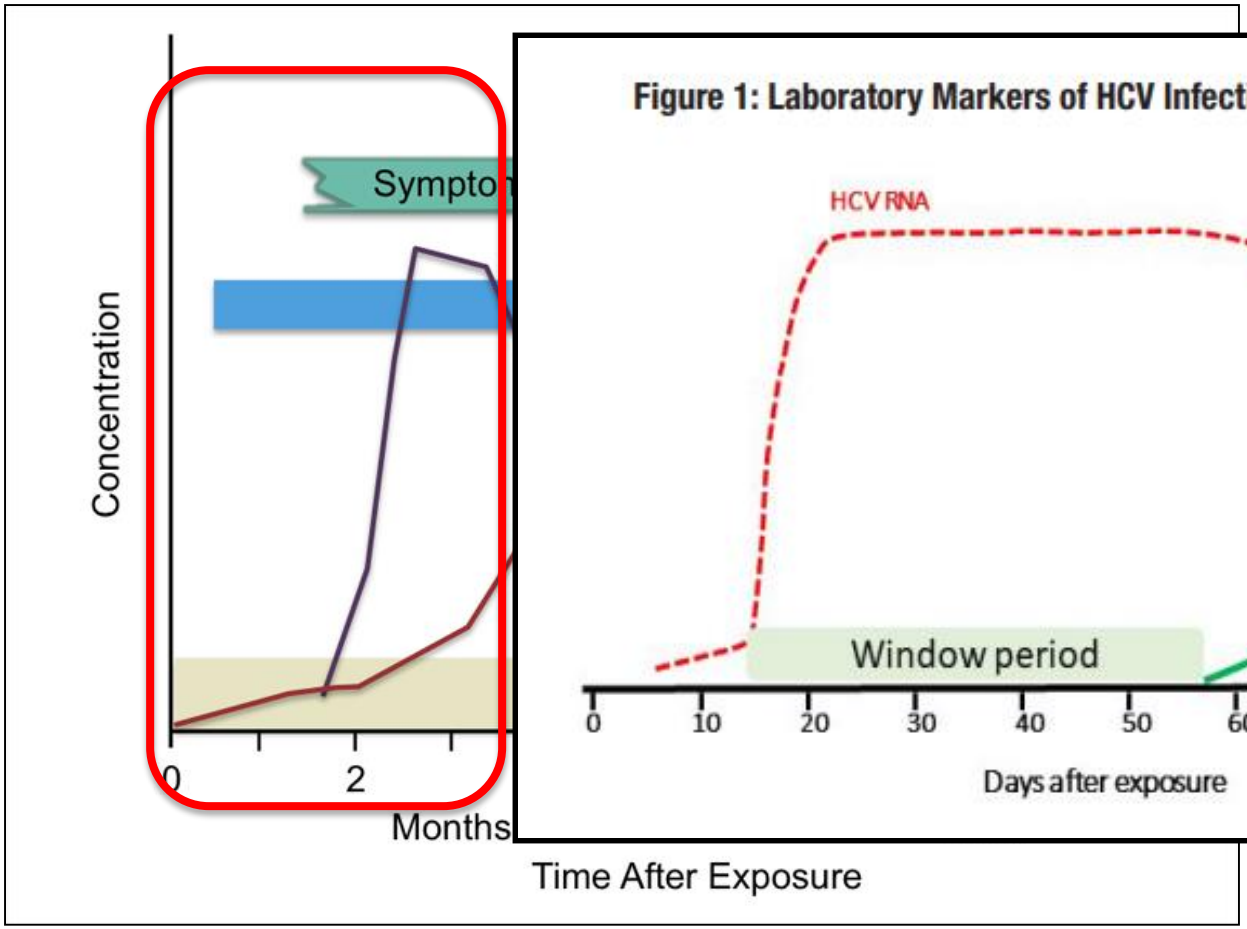
# Lab markers of HCV infection







*Hepatitis C Online- https://www.hepatitisc.uw.edu/go/screening-diagnosis/acute-diagnosis/core-concept/all ; also Association of Public Health Laboratories, "Interpretation of Hepatitis C Virus Test Results: Guidance for Laboratories (Jan 2019), accessed at: https://www.aphl.org/aboutAPHL/publications/Documents/ID-2019Jan-HCV-Test-Result-Interpretation-Guide.pdf.*

