

# RESEARCH INITIATIVE



**Treatment Action!**

## INTERVIEW WITH:

**Douglas T. Dieterich, MD**

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## **Research Initiative / Treatment Action!**

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*RI TA!* reports on issues in HIV/AIDS research and policy, and is intended for the HIV research, medical, and professional communities. The statements and opinions expressed herein do not imply recommendations or endorsement. Always consult your doctor before taking any drug or altering a prescribed drug regimen.

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## DAAs for HCV/HIV coinfection: lots more to learn

By Mark Mascolini .....

Writing about direct-acting antivirals (DAAs) for HCV infection in early 2014 is like writing a World Series wrap-up on the first day of spring training. Compared with the dazzling DAA dawn, the advent of HIV protease inhibitors and nonnucleosides in the mid-1990s seems almost sedate. For both infections, the debut of potent new antivirals transformed treatment. But there the similarities end (**Figure 1 page 9**).

HIV protease inhibitors and nonnucleosides did not replace nucleosides, the first antiretroviral class. They teamed with nucleosides to create potent triple regimens that could stop HIV replication but not cure the infection. HCV DAAs do cure a remarkably high percentage of patients—90% to 100%—and show every sign of consigning the time-worn anti-HCV duo—interferon and ribavirin—to the pharmacologic dustbin.

The antiretroviral classes new in the mid-1990s—protease inhibitors and nonnucleosides—were not joined by entry inhibitors and integrase inhibitors until 2003 and 2007. Already four classes of DAAs are on pharmacy shelves or in late stages of de-

velopment: NS3/NS4A protease inhibitors, NS5A nonenzyme replication complex inhibitors, NS5B polymerase nucleosides and nucleotides, and NS5B polymerase nonnucleosides (**Table 1**). Other non-DAA agents, such as host cyclophilin inhibitors, also figure in the mix.

And now that DAAs have (emphatically) arrived, keeping up with new agents, new combinations, and new treatment advice has become a full-time job. Or maybe several full-times jobs. [www.hcvguidelines.org](http://www.hcvguidelines.org), managed by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA), has a home page plastered with provisos about rapidly evolving therapeutic strategies and advice, including a home-page section on “Updates/Changes” where “notable changes are highlighted.” This regularly revised website warns that “guidance for hepatitis C treatment is changing constantly with the advent of new therapies and other developments. A static version of this guidance, such as a printout of this website material, booklet, slides, and other materials, may be outdated by the time you read this.”<sup>1</sup>

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But read this “static version” of DAA insights anyway, because it tries to outline some larger issues without shackling itself to last week’s trial results or last month’s treatment advice.

In the [hcvguidelines.org](http://hcvguidelines.org) section on HCV/HIV coinfection, the two HCV protease inhibitors licensed in 2011—telaprevir and boceprevir—no longer merit a recommendation for treatment-naïve people or those in whom pegylated interferon/ribavirin (PEG/RBV) failed.<sup>2</sup> Because of their toxicity and manifold interactions with antiretrovirals, these two vanguard DAAs have already been shouldered aside by the protease inhibitor simeprevir and the NS5B nucleo-

side sofosbuvir in the latest guidelines. But hold onto your hat. An eager army of other DAAs has reached late stages of development and could displace or combine with simeprevir and sofosbuvir for certain patients (**Table 1**).

Investigational interferon-free regimens, and interferon/ribavirin-free regimens, abound. And fixed-dose combinations of DAAs from different classes are on their way. Gilead Sciences has filed for approval of a once-daily pill melding the NS5A inhibitor ledipasvir with the already licensed NS5B inhibitor sofosbuvir. Ritonavir-boosted ABT-450 is coformulated with ombitasvir (ABT-267).

**Table 1.** Abbreviated list of licensed or late-stage DAAs for HCV infection

NS3/NS4A protease inhibitors	NS5A replication complex inhibitors	NS5B nucleoside/tide polymerase inhibitors	NS5B nonnucleoside polymerase inhibitors	Cyclophilin inhibitors
<ul style="list-style-type: none"> <li>• Simeprevir*</li> <li>• Boceprevir*</li> <li>• Telaprevir*</li> <li>• Asunaprevir</li> <li>• Danoprevir</li> <li>• Faldaprevir</li> <li>• Sovaprevir</li> <li>• ABT-450</li> <li>• GS-9451</li> <li>• MK-5172</li> </ul>	<ul style="list-style-type: none"> <li>• Daclatasvir</li> <li>• Ledipasvir</li> <li>• Samatasvir</li> <li>• Ombitasvir (ABT-267)</li> <li>• GS-8516</li> <li>• MK-8742</li> </ul>	<ul style="list-style-type: none"> <li>• Sofosbuvir*</li> <li>• Meracitabine</li> </ul>	<ul style="list-style-type: none"> <li>• Deleobuvir</li> <li>• Dasabuvir (ABT-333)</li> <li>• BMS-791325</li> <li>• GS-9669</li> </ul>	<ul style="list-style-type: none"> <li>• Alisporivir</li> <li>• SCY-635</li> </ul>

\*Licensed by FDA.

## Early findings on DAA-only regimens: a sampler

How strong are the new HCV drugs? Very strong. How fast do they work? Very fast. How much do they cost? Very much.

A thorough summary of DAA trials to date would be ponderous and largely pointless for HIV clinicians. Anyone interested in data on this or that drug in this or that trial can probably track it down at [www.natap.org](http://www.natap.org), which details results of most consequential trials published or presented at key meetings. A quick summary of some standout results will give a taste of how potent these new compounds can be.

A trial that randomized noncirrhotic HCV treatment-naïve or experienced people to ribavirin or no ribavirin plus once-daily daclatasvir plus sofosbuvir charted high sustained virologic responses 12 weeks after therapy ended (SVR12) in previously untreated people with HCV genotype 1 (98%), people in whom boceprevir or telaprevir plus PEG/RBV had failed (98%), previously untreated people with genotype 2 (92%), and untreated people with genotype 3 (89%).<sup>3</sup> Response rates stood above 90% for participants with genotype 1a and 1b, those with the CC or non-CC IL28B genotype (which affects response to PEG/IFN), and those who took or did not take ribavirin. Only 2 people stopped treatment because of adverse events—fibromyalgia and stroke.

In the daclatasvir/sofosbuvir trial,<sup>3</sup> treatment lasted 12 weeks in treatment-naïve participants and 24 weeks in previously treated people. A trial of two or three DAAs in 60 naïve people with genotype

1 charted excellent SVR12s after 6 to 12 weeks of therapy.<sup>4</sup> SYNERGY tested the fixed-dose sofosbuvir/ledipasvir pill with or without GS-9669 (a non-nucleoside) or GS-9451 (a protease inhibitor). Those taking only the fixed-dose combination got treated for 12 weeks; those taking triple therapy got treated for 6 weeks. Most trial participants (70%) had an HCV load above 800,000 IU/mL, and most (82%) had a non-CC IL28B genotype, which dims chances of responding to PEG/RBV.

Twenty of 20 in the sofosbuvir/ledipasvir arm, 19 of 20 in the GS-9669 arm, and 20 of 20 in the GS-9451 arm attained SVR12 in an intention-to-treat analysis. No one stopped treatment and no one had a grade 4 adverse event or serious adverse event related to study drugs. The National Institutes of Health team that headed SYNERGY suggested their results offer “a new paradigm of combination therapy to reduce HCV treatment duration, which may be vital to the treatment and eradication of HCV globally.”<sup>4</sup>

A three-drug DAA medley combining once-daily fixed-dose ABT-450/ritonavir/ ombitasvir with twice-daily dasabuvir in 419 noncirrhotic treatment-naïve people with HCV genotype 1b for 12 weeks yielded 99% SVR12 rates with or without ribavirin.<sup>5</sup> Response rates did not differ by gender, race, or IL28B genotype.

These three trials did not enroll people with HIV infection,<sup>3-5</sup> but work on DAA medleys in HCV/HIV-coinfected people has begun. Part B of the C-WORTHY trial tested MK-5172 plus MK-8742 with or without ribavirin for 12 weeks in 403 people with HCV genotype 1, including 59 with HIV.<sup>6</sup> Part

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A tested the same regimens in 65 people infected only with HCV genotype 1. Among 58 HIV-positive people who had reached 4 weeks of follow-up after treatment ended in part B, 28 of 29 people taking MK-5172/MK-8742 with ribavirin and 26 of 29 taking MK-5172/MK-8742 without ribavirin had a sustained virologic response (SVR4). There was 1 relapse in the ribavirin arm and 2 virologic breakthroughs and 1 loss to follow-up in the no-ribavirin arm. The two people with virologic breakthroughs had low plasma levels of MK-5172 and MK-8742. Response rates were similar in HCV-monoinfected people in Part A.

Fixed-dose formulation sofosbuvir/ledipasvir yielded 100% SVRs 12 and 4 weeks after treatment of HIV-coinfected people in interim results of the ERADICATE trial.<sup>7</sup> Of the 50 study participants, all had HCV genotype 1, none had taken anti-HCV agents, 13 were not taking antiretrovirals, and 37 had an undetectable HIV load with antiretroviral therapy. At the time of this report in May 2014, researchers had SVR12 results for the antiretroviral-untreated people and SVR4 results for the treated people. Regimens in the antiretroviral-treated group included efavirenz, raltegravir, and/or rilpivirine plus tenofovir/emtricitabine. No one discontinued treatment so far. CD4 count and HIV load did not change with sofosbuvir/ledipasvir.

Results like these indicate that DAAs will cure HCV in people with HIV as regularly as in those without HIV, but more enrollment of HIV subgroups in clinical trials—or more trials recruiting only people with HIV—are clearly needed.

Which PEG/RBV-free DAA combination(s) will come out on top? The answer may differ by HCV genotype, but hepatitis experts Marie-Louise Vachon and Douglas Dieterich of New York's Mount Sinai School of Medicine offer some guidance by listing five traits of a “perfect” DAA combination:<sup>8</sup>

1. High cure rates in all categories of patients (independent of host and viral characteristics)
2. Good side-effect profile
3. All oral, once-daily regimen with short treatment duration
4. Limited drug-drug interactions (especially with immunosuppressant medications\*)
5. Affordable in all countries of the world

*\*And, for HIV-positive people, with antiretrovirals.*

So far no single DAA—never mind a DAA combination—comes close to fulfilling criterion number 5. (More on that issue below.) And even experts eschew the task of picking leading contenders for routine use. Jürgen Rockstroh, a top HCV/HIV authority from the University of Bonn, explained why in his review of the 2013 AASLD conference: “With a constantly increasing number of DAAs in development from conference to conference,” he wrote, “it becomes increasingly difficult to foresee where and in whom the individual drugs will be used eventually.”<sup>9</sup>

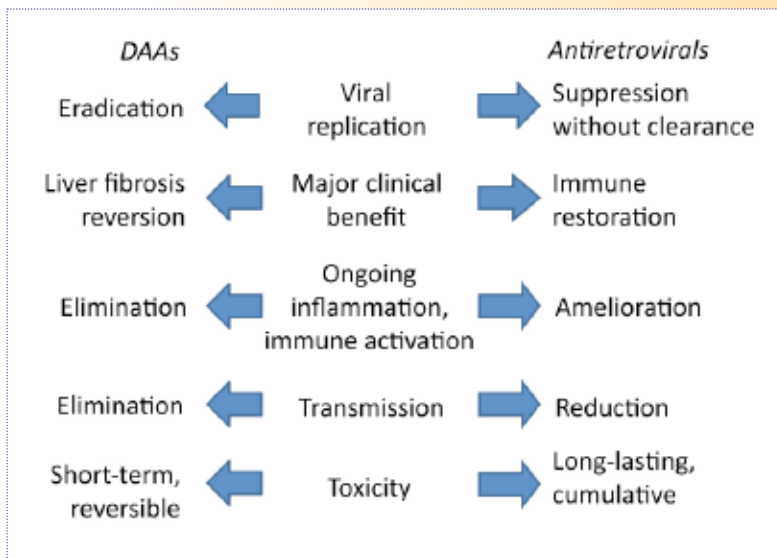
But it's easy to foresee why DAAs will remodel treatment of HCV infection even more than antiretrovirals revamped treatment of HIV (**Figure 1**).<sup>10</sup> In an essay on curing HCV infection, Harvard and Strasbourg University HCV experts Raymond Chung

and Thomas Baumert observe that HCV “replicates its genome directly into RNA without traversing a DNA intermediate, so that unlike HIV or hepatitis B virus, it lacks a latent, nuclear form that defies ready immunologic clearance.”<sup>11</sup> Instead, merely stopping continuous replication snuffs out HCV.

On the basis of DAA data so far, Chung and Baumert predict that DAA combinations “are capable of bridging most of the performance gap between more conventional populations of previously untreated patients and populations that have historically been

difficult to treat”—including people with HIV infection.<sup>11</sup> In April 2014 guidelines, the European Association for the Study of the Liver (EASL) advised that “indications for HCV treatment in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection.”<sup>12</sup> EASL guidelines (linked in the reference list) also offer advice on interactions between new HCV agents and antiretrovirals, as does the AIDS Clinical Trials Group Drug Interactions Database (<https://actgnetwork.org/ACTG-Drug-Interactions-Database>).

**How DAAs and antiretrovirals differ**



**Figure 1.** DAAs for HCV infection hold several advantages over antiretroviral for HIV, as indicated in this schematic based on a table by Vincent Soriano and colleagues at Madrid’s Hospital Carlos III.<sup>10</sup>

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### Remaining roles for interferon and ribavirin?

With interferon- and ribavirin-free regimens already here—and more on the way—will these two toxic agents remain in the anti-HCV arsenal? At a CROI 2014 press conference on DAA research, clinician-investigator Trevor Hawkins (Southwest CARE Center, Santa Fe) all but scoffed at a journalist's suggestion that some people may still be candidates for initial treatment with a non-DAA interferon regimen. The list of side effects caused by interferon and ribavirin is long, daunting, and agonizingly familiar to clinicians who treat HCV infection.<sup>13</sup>

At this writing, AASLD/IDSA HCV guidelines recommend pegylated interferon with sofosbuvir and ribavirin as a first choice for treatment-naïve interferon-eligible patients with HCV genotype 1, 4, 5, or 6 (but not 2 or 3), with or without HIV infection.<sup>1,2</sup> These guidelines also recommend interferon (1) plus ribavirin and sofosbuvir or simeprevir for retreatment of HCV genotype 1 infection after failure of PEG/RBV, and (2) plus ribavirin and sofosbuvir for retreatment of HCV genotype 4, 5, or 6 infection after failure of PEG/RBV.

In a 2014 review article, the University of Toronto's Jordan Feld wrote "it is likely interferon-free therapy will be a reality for most patients in the not too distant future."<sup>14</sup> But for now Feld sees several indications for pegylated interferon in first-line and later regimens: (1) with simeprevir or sofosbuvir for first-line treatment of genotype 1 infection, (2) with sofosbuvir and ribavirin for first-line treatment of genotype 3 infec-

tion, particularly in people with cirrhosis, (3) with two DAAs and ribavirin for null responders or people in whom a DAA regimen fails with multidrug-resistant HCV, and (4) in poor countries to lower the number and/or duration of DAAs needed.

DAA monotherapy makes as little sense as antiretroviral monotherapy and for the same reason. Both HCV and HIV replicate at such a furious pace that every resistant variant gets produced daily. One or more variants resistant to single drugs rapidly become the dominant circulating species if challenged with that single drug. Just as antiretroviral nucleosides protect third agents in a regimen from resistance by shutting off HIV replication (and thus emergence of resistant virus), so interferon and/or ribavirin protects single DAAs from emergence of HCV resistant to that DAA.

