Current HIV/AIDS Reports (2018) 15:155–161
https://doi.org/10.1007/s11904-018-0386-z

CO-INFECTIONS AND COMORBIDITY (S NAGGIE, SECTION EDITOR)

Treatment of Hepatitis C during Pregnancy-Weighing the Risks and Benefits in Contrast to HIV

A. Sidney Barritt IV[1] · Ravi Jhaveri[2]

Published online: 22 February 2018

Abstract

Purpose of Review Increasing hepatitis C virus (HCV) cases over the past decade have raised concerns about subsequent increased cases in infants due to mother to child transmission (MTCT). Many are reminded of the early days of HIV and the rationale for using antiretroviral agents during pregnancy.

Recent Findings Direct-acting antivirals (DAAs) that are highly potent, all-oral, short-duration regimens that cure HCV have led many to consider what it would entail to use DAAs for pregnant women. Considering HIV and Hepatitis B virus (HBV) as two infections with MTCT to draw lessons from, DAA use to interrupt HCV MTCT comes with risks, costs, and many potential benefits.

Summary When considering how to effectively curb the current epidemic of HCV in the US population, using DAAs to treat pregnant women with HCV offers potential benefits to the mother immediately, to the pair in the short-term and to the child, family, and society over a lifetime.

Keywords Hepatitis C · Pregnancy · Mother to children transmission · Vertical transmission

Abbreviations

HCV	Hepatitis C
MTCT	Mother to children transmission
DAAs	Directly acting antivirals
SVR	Sustained virologic response

Introduction

The treatment of chronic viral infections during pregnancy has now become the standard of care for many conditions. The concept of treatment also serving as prevention of mother to child transmission (MTCT) has taken many years to mature. The example of human immunodeficiency virus (HIV) has offered a wealth of experience and served as a model for intervention that benefits both mother and infant. Hepatitis B virus (HBV) offers an example of how a strategy has evolved over time to incorporate treatment as prevention of MTCT in high-risk cases. Hepatitis C virus (HCV) is often discussed as the potential next target. Similar to HIV and HBV, HCV also progresses to chronic infection and can spread via MTCT. With the advent of direct-acting antivirals (DAAs), the obvious question that arises is "Should we now be using these agents to treat pregnant women with HCV?" In this commentary, we will review some of the important examples learned from the HIV experience and how they relate to HCV. We will discuss how HCV treatment in pregnancy might be initiated and identify the perceived risks and expected benefits. Finally, we will discuss what research needs must be performed before widespread treatment can occur.

This article is part of the Topical Collection on *Co-infections and Comorbidity*

✉ Ravi Jhaveri
ravi.jhaveri@unc.edu

[1] Division of Gastroenterology, Department of Medicine, UNC School of Medicine, Chapel Hill, NC, USA

[2] Division of Infectious Diseases, Department of Pediatrics UNC School of Medicine, Chapel Hill, NC 27599-7231, USA

HCV Background

Natural History and Treatment

The cardinal features of HCV are well known. HCV progresses to chronic infection in the majority of adults, is a major

cause of chronic liver disease, and is responsible for many cases of cirrhosis and hepatocellular carcinoma [1]. It is currently the leading indication for liver transplantation [1]. What was once a difficult and complicated infection to treat with interferon-based therapy has now become a modern medical success story. DAAs offer very simple, oral, once- or twice-a-day dosing that offer sustained viral response (SVR) rates of greater than 95% in virtually every patient group [2–8]. As the DAA combinations treat more genotypes and more patients with prior concerning risk factors (cirrhosis, prior treatment failure), the decision-making becomes less complex and more amenable for treatment outside of a specialist's office.

HCV in Pregnancy and MTCT

Studies of pregnant women with HCV have demonstrated that they have largely equivalent outcomes to uninfected women. There are reports of increased rates of gestational diabetes with an approximate odds ratio of 2 [9]. HCV-infected pregnant women with cirrhosis are at risk for severe outcomes like bleeding and death, but this is largely due to the fragile nature of compensated cirrhosis [10].