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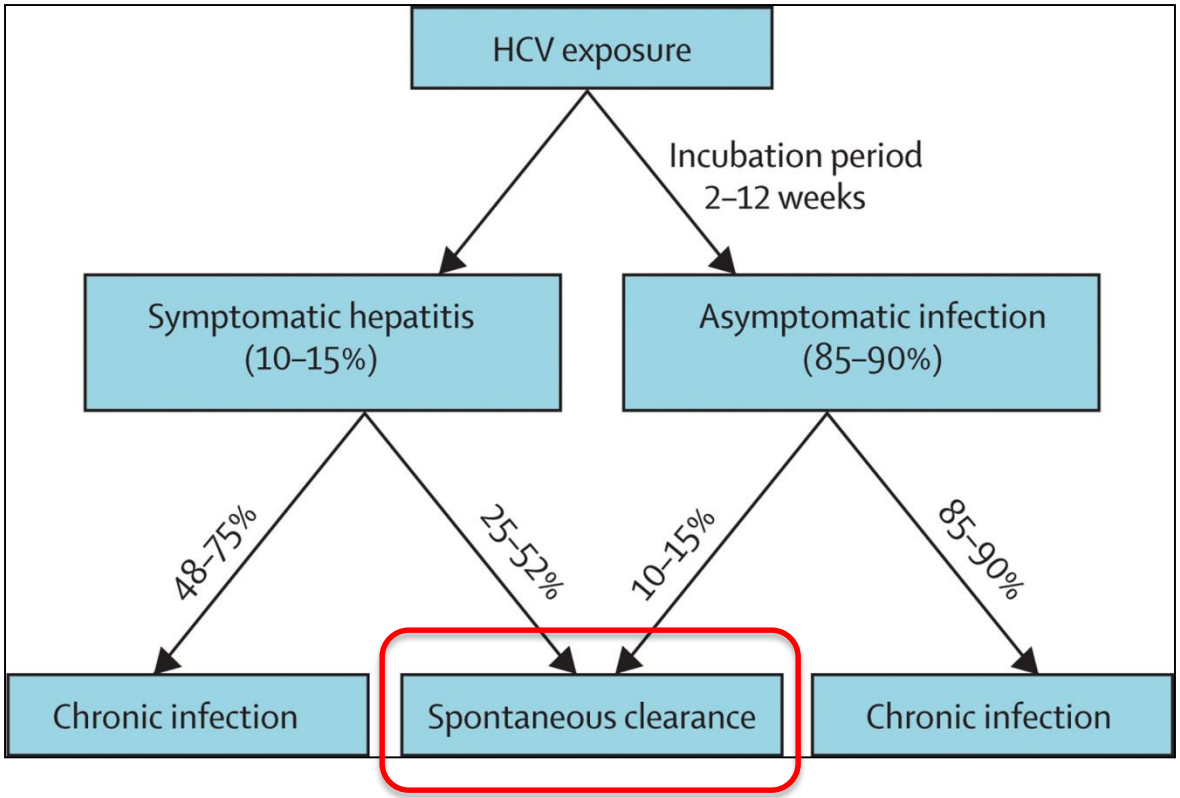
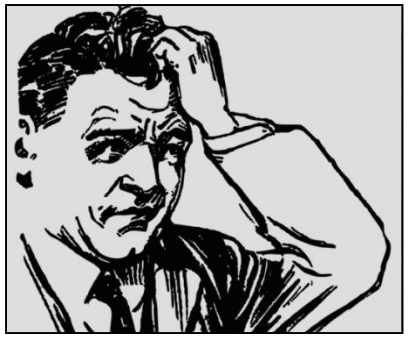
# *"I've heard people can sometimes 'clear' HCV on their own??"*




*Maheshwari A, Thuluvath PJ. Endocrine diseases and the liver. Clin Liver Dis. 2011 Feb; 15(1): 55-67.*
*Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. Lancet. 2008; 372:321-332. Accessed at:*
*https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=272*

# Comparison of HCV tests



## *HCV antibody ("anti-HCV")*

- Can screen for prior exposure to hepatitis C
- Positive, negative, or indeterminate result (reactive, non-reactive)
- Widely available and faster turnaround (doesn't require batching), POC assay available

## *HCV RNA*

- Confirms current "active" infection, assesses HCV treatment response
- Qualitative and quantitative (viral load)
- Longer turnaround: requires batching, many labs may not run in-house
- More sensitive and becomes positive sooner, can be more helpful/definitive when assessing transmission risk

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# Multiple HCV RNA assays available

**Table 1: Currently Available FDA-Approved HCV Qualitative and Quantitative RNA Tests**

| Manufacturer (PMA #) | Device[a] | LoD[b] Serum | LoD[b] Plasma | LLoQ[c] (serum or plasma) | ULoQ[d] (serum or plasma) |
|---|---|---|---|---|---|
| Abbott Molecular (P00017) | Abbott RealTime HCV | 1.08 $\log_{10}$ IU/mL **12.0 IU/mL** | 1.08 $\log_{10}$ IU/mL **12.0 IU/mL** | 1.08 $\log_{10}$ IU/mL **12.0 IU/mL** | 8 $\log_{10}$ IU/ml **100,000,000 IU/mL** |
| Hologic (P020011) | Aptima HCV Qual Dx Assay | **5.3 IU/mL** | **5.3 IU/mL** | N/A Qualitative Assay | N/A Qualitative Assay |
| Hologic (P160023) | Aptima HCV Quant Dx Assay | 0.53 $\log_{10}$ IU/mL **3.4 IU/mL** | 0.59 $\log_{10}$ IU/mL **3.9 IU/mL** | 1.0 $\log_{10}$ IU/ml **10.0 IU/mL** | 8 $\log_{10}$ IU/ml **100,000,000 IU/mL** |
| Roche Molecular (P150015) | cobas-HCV (for 6800/8800) | **13.7 IU/mL** | **12.0 IU/mL** | **15.0 IU/mL** | **100,000,000 IU/mL** |
| Roche Molecular (P060030)[e] | COBAS Ampliprep/ COBAS Taqman HCV Test | **15.0 IU/mL** | **15.0 IU/mL** | **15.0 IU/mL** | **100,000,000 IU/mL** |

*From: Association of Public Health Laboratories, "Interpretation of Hepatitis C Virus Test Results: Guidance for Laboratories (Jan 2019), available at https://www.aphl.org/aboutAPHL/publications/Documents/ID-2019Jan-HCV-Test-Result-Interpretation-Guide.pdf.*

*See also: Kamili S, Drobeniuc J, Araujo A, et al. Laboratory diagnostics for hepatitis C virus infection. Clin Inf Dis. 2012; 55(S1): S43-8.*

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# APHL guidance for laboratories, Jan 2019: select recommendations (related to BBFE management)

- For persons who had a negative anti-HCV and a potential HCV exposure within the past 6 months, testing for HCV RNA or follow-up testing for anti-HCV is recommended
- For persons with a positive anti-HCV and negative HCV RNA [at baseline], HCV RNA testing should be repeated if:
  - Potential HCV exposure within the past six months
  - Clinical evidence of HCV present
  - Concerns regarding specimen integrity

https://www.aphl.org/aboutAPHL/publications/Documents/ID-2019Jan-HCV-Test-Result-Interpretation-Guide.pdf *(Updated Jan 2019)*

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# More confusion? (…this time brought to you by the PEPline!) 😬

## Exposures to HCV

(dev'd early 2017; not yet updated)

**How are exposures to HCV managed?**

• The risk of HCV transmission after percutaneous exposure is about 1 in 56 (1.8%) when the so
person is HCV-infected. There is no post-exposure prophylaxis currently available/approved for H
prevention.
• After review of available studies, guidelines and summary documents, the CCC PEPline recom
the following approach:

**Testing Recommendations for the Exposed Person**

| Recommendations | | Baseline testing | Initial follow-up | Final follow-u |
|---|---|---|---|---|
| **PEPline 2017** | HCV+ SP [1] or SP has potential HCV risk factors [1] | HCV Ab [2] | 6 weeks [3] HCV RNA (HCV viral load) | ≥6 months [4 HCV Ab |
| | SP HCV status unknown [1] or SP is known and has no known HCV risk factors [1] | | Optional: 6 week HCV RNA | |
| CDC 2016 [6] | All source persons [1] | HCV Ab [2] | ≥3 weeks HCV RNA | Optional: ≥6 month HCV Ab [2] |
| CDC 2001 [7] | | HCV Ab and ALT | If earlier diagnosis desired: HCV RNA at 4-6 weeks | 4-6 months HCV Ab and ALT |

Abbreviations: HCV+ = hepatitis C positive; SP = source person; Ab = antibody; ALT = aminotransferase

[1] For purposes of initial post-exposure management, a source person is considered HCV-positive if either HCV RNA (HCV viral load) or HCV antibody is positive. HCV RNA, when performed on the SP within a few days of the exposure, is the more accurate indicator of infectivity. For the purpose of deciding whether the source can potentially transmit HCV, HCV antibody can be obtained. Positive HCV antibody, however does not always indicate infectivity because: some patients eradicate HCV naturally but retain HCV antibody; and those with active HCV infection can have fluctuating HCV RNA (viral load) as well as undetectable viral load (and are presumably un-infectious at that time when viral load was undetectable).
[2] If HCV antibody is positive at any point, follow-up HCV RNA testing is required. Persons with confirmed positive HCV RNA results should be referred for further evaluation and care.
[3] The PEPline recommends initial HCV follow-up test at 6 weeks, to coincide with the first HIV follow-up test. There are no data that establish a clinical advantage to testing at 3 weeks vs. 6 weeks [*Glynn, et al, Busch, et al, Hajarizadeh, et al*]. HCV RNA becomes detectable beginning at 3 weeks. Testing earlier than 6 weeks can be performed at the discretion of the managing clinician, especially if preliminary assessment is needed. Positive HCV RNA indicates likely infection. However, approximately 25% of new infections will clear spontaneously [*Naggie, et al*]. Refer to an experienced provider for additional counseling, testing, and follow-up if positive.

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# Ready for more?

**Table 2. Testing for Hepatitis C Virus Infection Following Exposure**

| | Laboratory Testing | | | |
|---|---|---|---|---|
| Timing After Exposure | HCV EIA | HCV RNA | ALT | Comment |
| Source patient Immediate | Yes | If HCV EIA positive: Yes<br>If HCV EIA negative: Recommend only if source is at risk for false-negative test | No | Although HCV RNA testing is not routinely recommended, it may be useful in immunocompromised source patients who may have false-negative serology. |
| Healthcare worker (if source patient has evidence of HCV infection) | | | | |
| Immediate | Yes | If HCV EIA positive: Yes | Yes | Healthcare worker does not require follow-up if source patient is HCV negative; however, baseline testing of HCW is prudent. |
| 4–6 wk | Yes | Yes | Consider | If earlier diagnosis of HCV infection is desired, testing for HCV RNA may be performed to help guide treatment decision making. Due to the intermittent nature of HCV viremia in acute HCV infection, RNA testing should not be the sole screening test. |
| 4–6 mo | Yes | Yes | Yes | HCV antibody testing 4–6 mo postexposure is considered the optimal means of detecting infection, although seronegative infections have been reported. |

Abbreviations: ALT, alanine aminotransferase; EIA, enzyme immunoassay; HCV, hepatitis C virus; HCW, healthcare worker; RNA, ribonucleic acid.

*Naggie S, Holland DP, Sulkowski D, Thomas DL. Hepatitis C virus postexposure prophylaxis in the healthcare worker: why direct-acting antivirals don't change a thing. Clin Inf Dis. 2017. 64(1): 92-9.*

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# Updated HCV transmission estimates!

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Seroconversion rates among health care workers exposed to hepatitis C virus–contaminated body fluids: The University of Pittsburgh 13-year experience

Francesco M. Egro MBChB, MSc, MRCS [a,*], Chibueze A. Nwaiwu BSN [b], Saundra Smith RN [c], Jay D. Harper MD, MPH [c], Alexander M. Spiess MD [a]

- Longitudinal analysis of prospectively maintained database of reported occupational injuries, 2002-2015, University of Pittsburgh Medical Center
  - 0.1% overall HCV seroconversion rate (0.2% for percutaneous injuries)
- Non-systematic literature review of select studies, 1991-2016
  - 0.7% seroconversion rate (0.8% for percutaneous events)

https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#Ref24

*Egro FM, Nwaiwu CA, Smith S, et al. Seroconversion rates among health care workers exposed to hepatitis C virus-contaminated body fluids: The University of Pittsburgh 13-year experience. Am J Inf Control. 2017. 45: 1001-5.*