But if an HCV regimen combines two or more DAAs from two or more antiviral classes with nonoverlapping resistance, each will protect the other(s) from emergence of resistant HCV. Thus advice on short-term use of interferon—as the AASLD/IDSA stresses<sup>1</sup>—must be regarded as transient. The likely imminent arrival of more DAAs, including coformulated DAAs, will make it harder and harder to justify weekly injections of a drug that is at best inconvenient and at worst corrosive.

Ribavirin has a side-effect profile as unnerving as interferon's but remains a mainstay of currently recommended first-line and retreatment regimens for all six HCV genotypes.<sup>1</sup> And many current DAA trials include ribavirin as a component, though some

studies found no SVR difference between regimens with or without ribavirin.<sup>3,5,6</sup> Ribavirin can cause hemolytic anemia and, in people with unstable cardiac disease, death from myocardial infarction.

This guanosine nucleoside analog does have one advantage over other licensed oral anti-HCV drugs: (relatively) low cost. On the minus side, after more than a decade of ribavirin use against HCV infection, no one knows how it works. This void is more than an annoyance to treatment purists, explain Christopher Koh and T. Jake Liang of the National Institutes of Health;<sup>15</sup> it frustrates attempts to improve ribavirin's efficacy.

In their analysis of the future of ribavirin, Koh and Liang make other interesting observations.<sup>15</sup>

1. Retrospective analysis of trials combining ribavirin with interferon and the first-generation DAAs boceprevir and telaprevir suggested that a ribavirin dose as low as 600 mg daily did not diminish response to triple therapy. That result, Koh and Liang write, “raises the intriguing possibility” that lower-dose ribavirin (with consequently fewer or milder side effects) may be feasible with newer DAAs.
2. In one study of sofosbuvir, adding ribavirin did not worsen overall side effects or quality of life.<sup>16</sup> If that finding holds true with other DAAs, Koh and Liang suggest, ribavirin “may continue to have added value in interferon-free regimens without the observed side effects and toxicities seen in combination with interferon.”<sup>15</sup>

Koh and Liang believe that “for the near future” infection with genotype 2 or 3 HCV will require ribavirin.<sup>15</sup> “In the more distant future, with increasingly potent DAAs to attack multiple HCV targets,” they propose, “the use of ribavirin may not be necessary, especially because of the lack of understanding of its mechanism of action in chronic HCV infection.” But in the interview following this article, Douglas Dieterich suggests a tiny percentage of patients—those with multiple regimen failures and DAA resistance—may remain candidates for ribavirin or interferon.

### Cure at what cost?

How much new DAAs cost attracts as much attention as how well they work. Both variables can be called astonishing, and the two are intimately linked. Twelve weeks of sofosbuvir therapy costs about \$84,000, while 12 weeks of simeprevir comes in at about \$66,000—not counting costs for coadministered ribavirin or interferon.<sup>17</sup>

Makers of these two potent antivirals—and some nonindustry experts<sup>18,19</sup>—argue that the high price tag can be justified by dollars saved in curing a chronic disease that will ultimately cost more as it gets worse, requiring HCV salvage therapy, treatment of hepatocellular carcinoma, and maybe liver transplantation (which costs more than a half-million dollars).<sup>18</sup> Aside from direct therapeutic costs, managing and monitoring people with a chronic disease that kills slowly inflate the bill considerably. “It’s very expensive to die from liver disease,” Douglas Dieterich observes in the interview following this article.

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Current antiretroviral regimens cost \$2000 to \$5000 monthly and have to be taken for life.<sup>18</sup> With life expectancy in HIV-positive people approaching that of the general population, “for life” means about 35 years for a 35-year-old. So at age 35 monthly treatment at \$2000 for life would ring up a lifetime bill of \$840,000 (just for the drugs), while monthly treatment at \$5000 for life would drain the till of \$2.1 million. So even at the \$2000-per-month price, lifelong antiretroviral therapy could cost 10 times as much as a curative 12-week course of sofosbuvir.

To some extent, modeling can account for expenditures saved by an expensive though curative therapy like sofosbuvir or simeprevir. The California Technology Assessment Forum (CTAF) tried to do that by reckoning the cost and costs saved in treating 1000 people with chronic HCV for 1, 5, or 20 years.<sup>20</sup> After 88 pages of exacting analysis, this group determined that initial treatment with sofosbuvir or simeprevir would run about \$88,000 per patient on the low end—and \$175,000 per patient on the high end. Incremental cost to achieve one sustained virologic response (or cure) came to more than \$300,000—much more than previously published estimates of cost per SVR with various PEG/IFN regimens (\$17,000 to \$24,000), cost per SVR with the first-generation HCV protease inhibitor telaprevir (\$189,000), and cost to achieve an undetectable HIV load with combination antiretroviral therapy (\$1000 to \$79,000).

Princeton health economist Uwe Reinhardt notes that countries like the UK “routinely undertake such studies and reject some therapies as too expensive,”

but such a thumbs-down in the United States “is quite a remarkable statement.”<sup>19</sup>

The CTAF model accounted for HCV genotype, prior treatment status, interferon eligibility, liver complications, and other medical care.<sup>20</sup> Notably, though, the model considered DAA treatment for a 60-year-old. A 40- or 50-year-old would stand to gain many more productive life years if cured of HCV infection in 12 or 24 weeks, yielding a more economically palatable lifetime cost per SVR.

Will insurers read the CTAF statement and say no to paying for sofosbuvir or simeprevir? Some insurers have already decided to limit coverage to people in whom PEG/IFN has already failed,<sup>21</sup> in effect condemning policyholders to a dangerous course of therapy no longer sanctioned by US experts.<sup>1</sup> Other insurers rule out coverage for people without at least moderately advanced HCV infection.<sup>21</sup>

In the United States, chronic HCV infection is almost 4 times more likely in low-income people,<sup>22</sup> who often rely on Medicaid to pay a big part of their health bills. Kaiser Health News reports that Medicaid managed care companies are scrambling to determine how state Medicaid directors will determine whether or when to pay for new DAA regimens.<sup>21</sup> Meanwhile, at least one of the biggest Medicaid managed care outfits will cover treatment only with older therapies. (Makers of sofosbuvir and simeprevir have patient assistance programs that can be accessed online at [www.MySupportPath.com](http://www.MySupportPath.com) and <https://support.olyzio.com/co-pay-assistance>).

Since many attractive, guideline-sanctioned DAA combinations will not be authorized by the FDA label, another question is whether insurers will pay for off-label DAA prescribing. A 2009 pre-DAA survey of 34 third-party payers representing about one quarter of US Medicare and Medicaid beneficiaries found that approximately 25% refused to pay for any off-label indications.<sup>23</sup> Those who did usually considered peer-reviewed literature (74%) and practice guidelines (53%) in deciding which off-label uses to reimburse. But there was a catch, a group from the University of Chicago reports<sup>24</sup>: Such reimbursement usually required previous authorization

or prior failure of less expensive therapies. The Chicago team predicts that, as newer DAAs “continue to minimize toxicity and optimize efficacy, payers will be less likely to reimburse potentially costly off-label regimens that offer only incremental benefits of efficacy, safety, or duration of therapy.”<sup>24</sup>

“Although DAA therapy may be \$1000 a pill,” write two of these University of Chicago liver specialists,<sup>18</sup> “SVR is arguably priceless.” And without one of the new DAA regimens, some fraction of chronic HCV patients will never see an SVR.

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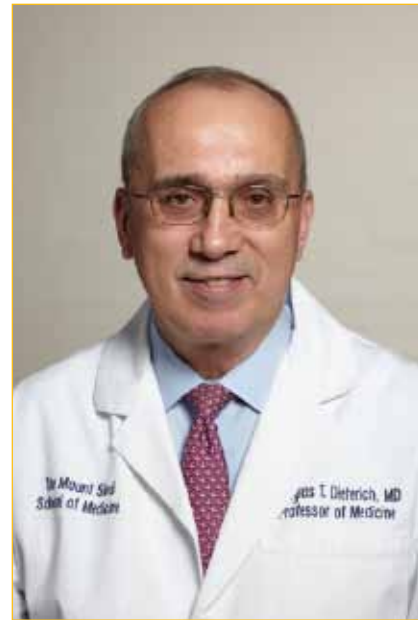
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## Advice on using DAAs for patients with HCV/HIV coinfection

An interview with **Douglas T. Dieterich, MD**

*Professor of Medicine  
Icahn School of Medicine at Mount Sinai  
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Dr. Dieterich is Professor of Medicine in the Division of Liver Diseases, Director of Continuing Medical Education in the Department of Medicine, and Director of Outpatient Hepatology at the Icahn School of Medicine at Mount Sinai in New York City. He also holds appointments in the divisions of Gastroenterology and Infectious Diseases at the Icahn School of Medicine. Dr. Dieterich's clinical work and research focus on HCV and HBV infection, often in people also infected with HIV. He has served on several committees of the AIDS Clinical Trials Group, including the Steering Committee of the Opportunistic Infections Core Committee. A PubMed search linking his name to HCV returns 71 articles.



**Mascolini:** Do DAAs—direct-acting antivirals—work in people with HIV as well as they do in HIV-negative people?

**Dieterich:** Absolutely, exactly the same. It's incredible. Ever since the beginning of the DAA era in 2011, all trials in HCV/HIV-coinfected patients show that DAAs work just as well as in people infected only with HCV<sup>1,2</sup> (**Table 1, page 16**). What's more interesting is that in the real world it looks like DAAs work even better in coinfecting patients than they do in trials.

**Mascolini:** Why do you suppose that is?

**Dieterich:** I think HIV patients probably take their medicine better. I'm presenting some data at the DDW [Digestive Diseases Week] meeting [May 4-6, 2014, Chicago] that shows one of the positive predictors of response to HCV treatment with faldaprevir is being HIV positive.

**Mascolini:** Is enough DAA research being done in HCV/HIV-coinfecting people?

*One of the positive predictors of response to HCV treatment with faldaprevir is being HIV positive.*

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**Table 1.** Two trials of DAA-only regimens for HCV/HIV coinfection

	ERADICATE Trial <sup>1</sup>	C-WORTHY Trial <sup>2</sup>
Study participants (all HCV treatment-naïve)	13 noncirrhotic HIV/HCV-G1 patients not taking antiretrovirals 37 noncirrhotic HIV/HCV-G1 patients taking antiretrovirals	59 noncirrhotic HIV/HCV-G1 patients taking raltegravir regimen
Treatment	Sofosbuvir/ledipasvir for 12 weeks	MK-5172/MK-8742 with or without ribavirin for 12 weeks
Response	13 not taking antiretrovirals: 13/13 EOT, 10/10 SVR12 37 taking antiretrovirals: 30/30 EOT, 22/22 SVR4	29 taking ribavirin: 29/29 EOT, 28/29 SVR4 30 not taking ribavirin: 27/30 EOT, 26/29 SVR4
Other findings	No CD4 change during HCV treatment No discontinuations due to adverse events	Mean CD4 change from baseline - 61.7 with ribavirin, +46.9 without ribavirin No discontinuations due to adverse events

EOT, end-of-treatment response (HCV RNA below lower limit of quantitation); G1, genotype 1; SVR4 or SVR12, sustained virologic response 4 or 12 weeks after treatment ends.

**Dieterich:** There's never enough research. But one huge step forward is that Merck is not separating out HIV patients in their phase 3 trials. HIV patients are included in overall analyses as well as in analyses stratified by HIV status.

### When to treat which virus with coinfection

**Mascolini:** How should clinicians who treat HCV infection decide whether to treat HIV-coinfected peo-

ple with HCV drugs available now or wait for simpler DAA-only combinations?

**Dieterich:** Some patients can be treated now with sofosbuvir/ribavirin, such as Child-Pugh B and C cirrhotics, though we shouldn't be treating those patients without liver transplant planning. Clinicians can prescribe sofosbuvir/ribavirin for HCV genotype 2 and 3 patients now. In selected patients who are Child-Pugh A or better and who don't have any potential drug interactions, clinicians could use simeprevir/sofosbuvir

in coinfecting patients, and we've been doing that in some HIV patients.

**Mascolini:** How close are we to having licensed interferon/ribavirin-free combinations?

**Dieterich:** Sometime between August and October 2014 for coformulated sofosbuvir/ledipasvir. For coformulated ABT-450/ABT-267, we should know by December.

**Mascolini:** If a coinfecting person has taken drugs for neither infection, how should clinicians decide whether to start treatment for both infections simultaneously or to start with HCV or HIV?

**Dieterich:** It's probably not a good idea to begin treating both infections simultaneously because of the potential for drug interactions or more side effects. Usually we recommend starting antiretroviral therapy first so we have a better quantity and quality of T cells when we start HCV therapy.

**Mascolini:** If an untreated person with HIV has a moderate viral load and relatively high CD4 count, does it make sense to try to knock out the HCV infection first with 12 weeks of therapy?

**Dieterich:** A very small study from the NIH found an SVR12 of 100% in coinfecting patients treated with sofosbuvir/ledipasvir for 12 weeks when not on antiretrovirals (**Table 1**).<sup>1</sup> In the future it's probably not going to make any difference whether people are on antiretrovirals or not, but for now I prefer starting antiretrovirals before HCV therapy. And with sofos-

buvir/ledipasvir, it looks like adding ribavirin doesn't make any difference. For ABT-450/ABT-267, it looks like adding ribavirin makes a difference only with HCV genotype 1a.

**Mascolini:** Two or three years from now, will anyone with HCV be taking interferon or ribavirin?

**Dieterich:** There always might be a tiny percentage of people, perhaps 1% to 5%, with multiple failures and with resistance to DAAs who will be candidates for interferon or ribavirin.

**Mascolini:** What are the treatment options for coinfecting people with cirrhosis in whom previous treatment failed?

**Dieterich:** If they're Child A cirrhotics, you could use simeprevir/sofosbuvir, provided they're screened for esophageal varices and for hepatocellular carcinoma and screened for transplant. If they're Child B or C, they need to be evaluated for liver transplant, and sofosbuvir/ribavirin is clearly the treatment of choice.

**Mascolini:** Are some coinfecting people at such an advanced stage that DAAs are not going to help them?

**Dieterich:** I don't think there is a stage that's too advanced for DAAs to help, unless it's metastatic liver cancer. Screening for liver cancer with ultrasound and alpha-fetoprotein is very important, and I think most HIV clinics are not screening enough or at all. Screening for esophageal varices with endoscopy is also crucial.

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*Screening for liver cancer with ultrasound and alpha-fetoprotein is very important, and I think most HIV clinics are not screening enough or at all.*

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### When should HIV clinicians be treating HCV?

**Mascolini:** When simple DAA-only regimens become available, will HIV clinicians still want to refer their HCV-coinfected patients to hepatitis specialists? Or will they be able to start prescribing for most coinfecting patients themselves?

**Dieterich:** They can do it themselves, as long as they know how to spot cirrhosis and what to prescribe. It's perfectly appropriate for noncirrhotic patients to be treated in the HIV clinic.\*

**Mascolini:** In your experience talking with HIV clinicians, do you think they're getting up to speed on DAA therapy and reaching a comfort level in prescribing them?

**Dieterich:** I think they're eager to start using DAAs, but they're still having trouble pulling the trigger. I don't know why. I've been trying for years to get HIV providers to treat hep C, and there are only a few who do. Everybody is interested now that DAAs are becoming available, but not many HIV clinicians are writing prescriptions yet. I don't think there are enough treaters to treat all the hep C that's out there. We need to increase our treatment base.

