DEFUSE HEPATITIS C, THE VIRAL TIME BOMB: TEST AND TREAT HEPATITIS C

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The World Health Organization (WHO) has referred to hepatitis C as a "viral time bomb."

In 2010, the 63rd World Health Assembly (WHA) adopted the first resolution on viral hepatitis; a new resolution will be presented at this Assembly.

Globally, an estimated 185 million people have been infected with the hepatitis C virus (HCV). Since 2010, more than a million of them have died from HCV-related liver disease, **although hepatitis C is treatable and curable**. Since 2010, nine to twelve million people have become infected with hepatitis C, **although it is preventable**. Most new infections occur among people who inject drugs (PWID), yet access to sterile injection equipment and other HCV prevention tools is staggeringly inadequate, reaching only a tiny percentage of those who need it. This shocking public health failure allows the epidemic to continue spreading.

Most people who have HCV live in low- and middle-income countries (LMICs), and have scarce access to HCV diagnostics, care, and treatment. Pegylated interferon (peginterferon, or PEG-IFN), the backbone of HCV treatment, is priced cruelly out of reach. And new direct-acting antiviral (DAA) medications will be even more expensive.

Even in places where HCV treatment is available, injection drug use is often used as a criterion for denying access: only 2–4 percent of the 10 million people who inject drugs (PWID) who are infected by HCV are currently receiving treatment.

We, people living with HCV, HIV/AIDS, people who use drugs, and our advocates, urge United Nations (UN) Member States to act with urgency to end the hepatitis C epidemic; it is possible!

1. Reducing the cost of existing and future treatments for hepatitis C must be an urgent priority for governments and the World Health Organization

■ HCV treatment: unaffordable for governments and people living with hepatitis C

Due to exorbitant prices, access to current HCV treatment is virtually nonexistent for most people living with hepatitis C. Two pharmaceutical companies—Roche and Merck—own the patents on PEG-IFN and share the global market. This duopoly allows them to fix prices. In LMICs, where the vast majority of people in need of treatment live, the cost of pegylated interferon can be as high as US$18,000; a 48-week treatment course can cost 10 times the average annual per capita income.

■ Drastic price reduction of PEG-IFN is possible

Additional supply sources are needed to create competition that will decrease drug prices.In Egypt, for example, a locally manufactured alternative pegylated interferon, Reiferon Retard, has been available since 2004. Market competition has supported a sixfold reduction in the price of both originator and alternative PEG-IFN products: a 48-week treatment course of pegylated interferon and ribavirin (RBV) currently costs less than US$2,000 in Egypt. This is the lowest price in the world, and demonstrates that substantial price reductions are possible if there is competition.

■ New treatments in the pipeline: direct-acting antivirals

Predicted Minimum Costs of Hepatitis C Virus Direct-Acting Antivirals[1]

Agent	Daily Dose, mg	Overall Dose Per 12 wk, g	Estimated Cost per Gram, USD	Predicted Cost, USD
Ribavirin	1000–1200	84–101	0.29–0.41[a]	34–48[b]
Daclatasvir	60	5	2–6	10–30
Sofosbuvir	400	34	2–4	68–136
Faldaprevir	120	10	10–21	100–210
Simeprevir	150	13	10–21	130–270

[a] Current range of active pharmaceutical ingredients cost per gram from 3 Chinese suppliers.
[b] Shows cost for 1,000 mg daily dose; US$41–58 for 1,200 mg daily dose of ribavirin; adjusted with a 40% mark-up for formulation.

In the coming years, interferon-free HCV treatment will be on the market, revolutionizing hepatitis C treatment. Oral direct-acting antivirals (DAAs) are dramatically increasing cure rates; in clinical trials, combinations of these drugs led to cure rates up to 100 percent, regardless of HCV treatment history, cirrhosis, or host genotype. DAAs have the potential to eradicate hepatitis C virus from the planet, but they must be affordable for the vast majority who need them. According to a recent study, [1] "large-scale manufacture of ribavirin plus two generic HCV DAAs is feasible, **with target prices of $100-$200 per 12 week treatment course," if the drugs can be produced generically.**

1. Hill A, Khoo S, Fortunak J, Simmons B, Ford N. Minimum costs for producing hepatitis C direct-acting antivirals for use in large-scale treatment access programs in developing countries. Clin Infect Dis. 2014 Feb 13. 2014 Apr;58(7):928–36. doi: 10.1093/cid/ciu012.

"If the prices [of new HCV treatments] were to be unaffordable once more in history, it would be one more scandal around inequity of access to health care."