Studies of HCV MTCT show that it is not a frequent event. Approximately 5–10% of exposed infants have detectable HCV RNA levels in the first several months of life [11–13]. Some studies have demonstrated the rate could be as high as 15%, and the early Women and Infants Transmission Study (WITS) analysis of mothers with HIV-HCV co-infection reported rates as high as 25% [13–15]. Those studies were conducted before highly active antiviral therapy (HAART) was available, and more current estimates demonstrate that the risk of HCV MTCT in HIV co-infected women on HAART is the same as HCV mono-infection [16]. The range of HCV MTCT that is most widely quoted is 3–8% [17]. What is different about infants and young children (less than 3 years old) compared to older children and adults is that there is a much higher rate of spontaneous resolution in these younger patients (25–50%) [11, 12, 13, 18]. The diagnosis of chronic HCV in a young child is not made until persistence of viremia is confirmed past the age of 3. The natural history of HCV-infected children with chronic infection is largely benign. Studies looking at children infected with HCV since birth show that only about 5% have detectable fibrosis up to 20 years after acquisition [19–21]. While cases do occur in adolescents, cirrhosis and hepatocellular carcinoma are rare events [22].

Studies that have attempted to define risk factors for MTCT have been conflicting or unsuccessful. Mode of delivery was identified in early studies, but large network studies have shown that cesarean section is not protective against MTCT [14, 23–25]. Higher maternal HCV RNA was also identified in some early studies, but MTCT can still occur with low levels of viremia [12, 14]. The IL28B allele that was so influential to the success of interferon-based therapies has no identified role in HCV MTCT, but it does impact spontaneous resolution in infants as well as in the women during the post-partum period [14, 26–28, 29].

The Contrast with HIV and HBV

When considering the possibility of treating pregnant women with HCV, the prior experience and context of HIV and HBV offer meaningful lessons to build upon. Each scenario illustrates some of the gaps in our knowledge of HCV MTCT that still need to be filled prior to moving forward with universal treatment. The important attributes of each virus are summarized in Table 1.

HIV-Emphasizing Maternal Treatment to Save the Infant

The overwhelming success of HIV MTCT efforts over the past 20 years has long overshadowed the urgency, novelty, and controversy of the initial studies to test if it would work. Prior to the ACTG 076 trial, the status quo of HIV MTCT was abysmal. In the early 1990s, about 25% of infants acquired HIV from their infected mother and a large percentage of infants infected developed opportunistic infections and rapidly progressed to AIDS or death within the first 2 years [30–32]. Treatment was still limited to azidothymidine (AZT) and a few other nucleoside analogs. Because MTCT was possible antepartum, intrapartum, and post-partum, the prevention strategy had to span the entire time frame. The resulting ACTG 076 trial did just that, with maternal AZT treatment during pregnancy, IV AZT in the delivery room, and oral AZT for all infants exposed to the virus [33]. The risk of this therapy that was previously unstudied in pregnancy was tangible, but the potential benefit was enormous. Indeed, the results were groundbreaking. This aggressive approach to treating mother to save infants worked well, with a $>66\%$ reduction in transmissions (25% in control group vs. 8% in AZT group) [33]. This approach opened the door to expanded treatment algorithms and mandated that future antiretroviral drugs be studied, be proven safe, and ultimately be used as part of MTCT prevention. In the USA, the rate of HIV MTCT is now $<2\%$ [34].