**Mascolini:** DAAs are expensive. Are public and private insurance paying for them?

**Dieterich:** They are paying for DAAs, and I think they'll continue to do so. DAAs are very cost-effective. It's very expensive to die from liver disease, and it's very expensive to get a liver transplant. So treating hep C can be incredibly cost-effective. When you figure quality-adjusted life-years, compared with colonoscopy, Pap smears, mammograms, and cholesterol therapy, treating hep C with all-oral DAAs is one of the most cost-effective things you can do because of the downside risk of liver failure.

**Mascolini:** Is there anything else you want to add about what HIV clinicians should know about DAAs or about HCV coinfection in general?

**Dieterich:** It's important for patients with cirrhosis to get referred to a liver center. Cirrhosis is relatively easy to diagnose, but HIV clinicians have got to remember how to do it: If a patient's platelets are less than 110,000 per mL, if their albumin is less than 3.5 g/dL, if they have any physical signs of liver disease, they need to get referred.

HIV clinicians also need to be screening all their hepatitis B surface antigen-positive patients for hepatocellular carcinoma, especially patients who are hep C infected, because they're at increased risk of liver cancer. Tenofovir and emtricitabine are so effective in treating hep B, we've forgotten who among our patients is surface antigen-positive. And those patients are at extra risk for liver failure.

*It's very expensive to die from liver disease,  
so treating hep C can be incredibly cost-effective.*

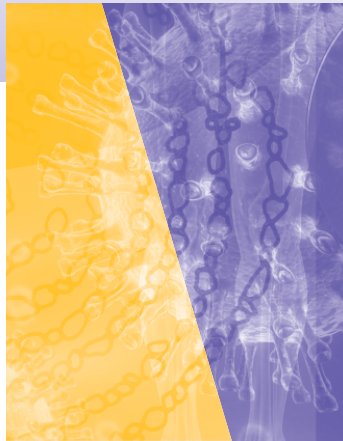
\*The American Association for the Study of Liver Diseases (AASLD) launched ACT-First, a comprehensive online guide for first-line HCV treaters, at <http://www.aasld.org/LiverLearning%20AE/Pages/LiverProgramforPrimaryCareProviders.aspx>

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## Does HCV make HIV infection worse?

By Mark Mascolini .....

HIV makes HCV infection worse. Compared with people infected only with HCV, those burdened by both viruses get cirrhosis faster<sup>1,2</sup> and die sooner.<sup>3,4</sup> Taking combination antiretroviral therapy (cART) eased HIV's baneful impact on HCV progression in a 3567-person meta-analysis, but not completely.<sup>1</sup>

Does HCV infection make HIV infection worse? Studies addressing this question yield different—and sometimes conflicting—answers. No one should be surprised. These studies used different methods to analyze different populations, different endpoints, and different periods (before and after the arrival of cART). And some of the cART-era studies involve more toxic and inconvenient antiretrovirals rarely used today. According to an AIDS Clinical Trials Group (ACTG) team that recently explored these issues,<sup>5</sup> the controversy breaks down this way:

- Natural history studies show that—before HCV/HIV-coinfected people start cART—their HIV disease progression largely tracks with that of people infected only with HIV.<sup>6-8</sup>
- After people begin cART, some studies found that HCV/HIV-coinfected people have smaller or delayed CD4 gains than HIV-monoinfected people.<sup>9-15</sup>
- A few studies found, though, that CD4 differences between coinfecting and monoinfected people wane as cART continues.<sup>16,17</sup>
- And a cluster of other studies found no link between coinfection and dampened CD4 gains.<sup>18-25</sup>
- Three studies that examined the impact of coinfection on virologic response to cART found no link.<sup>10,11,26</sup>
- A 2009 meta-analysis<sup>13</sup> and other studies<sup>27,28</sup> discerned no tie between HCV/HIV coinfection and AIDS-defining endpoints.
- But one study did link coinfection with AIDS endpoints.<sup>29</sup>

This article dissects these and other studies to answer three questions:

1. How does HCV infection affect mortality in people with HIV?
2. How does HCV infection affect progression to AIDS and other clinical outcomes?
3. How does HCV infection affect response to cART?

Answers to these questions have already informed guidelines on caring for people with potential and confirmed HCV/HIV coinfection. **Tables 1** and **2** outline current guidelines. A 1-page handout following this article offers HCV/HIV patients 10 pointers on preventing transmission of these viruses and avoiding treatment complications.



**Table 1.** Screening and prevention guidelines for HCV and HIV coinfection

<b>Screening</b>
<p>Everyone with HIV should be screened for HCV infection when entering care, preferably before starting cART (DHHS Adult),<sup>30</sup> and annually thereafter (HIVMA/IDSA).<sup>31</sup></p> <p>People positive for HCV antibody should have HCV RNA measured to determine whether HCV infection is active (HIVMA/IDSA).<sup>31</sup></p> <p>HCV RNA should be measured in HCV antibody-negative people with a history of injection drug use or unexplained increased serum transaminases because HCV antibodies do not develop in approximately 6% of HCV/HIV-coinfected people (HIVMA/IDSA).<sup>31</sup></p> <p>Infants born to HCV- or HBV-infected women should be screened for HCV and HBV. Infants can be tested for HCV RNA after age 2 months and for HCV antibody after 18 months of age (HIVMA/IDSA).<sup>31</sup></p>
<b>Prevention</b>
<p>To assess kidney function, HCV/HIV-coinfected people should be screened for proteinuria when they begin care and annually thereafter (HIVMA/IDSA).<sup>31</sup></p> <p>All HCV/HIV-coinfected people should be tested for hepatitis A virus (HAV) and hepatitis B virus (HBV) and vaccinated if not immune (HRSA).<sup>32</sup></p> <p>HCV/HIV-coinfected people vaccinated against HBV in the past should have their anti-HBV titer checked to make sure they remain protected (HRSA).<sup>32</sup></p>
<b>Patient counseling</b>
<p>People with HCV infection should be counseled to avoid alcohol and medications toxic to the liver, including fluconazole, isoniazid, and large doses of acetaminophen (HRSA).<sup>32</sup></p> <p>People with HCV infection should be counseled to reduce risk of HCV transmission through unprotected sex, perinatal exposure, or sharing drug-injecting equipment, razors, tattoo equipment, or sex toys (HRSA).<sup>32</sup></p> <p><i>See the 1-page patient guide at the end of this article.</i></p>

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**Table 2.** HIV and HCV care guidelines for people with coinfection

Combination antiretroviral therapy (cART) should be considered for coinfecting patients regardless of CD4 count because cART may slow liver disease progression by preserving or restoring immune function and reducing HIV-related immune activation (DHHS Adult).<sup>30</sup>

Liver function should be monitored closely in coinfecting people on cART (HRSA).<sup>32</sup>

Consideration of potential drug-drug interactions and overlapping toxicities should guide antiretroviral selection in coinfecting people receiving treatment for HCV infection (DHHS Adult).<sup>30</sup>

Because of pill burden, drug-drug interactions, and overlapping toxicities when treating coinfecting people, some clinicians may choose to defer cART until antiretroviral-naïve people with a CD4 count at or above 500 cells/mm<sup>3</sup> complete anti-HCV therapy\* (DHHS Adult).<sup>30</sup>

For people with a CD4 count below 200 cells/mm<sup>3</sup>, it may be preferable to start cART first and begin HCV therapy after the CD4 count rises (DHHS Adult).<sup>30</sup>

Interferon alfa and pegylated interferon are not recommended during pregnancy, and ribavirin is contraindicated during pregnancy (DHHS Perinatal).<sup>33</sup>

Men and women taking ribavirin should use contraception consistently during ribavirin therapy and for 6 months after completing ribavirin therapy (HRSA).<sup>32</sup>

Treatment of HCV infection in HIV-positive people is evolving rapidly as direct-acting antivirals (DAAs) become available and their interactions with antiretrovirals are defined. For the latest treatment advice, see the table “Unique Patient Populations: HIV/HCV Coinfection” in *Recommendations for Testing, Managing, and Treating Hepatitis C*, from the Infectious Diseases Society of America: <http://hcvguidelines.org/full-report-view>. Also see the article on DAAs in this issue of *Research Initiative, Treatment Action!* and the interview with Douglas Dieterich.

People with HCV infection who inject drugs should be strongly counseled to enter a treatment program to end their dependence (HRSA).<sup>32</sup>

\*Recent and ongoing approval of stronger direct-acting antivirals (DAAs) for HCV infection with 8- to 24-week courses could strengthen the rationale for treating HCV infection before starting cART.<sup>34</sup>

## IMPACT OF HCV ON MORTALITY WITH HIV

The impression that HCV does not affect survival in people with HIV dates to the pre-cART era, when HIV-positive people died of AIDS long before they could die of heart, kidney, or liver disease. Two emblematic studies involve medium-size US HIV cohorts—one largely male and one entirely female.<sup>35,36</sup>

Researchers compared survival in 115 HIV-positive veterans with HCV and 235 without HCV in the HIV Atlanta Veterans Affairs Medical Cohort Study (**Table 3**).<sup>35</sup> These people were in care at some point from January 1992 to May 1997, and all but 5 were men. Most participants had taken antiretrovirals, but only 20% had taken a protease inhibitor, so this was a largely cART-naïve cohort. Multivariate analysis identified no links between antiretroviral treatment history and HCV antibody positivity.

The same proportion of people in the coinfecting group and the HIV-only group—70%—had AIDS.<sup>35</sup> Twenty-four people with coinfection (21%) and 46 with HIV alone (20%) died during the study period (**Table 3**). Cox proportional hazards models discerned no difference between the coinfecting group and the monoinfected group in time from HIV diagnosis to death or time from AIDS diagnosis to death. In this group, largely in care before the benefits of cART took hold, HCV coinfection did not shorten survival.

A Women and Infants Transmission Study (WITS) analysis involved 652 women—190 (29%) with HCV and none with an AIDS diagnosis—who enrolled in the cohort when pregnant from 1989 through 1995, before cART arrived.<sup>36</sup> Only 124 women (19%) tried a cART combination during follow-up (with no difference between coinfecting and monoinfected women). Forty-three women (7%) died, 26 of them (4%) with-

out a documented AIDS diagnosis. Cox proportional hazards analysis determined that coinfecting women did not have faster progression to an initial class C AIDS diagnosis or death (relative hazard 0.75, 95% confidence interval [CI] 0.37 to 1.53).

## AIDS as a king-size competing risk

These two studies<sup>35,36</sup> share a key limitation: The investigators did not report (and perhaps did not know) what caused the deaths in their cohort. Was it AIDS, liver failure, or something else? Knowing the cause of death is critical to understanding whether HCV infection shortens survival in people with HIV because of a statistical bugbear called competing risk. A person who runs a risk of more than one mutually exclusive mortal event—such as death from AIDS and death from HCV-induced liver failure—has competing risks.<sup>37</sup> The risks compete because if one happens, the other can't.

From the dawn of the HIV epidemic until wide use of cART, AIDS became a competing risk as population-shredding as the black death in 1666 London or influenza in 1918 across the globe. Until the mid-1990s HIV-positive men and women died of AIDS in their 30s and 40s—long before they could succumb to heart disease or lung cancer—even if they had relatively high heart or cancer risks. Compared with HIV infection, HCV infection is an indolent disease. About 10 years elapse between untreated HIV infection and AIDS in the United States,<sup>38</sup> and perhaps another 2 years between untreated AIDS and death.<sup>39,40</sup> In contrast, people with untreated HCV infection can live without cirrhosis for 20 to 30 years and sidestep liver failure for years beyond that.<sup>41</sup> So a person infected with both viruses runs a much higher risk of dying from AIDS than from liver disease, even if infected with HCV 5 or 10 years earlier than with HIV.

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A pre-cART study from Spain shows how handily AIDS outcompetes liver disease in coinfecting and inadequately treated people.<sup>42</sup> The cohort included 328 antiretroviral-treated people seen from 1989 through 1996—before wide cART use. The group had a median initial CD4 count of 303 cells/mm<sup>3</sup>. Two thirds (65%) had HCV, 5% HBV, and 3% hepatitis D virus. The researchers did not know whether 36 people (11%) lived or died. Among the remaining people, 67 died. Forty-nine of those 67 (73.1%) died of AIDS, while only 3 (4.5%) died of liver failure and 15 (22.4%) of other causes. As in the two US studies,<sup>35,36</sup> mortality did not differ between people with and without hepatitis virus infection. But AIDS killed 22 times more

people than hepatitis in this group receiving inadequate treatment for their viral infections.

### cART makes liver disease a top killer

What happened when HCV/HIV-coinfecting people started taking three antiretrovirals at the same time? They stopped dying of AIDS as quickly, and growing proportions began living so long with HIV they started dying of other diseases—including liver failure and liver cancer. And study after study began showing that HCV coinfection boosted chances of death in people with HIV.

**Table 3.** Impact of HCV infection on survival in Atlanta VA Cohort before cART and with cART

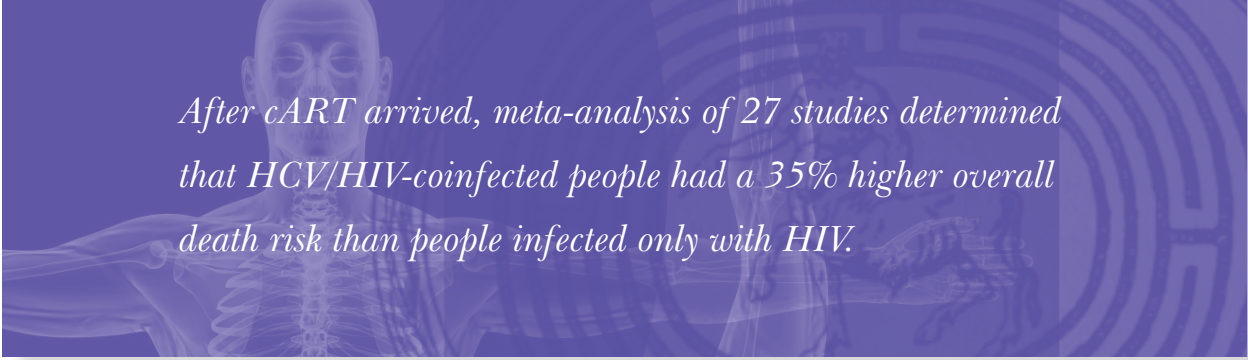
	<b>Staples<sup>35</sup></b>		<b>Anderson<sup>43</sup></b>	
Observation period	January 1992 through May 1997		January 1997 through May 2001	
	HCV plus HIV (n = 115)	HIV only (n = 235)	HCV plus HIV (n = 306)	HIV only (n = 664)
Had AIDS	81 (70%)	164 (70%)	213 (70%)	433 (65%)
Took cART	19 (16%)*	50 (21%)*	199 (65%)†	509 (77%)†
Died	24 (21%)	46 (20%)	67 (22%)‡	72 (11%)‡
Time from HIV Dx to death	No difference by Cox proportional hazards model		aHR HCV+ vs HCV-: 2.47 (95% CI 1.26 to 4.82, P = 0.0085)	
Time from AIDS Dx to death	No difference by Cox proportional hazards model		aHR HCV+ vs HCV-: 1.84 (95% CI 1.09 to 3.10, P = 0.022)	

aHR, adjusted hazard ratio; Dx, diagnosis.