—Michel Kazatchkine, the United Nations Secretary-General's Special Envoy on HIV/AIDS in Eastern Europe and Central Asia

Where there is competition from generics and biosimilars, prices can be driven down dramatically

Neither tiered-pricing nor voluntary licensing strategies (both widely used by originator companies) have prevented monopolies. In fact, the restrictive terms of these agreements have severely delayed or impaired governments' use of legal flexibilities in their intellectual property laws to access essential medications.

Patent Opposition

National legislative mechanisms also allow most countries to revoke patents when "new" medicines do not meet their criteria for patentability. For example, in November 2012, Roche's patent for Pegasys was opposed and revoked in India.[3] As a result, Indian producers can now produce a biosimilar peginterferon alfa-2b and export it to any country where Pegasys is not patented.

In November 2013 (also in India), another patent opposition was filed, this time against Gilead's sofosbuvir, one of the new DAAs (see the box above). As sofosbuvir is not innovative enough at the molecular level to warrant a patent --according to several legal and pharmacology organizations-- the strategy of patent opposition is therefore a relevant option. And as India is the largest producer of generics in the world, if Gilead's patent is revoked there, it may help to extend access to generics worldwide.

Focus on Gilead's sofosbuvir

Gilead's DAA, sofosbuvir, was approved by the European Medicines Agency (EMA) in November 2013, and by the U.S. Food and Drug Administration (FDA) in December 2013.

Gilead is charging US$84,000 for 12 weeks of sofosbuvir—US$1,000 per day. Sofosbuvir needs to be used with other medicines, sometimes for 24 weeks. But sofosbuvir and many other DAAs in late-stage development can be produced generically for a tiny fraction of that price, just like HIV medicines. For example, a generic version of sofosbuvir could be produced for as little as US$68–136.[2]

In countries where patents have been granted and cannot be opposed, and for molecules that are considered to be true therapeutic novelties, a compulsory license could prove an appropriate option for providing access.

Compulsory Licensing

One of the key lessons from the global AIDS treatment access movement is that countries can use legal flexibilities such as compulsory licensing to make essential medications available. Issuing **a compulsory license (CL) allows generics producers to produce affordable drugs, despite patents**. For example, in 2000, the originator price for first-line HIV antiretroviral (ARV) therapy was US$10,430; when compulsory licenses allowed several generic versions to enter the market, the price for these drugs was driven down to US$62.[4]

The use of compulsory licensing is recommended in the WHA's 2010 resolution on viral hepatitis: "to consider, as necessary, national legislative mechanisms for the use of the flexibilities contained in the Agreement on Trade-Related Aspects of Intellectual Property Rights [TRIPs] in order to promote access to specific pharmaceutical products." LMIC governments that elect to issue CLs must not be threatened or punished—with sanctions or by other means—by governments in upper-income countries. The WHO must reaffirm and vocally support governments' right to issue compulsory licenses.

Financing hepatitis C treatment

Another key lesson from the global AIDS treatment access movement is that **bulk-buying prequalified generics substantially reduces drug price**. Currently, neither governments nor international agencies on the hepatitis C frontline have allocated adequate resources for tackling this global epidemic. Only a few LMICs (e.g., Georgia, Ukraine, and Macedonia) have HCV treatment programs for people with HIV/HCV coinfection, which are funded by the Global Fund to Fight AIDS, Tuberculosis and Malaria.

There is an urgent need for adequate resources in order to effectively tackle hepatitis C

2. Ibid.
3. Lynne Taylor, "India Revokes Roche's Patent on Pegasys," PharmaTimes. November 5, 2012. Available from: http://www.pharmatimes.com/article/12-11-05/India_revokes_Roche_s_patent_on_Pegasys.aspx. (Accessed 1 May 2014)
4. MSF Access Campaign. Untangling the web of antiretroviral price reductions, 14th edition. Geneva: Médecins Sans Frontières; July 2011. Available from: http://www.msf.org/sites/msf.org/files/utw_14_eng_july2011.pdf. (Accessed 1 May 2014)

2. Identify and prioritize people with urgent need for treatment

■ People who inject drugs (PWID) are disproportionately affected by hepatitis C

- An estimated 10 million PWID are infected with HCV, or 67% of the estimated 16 million people who inject drugs globally.
- About 80% of HIV-positive PWID are coinfected with hepatitis C.
- 90% of new infections result from lack of access to sterile injecting equipment.
- HCV incidence is high among PWID: 5–25% are newly infected each year.

■ Harm reduction services must be massively scaled up

- Globally, an average of 2 needles and syringes are distributed per person who injects drugs per month.[6]
- Only 8 (range: 6–12) of 100 PWID receive opioid substitution therapy (OST).
- Only 4 HIV-positive PWID (range: 2–18) of 100 receive ART.

