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HCV Treatment

HCV Treatment Pipeline 2020

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In December 2013, a new chapter in the history of infectious disease began with the U.S. Food and Drug Administration (FDA) approval of sofosbuvir, the first highly effective, all-oral, direct acting antiviral (DAA) against hepatitis C virus (HCV). The arrival of a long sought-after cure for a chronic infection responsible for 400,000 deaths annually from HCV-related liver disease and cancer should have been cause for unreserved celebration. Yet, as of December 2018, the fifth anniversary of sofosbuvir's FDA approval, less than 3 percent of the estimated 71 million people living with HCV had received sofosbuvir-based treatments. As of 2019, only five countries—Egypt, France, Iceland, Spain, and Switzerland—were on track to achieve World Health Organization (WHO) 2030 HCV elimination targets.

HCV remains a deadly viral infection, but the DAA breakthrough and WHO viral hepatitis elimination targets may seem like distant abstractions when considered in the context of the ongoing global COVID-19 pandemic. The global viral hepatitis response been profoundly impacted by COVID-19: the pandemic has not only paused HCV community outreach, education, screening, and linkage to care programs, but the lack of personal protective equipment, overwhelmed health systems, and looming austerity budgets threaten to roll back even the limited progress achieved since the debut of the HCV cure. The syndemic of blood borne infectious disease, substance misuse, and overdose continues to take lives, and shows signs of worsening as a result of the COVID-19 crisis. Even before the pandemic shuttered economies across the globe, the HCV response had been woefully underfunded, with less than 10 percent of needs met. Political apathy, the challenges of mobilizing highly marginalized and criminalized communities for advocacy, limited licenses for affordable generics that exclude middle-income countries, and slow registration for generic production by both originator companies and national governments continue to be barriers to expanded access and scale up. While our understanding of COVID-19 continues to evolve, as of press time, elevated liver enzymes have been observed among people who have recovered from COVID-19 infection. This highlights the ongoing, and often unmet, need for life-long liver health and function monitoring for all those with current or past viral hepatitis, cirrhosis, or other hepatic conditions.

As reported last year, prior to the COVID-19 pandemic, generic sofosbuvir/velpatasvir (SOF/VEL), largely manufactured in India, had reached sufficient scale to approach affordability for patients in India. However, while AbbVie's glecaprevir/pibrentasvir (G/P)

has been licensed to the Medicine Patent Pool for generic production, India is excluded from the license as a purchaser, but not a manufacturer. As a result, the recent agreement with generic manufacturer Mylan will see Indian workers producing an essential medicine for the benefit—and profit—of others.

The End of the Beginning

For all intents and purposes, the HCV treatment pipeline is closed and no novel oral DAA combinations are expected for the global market. Pangenotypic DAAs continue to demonstrate high efficacy in post approval studies and real-world clinical settings, including among patients with co-morbidities and coinfections. SOF/VEL demonstrated safety and 95 percent sustained virologic response at 12 weeks post treatment (SVR12) among patients with end stage renal disease undergoing dialysis. Triple combination sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) demonstrated high efficacy for its approved retreatment indication, including retreatment in patients coinfected with HIV. However, lower SVR12 rates continue to be observed with SOF/VEL/VOX in genotype 3 patients receiving retreatment.

A meta-analysis of G/P found greater than 95 percent overall efficacy in real world clinical settings, which is consistent with clinical trial data. A greater than 90 percent cure rate was also observed with G/P using a simplified monitoring algorithm, with clinical visits only at treatment initiation and 12 weeks post treatment completion (see Table 1). In addition, a pilot study of short duration treatment with six weeks of G/P among men with recent or acute HCV infection achieved 90 percent SVR12 (Table 1). Short course treatment for acute infection among men who have sex with men is essential given the relatively high rates of HCV infection among men using pre-exposure prophylaxis, known as PrEP, for HIV prevention.

Notably, when compared to ledipasvir and daclatasvir, other NS5A inhibitors, pibrentasvir demonstrated the greatest activity against emerging difficult-to-treat HCV subtypes prevalent in Sub-Saharan Africa. This further underscores the urgency of expanded access and scale up of generic SOF/VEL and G/P in low- and middle-income countries, particularly in Sub-Saharan Africa and South East Asia regions.

Table 1:

G/P	NS3-4A/NS5A inhibitor	AbbVie	Simplified and shortened treatment algorithms	FDA approved

Multi-center, open-label, randomized phase IIIb non-inferiority trial comparing standard on-treatment clinical monitoring at baseline and weeks 4, 8, 12 post treatment vs. baseline/week 12 post treatment only.

- N = 380 participants (40% female); simplified (n = 253) vs standard (n = 127) arms.
- 92% (233/253) SVR12 in simplified arm.
- 95% (121/127) SVR12 in standard arm.
- Two transgender participants in the standard arm.
- No treatment-related serious adverse events reported.

Multi-center, open-label, single arm pilot study of six weeks of G/P in recent or acute HCV infection, defined as positive antibody and/or HCV RNA within six months of enrollment and either acute clinical hepatitis within the past 12 months or antibody seroconversion within 18 months.