\*Reported as protease inhibitor use.

†P = 0.001.

‡P < 0.0001.



*After cART arrived, meta-analysis of 27 studies determined that HCV/HIV-coinfected people had a 35% higher overall death risk than people infected only with HIV.*

For example, whereas the pre-cART analysis of the Atlanta VA Cohort found that HCV coinfection did not affect survival,<sup>35</sup> an early cART-era analysis of the same group did.<sup>43</sup> The later study involved 970 HIV-positive people in care from January 1997 through May 2001, 306 of whom (32%) had HCV infection (**Table 3**). About two thirds in each group had AIDS, and CD4 counts when cART began were similar. During follow-up in the later study 67 coinfecting people and 72 mono-infected people died, a highly significant difference (21.9% versus 10.8%,  $P < 0.0001$ ).<sup>43</sup>

Multivariate survival analysis determined that coinfecting people had significantly shorter survival after HIV diagnosis than did mono-infected people (hazard ratio [HR] 2.47, 95% CI 1.26 to 4.82,  $P = 0.0085$ ) (**Table 3**).<sup>43</sup> Survival after AIDS diagnosis was also significantly shorter in the coinfecting group (HR 1.84, 95% CI 1.09 to 3.10,  $P = 0.022$ ). Taking cART for at least 1 month was independently associated with longer survival after HIV diagnosis (HR 0.25, 95% CI 0.16 to 0.39,  $P < 0.0001$ ) and after AIDS diagnosis (HR 0.26, 95% CI 0.16 to 0.42,  $P < 0.0001$ ). HCV coinfection did not affect short- or long-term CD4 recovery in this cohort.

Before long, enough HCV/HIV mortality studies got published to allow meta-analysis. In 2009 researchers analyzed 10 studies from pre-CART days and 27 from

the cART era, all of them including HIV-positive people with or without HCV infection.<sup>13</sup> The 10 pre-cART studies (5 US/Canada, 4 Western Europe) involved 4413 people with HCV plus HIV and 10,213 with HIV alone. The 27 cART studies (12 US/Canada/Puerto Rico, 9 Western Europe) included 25,319 coinfecting people and 61,697 with HIV alone. In the pre-cART era, a random effects model determined that coinfecting people had a lower overall mortality risk than people infected only with HIV (risk ratio 0.68, 95% CI 0.53 to 0.87). (A single large study drove that outcome; because that study included only in-hospital patients, the meta-analysis authors believe it may suffer from survival bias.<sup>13</sup>)

After cART arrived, that risk flip-flopped. Statistical analysis adjusted for cART use, proportion of IDUs, study duration, and sex determined that coinfecting people had a 35% higher overall death risk than mono-infected people in the cART era (RR 1.35, 95% CI 1.11 to 1.6) (**Table 4, Figure 1**). And, notably, the risk of AIDS in the cART era did not differ significantly between coinfecting and mono-infected people (RR 1.12, 95% CI 0.82 to 1.51). “Given the lack of an association between progression to AIDS and HCV coinfection,” the authors observed, “the major contributor to mortality among coinfecting subjects during the HAART era is likely to be liver disease.”<sup>13</sup>

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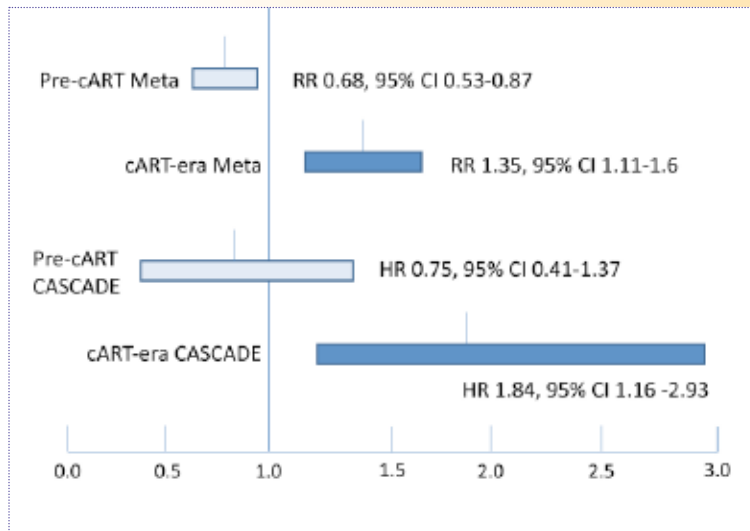
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**Table 4.** Five studies of HCV mortality impact in cART era

Author	n, years	Population	Site(s)	Key outcomes*
Sulkowski (2002) <sup>20</sup> <b>HCV does not have impact</b>	1995, 873 (44%) HCV+; 1995-2001; median follow-up 2.19 y in HCV+, 2.00 y in HCV-	Prospective cohort of patients without AIDS starting cART; 85% of HCV+, 13% HIV- IDU	Baltimore	In cART-treated people with a baseline CD4 count of 50-200, HCV raised death risk (RH 1.85, 95% CI 1.11 to 3.07); in final model including cART use and HIV suppression, HCV had no impact on mortality (RH 1.01, 95% CI 0.65 to 1.56).
Rockstroh (2005) <sup>26</sup> <b>HCV has impact</b>	5957, 1960 (33%) HCV+; 1994-2004; follow-up 3.75 y in HCV+, 2.7 y in HCV-	Prospective study of EuroSIDA cohort; 77.5% of HCV+, 3.2% HCV- IDU	Europe, Israel	HCV raised risk of any-cause death in fixed-factor model (IRR 1.41, 95% CI 1.13 to 1.76, $P = 0.0024$ ) and updated factor model (IRR 1.80, 95% CI 1.44 to 2.25, $P < 0.0001$ ), largely because of liver-related death.
Sullivan (2006) <sup>46</sup> <b>HCV does not have impact</b>	10,481, 2024 (19%) HCV+; 1998-2004; follow-up 1.9 y	Adult and Adolescent Spectrum of HIV Disease participants starting cART; 47% HCV+, 7.5% HCV- IDU	10 US cities	HCV did not raise risk of death (HR 1.1, 95% CI 0.9 to 1.2, $P = 0.38$ ).
Chen (2009) <sup>13</sup> <b>HCV has impact</b>	87,016, 21,607 (25%) HCV+; 1996-2004; 8 studies 1-3 y follow-up, 10 >3 y, 5 did not report follow-up	Meta-analysis of cART patients in 27 trials; 3%-64% IDU	12 studies in US, Canada, Puerto Rico; 9 studies W Europe	HCV raised risk of death (RR 1.35, 95% CI 1.11 to 1.6).
van der Helm (2013) <sup>45</sup> <b>HCV has impact</b>	8674, 1767 (20%) HCV+; Pre-1989-2007	Europeans and Canadians with known date of HIV seroconversion	Europe, Canada	HCV raised risk of death (HR 1.84, 95% CI 1.16 to 2.93).

HR, hazard ratio; IDU, injection drug user; IRR, incidence rate ratio; RH, relative hazard.

### Risk of all-cause mortality with vs without HCV



**Figure 1.** A 37-study meta-analysis<sup>13</sup> and a CASCADE Collaboration study<sup>45</sup> both found a higher risk of all-cause mortality with HCV/HIV coinfection than with HIV alone in the cART era but not in the pre-cART era. (HR, hazard ratio; RR; risk ratio.)

A 5974-person Spanish HIV cohort study published after this meta-analysis found that all-cause mortality in HCV-negative people fell by half from 1997-2003 to 2004-2008 (adjusted incidence rate ratio [aIRR] 0.52, 95% CI 0.32 to 0.85).<sup>44</sup> But among HCV-coinfected people, overall mortality rose nonsignificantly from 1997-2003 to 2004-2008 (aIRR 1.27, 95% CI 0.90 to 1.79).

A recent analysis of the largely European CASCADE collaboration included 936 coinfecting people and 833 monoinfected people in the pre-cART era, and 1767 coinfecting and 6907 monoinfected people in the cART era.<sup>45</sup> All-cause pre-cART mortality within 15 years of HIV seroconversion was higher, but not significantly higher, in the monoinfected group (78% versus 58%). In the cART era, in contrast, a significantly higher proportion of coinfecting people died of any cause within 15 years of HIV seroconversion (35%, 95% CI 31% to 39%, versus 11%, 95% CI 9% to

14%). After statistical adjustment for HIV risk group, age, and sex, coinfecting people had an 84% higher risk of death from any cause than did monoinfected people in the cART era (adjusted hazard ratio [aHR] 1.84, 95% CI 1.16 to 2.93) (**Figure 1**).

AIDS-related mortality dropped sharply in both coinfecting and monoinfected people in the cART era, although AIDS (and non-natural causes) remained the leading causes of death in the coinfecting group, while AIDS (and natural causes) remained the leading causes in the monoinfected group.<sup>45</sup> But unlike the meta-analysis,<sup>13</sup> the CASCADE study determined that coinfecting people had a higher risk of AIDS death than monoinfected people—regardless of HIV transmission group—in the cART era.<sup>45</sup>

The CASCADE team speculated that this difference from the meta-analysis could reflect “differences in

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follow-up duration, inability to correct for duration of HIV infection, different statistical methods, and [racial/ethnic] differences in patient population.”<sup>45</sup> Why would AIDS-related mortality be significantly greater in the coinfecting group after cART’s advent? The CASCADE team speculated that higher T-cell activation with HCV infection could upset immune function in coinfecting people as cART quiets HIV-induced immune activation in both coinfecting and mono-infected people. Cirrhosis and advanced liver disease in coinfecting people would further promote AIDS conditions. So although AIDS deaths dropped steeply in both coinfecting and mono-infected people, the drop was less acute in the coinfecting group. Finally, although liver-related mortality fell among coinfecting people in the cART era compared with earlier years, coinfecting people still died more from liver-specific causes than mono-infected people after cART arrived.

These two large analyses concurred on the key finding that HCV/HIV-coinfecting people began running a higher risk of death from any cause than did HIV-mono-infected people once cART arrived. The CASCADE investigators proposed that “an increased risk of both HIV and/or AIDS and hepatitis or liver-related mortality among co-infected individuals in the cART era might suggest that co-infected patients should start HIV and HCV treatment sooner after diagnosis to reduce the likelihood of disease progression, even in the absence of liver fibrosis,”<sup>45</sup> a stance reflecting current US guidelines (**Table 2**).<sup>30</sup>

A large EuroSIDA study confirmed the higher risk of death from any cause with HCV/HIV coinfection than with HIV infection alone (**Table 4**).<sup>26</sup> The study involved 5957 HIV-positive people, 1960 of them (33%) positive for HCV antibody. People began entering EuroSIDA in May 2004, when 3117 participants

signed up. Another 1365 people joined in December 1995, the cusp of the cART era. A further 6747 people enrolled in four more waves through 2003. Follow-up for the HCV/HIV analysis continued until the autumn of 2004, by which time everyone in this analysis had started cART. Median follow-up measured 45 months in the HCV/HIV group and 32 months in the HIV-only group.

The EuroSIDA team used two multivariate models to calculate the impact of HCV coinfection on virologic response, CD4 gains, progression to AIDS, any death, and liver-related death: The first model considered fixed factors known at baseline, and the second model considered updated CD4 count, cART initiation, and diagnosis of a new AIDS illness.<sup>26</sup> HCV coinfection raised the risk of any death 41% in the fixed-factor model (IRR 1.41, 95% CI 1.13 to 1.76,  $P = 0.0024$ ) and 80% in the updated factor model (IRR 1.80, 95% CI 1.44 to 2.25,  $P < 0.0001$ ). The investigators attributed these higher death rates to more than a 10-fold higher risk of liver-related death with HCV in either statistical model.

### Two US studies do not link coinfection to higher death risk

But two US studies saw no link between HCV and a higher death risk in people with HIV.<sup>20,46</sup> A 10-city US study involved 10,481 US adults and adolescents, 2024 of them (19%) with a positive HCV test (**Table 4**).<sup>46</sup> Only 7% of the HIV-negative group and 2% of the HCV positive group were younger than 24. Two thirds of the HCV-positive group and almost three quarters of the negative group took cART (66.2% versus 71.2%,  $P < 0.0001$ ) during a median follow-up of 1.9 years between 1998 and 2004. The HCV group included a significantly higher proportion of

IDUs (47.4% versus 7.5%), as well as gay/bisexual men who injected drugs (11.8% versus 3.9%) ( $P < 0.0001$ ) and people who injected drugs in the past 6 months (13.2% versus 2.0%,  $P < 0.0001$ ).

During follow-up, 16% of HCV-coinfected people died, compared with 9.3% of the HCV-negative group. Statistical analysis controlling for alcoholism, alcoholic hepatitis, drug-induced hepatitis, being prescribed ART, a previous AIDS diagnosis, lower CD4 cell count, and age found that coinfection did not affect the risk of death (aHR 1.1, 95% CI 0.9 to 1.2,  $P = 0.38$ ).

A study of people in care from January 1995 to January 2001 at the Johns Hopkins Hospital HIV Clinic in Baltimore found that HCV coinfection raised the risk of death in certain analyses but not in others (**Table 4**).<sup>20</sup> The 1955 HIV-positive people in this study included 873 (44%) with a repeatedly reactive HCV antibody test. Median follow-up lasted 2.19 years in the HCV group and 2.0 years in the HCV-negative group. The HCV group was significantly older and included a higher proportion of African Americans (86% versus 68%,  $P < 0.001$ ) and a higher proportion of IDUs (85% versus 13%,  $P < 0.001$ ). People with HCV had a significantly lower baseline CD4 count (237 versus 266 cells/mm<sup>3</sup>,  $P = 0.02$ ). No one had an AIDS illness before enrollment.

During follow-up 153 HCV-positive people (17.5%) and 168 HCV-negative people (15.5%) died.<sup>20</sup> Cox proportional hazards regression analysis (adjusted for HCV status, age, sex, race, baseline CD4 count, and baseline viral load) discerned no mortality risk difference with versus without HCV (RH 1.05, 95% CI 0.85 to 1.30). Analysis limited to 1199 people who eventually took cART also found no mortality difference with versus without HCV (RH 1.22, 95% CI 0.22 to 1.61). The same proved true in 208 people with cART-controlled HIV replication, defined as having a viral load below 400 in 75% or more measurements (RH 1.49, 95% CI 0.33 to 6.68).

HCV did boost the risk of death in 429 people with a pre-cART CD4 count between 50 and 200 cells/mm<sup>3</sup> (RH 1.51, 95% CI 1.01 to 2.27) and in those in this subgroup who received cART (RH 1.85, 95% CI 1.11 to 3.07).<sup>20</sup> But in this 50-200 CD4 subgroup, multivariate Cox regression also adjusted for cART use and HIV suppression saw no HCV impact on death risk (RH 1.01, 95% CI 0.65 to 1.56). Notably, the Hopkins team found that 187 of all 1199 people (15.6%) taking cART died, compared with 6 of 208 (2.9%) with well-controlled HIV replication. In the final multivariate model, longer time on cART independently halved the risk of death (RH 0.47, 95% CI 0.36 to 0.63), while more clinic visits with a detectable HIV load raised the death risk 8 times (RH 7.96, 95% CI 2.00 to 31.66).