Promotion of evidence-based harm reduction services can affect HCV transmission rates

HCV prevalence among PWID in selected countries[5]

Country	Adult HCV prevalence among PWID
Brazil	39.5–69.6%
Estonia	90%
Germany	75%
India	92%
Indonesia	60–98%
Mauritius	95%
New Zealand	70%
Pakistan	89%
Thailand	90%
Ukraine	70–90%
United States	50–80%

■ To be effective, HCV prevention requires an approach that combines prevention (high-coverage needle and syringe programs [NSP], OST, and peer education) with HCV treatment programs

Implementation and scale-up of evidence-based harm reduction programs, particularly NSP and OST have successfully lowered the rate of HIV infections among people who inject drugs.[7] Similar actions should be taken to control HCV, which is 10 times more infectious than HIV. According to recent studies, "each intervention alone will achieve modest reductions in HCV transmission, and prevention of HCV transmission necessitates high-coverage and combined approaches."[8] A meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs found a "substantial and statistically significant reduction in HCV incidence in PWID—of approximately 75 percent—when combination prevention strategies were applied."[9]

A standard package for HCV control in PWID as recommended by the WHO[10] must consist of:

- high-coverage needle and syringe programs (HCNSP) defined as obtaining one or more sterile needle and syringe from an NSP for each injection;
- opioid substitution treatment (OST);
- peer education programs; and
- treatment programs.

HCV care and treatment is almost always withheld from people who inject drugs; two to four percent of PWID in LMICs have access to HCV treatment. **However, HCV treatment is equally likely to cure PWID as it is people who do not inject drugs.**[11] PWID "demonstrate high adherence, low discontinuation of therapy, and a low rate of reinfection (1–5% per year)."[12] In accordance with human rights norms and guidelines from medical experts, "decisions about treatment should be made independently of an individual's injection drug use status."[13]

■ A large proportion of people who inject drugs are coinfected with HIV and HCV

An estimated 80 percent of HIV-positive people who inject drugs also have HCV.[14] In Asia and Eastern Europe, HIV/HCV coinfection rates among PWID range from 70 percent to 95 percent. In fact, the vast majority of people living with HIV/HCV coinfection acquired both viruses because they did not have access to sterile injection equipment.

Worldwide, an estimated 4–5 million people are HCV/HIV-coinfected.[15] Although antiretroviral therapy has extended the life expectancy of people with HIV/AIDS, they remain vulnerable to liver disease from HCV—in fact, it has become a leading cause of death among HIV-positive people. HIV accelerates HCV disease progression, and more than triples the risk for liver disease and liver failure.

But HCV is curable, regardless of HIV status. Treating—and curing—HCV is recommended for all HCV/HIV-coinfected people, because it reduces the risk of AIDS-related, liver-related, and all-cause mortality.[16]

Governments must make it a priority to screen and treat people who inject drugs and people with HIV coinfection

5. Table Sources: Cook C, Kanaef N. Global state of harm reduction: mapping the response to drug-related HIV and hepatitis C epidemics. London: International Harm Reduction Association; 2008. Available from: www.ihra.net/files/2010/06/16/GSHRFullReport1.pdf **6.** For instance, just an estimated 10 percent of PWID in Eastern Europe, and 36 percent in Central Asia, access NSPs. See: Stuikyte R, Votyagov S, Pinkham S. Quitting while not ahead. The Global Fund's retrenchment and the looming crisis for harm reduction in Eastern Europe & Central Asia. Vilnius: Eurasian Harm Reduction Network; 2012. **7.** UNAIDS. Global report: UNAIDS report on the global AIDS epidemic, 2010. Geneva: UNAIDS; 2010. **8.** Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. Lancet. 2010 Jul 24;376(9737):285–301. doi: 10.1016/S0140-6736(10)60742-8. **9.** Hagan H, Pouget ER, Des Jarlais DC. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. J Infect Dis. 2011 Jul 1;204(1):74–83. doi: 10.1093/infdis/jir196 **10.** World Health Organization. Guidance on prevention of hepatitis B and C among people who use drugs. Geneva: World Health Organization; July 2012. **11.** Harris M, Rhodes T. Hepatitis C treatment access and uptake for people who inject drugs: a review mapping the role of social factors. Harm Reduct J. 2013 May 7;10:7. doi: 10.1186/1477-7517-10-7. **12.** Grady BP, Schinkel J, Thomas XV, Dalgard O. Hepatitis C virus reinfection following treatment among people who use drugs. Clin Infect Dis. 2013 Aug; 57 Suppl 2:S105–10. doi: 10.1093/cid/cit301. **13.** Aspinall EJ, Corson S, Doyle JS, et al. Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis. Clin Infect Dis. 2013 Aug;57 Suppl 2:S80–9. doi: 10.1093/cid/cit306. **14.** Centers for Disease Control and Prevention (U.S.) (Fact Sheet). HIV and viral hepatitis. Atlanta : Centers for Disease Control and Prevention; May 2013. **15.** Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. J Hepatol. 2006;44 (1 Suppl):S6–9. **16.** Berenguer J, Rodríguez E, Miralles P, et al. GESIDA HIV/HCV Cohort Study Group. Sustained virological response to interferon plus ribavirin reduces non-liver-related mortality in patients coinfected with HIV and hepatitis C virus. Clin Infect Dis. 2012 Sep;55(5):728–36.