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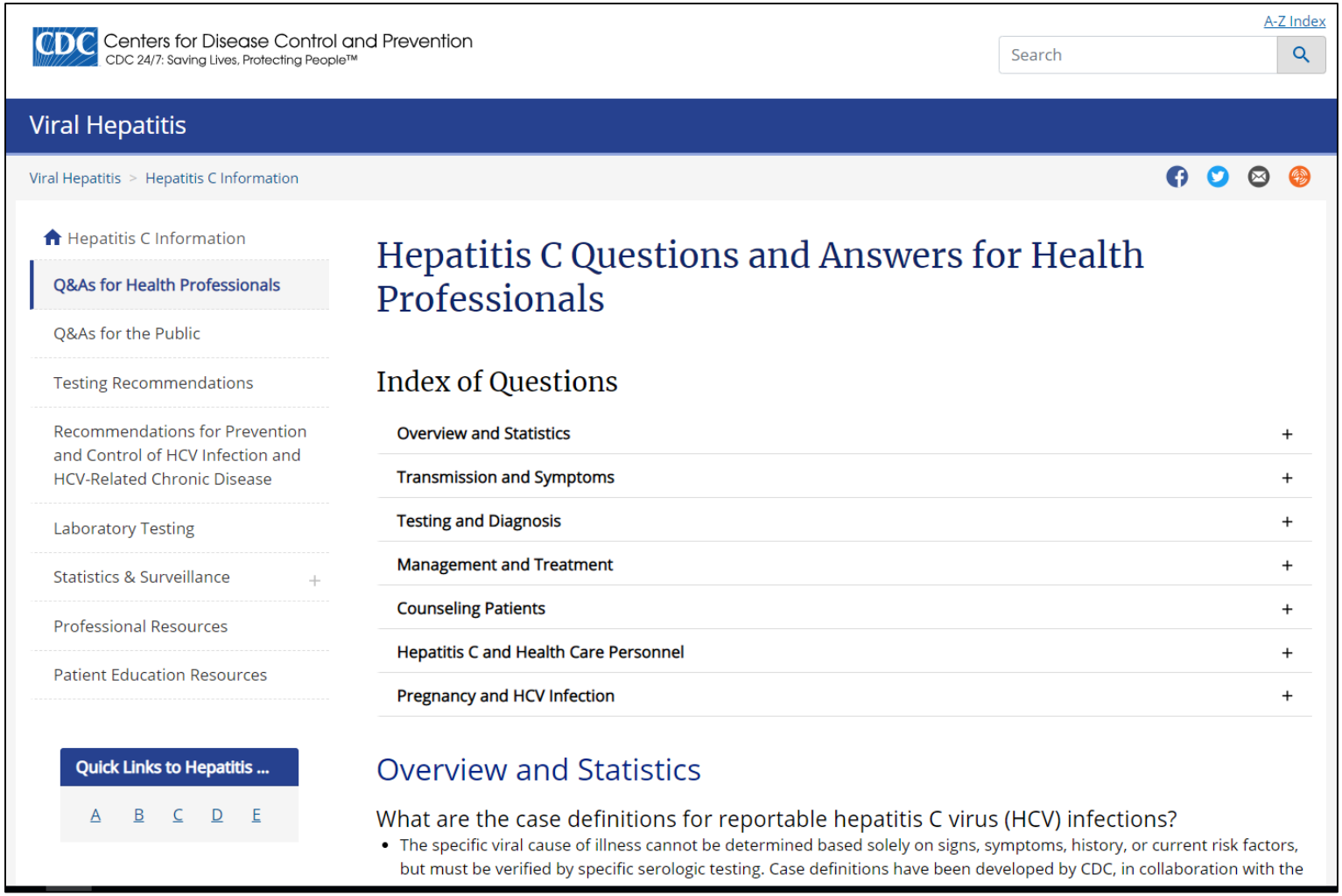


https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#Ref24

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# One thing remains: no HCV PEP recommended

*Clinical Infectious Diseases*

INVITED ARTICLE

VIRAL HEPATITIS: Camilla S. Graham, Section Editor

## Hepatitis C Virus Postexposure Prophylaxis in the Healthcare Worker: Why Direct-Acting Antivirals Don't Change a Thing

Susanne Naggie,[1,2] David P. Holland,[3] Mark S. Sulkowski,[4] and David L. Thomas[4]

[1]Duke Clinical Research Institute, and [2]Duke University School of Medicine, Durham, North Carolina; [3]Emory University School of Medicine, Atlanta, Georgia; and [4]Johns Hopkins School of Medicine, Baltimore, Maryland

(See the Editorial Commentary by Barocas and Linas on pages 108–9.)

Currently, 380 000–400 000 occupational exposures to blood-borne pathogens occur annually in the United States. The management for occupational HIV or hepatitis B virus exposures includes postexposure prophylaxis (PEP) when necessary; however, PEP is not recommended for hepatitis C virus (HCV) exposures. Recent approval of HCV direct-acting antivirals (DAAs) has renewed discussions as to whether these therapies could be used to prevent infection after exposure. There are no published studies addressing this question, but the prescribing of DAAs for PEP has been reported. We will discuss the differences in transmission of the 3 most common blood-borne pathogens, the natural history of early HCV infection, and the scientific rationale for PEP. In particular, we will discuss how the low feasibility of conducting an adequately powered clinical trial of DAA use for PEP and the low cost-effectiveness of such an intervention is not supportive of targeting limited resources for such use.

Keywords. hepatitis C virus; occupational exposure; direct acting antivirals; postexposure prophylaxis; cost-analysis.

Occupational exposure to blood-borne pathogens is a recognized risk for all healthcare workers (HCWs). A total of 380 000–400 000 occupational exposures occur annually in the United States [1, 2]. Three blood-borne pathogens account for the majority of cases: human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) [3]. Specific management for HIV or HBV exposures includes postexposure prophylaxis (PEP) and, in the case of HBV, vaccination [4–6]. Currently, PEP is not recommended for HCV exposures. We will discuss the differences in transmission, the natural history of early HCV infection, and the scientific rationale for and against PEP. In particular, we will discuss what role, if any, direct-acting antivirals (DAAs) for HCV should play in PEP. Due to the rapidly changing standard of care of HCV treatment, we will not focus on specific DAA therapies, but the principle of DAAs for HCV PEP.

### OCCUPATIONAL TRANSMISSION OF HCV

The occupational transmission of HCV is well documented, although the variation in reported rates is wide (0%–10%) [7–18](Table 1). The majority of reports support a low estimated transmission rate, and pooled longitudinal data following parenteral exposure to blood from HCV-infected source patients reported an estimated incidence of 1.9% per exposure [19]. This is compared to a 0.32% risk (approximately 1 infection for every 325 documented exposures) and 19%–37% risk (approximately 1 infection for every 3–5 documented exposures among HCWs without protective immunity from HBV vaccination) per percutaneous exposure to blood from HIV-infected and HBV-infected source patients, respectively [20–23].