Why do the two US studies<sup>20,46</sup> find no association between HCV coinfection and death while the cART-era meta-analysis,<sup>13</sup> the European CASCADE study,<sup>45</sup> and the EuroSIDA study<sup>26</sup> do? The list of differences between these analyses could run several paragraphs, starting with utterly different populations, formats, years of cART, and statistical methods, then grinding down to nitty-gritties like confounders controlled for versus not considered. The meta-analysis, CASCADE, and EuroSIDA combined included three times as many people as the Hopkins and 10-city US study combined. The Hopkins study<sup>20</sup> and the 10-city study<sup>46</sup> each had about 2 years of follow-up for people with and without HIV. EuroSIDA had 3.75 years of follow-up in the HCV group and 2.7 in the HCV-negative group. In 27 cART-era meta-analysis studies,<sup>13</sup> 8 studies had 1 to 3 years of follow-up, 10 had more than 3, and 5 did not report follow-up. CASCADE did not report follow-up years. So the studies finding that HCV coinfection shortened survival generally had longer follow-up than the studies that did not. The 10-city US study controlled for alcoholism, alcoholic hepatitis, and drug-induced hepatitis, whereas CASCADE and EuroSIDA did not. This US

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study did not control for injection drug use or recent injection drug use, both of which were significantly more prevalent in the HCV-positive group, though controlling for drug-induced hepatitis may amount to the same thing.

One could go on, but probably to little avail. If compelled to boil all these data down to a single take-home dictate, it might be, HCV coinfection may shorten survival in people with HIV, and clinicians should do what they can to improve survival chances, notably by starting cART as quickly as feasible, working with an HIV/liver consultant to plan an optimal HCV treatment program, and working with coinfecting patients to limit other prime risk factors, such as drinking, smoking, and injection drug use.

SMART trial investigators added a compelling footnote to these analyses of how HCV coinfection affects mortality.<sup>47</sup> SMART famously found that people who suspended cART based on CD4 count had a higher risk of opportunistic disease and/or death from any cause than did people who took continuous cART. Of the 5472 study participants, 930 (17%) had HCV or HBV coinfection. Coinfecting people had more than a tripled risk of death due to nonopportunistic causes compared with monoinfected people (HR 3.6, 95% CI 2.3 to 5.6), while the risk of death from opportunistic disease proved comparable in coinfecting and monoinfected people. Almost half of all nonopportunistic deaths in SMART involved coinfecting people, even though they made up only 17% of the study group. Substance abuse and non-AIDS cancer were the two most-identified causes of nonopportunistic death in coinfecting SMART participants. The SMART team concluded that “interruption of antiretroviral therapy is particularly unsafe in persons with hepatitis virus coinfection.”<sup>47</sup>

## IMPACT OF HCV ON HIV CLINICAL OUTCOMES

As with studies analyzing the impact of HCV/HIV coinfection on mortality, studies examining how HCV affects chances of HIV disease progression tell different stories before and after people started taking cART (**Table 5**). In pre-cART days, a 416-person Italian study<sup>48</sup> and a 1649-person analysis of Canadians, Australians, Europeans, and South Africans enrolled in the CAESAR trial<sup>27</sup> determined that HCV infection had no impact on CD4 declines or progression to AIDS. Everyone with HIV—with or without HCV—had an inexorably downward disease course.

But that changed when cART came along. Triple therapy usually halted HIV disease progression by bolstering immune function and putting HIV replication in check. Yet studies began showing that cART did not rescue HCV-coinfecting people as consistently as patients without the hepatitis virus. With follow-up beginning soon after cART came online, a 1467-person study at a large London HIV clinic<sup>21</sup> and a 5397-person analysis of the Italian Icona cohort<sup>29</sup> found that HCV coinfection raised chances of CD4 tallies dwindling below 200 cells/mm<sup>3</sup> or a new AIDS diagnosis (**Table 5**). A study of 343 HIV-positive people in Saskatchewan—79% with a drug-injecting history and 77% with HCV—figured that HCV tripled chances that CD4s would dwindle below 200 cells/mm<sup>3</sup> (HR 2.9, 95% CI 1.2 to 6.9).<sup>49</sup>

The 2009 meta-analysis of 7 HCV/HIV studies in Canada, Europe, the United States, and Taiwan during the cART era found that HCV infection barely budged chances of a new AIDS diagnosis when compared with HIV alone (aRR 1.12, 95% CI 0.82 to 1.51).<sup>13</sup> But this meta-analysis did not include the

**Table 5.** Impact of HCV on HIV disease progression

Author	n	Population	Site(s)	Year(s)	Key outcomes
Dorrucchi (1995) <sup>48</sup>	416, 214 (51%) HCV+	AIDS-free, IDU or sexual transmission; known HIV sero-conversion date	Italy	Pre-cART longi-tudinal study	HCV had no impact on progression to AIDS or CD4 decline <100.
Amin (2004) <sup>27</sup>	1649, 265 (16%) HCV+	People adding 3TC or 3TC/loviride to single or dual nucleosides	Canada, Australia, Europe, South Africa	Pre-cART 1995-1996 (52-wk FU)	Median change in CD4 count and progression to new AIDS event similar with/without coinfection.
Stebbing (2005) <sup>21</sup>	1467, 85 (6%) HCV+	Patients with >200 CD4s in care since cART availability in 1/1996	Chelsea and Westminster Hospital, London	1996-2005	HCV raised chance of <200 CD4s or first AIDS event (aHR 1.52, 95% CI 1.07 to 2.17, P = 0.019).
d'Arminio Monforte (2009) <sup>29</sup>	5397, 2421 (49%) HCV+	Icona cohort patients enrolled when ART-naive	Italy	1997-2008	HCV raised chances of AIDS diagnosis (aRR 2.61, 95% CI 1.88 to 3.61).*
Konrad (2013) <sup>49</sup>	343, 264 (77%) HCV+	Mainly (79%) IDU HIV+ population	Two clinics in Saskatchewan	Diagnosed 2005-2010	HCV tripled risk of CD4 decline <200 (HR 2.9, 95% CI 1.2 to 6.9).
Chen (2009) <sup>13</sup>	21,607, 5334 (25%) HCV+	Meta-analysis of cART patients	7 studies in Canada, Europe, US, Taiwan	1996-2004	In pooled analysis, HCV did not raise chance of new AIDS diagnosis (aRR 1.12, 95% CI 0.82 to 1.51).†¶
van der Helm (2013) <sup>45</sup>	9164, 2015 (22%) HCV+	Europeans and Canadians with known date of HIV seroconversion	Europe, Canada	Pre-1989-2007	HCV raised chances of AIDS-related mortality in cART era in IDUs (aHR 2.43), MSM (aHR 3.11), and others‡ (aHR 3.43).

aRR, adjusted relative rate; FU, follow-up; MSM, men who have sex with men.

\* AIDS-defining illnesses included bacterial infection (aRR 3.15, 95% CI 1.76 to 5.67), HIV-related disease (wasting and dementia, aRR 2.68, 95% CI 1.03 to 6.97), and mycotic disease (aRR 3.87, 95% CI, 2.28 to 6.59).

† Did not include d'Arminio Monforte<sup>29</sup> or Konrad.<sup>49</sup>

¶ Analysis of 7 other studies defining progression as either an AIDS diagnosis or death determined that HCV coinfection raised the risk of progression almost 50% (aRR 1.49, 95% CI 1.08 to 2.05).

‡ People infected heterosexually or via blood products.

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large Italian study that found more than a doubled risk of an AIDS diagnosis with versus without HCV,<sup>29</sup> and it did not include the small Saskatchewan study that linked HCV coinfection to a CD4 drop below 200 cells/mm<sup>3</sup> or a new AIDS diagnosis.<sup>49</sup> Adding those 5740 patients to the meta-analysis would have boosted the risk of HIV disease progression with HCV, perhaps into significant terrain. The meta-analysis did find that coinfection inflated chances of an AIDS diagnosis *or* death about 50% (aRR 1.49, 95% CI 1.08 to 2.05).

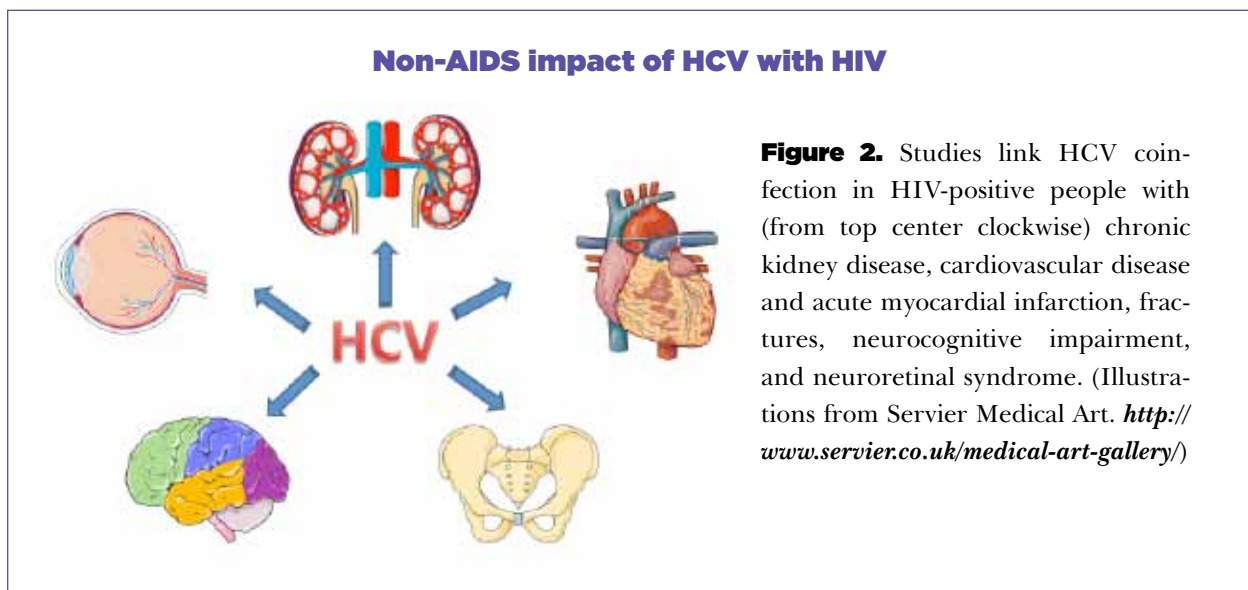
The 2013 CASCADE cohort analysis did not consider a new AIDS diagnosis or waning CD4 counts as an endpoint.<sup>45</sup> But HCV coinfection more than doubled or tripled chances of AIDS-related mortality in the cART era, depending on HIV transmission group (**Table 5**).

Together these studies (**Table 5**) offer compelling evidence that—as cART began to rescue people from AIDS—it left behind many coinfecting with HCV. With these findings in mind, the CASCADE team stressed

“the importance of early diagnosis of HCV infection in HIV-infected individuals and the need for routine screening of HCV among high-risk groups, including those not (yet) infected with HIV.”<sup>45</sup> They proposed that their results “highlight the importance of interventions to increase the uptake of HCV treatment in co-infected individuals.” Findings in multiple populations that HCV raises chances of AIDS or a falling CD4 count lend credence to data indicating that HCV boosts mortality in people with HIV, the issue examined in the preceding section.

### HCV COINFECTION AND NONAIDS DISEASE RISK

HCV has a profound impact on mortality in people with HIV not only because it leaves many vulnerable to AIDS (preceding section), but also because it has far-flung repercussions on risk and progression of deadly non-AIDS diseases. Research indicates that HCV affects kidneys, heart, bones, brain, and eyes—all highly pregnable organs in people with HIV infection (**Figure 2**).



HCV coinfection did not heighten renal or cardiovascular disease prevalence in a 1996-2001 age-adjusted analysis of 823 HIV-positive people in the HIV Out-patient Study.<sup>50</sup> But more recent and larger analyses did find ties between HCV and damaged kidneys or heart. Analysis of 3441 cART-treated people enrolled in the SMART and ESPRIT trials included 473 (14%) positive for HCV antibody and 363 (10.5%) with detectable HCV RNA.<sup>51</sup> After adjustment for renal risk factors, statistical analysis determined that HCV coinfection bolstered odds of progressive chronic kidney disease (CKD) almost 75% (adjusted odds ratio [aOR] 1.72, 95% CI 1.07 to 2.76). People with low or undetectable HCV RNA had a CKD progression risk similar to that of HCV-negative people, but those with an HCV load above 800,000 IU/mL had tripled odds of progression (aOR 3.07, 95% CI 1.60 to 5.90).

An 8235-person EuroSIDA group included 2025 (25%) positive for HCV and 983 (12%) with detectable HCV RNA.<sup>52</sup> During follow-up starting in January 2004, CKD developed in 495 people (6%) for an incidence of 13.7 per 1000 person-years. After statistical adjustment for kidney risk factors, HCV positivity nearly doubled the risk of incident CKD (IRR 1.85, 95% CI 1.49 to 2.30,  $P < 0.0001$ ). People who cleared their HCV had a CKD risk similar to that of HCV-negative people (IRR 1.17, 95% CI 0.65 to 2.09,  $P = 0.60$ ). But people with HCV RNA between 615 and 500,000 IU/mL had almost a twice higher CKD incidence (IRR 1.88, 95% CI 1.31 to 2.71,  $P = 0.0006$ ), and people with an HCV load above 500,000 IU/mL had more than a doubled risk of progression to CKD (IRR 2.10, 95% CI 1.54 to 2.87,  $P < 0.0001$ ). Results of both studies<sup>51,52</sup> endorse calls for early HCV therapy in coinfecting people.

HCV coinfection swelled risk of cardiovascular disease and acute myocardial infarction (MI) in a study of 19,424 US veterans, 32% of whom had HCV coinfection.<sup>53</sup> As in previous research, this study recorded lower cholesterol levels in people with HCV,

but HCV-positive veterans had significantly higher rates of hypertension, type 2 diabetes, and smoking. Through more than 76,000 person-years of follow-up in the cART era (1996-2004), cardiovascular disease and acute MI incidence were significantly higher in HCV-coinfecting veterans. After statistical adjustment for diabetes, hypertension, age, and cART duration, HCV inflated acute MI risk 25%, though that association stopped short of statistical significance (aHR 1.25, 95% CI 0.98 to 1.61,  $P = 0.072$ ). HCV boosted cardiovascular disease risk 20%, and that association was significant (aHR 1.20, 95% CI 1.04 to 1.38,  $P = 0.013$ ).

The French prospective APROCO-COPILOTE cohort involved 1281 people who began cART in 1997-1999, 26 of whom had 27 fractures during a median follow-up of 7.1 years between March 1997 and August 2007.<sup>54</sup> Body mass index did not differ between those with and without a fracture, but people who broke a bone were more often heavy drinkers (44% versus 19.5%), more likely to have HCV coinfection (48% versus 24.5%), and had a lower baseline CD4 count (194 versus 277 cells/mm<sup>3</sup>). Multivariate analysis determined that heavy drinkers had almost tripled odds of fracture (aOR 2.9, 95% CI 1.3 to 6.5). Fracture risk was even higher in people coinfecting with HCV (aOR 3.6, 95% CI 1.6 to 8.1).

Both HCV and HIV penetrate the central nervous system, so there's no surprise that studies link HCV coinfection to neurologic problems, including neurocognitive impairment and neuroretinal disorder. A small study at the University of North Carolina, Chapel Hill documented worse visual memory and fine-motor functioning in 20 HCV/HIV-coinfecting people than in 45 infected only with HIV before they started cART.<sup>55</sup> The groups had comparable HIV progression before treatment started, and no one had a history of neurologic conditions. Six months after cART began, follow-up neuropsychological testing in

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13 coinfecting and 31 monoinfected people indicated that coinfecting people no longer had worse neurocognitive function than the monoinfected group.