- 90% SVR12 (27/30).
- 90% of participants were men who have sex with men.
- 77% (n = 23) of participants were coinfected with HIV.
- 47% (n = 14) had ever injected drugs.
- 13% (n = 4) had HCV reinfection.
- One relapse.
- One lost to follow-up.
- One death not related to treatment.

Treating Pediatric and Pregnant Patients

Despite modeling done in 2018 that estimated that 3.26 million children under the age of 18 were living with HCV, the global prevalence of HCV among children continues to be poorly understood. Although there are currently no FDA approved DAA treatments for children younger than six years of age, the American Association for the Study of Liver Diseases (AASLD) recommends treatment for all children three years of age or older when approved medications are available. Data on the safety and efficacy of DAA treatment in pregnant individuals is still pending, but a similar recommendation will likely follow positive results of ongoing studies. Investments in research on the use of DAAs to prevent parent to child transmission are also needed.

Universal Screening

The U.S. Centers for Disease Control and Prevention, the U.S. Preventative Services Task Force, and AASLD all now recommend universal, one-time HCV screening for all individuals 18 years and older. This significant step forward for identifying HCV cases must be met with equally significant investments and regulatory reforms to provide antibody screening and confirmatory testing at primary care, community clinic, and harm

reduction sites. The funding, development, and scale up of affordable point-of-care confirmatory testing is the central challenge of global effort to eliminate viral hepatitis, the impact of COVID-19 notwithstanding.

The Future of an HCV Vaccine

The case for an HCV vaccine is strong, yet the future of an HCV vaccine remains uncertain. While a randomized, controlled trial of an HCV vaccine candidate in people who inject drugs did not demonstrate efficacy, U.S. federal appropriations included $8 million in funding for continuing research into an HCV vaccine; this story continues.

The End of an Era

This will be the final HCV treatment chapter for the Pipeline report. In this unprecedented time, with so much uncertainty on the path to elimination, the future truly cannot be predicted. At press time, reports from small, open-label trials showed that hospitalized patients with SARS-CoV-2 who received the HCV DAA combination SOF/DAC had shorter stays compared to the standard of care (hydroxychloroquine with or without lopinavir/ritonavir). Obviously more study is needed, in particular with other comparator treatments.

The following recommendations will, unfortunately, be all too familiar. The persistence of barriers to HCV cure is inseparable from the systemic oppression faced by people at risk for and living with HCV infection, including: histories of colonization and neo-colonialism; racism; the criminal human rights violations of the drug war and mass incarceration; state violence; gendered violence; disregard for mental health and the rights and dignity of those living with mental illness, including substance misuse; and poverty. The COVID-19 pandemic has made visible to allthat which has always been known to those living under these intersecting, oppressive systems. It is our shared hope that this moment will bring the clarity and courage necessary to bring these systems to an end.

Advocacy points

For companies:

- Ensure generic sofosbuvir, daclatasvir, and velpatasvir are registered and available for sale in all countries covered under voluntary licenses.
- Accelerate registration and access to generic glecaprevir/pibrentasvir (G/P) via voluntary licenses.
- Secure alicense for the sale of affordable generic G/P in India.
- Complete phase II/III clinical trials of sofosbuvir/ravidasvir (SOF/RAV) in genotype 5 and 6 patients.
- Complete phase II/III clinical trials in pregnant people to assess the safety and efficacy of DAAs as curative treatment and prophylaxis to prevent vertical transmission.

- Complete phase II/III clinical trials of sofosbuvir-based regimes and G/P in patients younger than six years of age and weighing less than 17 kilograms.
- Conduct phase II/III clinical trials of pangenotypic regimes, including sofosbuvir/daclatasvir (SOF/DAC) and SOF/RAV, in patients younger than 17 years of age and children weighing less than 35 kilograms.
- Continue phase II/III trials of short-term (less than eight-week) treatment courses for acute infection.

For WHO:

- Gather and review evidence and issue recommendations regarding universal adult screening for HCV.

For national governments:

- Waive any requirement for in-country clinical registration trials for proven DAA combinations from validated generic manufacturers.
- Decriminalize the possession and distribution of harm reduction tools and interventions: syringe service programs, direct purchase and possession of syringes, and safe drug consumption spaces/safe-injection facilities.
- Ensure competition between generics manufacturers.
- Explore all available means to accelerate and expand access to generics: compulsory licenses using TRIPS flexibilities or other legal approaches, parallel importation, and patent challenges.
- For high-income countries, refrain from retaliatory trade practices in response to the use of TRIPS flexibilities for access to medicines.
- Enact opt-out HCV screening of all people upon incarceration, with robust linkage to care during incarceration and after release.
- Align public health system payment/reimbursement to expand HCV screening to all adults 18 years and older, including pregnant people.

For donors:

- Commit to multilateral and bilateral funding for universal access to generic DAA treatment in LMICs.
- Facilitate the integration of disease-specific programs by supporting treatment of HCV-monoinfected people who are at risk for HIV and other infectious diseases.
- Expand access to regional and central procurement platforms, such as the Global Fund's Pooled Procurement Mechanism, beyond HIV, TB, and malaria, at a minimum for DAA treatment for those with coinfections.