These data conform to the conceptual model that transmission risk is directly proportional to the infectivity of the body fluid and the susceptibility of the tissue exposed [24]. The infectivity of the body fluid is assumed to correlate with both the concentration of viral particles in the body fluid and the volume of inoculation. Supporting this model is the observation that transmission is high with hollow-bore needlesticks that can transfer a larger inoculum and greatest with deep penetration of a scalpel into muscle [18, 22].

While HCV RNA has been detected in other body fluids including saliva, semen, and vaginal secretions, HCV RNA levels are consistently higher in serum [25–27]. Existing data suggest that a higher level of HCV RNA in serum correlates to higher risk of transmission [22, 28–30]. Chimpanzee challenge studies have suggested that there is an infectious titer (chimpanzee infective dose) required to transmit infection, and that this level of inoculum is different in other animal models (humanized liver-mouse models) [31]. Whereas these studies have unequivocally established the infectivity of blood, it is possible that RNA detected in other body fluids might not correspond as directly with infectious virions.

Received 18 May 2016; accepted 5 August 2016; published online 26 September 2016.
Correspondence: S. Naggie, 2400 Pratt St, Rm 8311 Terrace level, Durham, NC 27705
Clinical Infectious Diseases® 2017;64(1):92–9

DOI: 10.1093/cid/ciw678





- Risk of transmission in healthcare workers is very low
- For the rare employee who develops acute infection, eradication rate with highly efficacious and safe DAA combination therapies is near 100%
- *"There is unlikely to be a scenario by which PEP is cost-effective compared with early HCV treatment, with the exception of a 2-day course of PEP"*

*Naggie S, Holland DP, Sulkowski D, Thomas DL. Hepatitis C virus postexposure prophylaxis in the healthcare worker: why direct-acting antivirals don't change a thing. Clin Inf Dis. 2017. 64(1): 92-9.*

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# ClinicalTrials.gov: NCT03313414

- Sponsor: Massachusetts General Hospital, with Gilead Sciences listed as collaborator, PI: Chung

- Unblinded, open label, observational Phase 4 trial of sofosbuvir-velpatasvir (x14 days) in adult HCW who are exposed to hepatitis C virus from needlestick injuries involving hollow-bore needles
- Estimated study start: March 15, 2019; estimated study completion: July 1, 2022 (60 participants estimated)

https://clinicaltrials.gov/ct2/show/NCT03313414?cond=hepatitis+C+post-exposure+prophylaxis&rank=2

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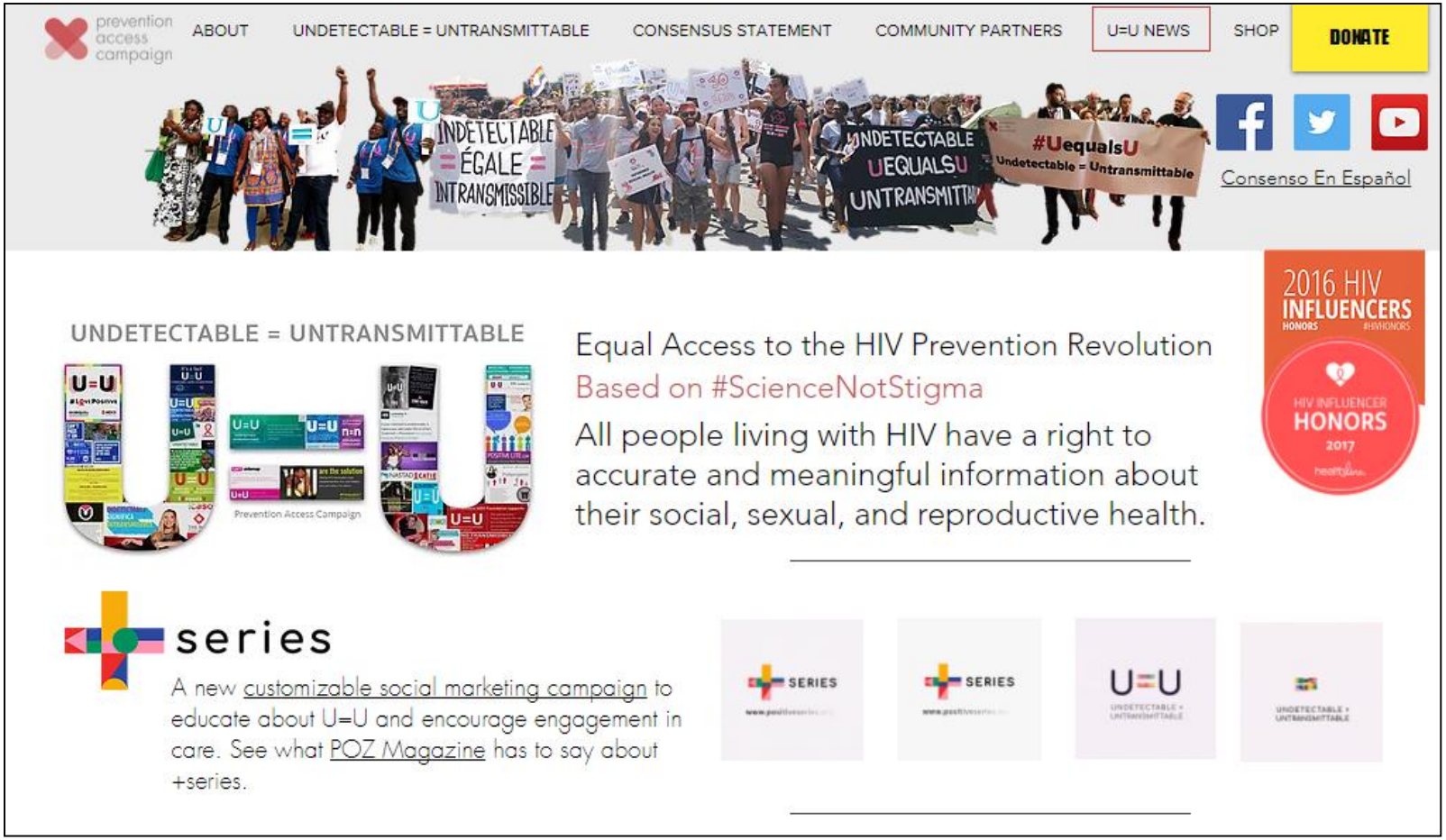
# U=U