A 1998-2010 study at two HIV clinics in Alberta, Canada involved 456 HIV-positive people without a substance abuse history, 91 of them (20%) positive for HCV.<sup>56</sup> The coinfecting group had a higher prevalence of multiple neurologic disorders (60.4% versus 46.6%,  $P < 0.05$ ) and a higher seizure frequency (28.6% versus 17.8%,  $P < 0.05$ ). Seizure risk was independent of immune status in the coinfecting group but not the monoinfected group. Symptomatic HIV-associated neurocognitive disorder (HAND) was more severe in coinfecting than monoinfected people. Reflecting most studies reviewed in the mortality analysis above, a significantly higher proportion of people with than without HCV in the Alberta analysis died during the study period (24.2% versus 14.5%,  $P < 0.05$ ). The coinfecting group had a 2.4 times higher death risk after adjustment for demographic and clinical variables.

A 2013 study by researchers at New York's Mount Sinai Medical Center and Baltimore's Johns Hopkins University focused on 1576 HIV-positive people with no record of ocular opportunistic infection.<sup>57</sup> The group included 290 people (18%) with chronic HCV infection, 74 (5%) with cleared HCV infection, and 1212 (77%) with no HCV markers. The investigators counted 244 prevalent cases of HIV-associated neuroretinal disorder (15.5%)—visual impairment marked by reduced contrast sensitivity and reading ability. During a median follow-up of 4.9 years, neuroretinal disorder developed in another 263 people (17%). Statistical analysis adjusted for demographics, HIV treatment, liver function, and immune status determined that people with chronic HCV infection had 54% higher odds of prevalent neuroretinal disorder (95% CI 1.03 to 2.31) and 62% higher odds of

incident neuroretinal disorder (95% CI 1.13 to 2.34) when compared with HCV-negative people.

### IMPACT OF HCV ON RESPONSE TO cART

Among 10 large studies analyzing antiretroviral response in people starting cART, five (including an 8-cohort meta-analysis<sup>14</sup>) found that HCV coinfection impaired CD4 or virologic response to cART, four did not, and one found an early impact on CD4 gain that disappeared over 4 years<sup>17</sup> (**Table 6**). No easy explanation of this disagreement screams for attention.

One of the no-impact studies, an analysis of 970 US veterans in a prospective cohort,<sup>43</sup> included a relatively low proportion of IDUs and assessed CD4 changes after only 6 months of treatment. But the other three no-impact studies, a Johns Hopkins cohort study,<sup>20</sup> a EuroSIDA study<sup>26</sup> and a 10-city US analysis,<sup>46</sup> had higher proportions of IDUs and longer follow-up. All told, the no-impact studies assessed 19,403 people, including 5163 (27%) positive for HCV. The five studies finding that HCV worsens response to cART tallied 14,110 participants, 4192 (30%) with HCV. Almost all cohort members in every study lived in Western Europe or the United States.

The 2005 meta-analysis focused on 8 cohorts of people starting cART from 1995 through the early 2000s.<sup>14</sup> After 48 weeks of treatment, people positive for HCV had a 33.4-cell lower CD4 gain than people negative for HCV. No single study had an undue influence on the results, and cART begun before or after the year 2000 did not affect the key finding. These investigators noted that their analysis is limited by an inability to determine pretreatment CD4 counts in the cohorts assessed. Also, seven of the eight studies that reported virologic response to cART saw no difference by HCV status.

**Table 6.** Impact of HCV coinfection on response to cART

Author	n	Population	Site(s)	Year(s)	Key outcomes*
Sulkowski (2002) <sup>20</sup> <b>HCV does not have impact</b>	1995, 873 (44%) HCV+	Prospective cohort of patients without AIDS starting cART; 85% of HCV+ IDU	Baltimore	1995-2001, median follow-up 2.19 y with HCV, 2.00 y without HCV	HCV had no impact on CD4-cell or CD4-percent gains with cART.
De Luca (2002) <sup>10</sup> <b>HCV has impact</b>	1320, 600 (45%) HCV+	Prospective study in Icona cohort patients starting cART, 39% IDU	Italy	Median 37 mo follow-up in 1997-2001	HCV+ had shorter time to AIDS or death (aHR 1.55, 95% CI 1.00 to 2.41); mean CD4 gain 30 cells/mm <sup>3</sup> less with HCV; no HCV impact on virologic response.
Kaufmann (2003) <sup>17</sup> <b>HCV has transient impact</b>	985 on continuous cART, 300 (30.5%) HCV+	Prospective Swiss HIV Cohort Study patients starting cART, 23% IDU	Switzerland	Began cART 1996-1997, 4 years follow-up	HCV+ had lower CD4 gain in first year of cART (126 vs 151 cells/mm <sup>3</sup> , <i>P</i> = 0.004) but not after 4 years of cART.
Anderson (2004) <sup>43</sup> <b>HCV does not have impact</b>	970, 306 (32%) HCV+	Atlanta VA Cohort Study patients starting cART, 22% IDU	Atlanta area	1997-2001	HCV did not affect CD4 gain in first 6 months of cART; IDU associated with lower CD4 gain.
Miller (2005) <sup>14</sup> <b>HCV has impact</b>	6216, 2179 (35%) HCV+	Meta-analysis of patients starting cART in 8 cohorts, 3% to 88% IDU	Australia, Canada, France, Italy, Spain, Switzerland, US	1995-early 2000s	HCV+ had mean 33.4 cells/mm <sup>3</sup> lower gain through 48 weeks of cART.
Rockstroh (2005) <sup>26</sup> <b>HCV does not have impact</b>	5957, 1960 (33%) HCV+	Prospective study of EuroSIDA cohort, 77.5% of HCV+ IDU	Europe, Israel	1994-2004	HCV had no impact on virologic or CD4 response (measured as 50% or 50-cell increase).
Sullivan (2006) <sup>46</sup> <b>HCV does not have impact</b>	10,481, 2024 (19%) HCV+	Adult and Adolescent Spectrum of HIV Disease participants starting cART, 47% HCV+ IDU	10 US cities	1998-2004, median 1.9 y follow-up	HCV did not affect CD4 gains or virologic response in first 12 months of cART.

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**Table 6.** Impact of HCV coinfection on response to cART

Author	n	Population	Site(s)	Year(s)	Key outcomes*
Potter (2010) <sup>6</sup> <b>HCV has impact</b>	271 HCV+, 236 (87%) with detectable HCV RNA, 35 with cleared HCV RNA	Canadian Co-infection Cohort Study participants starting cART, 76% HCV RNA+ and 71% HCV RNA- IDU	16 centers in Canada	2003-2009	Yearly CD4 gain 4 cells/mm <sup>3</sup> in HCV RNA+ vs 26 cells/mm <sup>3</sup> in HCV RNA- ( <i>P</i> < 0.001).
Motta (2012) <sup>16</sup> <b>HCV has impact</b>	3262, 863 (26%) HCV+	Italian MASTER cohort starting cART in 2000- 2008	9 centers in Italy	Mean 4.3 y follow-up	HCV lowers odds of reaching <500 HIV RNA in 1st 8 mo (OR 0.612, <i>P</i> = 0.01 with PIs, OR 0.717, <i>P</i> = 0.006 with NNRTIs); HCV lowers odds of gaining 100 CD4s in 8 months (OR 0.662, <i>P</i> = 0.003 with PIs, OR 0.595, <i>P</i> < 0.001 with NNRTIs); HCV lowers 24-mo absolute CD4 gain.†
Hua (2013) <sup>5</sup> <b>HCV has impact</b>	3041, 279 (9%) HCV+	Participants in 4 ACTG cART trials; 52% HCV+ IDU	ACTG sites in US	NR, ~early to late 2000s	Through median 132 wk follow-up, HCV linked to earlier virologic fail- ure (HR 1.43, 95% CI 1.07 to 1.91), smaller mean CD4 increase (-33.8 cells/ mm <sup>3</sup> , 95% CI -52.2 to -15.4), earlier grade 3/4 safety event (HR 1.51, 95% CI 1.26 to 1.81), increased progression to AIDS or death (HR 2.10, 95% CI 1.31 to 3.37).

\* All analyses adjusted for potential confounders.

† CD4 response analysis included only virologic responders.

ACTG, AIDS Clinical Trials Group; IDU, injection drug user; NR, not reported.

The most recent analysis compared HCV-positive and negative people enrolled in four AIDS Clinical Trials Group (ACTG) trials of first-line cART.<sup>5</sup> All trials assessed contemporary cART regimens including efavirenz, atazanavir/ritonavir, or lopinavir/ritonavir. After substantial follow-up (median 132 weeks), HCV-positive people had worse virologic, CD4 count, and CD4 percent responses in adjusted analyses. They also ran a 50% higher risk of grade 3 or 4 safety events and a doubled risk of AIDS or death. Antiretroviral adherence was good in both the HCV-positive and negative groups. Strengths of this analysis, the researchers observed, include “randomization, rigorous study monitoring, and extensive and similar data collection.” And the worse CD4 response with HCV held true when the investigators limited the analysis to people without virologic failure. The ACTG team noted that their study (like the meta-analysis<sup>14</sup>) suffers from dependence on HCV antibody testing rather than HCV RNA assessment and the relatively small proportion of HCV-positive people.

This ACTG analysis checked cART responses through 2.5 years of therapy.<sup>5</sup> The (earlier and smaller) Swiss HIV Cohort Study (SHCS) reckoned cART responses through 4 years of treatment and determined that HCV positivity did not imperil CD4 gains over that span.<sup>17</sup> The SHCS analysis *did* find worse 1-year CD4 gains in coinfecting people (**Table 6**), but that deficit disappeared with continued cART.

The Canadian Co-infection Cohort Study was the only study that distinguished between HCV RNA-positive people with chronic HCV infection and HCV antibody-positive people with cleared infection.<sup>6</sup> This 16-center study monitoring people from 2003 through 2009 found that those who cleared their HCV gained 26 CD4 cells/mm<sup>3</sup> yearly, compared with a meager 4 cells/mm<sup>3</sup> yearly in the chronically infected HCV RNA-positive group ( $P < 0.001$ ). Researchers figure that 85% of HCV antibody-positive

people have chronic infection.<sup>58</sup> But the remaining 15% could have some impact on results of the 7 studies relying solely on HCV antibody testing.

If one believes the apparently preponderant evidence that HCV coinfection heightens the risk of AIDS (**Table 5**), believing that HCV does not affect CD4 counts or viral load requires some gymnastic reasoning.

## DISCUSSION, REDUCTION, DEDUCTION

Can the harried clinician put all these HCV and HIV pieces together to decide how HCV affects HIV progression? A quick check of the reference list indicates that—after excluding HIV care guidelines—there are a lot of pieces: 55 if you count each study cited so far, many more if you pick out key data points from each study. One answer—as frivolous as sounds—is it doesn’t matter which studies are right and which wrong (or less right).

A first step toward groping one’s way through the research labyrinth to slay the data-spouting minotaur (**Figure 3**) is to ask whether an HCV impact on HIV’s course makes pathophysiologic sense. It does:

- Activated CD4 and CD8 cells (reflecting poorly controlled infection and signaling progression) reach higher levels in HCV/HIV-coinfecting people than in those infected with only one or the other virus.<sup>59</sup> T-cell activation and exhaustion in this 58-person study correlated with HCV RNA load.
- Activated CD8 cell percentages proved higher in women positive for HIV, HCV antibody, and HCV RNA than in women positive for HIV but not HCV antibody in a 218-woman study.<sup>60</sup>

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- HCV-positive women with measurable HCV RNA had significantly higher levels of activated CD8 cells and a higher AIDS incidence than HCV-negative women, according to results of a 1307-woman analysis.<sup>61</sup>
- HCV coinfection boosted T-lymphocyte apoptosis (cell death) in 30 HIV-positive people not taking antiretrovirals more than in 31 people infected only with HIV.<sup>62</sup>

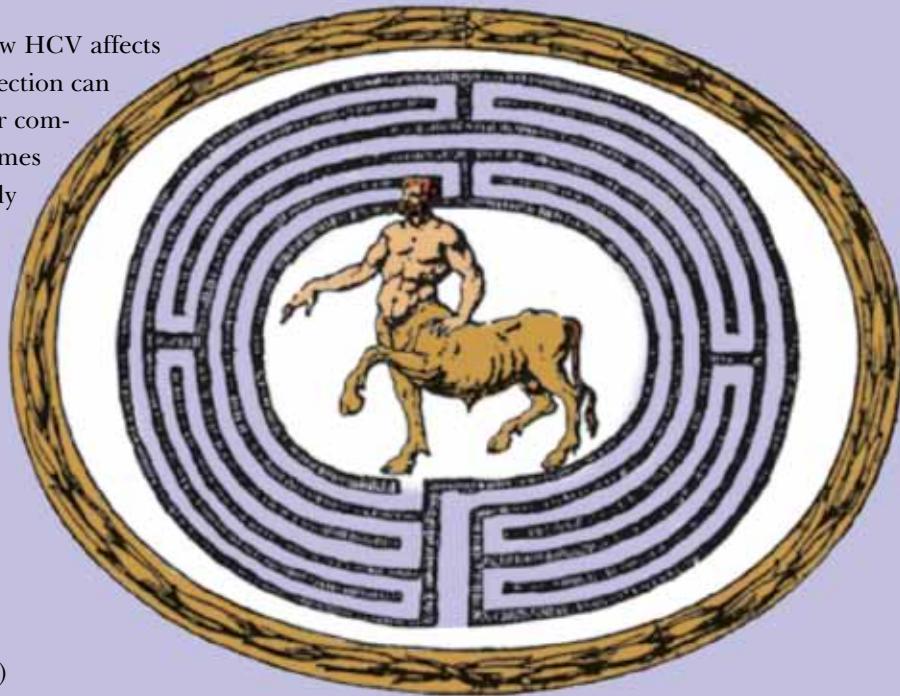
Thus reassured, the clinician can acknowledge that a mountain of data—reasonably interpreted—says HCV infection makes people with HIV get sick and die faster than people without HCV. Yet there's no denying that another mountain of data says the op-

posite. Does it matter which mountain one decides to plant one's flag upon? The apparent answer seems to be "certainly"—because the outcomes are sickness versus health, life versus death.

But from a different perspective—one that offers a view of the minotaur's maze from above rather than within (**Figure 3**)—debates over the clinical impact of HCV on HIV disease are academic. Would anyone suggest that failure to find an association between HCV and HIV disease progression in some studies means clinicians can relax when treating coinfecting people? Or stop worrying about sky-scraping HCV loads? Or delay deciding how and when to treat HCV infection?

### Finding a way through the HCV/HIV data maze

**Figure 3.** Data on how HCV affects the course of HIV infection can seem mazelike in their complexity. But sometimes the most apparently daunting maze—seen from above like the minotaur's maze—has a simple solution: There's only one way in and one way out.



(Illustration from  
Wikipedia Commons.)

With direct-acting antivirals (DAAs) already on hand and rapidly growing more numerous (see the first article in this issue of *RITA!*), would anyone suggest delaying HCV therapy and denying a coinfecting person a 90% or higher chance of cure makes sense because HCV does not, or may not, worsen the course of HIV infection? DAAs have not only transformed treatment of HCV infection; they have also radically reshaped interpretation of how HCV and HIV interact to make someone sicker or closer to death. One might delay DAA therapy to wait for an appropriate all-DAA regimen, but not because of HCV's impact on HIV.