HBV-Identifying Women with Increased MTCT Risk for Targeted Therapy

The case of HBV illustrated different circumstances and an evolved approach to MTCT prevention. Unlike adults infected with HBV where only 10% or less progress to chronic infection, infants with MTCT progress to chronic infection 90% of the time [35]. This differential created the urgency for preventing MTCT to counter this unique susceptibility. After

Table 1 Comparison of mother to child transmission features for HIV, HBV, and HCV

	HIV	HBV	HCV
Rate of transmission	17–25% pre-HAART; 1–2% w/HAART	30–40% before prophylaxis; 3–4% with prophylaxis	3–8%
High-risk groups for MTCT	Detectable HIV RNA at delivery	HBV DNA > 10^7 copies/μl	HCV viremia
Methods for interruption of MTCT	Maternal treatment before during and after delivery; infant treatment for 6 weeks after delivery	HBIG and HBV vaccine for all infants at birth; tenofovir for high-risk pregnant women from 28 to 32 weeks gestation to 4–6 weeks post-partum	None currently; possible future DAAs
Short-term/long-term benefits of maternal/neonatal interventions	Prevention of infant infections; reduction of infant mortality due to HIV infection; improved maternal health; reduced breastmilk transmission	Prevention of neonatal hepatitis; prevention of breakthrough transmissions after HBIG and HBV vaccine (with tenofovir)	Potential benefits: HCV cure for mother; elimination of MTCT; elimination of need for screening of exposed infants

the advent of using both HBV vaccine and high-titer HBV immunoglobulin (HBIG), approximately 90% of the transmission events were prevented which subsequently saved many infants from chronic HBV [36]. Despite the current widespread testing and administration of this effective prophylactic regimen, a consistent minority of infants are still infected with HBV via MTCT [37]. The profile of the high-risk pregnant women was a predictable one: those pregnant women with the highest burden of HBV (very high HBV DNA levels and/or HBV e antigen positive) [37]. Due to the predictable nature of this subgroup of women, studies designed to routinely perform subsequent testing of any pregnant woman that tested positive for HBV surface antigen to identify those at increased risk of breakthrough MTCT and start pre-emptive antiviral therapy. Initial attempts to suppress viremia with lamivudine had minimal effect, likely because of the low potency and low barrier to resistance of this agent [38]. Subsequent efforts with tenofovir have been much more successful and several studies have demonstrated marked reductions in MTCT in high-risk pregnant women with an antiviral in addition to standard of care prophylaxis [39–41]. This practice is now part of AASLD recommendations for HBV management [42].

HCV in Comparison to HIV and HBV: Challenges and Opportunities

In contrast to both HIV and HBV, HCV treatment during pregnancy lacks the obvious urgency of the other viruses. There is no neonatal mortality or even early childhood morbidity associated with HCV infection, and symptoms may take 10–15 years to manifest. The overall transmission rate is low in comparison (HCV 3–8% vs. HIV 17–25% or HBV at 30–40% without any intervention) to the other chronic viruses. Unlike HBV, there is no reliable way to identify the women that are at higher risk for MTCT for targeted therapy. The one overwhelming benefit when considering HCV is that using DAAs offers the potential for viral eradication, a cure that is not possible for either HIV or HBV. This reason among others is why HCV therapy in pregnant women is such a compelling opportunity.

Rationale for HCV Therapy in Pregnant Women

Given that the current DAAs offer potent and rapid suppression of HCV RNA levels and the presence of viremia is an absolute criteria for MTCT to occur, it is very reasonable to expect almost complete prevention of HCV MTCT [11, 13, 43]. Even though the risk for MTCT in HCV is less than that of HIV and HBV as outlined above, the risk reduction from 3 to 8% to near zero should be sufficient to justify therapy for HCV-infected women during pregnancy [17]. The benefits of HCV cure during pregnancy, however, go beyond MTCT reduction and are multifaceted and include direct benefits to the mother, child, and society (Table 2).