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*"Scientists never like to use the word 'never' of a possible risk.* ***But I think in this case we can say that the risk of transmission from an HIV-positive person who takes treatment and has an undetectable viral load may be so low as to be unmeasurable, and that's equivalent to saying they are uninfectious.*** *It's an unusual situation when the overwhelming evidence base in science allows us to be confident that what we are saying is fact."*

- Anthony S. Fauci, MD, Director, NIAID, NIH
(July, 2017)

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# What has this meant for the PEPline?



the risk for infection). One laboratory study that demonstrated that more blood is transferred by deeper injuries and hollow-bore needles lends further credence to the observed variation in risk related to inoculum size.[23]

Exposure to a source patient with an undetectable serum viral load does not eliminate the possibility of HIV transmission or the need for PEP and follow-up testing. While the risk of transmission from an occupational exposure to a source patient with an undetectable serum viral load is thought to be very low, PEP should still be offered. Plasma viral load (eg, HIV RNA) reflects only the level of cell-free virus in the peripheral blood; persistence of HIV in latently infected cells, despite patient treatment with antiretroviral drugs, has been demonstrated,[24,25] and such cells might trans-

primarily for persons wi
prolonged antiretroviral
flect the experience of
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infected patients on anti
have been cited as a m
regimens as prescribed,
heavily influenced towa
HCP receiving PEP. P
agents should be discuss
anticipated, preemptive
side effects (eg, antiemet

*Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis. Kuhar DT, Henderson DK, Struble KA, et al. US Public Health Service Working Group. Inf Control Hosp Epi. 2013. 34(9): 875-892.*

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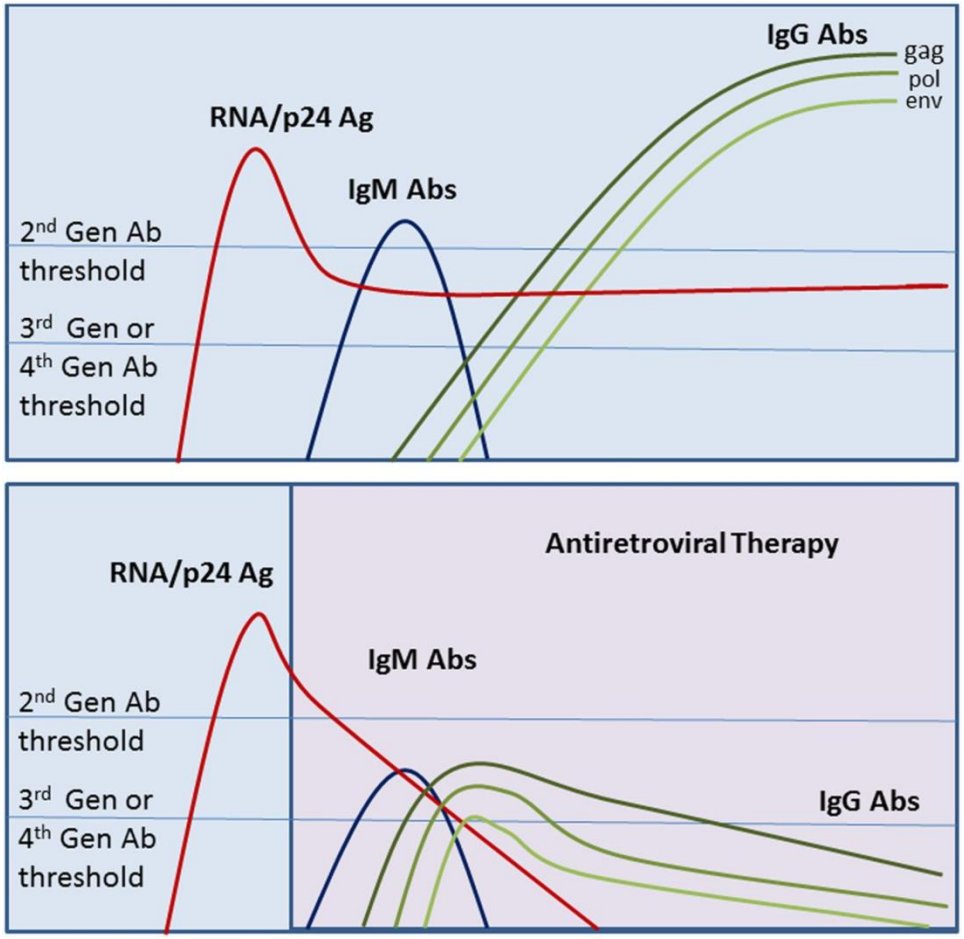
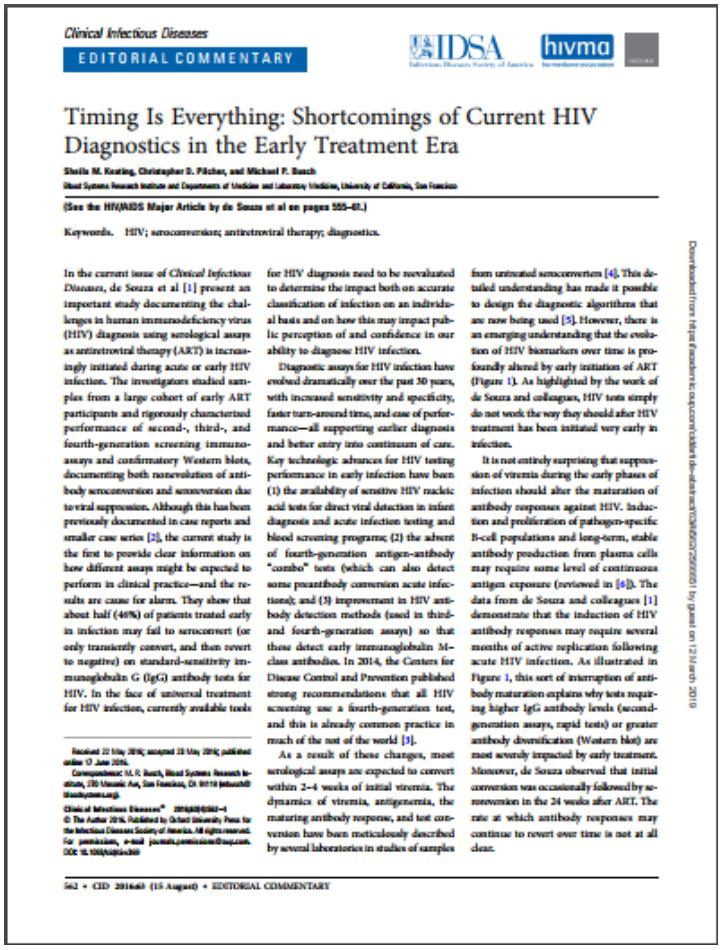
Table 1.
**Estimated Per-Act Probability of Acquiring HIV from an Infected Source, by Exposure Act***