What about conflicting data on how HCV affects antiretroviral response? If a clinician believes the five studies that saw no impact of HCV coinfection on cART response (**Table 6**), that clinician will have no concerns over timing treatment of HCV and HIV in the same person. If a clinician believes the four

studies (including one meta-analysis) that found a diminished response to cART in people with HCV, that clinician may want to start cART first in people with advanced HIV infection (as suggested in US guidelines<sup>30</sup>) and probably wants to monitor antiretroviral response more closely in people being treated for HIV and HCV at the same time.

But for both sets of providers, the imminent arrival of multiple-DAA regimens may largely render cART timing decisions moot. Delaying cART for 6 months or more in HCV-coinfecting people taking pegylated interferon plus ribavirin may be an unpalatable option—or completely out of the question—for patients with low CD4 counts or clinical AIDS. But if DAA combinations can cure HCV infection in 6 to 12 weeks, many more HIV-positive people may be candidates for (briefly) delayed cART during HCV therapy.

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# PatientGuide

## Ten pointers for people with hepatitis C virus (HCV) and HIV infection\*

1. HCV may not make you feel sick for many years after you become infected. But HCV continues to damage the liver during this period. People who run a risk of HCV infection (see points 3, 4, and 5) should get tested for HCV.
2. You can slow liver damage by avoiding alcohol and drugs that affect the liver, including some nonprescription drugs and party drugs. Your health care provider can tell you which drugs are most likely to affect the liver.
3. You can avoid passing HCV to a sex partner by always using a condom during sex.
4. You can avoid passing HCV to someone else by not sharing sex toys, razors, toothbrushes, dental appliances, or tattoo equipment.
5. The most frequent way HCV gets spread is by sharing drug-injecting equipment. Sharing injecting equipment can also pass HIV to an injecting partner. Never share injecting equipment.
6. Tell sex partners you have HCV and suggest that sex partners get tested for HCV.
7. Pregnant women can pass HCV to the fetus. Pregnant women both HCV and HIV run a higher risk of transmitting either virus to the fetus than do women infected with only HCV or HIV.
8. Pregnant women should not take the HCV drugs ribavirin and interferon. Women and men taking ribavirin should use contraceptive methods throughout ribavirin therapy and for 6 months after completing ribavirin therapy.
9. Children born to HCV-infected mothers should be tested for HCV.
10. Some anti-HIV drugs (antiretrovirals) may affect the liver more in people with HCV. Your health care provider will want to check your liver function regularly if you are taking anti-HIV drugs.

\*From US Department of Health and Human Services Health Resources and Services Administration. Guide for HIV/AIDS clinical care. January 2011. <http://hab.hrsa.gov/deliverhivaidsare/clinicalguide11/>



## Soaring sexually transmitted HCV rates in gay/bisexual men

By Mark Mascolini .....

“Tentative” may be the kindest word to describe Centers for Disease Control and Prevention (CDC) online statements about sexual transmission of HCV. The CDC does recommend testing some gay and bisexual men for HCV infection, but in a statement that starts with a negative clause: “Testing for Hepatitis C is not recommended for gay and bisexual men unless they were born from 1945 through 1965, have HIV, or are engaging in risky behaviors.”<sup>1</sup>

That fact sheet for gays, as well as CDC advice for professionals, make sexual transmission of HCV seem almost an anomaly: “While rare, spreading Hepatitis C through sex is possible.”<sup>2</sup>

The CDC’s longest factsheet declaration on HCV transmission clearly states that “HCV is most efficiently transmitted through large or repeated percutaneous exposure to infected blood (e.g., through transfusion of blood from unscreened donors or through use of injecting drugs).”<sup>3</sup> No one would argue with that. This transmission summary goes on to note that “although much less frequent, occupational, perinatal, and sexual exposures also can result in transmission of HCV.” Sexual transmission takes third place in this list of “much less frequent” transmissions, though overwhelming evidence from the past decade documents an explosive HCV epidemic among men who have sex with men (MSM) throughout the United States, Europe, and Australia. No research suggests

occupational or perinatal HCV transmission has grown at anywhere near the riptide pace seen in gay and bisexual men with and without HIV.

The most recent opportunistic infection guidelines from the CDC, National Institutes of Health, and HIV Medicine Association better reflect current research in MSM.<sup>4</sup> “In HIV-infected MSM,” this document notes, “multiple outbreaks of acute HCV infection demonstrate that sexual transmission is an important mode of acquisition in this population,” adding that risk factors include condomless receptive anal intercourse, using sex toys or noninjection recreational drugs, and sexually transmitted infections (STIs).

In these guidelines the CDC recommends routine HCV testing for “all HIV-infected patients.”<sup>4</sup> For “at risk HCV-seronegative persons,” the CDC advises HCV antibody testing “annually or as indicated by risk exposure.” A positive antibody result calls for confirmatory HCV RNA testing to identify chronic—versus cleared—HCV infection.

But if a provider or layperson clicks their way to handy HCV summaries at the CDC website,<sup>1-3</sup> they may easily come away with the impression that HCV jumps from one sex partner to the other too rarely to justify routine testing.

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The perception that HCV seldom roves between sex partners reflects some US/Canadian research from the early 2000s in MSM and people with HIV.<sup>5-7</sup> But other research from that era—and volumes of more recent work—amply demonstrate an epidemic of sexually transmitted HCV in MSM. Studies that identify transmission risk factors show why gay sex poses a much higher HCV transmission risk than heterosexual sex: it can be bloody. Rough anal sex, including sex toy use and fisting (inserting the fist into the rectum), and high rates of lesion-producing STIs offer HCV a direct route to the bloodstream and target cells throughout the body. Injection drug use and un-screened transfusions pose the highest risk of HCV transmission because big loads of blood carry more HCV than small loads. Less blood—often no blood—flows between partners during sex, but more blood typically gets mixed during gay sex than straight sex. Semen can also carry HCV RNA.

### **Doubled chance of HCV with HIV/HCV-positive sex partner**

A clever analysis by Swiss HIV Cohort Study (SHCS) investigators offers strong evidence that, within HIV transmission pairs, having an HCV-positive sex partner doubles the risk of getting infected with HCV.<sup>8</sup> The SHCS team turned to its antiretroviral resistance database and compared HIV genetic sequences to find 1555 HIV transmission pairs with known HCV status. Most pair members (78.5%) were men. Almost half (48.5%) picked up HIV during sex between men, while about one quarter became infected heterosexually and one quarter when injecting drugs.

Within likely HIV transmission pairs, having an HCV-positive partner boosted odds that the second partner would also have HCV more than 13 times (odds ratio [OR] 13.6, 95% confidence interval [CI] 10.5 to 17.6).

These higher odds held true when the researchers considered HIV transmission groups separately: 3.1 (95% CI 1.4 to 7.0) for MSM, 4.5 (95% CI 1.2 to 16.3) for MSM who injected drugs but attributed their HIV to sex, 5.4 (95% CI 2.9 to 10.3) for heterosexuals, 2.1 (95% CI 0.9 to 5.1) for heterosexuals who injected drugs but attributed their HIV to sex, and 2.7 (95% CI 1.3 to 5.5) for injection drug users (IDUs). Overall chances of having HCV if one's sex partner has HCV remained significant after statistical adjustment for HIV transmission group, calendar year, age, and sex (OR 3.2, 95% CI 2.2 to 4.7).

The SHCS team figured HCV incidence (the new-infection rate) by determining how many members of a likely HIV transmission pair tested negative for HCV then later tested positive. HCV-negative people who belonged to an HIV transmission pair in which the partner already had HCV proved twice as likely to acquire HCV infection as HCV-negative pair members whose partner did not already have HCV (hazard ratio [HR] 2.1, 95% confidence interval 1.1 to 3.8). This analysis adjusted for HIV transmission risk factor and calendar year.

The researchers stressed that their study does not involve confirmed sex partners: They relied on HIV phylogenetic analysis to infer partnerships (a well-accepted technique), and they did not phylogenetically analyze HCV in likely HIV pairs. The authors cautioned that the results may not apply to other HIV populations, but other Western HIV populations share more similarities than differences with the Swiss population. The twice higher risk of picking up HCV if a sex partner has HCV encouraged the SHCS team to underline “the importance of safe sex practices in HCV-discordant MSM couples and in sex with unknown partners even if HIV is suppressed by highly active antiretroviral therapy.”<sup>8</sup>

The CDC's own research provides evidence strongly implicating sexual transmission of HCV in the United States. CDC analysis of 30,074 National Health and Nutrition Examination Survey (NHANES) participants from 2003 and 2010 identified illicit drug use (including injecting drugs) and getting a blood transfusion before 1992 as predictors of chronic HCV infection.<sup>9</sup> Yet 49% of HCV-infected people in this analysis did not report either risk factor, a result leading the CDC team to propose that "risk-based screening alone is an incomplete approach to identifying chronically infected persons."

### Epidemic sexual transmission of HCV in MSM

The impression that HCV rarely migrates between sex partners rests on research in monogamous heterosexual couples and in sexually active MSM, other men, and women tracked largely in the early 2000s. In Italy a study of 776 HCV-negative monogamous heterosexual partners of people with HCV found *no* HCV transmissions through 10 years of follow-up.<sup>10</sup> No one in this study reported anal intercourse, sex during menstruation, or condom use. In a prospective study of 1085 Montreal MSM from January to September 2001, initial HCV prevalence stood at 2.9% and was attributed to injecting drugs much more often than to having sex (32.9% versus 0.3%,  $P < 0.0001$ ).<sup>11</sup> During 2653 person-years of follow-up, only 1 man picked up HCV, and he shared needles when injecting drugs.

A 1999-2003 study involved men and women offered HCV testing while attending STI clinics or seeking HIV testing in Seattle, San Diego, and New York City.<sup>12</sup> Among 1699 MSM who did not inject drugs, only 26 (1.5%) tested positive for HCV. That rate proved almost 60% lower than the 3.6% prevalence among 3455 heterosexual men who did not inject drugs (prevalence ratio 0.42, 95% CI 0.28 to 0.64). Retrospective review of 5639 people attending a New

York City hospital HIV clinic from January 1999 to May 2007 determined that MSM had lower odds of HCV coinfection than non-MSM (OR 0.565,  $P < 0.001$ ).<sup>13</sup> In contrast, coinfection odds were higher in heterosexual IDUs, MSM IDUs, and people who had transfusions.

Then clinicians started seeing something new. In mid-2004 three Paris hospitals told city public health officials they admitted several HIV-positive MSM with acute HCV infection who reported condom-free sex but denied injecting drugs.<sup>14</sup> Checking records of those three hospitals from April 2001 to October 2004, authorities identified 29 cases of acute HCV in MSM with HIV. All these men had anal sex without condoms, and many reported "hard" sex, bleeding during sex, fisting, or STIs. No men injected drugs. The Paris team concluded that "HCV transmission probably occurred through bleeding during unprotected traumatic anal sex among HIV+ MSM and may be facilitated by STI mucosal lesions."<sup>14</sup>

Around the same time in Rotterdam, 275 miles north of Paris, clinicians reported a case of acute HCV in an HIV-positive man to the Municipal Health Service.<sup>15</sup> The man had rectal lymphogranuloma venereum (LGV) at the time of acute HCV infection and belonged to a 2003 cluster of 15 LGV cases. A public health team studied this man, 2 recent sex partners, and 14 area men with LGV. Seven of these 17 (41%) recently became infected with HCV. Six of the 7 had HIV infection and 6 had LGV proctitis when they picked up HCV. None of these men injected drugs, but most used noninjection drugs. All 7 men with HCV practiced passive or active fisting. These men had many sex partners—often anonymous partners—throughout Europe.

As the millennium matured, reports of rocketing HCV incidence among MSM followed from Amsterdam,<sup>16</sup>

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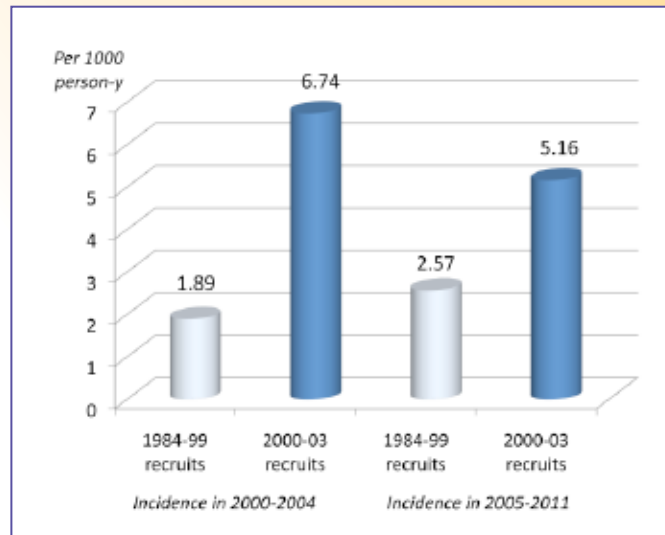
London and Brighton,<sup>17</sup> Antwerp,<sup>18</sup> Melbourne,<sup>19</sup> Amsterdam again<sup>20</sup>—then from whole countries (France,<sup>21</sup> Switzerland<sup>22</sup> and the United States<sup>23</sup>) and international cohorts.<sup>24,25</sup> Typically pussyfooted article headlines assumed a stampeding sense of urgency: “Is this an outbreak?”<sup>17</sup> “An expanding epidemic.”<sup>20</sup> “A rapidly evolving epidemic.”<sup>22</sup> “A large international network.”<sup>24</sup> And consistent findings appeared from study to study: little or no injection drug use or other parenteral exposure to HCV, anal sex without condoms, rough anal sex without condoms, heavy recreational drug use, and lesion-leaving STIs.

In Amsterdam HCV incidence in HIV-positive MSM jumped 10-fold after 2000 to 0.87 per 100 person-years, meaning almost 1 in every 100 men with HIV

picked up HCV every year.<sup>16</sup> In a London/Brighton study of MSM with HIV, HCV incidence leapt 70% from 0.686 per 100 in 2002 to 1.158 per 100 during January-June 2006.<sup>17</sup> An Antwerp study of HCV incidence in MSM with HIV traced an explosive surge from 0.2 per 100 in 2001, to 1.51 in 2008, all the way up to 2.9 in 2009.<sup>18</sup>

French researchers charted HCV incidence from 1996 through 2005 in the national PRIMO Cohort of people enrolled with primary HIV infection.<sup>21</sup> Through a median follow-up of 36 months, the 402 cohort members had an HCV incidence of 0.43 per 100 person-years. Incidence measured 0.12 per 100 before January 2003 and 0.83 per 100 after that date—almost a 7-fold spurt.

### Rising HCV incidence in HIV+ MSM in MACS



**Figure 1.** Among HIV-positive MSM in the Multicenter AIDS Cohort Study (MACS), those recruited in 2000-2003 had higher HCV incidence than those recruited in 1984-1999.<sup>23</sup> Higher incidence in later recruits held true for incidence in 2000-2004 and 2005-2011.

From 1998 through 2011, Swiss HIV Cohort Study investigators gauged HCV incidence in 3333 initially HCV-negative MSM, 123 IDUs, and 3078 heterosexuals.<sup>22</sup> Everyone had HIV. Among MSM HCV incidence ballooned from 0.23 per 100 person-years in 1998 to 4.09 in 2011, almost an 18-fold leap. Overall HCV incidence was higher in IDUs than in MSM but fell during the study period among IDUs, while HCV incidence in heterosexuals remained below 1 per 100 person-years.