Benefits of HCV Therapy for Pregnant Women

Access to Care

For young adults who may not seek regular medical attention, pregnancy represents a unique opportunity for access to care. Any chronic illness diagnosed early offers an improved chance at cure or control and greater potential cost savings as well. In a Canadian study of birth outcomes among immigrant mothers, researchers found an unanticipated high rate of diabetes and hypertension [44]. Without the opportunity to access care via antenatal programs, these problems may go undiagnosed until symptomatic end organ damage results [45]. HCV often follows a similar model of asymptomatic disease until there are manifestations of cirrhosis, where the cost of care then increases and the opportunity to cure may be lower. While only risk-based screening for HCV in pregnant women is currently part of antenatal care guidelines, the doubling of HCV infections in women of reproductive aged from

Table 2 Rationale for HCV therapy in pregnant women

Beneficiary	Benefit of therapy	Risks of delayed therapy
Pregnant women	• Opportunity to access care • Completion of therapy during pregnancy • HCV cure	• Delayed screening and diagnosis • Gestational diabetes • Loss to follow up • Systemic disease associated with HCV • Advancing disease • Medical costs
Unborn child and children	• Safety—new DAA are not teratogenic like former therapies • HCV cure	• Risk of mother to child transmission • Need for future HCV therapy • Small for gestational age • Low birth weight
Society	• Closer to HCV eradication • Cost savings over treating more advanced disease and complications of cirrhosis	• HCV transmission • Progression to cirrhosis • Increased costs to healthcare system

2006 to 2014 serves as a potent justification for universal screening [46]. The lack of urgency for identifying HCV in pregnancy was previously justified by the lack of a direct intervention, but the availability, safety, and efficacy of DAAs undermine the legitimacy of that justification.

Left untreated, HCV infection is associated with excess weight gain and gestational diabetes in pregnant women [9]. HCV cure prevents the development of insulin resistance and HCV replication is associated with higher all-cause mortality in the general population [47, 48]. HCV has surpassed HIV and HBV as a cause of death as well [47]. Seizing the opportunity to treat at this juncture may prevent subsequent excess morbidity and mortality in the mother later.

Treatment Duration within Confines of Pregnancy

HCV can be cured in as little as 8 weeks for treatment-naïve patients without cirrhosis [49]. Assessment for cure takes place 12 weeks after the completion of therapy [49]. Thus, screening, treatment, and assessment of cure can now take place during pregnancy. This is critically important as many patients identified with HCV are ultimately lost to follow up, and there are significant gaps in linkage to care [50]. Curing HCV during pregnancy would significantly reduce the challenge of following and testing those infants with perinatal HCV exposure. A study from Philadelphia has demonstrated that almost 90% of HCV-exposed infants never receive any follow up testing [51].

Safety

In order for HCV therapy to be feasible, it must be safe for mother and fetus. Prior treatment regimen that included ribavirin was FDA category X due to the significant teratogenic effects of ribavirin. While there are limited data for their use in pregnancy, sofosbuvir, ledipasvir (Harvoni in combination, Gilead Sciences, Inc.), paritaprevir, ombitasvir, and dasabuvir (Vikeria Pak, Abbvie) were classified as FDA pregnancy category B prior to the redesigned labeling system, rendering them in the same safety category as oral nucleoside analogs and other antiretrovirals already in widespread use during pregnancy.

Benefits of HCV Therapy for the Child

Children born to HCV-infected mothers are at risk to be small for gestational age, low birth weight, and to require assisted ventilation and neonatal intensive care [9]. Chronic infection may only develop in a minority of children, but these infections will need to be addressed at some point in the future, potentially doubling costs by treating mother and child. Mode of delivery, avoidance of breast feeding, and other interventions have not been shown to reduce the risk of MTCT, thus HCV therapy for the mother is the one certain way to stop transmission.

Symptomatic liver disease is uncommon in children, but the most severe and/or problematic consequences of chronic HCV are still seen. Children can progress to cirrhosis that may require liver transplantation. There are children that have developed hepatocellular carcinoma as a result of their HCV infection. As a result, regular monitoring is required for any child with chronic HCV. With treatment of pregnant women, the need for monitoring and all of these subsequent sequelae would be eliminated.