| Exposure Type | Rate for HIV Acquisition per 10,000 Exposures |
|---|---|
| **Parenteral** | |
| Blood transfusion | 9,250 |
| Needle sharing during injection drug use | 63 |
| Percutaneous (needlestick) | 23 |
| **Sexual** | |
| Receptive anal intercourse | 138 |
| Insertive anal intercourse | 11 |
| Receptive penile-vaginal intercourse | 8 |
| Insertive penile-vaginal intercourse | 4 |
| Receptive oral intercourse | Low |
| Insertive oral intercourse | Low |
| **Other**^ | |
| Biting | Negligible |
| Spitting | Negligible |
| Throwing body fluids (including semen or saliva) | Negligible |
| Sharing sex toys | Negligible |

*Factors that may increase the risk of HIV transmission include sexually transmitted diseases, acute and late-stage HIV infection, and high viral load. Factors that may

# Additional considerations: early ART for HIV and possible implications for testing



Clinical Infectious Diseases

EDITORIAL COMMENTARY

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Timing Is Everything: Shortcomings of Current HIV Diagnostics in the Early Treatment Era

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(See the HIV/AIDS Major Article by de Souza et al on pages 555–61.)

Keywords. HIV; seroconversion; antiretroviral therapy; diagnostics.

In the current issue of *Clinical Infectious Diseases*, de Souza et al [1] present an important study documenting the challenges in human immunodeficiency virus (HIV) diagnosis using serological assays as antiretroviral therapy (ART) is increasingly initiated during acute or early HIV infection. The investigators studied samples from a large cohort of early ART participants and rigorously characterized performance of second-, third-, and fourth-generation screening immunoassays and confirmatory Western blots, documenting both nonevolution of antibody seroconversion and seroreversion due to viral suppression. Although this has been previously documented in case reports and smaller case series [2], the current study is the first to provide clear information on how different assays might be expected to perform in clinical practice—and the results are cause for alarm. They show that about half (46%) of patients treated early in infection may fail to seroconvert (or only transiently convert, and then revert to negative) on standard-sensitivity immunoglobulin G (IgG) antibody tests for HIV. In the face of universal treatment for HIV infection, currently available tools for HIV diagnosis need to be reevaluated to determine the impact both on accurate classification of infection on an individual basis and on how this may impact public perception of and confidence in our ability to diagnose HIV infection.

Diagnostic assays for HIV infection have evolved dramatically over the past 30 years, with increased sensitivity and specificity, faster turn-around time, and ease of performance—all supporting earlier diagnosis and better entry into continuum of care. Key technologic advances for HIV testing performance in early infection have been (1) the availability of sensitive HIV nucleic acid tests for direct viral detection in infant diagnosis and acute infection testing and blood screening programs; (2) the advent of fourth-generation antigen-antibody "combo" tests (which can also detect some preantibody conversion acute infections); and (3) improvement in HIV antibody detection methods (used in third- and fourth-generation assays) so that these detect early immunoglobulin M–class antibodies. In 2014, the Centers for Disease Control and Prevention published strong recommendations that all HIV screening use a fourth-generation test, and this is already common practice in much of the rest of the world [3].

As a result of these changes, most serological assays are expected to convert within 2–4 weeks of initial viremia. The dynamics of viremia, antigenemia, the maturing antibody response, and test conversion have been meticulously described by several laboratories in studies of samples from untreated seroconverters [4]. This detailed understanding has made it possible to design the diagnostic algorithms that are now being used [5]. However, there is an emerging understanding that the evolution of HIV biomarkers over time is profoundly altered by early initiation of ART (Figure 1). As highlighted by the work of de Souza and colleagues, HIV tests simply do not work the way they should after HIV treatment has been initiated very early in infection.

It is not entirely surprising that suppression of viremia during the early phases of infection should alter the maturation of antibody responses against HIV. Induction and proliferation of pathogen-specific B-cell populations and long-term, stable antibody production from plasma cells may require some level of continuous antigen exposure (reviewed in [6]). The data from de Souza and colleagues [1] demonstrate that the induction of HIV antibody responses may require several months of active replication following acute HIV infection. As illustrated in Figure 1, this sort of interruption of antibody maturation explains why tests requiring higher IgG antibody levels (second-generation assays, rapid tests) or greater antibody diversification (Western blot) are most severely impacted by early treatment. Moreover, de Souza observed that initial conversion was occasionally followed by seroreversion in the 24 weeks after ART. The rate at which antibody responses may continue to revert over time is not at all clear.