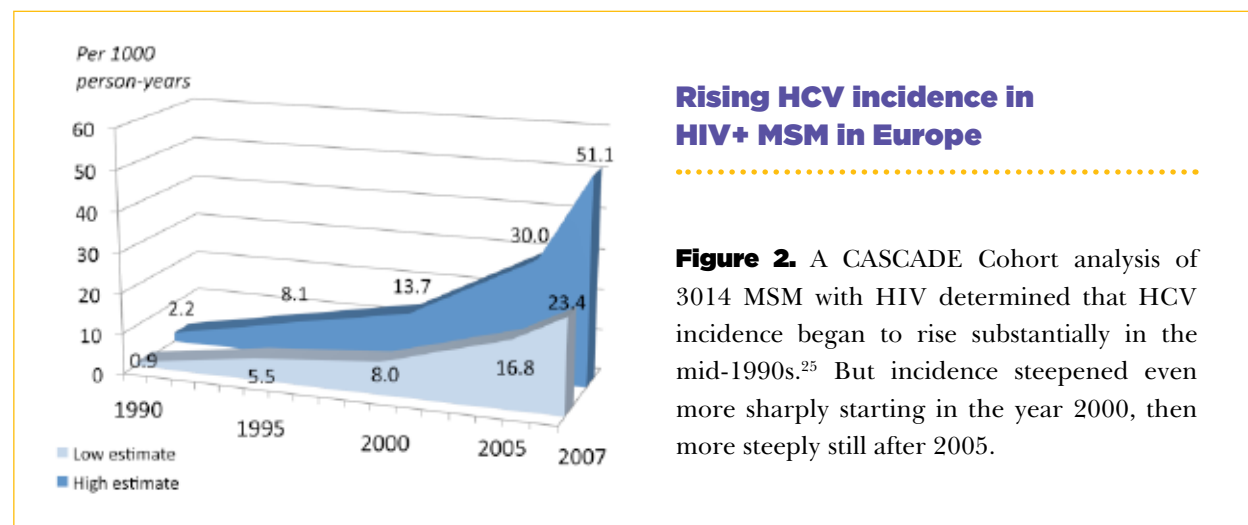
In the United States, Multicenter AIDS Cohort Study (MACS) investigators charted HCV incidence in 6417 MSM with and without HIV from the early days of the HIV epidemic (1984) until 2011.<sup>23</sup> HCV incidence proved almost 4 times greater in a later MACS recruitment period, 2001-2003, than in the 1980s or 1990s (incidence rate ratio [IRR] 3.80, 95% CI 1.67 to 8.64,  $P = 0.001$ ) (**Figure 1**). HIV-positive men had a 6 times higher HCV incidence than HIV-negative men (IRR 5.98, 95% CI 4.85 to 7.39,  $P < 0.001$ ).

An international team compared HCV NS5B sequences from 200 HIV-positive MSM diagnosed with HCV from 2000 through 2006 in England, the Netherlands, France, Germany, and Australia.<sup>24</sup> Sequence analysis determined that HCV from 156 men (78%) matched sequences from other men in the study. The

investigators mapped 11 HCV transmission clusters, each involving between 4 and 37 men. Molecular clock analysis indicated that 15% of HCV transmissions happened before 1996, 22% from 1996 to 2000, and 63% after 2000. Among European men in the study, 74% carried an HCV strain circulating in several European countries.

A similar, smaller phylogenetic analysis involved 74 HIV-positive MSM with recent HCV infection seen from 2005 through 2010 at New York’s Mount Sinai Medical Center.<sup>26</sup> None of the men injected drugs. HCV sequencing disclosed five clusters of closely related HCV variants. A case-control comparison matching 22 HCV/HIV-infected men with 53 HIV-infected men without HCV found that receptive anal intercourse without a condom raised chances of HCV infection 23 times. Having sex while using methamphetamine boosted HCV risk 28 times.

Finally, an international CASCADE cohort analysis found evidence that HCV incidence has been climbing among HIV-positive MSM since the mid-1990s.<sup>25</sup> But incidence steepened sharply starting in 2002, and even more so around 2005 (**Figure 2**). This analysis involved 3014 MSM with HIV, 43 from Canada and the rest from Western Europe.



### Rising HCV incidence in HIV+ MSM in Europe

**Figure 2.** A CASCADE Cohort analysis of 3014 MSM with HIV determined that HCV incidence began to rise substantially in the mid-1990s.<sup>25</sup> But incidence steepened even more sharply starting in the year 2000, then more steeply still after 2005.

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The investigators used three methods to estimate HCV incidence from 1990 through 2007. In 1990 estimated HCV incidence ranged from 0.9 to 2.2 per 1000 person-years (**Figure 2**).<sup>25</sup> By 1995 that range climbed to between 5.5 and 8.1 per 1000. In 2000 estimated HCV incidence stood between 8.0 and 13.7 per 1000. A big surge took HCV incidence up to 16.8 to 30.0 per 1000 in 2005. And by 2007 estimated HCV incidence ranged from 23.4 to 51.1 per 1000. Across these years the lowest and highest estimates mean that 1 per 1000 HIV-positive MSM picked up HCV in 1990, whereas 50 per 1000 got HCV infection in 2007.

### Risk factors for HCV infection in MSM

Reasons gay and bisexual men have become so vulnerable to HCV infection parallel reasons for surging HIV incidence among MSM in many Western countries: They're having more sex with more partners while taking party drugs and bearing anogenital lesions that give viral intruders easy entry. And they don't wear condoms. To protect themselves from HIV, some MSM have adopted serosorting—having condom-free anal sex with partners of the same HIV status. The value of serosorting in HIV prevention remains controversial, but HIV-serosorting clearly does nothing to protect an HCV-negative sex partner from hepatitis viruses. Rough anal sex including fisting has long been a feature of gay sex life, and studies dating to the early years of the HCV epidemic in gay men indicate that fisting plays a prominent role.<sup>14,15</sup>

HIV providers should be familiar with HCV risk factors in MSM, and they should make their HIV-positive and negative gay patients aware of these risks. (See **Table 1** and the patient handout on page 42 of this issue of *RITA!*.) Ample research analyzed in the first article of this issue of *RITA!* indicates that HCV infection complicates the course of HIV. Direct-acting antivirals (DAAs) have transformed treatment of

HCV infection, yielding high cure rates in 12 or fewer weeks. But these drugs are hugely expensive and may not be an option for people without excellent insurance. Avoiding HCV infection should be among the priorities of everyone with HIV.

**Table 1** summarizes what's known about HCV risk factors in MSM based on research over the past decade.

### “Alarmingly high” HCV reinfection rate in MSM

Getting infected with HCV does not protect a person from reinfection, even after spontaneous clearance of the first infection or curative therapy. Researchers working with Amsterdam's MSM Observational Study of Acute Infection With Hepatitis C (MOSAIC) charted HCV reinfection in 51 HIV-positive MSM with sexually acquired HCV.<sup>29</sup> All men got treated for HCV during acute primary infection and tested negative for HCV RNA after treatment, without relapse. The MOSAIC team defined HCV reinfection as detectable HCV RNA of a different HCV genotype or clade after undetectable HCV RNA at the end of treatment.

Eleven men (22% of 51) became reinfected for an incidence of 15.2 per 100 person-years (95% CI 8.0 to 26.5), meaning 15 of 100 men cured of HCV would become infected again in 1 year. Cumulative HCV reinfection incidence was 33% within 2 years. Calling the HCV reinfection rate “alarmingly high,” the Amsterdam group offered three recommendations:<sup>29</sup>

1. Discuss HCV prevention with people who test HCV RNA negative after being infected.
2. Test for HCV RNA frequently after successful treatment.
3. In cases of possible relapse after treatment, perform clade typing to rule out reinfection.

**Table 1.** Risk factors for HCV infection in gay or bisexual men\*

Sex	Drugs
<ul style="list-style-type: none"> <li>• Having many sex partners<sup>27</sup></li> <li>• Meeting sex partners online<sup>28</sup></li> <li>• Group sex<sup>27</sup></li> <li>• Fisting<sup>14,15,20,26,28</sup></li> <li>• Rough sex<sup>14,16</sup></li> <li>• Bleeding during sex<sup>14,28</sup></li> <li>• Receptive anal sex without condom<sup>14,23,26,28</sup></li> <li>• Inconsistent condom use<sup>22</sup></li> <li>• Using sex toys<sup>26</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Sex while high on drugs<sup>26,29</sup></li> <li>• Sex while using methamphetamine<sup>26</sup></li> <li>• Sex while using gamma hydroxybutyrate (GHB, cherry meth, liquid X)<sup>20,26</sup></li> <li>• Shared intranasal drugs<sup>27†</sup></li> <li>• More than 13 alcoholic drinks weekly<sup>23</sup></li> </ul>
Sexually transmitted infections (STIs)	HIV-related factors
<ul style="list-style-type: none"> <li>• Having an STI<sup>14,17</sup></li> <li>• Syphilis<sup>20,22,23,26</sup></li> <li>• Lymphogranuloma venereum (LGV)<sup>15,20</sup></li> <li>• Gonorrhea<sup>26</sup></li> <li>• Hepatitis B virus (HBV) infection<sup>23</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Lower CD4 count<sup>23</sup></li> </ul>

\* Risk factors identified by both univariate and multivariate analysis.

† [hcvguidelines.org](http://hcvguidelines.org), from the American Association for the Study of Liver Disease and the Infectious Diseases Society of America, cites intranasal illicit drug use as an HCV risk factor that should prompt testing.

Researchers at London’s Chelsea and Westminster Hospital tracked HCV reinfection in 191 sexually infected HIV-positive MSM who spontaneously cleared HCV or had successful treatment between January 2004 and April 2012.<sup>30</sup> They defined reinfection as any newly detectable HCV RNA after (24-week) sustained virologic response in treated men or 24 weeks after spontaneous clearance. All reinfections involved virus with an HCV genotype different from that of the first infection.

Forty-four of these men (23%) became reinfected for an incidence of 7.8 per 100 person-years (95% CI 5.8 to 10.5). Eight men became reinfected a second time for an incidence of 15.5 per 100 person-years (95% CI 7.7 to 31.0). Among 145 men whose initial infection could be documented as their first-ever HCV infection, the overall reinfection rate was 8.0 per 100 person-years (95% CI 5.7 to 11.3). In this 145-man analysis, reinfection incidence was 9.6 per 100 person-years (95% CI 6.6 to 14.1) among men with suc-

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cessfully treated primary infection and 4.2 per 100 person-years (95% CI 1.7 to 10.0) among men who spontaneously cleared their primary infection.

UK hepatitis virus guidelines for people with HIV now recommend HCV RNA testing every 3 to 6 months after spontaneous clearance or successful therapy in people who remain at risk for HCV infection.<sup>31</sup> The London team also recommends “directed education and prevention interventions” for HIV-positive MSM with HCV infection.<sup>30</sup>

### What about HIV-negative MSM?

Do sexually active HIV-negative MSM run a higher risk of sexually transmitted HCV infection than heterosexual men and women? Logic suggests that HIV-negative men may pick up HCV as often as HIV-positive men if they have condom-free sex, including fisting, while using party drugs. But studies in the US MACS cohort,<sup>23</sup> London,<sup>32</sup> Sydney,<sup>33</sup> and Zurich<sup>34</sup> found much lower HCV prevalence or incidence in HIV-negative MSM than HIV-positive MSM. The reasons for this difference may not be abstruse. The same sex habits that put MSM at risk for HIV infection put them at risk for HCV. An MSM group without HIV probably has less membrane-rending, drug-propelled sex than men with HIV—so they get HCV infection less often.

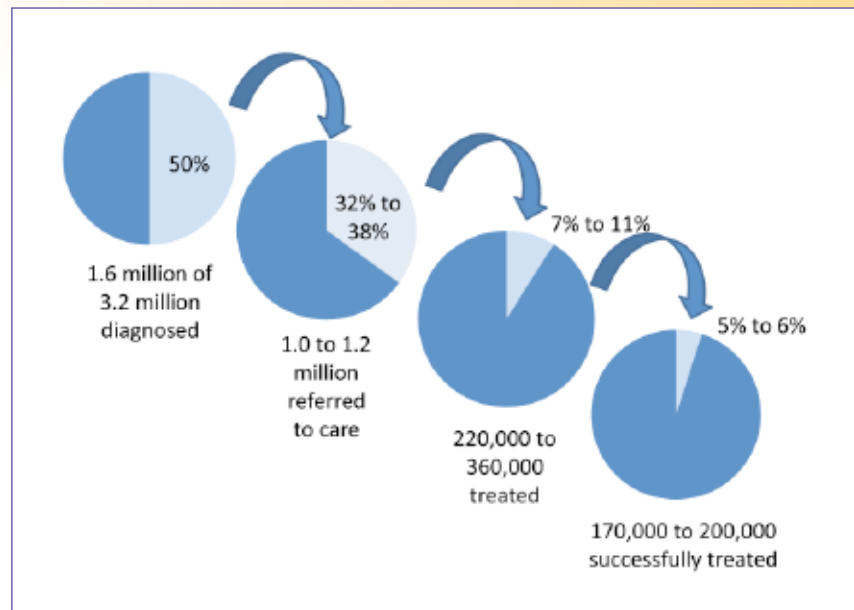
Systematic review of 21 published studies and four conference abstracts that appeared from January 2000 through May 2012 calculated a pooled HCV incidence of 1.48 per 1000 person-years (95% CI 0.75 to 2.21) in HIV-negative MSM and 6.08 per 1000 (95% CI 5.18 to 6.99) in HIV-positive MSM.<sup>35</sup> (In contrast, estimated 2009 HCV incidence in the United States stood at 0.3 per 100,000.<sup>36</sup>) In studies that directly compared HIV-negative and HIV-posi-

tive men, HCV incidence was significantly higher in the HIV group (pooled risk difference 3.45 per 1000 person-years, 95% CI 1.63 to 5.27). Although these investigators concluded that evidence does not support routine HCV screening of HIV-negative MSM, they suggested that some HIV-negative MSM—those who have high-risk sex—should get tested for HCV.

HIV clinicians should bear in mind that HIV-negative MSM (and positive MSM) often have other recognized nonsexual risks for HCV infection, and providers should ask men about these risks. Most importantly, more than a few MSM inject drugs, and injection drug use easily accounts for most HCV infections in the United States. Other risk factors are (1) being born between 1945 and 1965 (regardless of other risk factors), (2) unexplained chronic liver disease or chronic hepatitis including elevated alanine aminotransferase, (3) incarceration, (4) intranasal illicit drug use, (5) getting tattooed, (6) long-term hemodialysis (ever), (7) organ transplantation before 1992, and (8) getting clotting factor before 1987.<sup>37</sup>

An HCV testing and treatment cascade framed by the CDC suggests that erring on the aggressive side in HCV screening makes sense.<sup>38</sup> Crunching numbers from two large US patient databases, CDC researchers figured that only half of an estimated 3.2 million people with HCV infection get diagnosed, about one third get referred to care, and about 10% get treated (**Figure 3**). There’s no way to tell how many of the 1.6 million undiagnosed people are gay or bisexual men—with or without HIV. But pushing for more HCV testing in MSM—from the top (the US government) and from the trenches (front-line clinicians)—would probably make the CDC cascade less dreary. And with rapidly effective direct-acting antiviral regimens becoming available, aggressive HCV screening would get more people into care and cure them.

### HCV diagnosis and treatment cascade in United States



**Figure 3.** Analyzing numbers from two large US cohorts, the CDC figures that only half of HCV-infected people in the United States get diagnosed and only 7% to 11% get treated.<sup>38</sup>

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