Because there are few clinical symptoms that can be attributed to HCV during childhood, one must also consider the other potential non-medical benefits to parents and children. Many parents feel guilt and remorse at having their offspring

potentially acquire a chronic infection that is the result of their past indiscretions. Many children that are chronically infected face significant stigma in schools, daycares, and from communities that are ignorant of the facts about the lack of transmission of HCV with normal childhood behavior. These could all potentially be eliminated with systematic treatment during pregnancy.

Benefits of HCV Therapy for Society

Virus Eradication

From a societal perspective, the epidemic of HCV will not be curbed by highly effective DAA alone [52]. Of 4 million people living with HCV in the USA, only a third are referred for care and only 7–11% are actually treated [53]. Treatment must be offered to all infected patients inclusive of pregnant women to impact the overall disease burden. Groups of patients traditionally classified as difficult to treat have shown equivalent cure rates, and traditional arguments "not to treat" have been discredited [54]. Now that HCV therapy is highly effective and safe, and interferon and ribavirin are no longer part of treatment regimen, treatment of pregnant women needs to be reconsidered in the same manner.

Cost Effectiveness

While expensive at first glance, multiple studies have shown that HCV therapy is cost effective, even at early stages of disease and improves health outcomes [55, 56]. Furthermore, the costs of *not treating*, measured strictly in financial terms, and ignoring the significant psychosocial burden of HCV infection, are significant. A patient without HCV infection has a mean annual all-cause healthcare cost of US$9979 [57]. This cost nearly doubles for non-cirrhotic HCV-infected patients to $17,277 annually. Once cirrhosis develops, annual costs are US$22,752 and skyrocket to US$59,995 with decompensated disease [58]. Billed charges per liver transplant are $577,100 [59].

Treating and curing HCV will have enduring long-term implications for large patient populations of pregnant women and their children, manifest by less hepatocellular carcinoma, less end-stage liver disease, reduced morbidity, and ultimately reduced mortality. These are the motives that should drive policy for screening and treatment. Equally important, however, is the fact that HCV cure will have enduring long-term effects for individual pregnant women and their children by eliminating psychological stress and social stigma, stopping vertical transmission and ending the complications associated with HCV where morbidity and mortality are not measured by a percentage, but by a zero or one. At this level, SVR is "priceless" [59].

Conclusion

As one can see, HCV MTCT and the use of DAAs to interrupt transmission evoke some of the lessons of both HIV and HBV. While the initial medical urgency is not there, the power of cure and the need to use additional measures to control the growing HCV epidemic should be a call to action. Future studies should ensure that DAAs could be used safely and effectively in pregnant women and that providers are ready, willing, and able to intervene at the appropriate time.

Compliance with Ethical Standards

Conflict of Interest A. Sidney Barritt IV declares no conflict of interest. Ravi Jhaveri received a grant from Merck and has participated in clinical trials with Gilead and Abbvie.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med. 2001;345(1):41–52. https://doi.org/10.1056/NEJM200107053450107.
2. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370(20):1889–98. https://doi.org/10.1056/NEJMoa1402454.
3. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370(17):1594–603. https://doi.org/10.1056/NEJMoa1315722.
4. Hezode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet. 2015;385:2502–9. https://doi.org/10.1016/S0140-6736(15)60159-3.
5. Sulkowski M, Hezode C, Gerstoft J, Vierling JM, Mallolas J, Pol S, et al. Efficacy and safety of 8 weeks versus 12 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin in patients with hepatitis C virus genotype 1 mono-infection and HIV/hepatitis C virus co-infection (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015;385(9973):1087–97. https://doi.org/10.1016/S0140-6736(14)61793-1.
6. Balistreri WF, Murray KF, Rosenthal P, Bansal S, Lin CH, Kersey K, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. Hepatology. 2017;66(2):371–8. https://doi.org/10.1002/hep.28995.
7. Forns X, Lee SS, Valdes J, Lens S, Ghalib R, Aguilar H, et al. Glecaprevir plus pibrentasvir for chronic hepatitis C virus genotype 1, 2, 4, 5, or 6 infection in adults with compensated cirrhosis (EXPEDITION-1): a single-arm, open-label, multicentre phase 3 trial. Lancet Infect Dis. 2017;17:1062–8. https://doi.org/10.1016/S1473-3099(17)30496-6.
8. Kwo PY, Poordad F, Asatryan A, Wang S, Wyles DL, Hassanein T, et al. Glecaprevir and pibrentasvir yield high response rates in