3. The World Health Organization must act!

■ The WHO must urgently prequalify biosimilars and the coming generic DAAs

The WHO's prequalification program was launched in 2001 and aims to "make quality priority medicines available for the benefit of those in need." The prequalification program assesses safety and efficacy of medicines for HIV/AIDS, malaria, and tuberculosis, and runs inspection activities to guarantee that manufacturing sites are compliant with WHO "good manufacturing practices." Since 2001, the program has played a key role in improving access to cheap and high-quality medicines.

WHO quality assurance for pegylated interferon and HCV DAAs will give confidence to donors, people living with HCV, and implementing organizations. It will allow developing countries to fast-track registration of generics and biosimilars to treat HCV.[17]

■ The WHO's Essential Medicines List (EML)

The WHO EML is a powerful tool. Many governments refer to WHO recommendations when making decisions on health spending. Drugs that are included on the WHO EML are more likely to appear on a country's national EML and given priority for national health care coverage.

Until 2013, hepatitis C treatment was not included on the WHO's EML. In July 2013, following a strong civil-society advocacy campaign, PEG-IFN was included on the "complementary list" (rather than the main list) to the EML because of "consistent higher costs."[18]

Including DAAs on the EML is critical, both symbolically and practically, since it facilitates procurement of affordable HCV treatment in LMICs.

The WHO must include HCV treatment on its Essential Medicines List , prequalify biosimilar peginterferon, and be prepared to include future generic DAAs

Recommendations to effectively address the global hepatitis C virus epidemic:

To UN Member States:

- ▸ Give hepatitis C global priority, on par with HIV/AIDS, TB, and malaria in the post-2015 health agenda, and provide adequate resources for a continuum of hepatitis C prevention, treatment, care, and support programs for all who need these services—especially people who inject drugs—through national, regional, and international mechanisms;
- ▸ Ensure access to safe, effective, and affordable HCV treatment to the vast majority who currently lack access, by importing cheaper biosimilars/generics and using flexibilities of the TRIPs agreement in every country where intellectual property rights (IPR) pose a significant obstacle to access;
- ▸ Massively increase provision of evidence-based harm reduction services, in particular NSP and OST, using a combination approach that includes HCV care and treatment, to effectively stop hepatitis C transmission and ensure that people who use drugs are not excluded from these lifesaving services;
- ▸ Meaningfully involve civil society—specifically people who use and inject drugs—in the creation of tailored hepatitis C control plans. PWID and their organizations should be involved in the design, implementation, and monitoring of these programs; and
- ▸ Decriminalize drug use and remove legal, structural, and institutional barriers to health care and HCV services for PWID, as well as those legal and structural factors that actively drive the epidemic in the injecting community. Immediately put an end to human rights abuses and discrimination in the health care setting.

To Dr. Margaret Chan, WHO Director–General:

- ▸ Include hepatitis C products in the WHO prequalification program: both biosimilar pegylated interferon and, once approved, generic direct-acting antivirals;
- ▸ Prioritize the inclusion of key DAAs on the WHO Essential Medicines List and add newly approved;
- ▸ Produce regulatory guidance on biosimilars;
- ▸ Vocally and unequivocally support governments' right to utilize TRIPS flexibilities to ensure access to lifesaving tests, diagnostics, and treatment; and
- ▸ Allocate adequate resources, both human and financial, to the WHO's Global Hepatitis Programme, to help effectively address the global HCV epidemic.

17. Ford N, Singh K, Cooke GS, et al. Expanding access to treatment for hepatitis C in resource-limited settings: lessons from HIV/AIDS. Clin Infect Dis. 2012 May;54(10):1465–72. doi: 10.1093/cid/cis227.
18. Available from: http://apps.who.int/iris/bitstream/10665/93142/1/EML_18_eng.pdf?ua=1