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# So when should I consider ordering HIV viral load?**

- "High risk" source persons who test negative on point-of-care assay (especially if not a 4th generation POC) or lab-based antibody-only screening assay
  - If clinical signs/symptoms suggestive of acute HIV
  - If source screens negative and no significant/recent risks identified, no follow-up testing clinically indicated*
- Exposed persons for whom timely HIV diagnosis would be of particularly critical importance (e.g. pregnancy, breastfeeding)

IF SP known to be PLWH and on ART, consider getting VL, as low/undetectable VL may be highly reassuring; *likely little value in ordering VL if SP is **not** on ART.*

*Ditto for HBV, HCV; however note many institutions may routinely conduct surveillance for medico-legal purposes

** Additional, less common scenarios for consideration of VL include SP/EP with known/documented history of "false positive" results on HIV screening assays, as may occur with receipt of certain investigational HIV vaccine, etc. ???recent PrEP/PEP ???

# Two-way (bilateral) exposures

- Appropriate recognition/management of bilateral exposures is important, as post-exposure testing and follow-up are necessarily more complex because these incidents potentially involved 2 source persons (and 2 exposed persons)!
  - *Who does what? How to best coordinate and communicate testing and follow-up?*
  - *What are best practices?*

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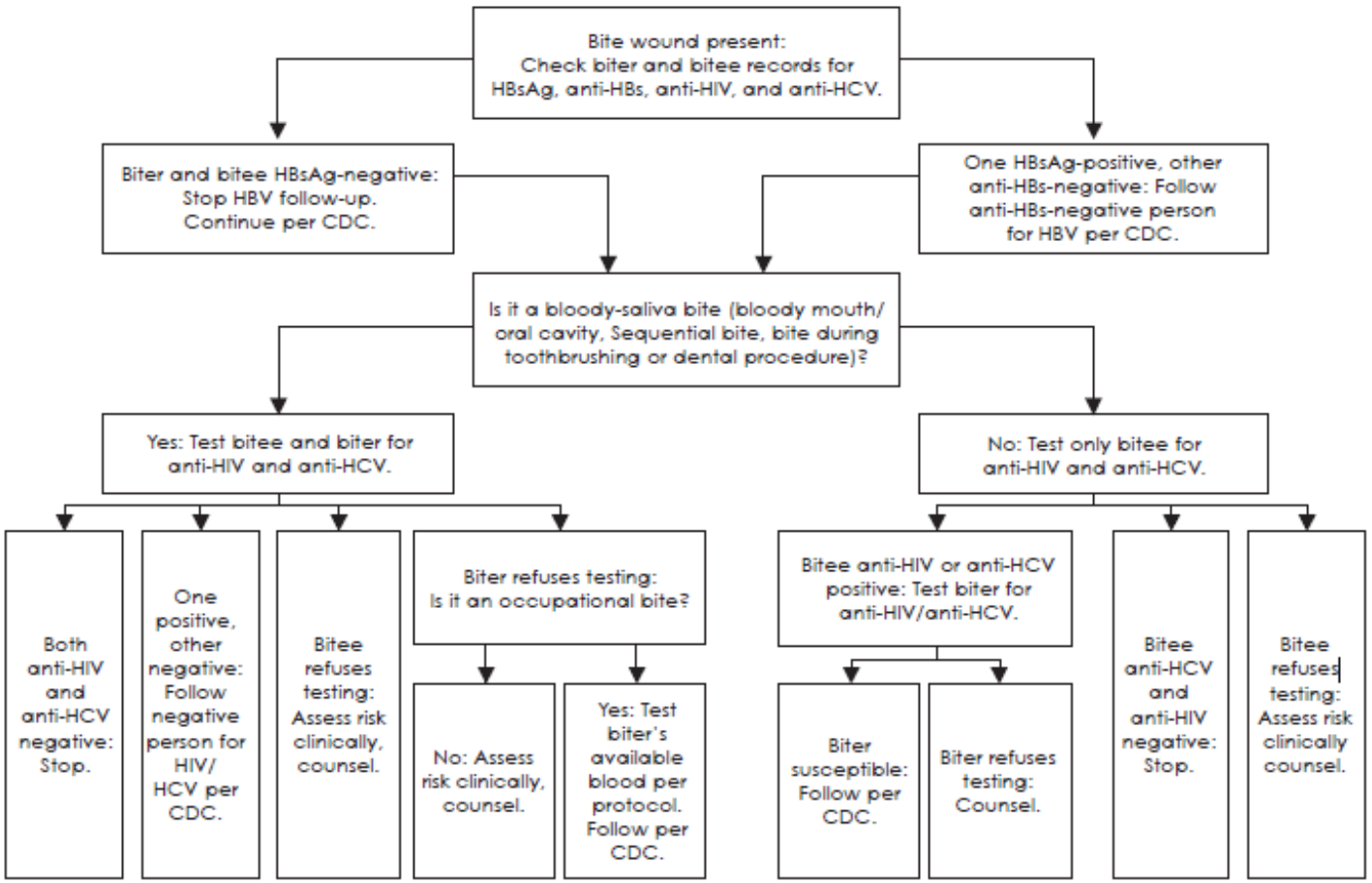
**Figure.** Algorithm for Postexposure Testing and Follow-up of Bites for Bloodborne Pathogen Transmission




Follow per CDC: Follow per CDC's guidelines for contaminated needlesticks.[1] Postexposure follow-up algorithm is necessarily more complex for bites than needlesticks because bites expose 2 persons and involve the variable of "visible blood in saliva." In contrast, although far more riskier, contaminated needlesticks expose only 1 person (the recipient) and involve no "visible blood" variable.

Anti-HBs indicates hepatitis B surface antibody; anti-HCV, hepatitis C antibody; anti-HIV, human immunodeficiency virus antibody; BP, bloodborne pathogens; CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus.

*Lohiya G-S, Tan-Figueroa L, Lohiya S, et al. Human bites: BBP risk and postexposure follow-up algorithm. J Natl Med Assoc. 2013: 105; 92-95.*

# Key points

(1) The CDC now prefers HCV viral load testing, if/when possible.

(2) The HIV scientific and clinical communities have embraced the concept of "*Undetectable = Untransmittable*", underscoring the potential role and value of HIV viral load testing with BBFE in certain situations.

(3) It is important to appropriately recognize and report bilateral exposures, due to necessary baseline testing and follow-up coordination involving multiple responsible parties.

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# Thank you!

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