patients with HCV genotype 1-6 without cirrhosis. J Hepatol. 2017;67(2):263–71. https://doi.org/10.1016/j.jhep.2017.03.039.
9. Pergam SA, Wang CC, Gardella CM, Sandison TG, Phipps WT, Hawes SE. Pregnancy complications associated with hepatitis C: data from a 2003–2005 Washington state birth cohort. Am J Obstet Gynecol. 2008;199(1):38 e1–9. https://doi.org/10.1016/j.ajog.2008.03.052.
10. Puljic A, Salati J, Doss A, Caughey AB. Outcomes of pregnancies complicated by liver cirrhosis, portal hypertension, or esophageal varices. J Matern Fetal Neona. 2016;29(3):506–9. https://doi.org/10.3109/14767058.2015.1009438.
11. Ceci O, Margiotta M, Marello F, Francavilla R, Loizzi P, Francavilla A, et al. Vertical transmission of hepatitis C virus in a cohort of 2,447 HIV-seronegative pregnant women: a 24-month prospective study. J Pediatr Gastroenterol Nutr. 2001;33(5):570–5.
12. Mast EE, Hwang LY, Seto DS, Nolte FS, Nainan OV, Wurtzel H, et al. Risk factors for perinatal transmission of hepatitis C virus (HCV) and the natural history of HCV infection acquired in infancy. J Infect Dis. 2005;192(11):1880–9. https://doi.org/10.1086/497701.
13. Shebl FM, El-Kamary SS, Saleh DA, Abdel-Hamid M, Mikhail N, Allam A, et al. Prospective cohort study of mother-to-infant infection and clearance of hepatitis C in rural Egyptian villages. J Med Virol. 2009;81(6):1024–31. https://doi.org/10.1002/jmv.21480.
14. Jhaveri R, Hashem M, El-Kamary SS, Saleh DA, Sharaf S, El-Mougy F, et al. Hepatitis C virus (HCV) vertical transmission in 12-month-old infants born to HCV-infected women and assessment of maternal risk factors. Open Forum Infect Dis. 2015;2(2):ofv089. https://doi.org/10.1093/ofid/ofv089.
15. Thomas DL, Villano SA, Riester KA, Hershow R, Mofenson LM, Landesman SH, et al. Perinatal transmission of hepatitis C virus from human immunodeficiency virus type 1-infected mothers. Women and infants transmission study. J Infect Dis. 1998;177(6):1480–8.
16. Checa Cabot CA, Stoszek SK, Quarleri J, Losso MH, Ivalo S, Peixoto MF, et al. Mother-to-child transmission of hepatitis C virus (HCV) among HIV/HCV-coinfected women. J Pediatr Infect Dis Soc. 2013;2(2):126–35. https://doi.org/10.1093/jpids/pis091.
17. Jhaveri R, Swamy GK. Hepatitis C virus in pregnancy and early childhood: current understanding and knowledge deficits. J Pediatr Infect Dis Soc. 2014;3(Suppl 1):S13–8. https://doi.org/10.1093/jpids/piu045.
18. Padula D, Rodella A, Spandrio M, Rossini A, Cariani E. Spontaneous recovery from perinatal infection due to hepatitis C virus. Clin Infect Dis. 1999;28(1):141–2.
19. European Paediatric Hepatitis C Virus Network. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. Clin Infect Dis. 2005;41(1):45–51.
20. Jonas MM. Children with hepatitis C. Hepatology. 2002;36(5 Suppl 1):S173–8. https://doi.org/10.1053/jhep.2002.36799.
21. Goodman ZD, Makhlouf HR, Liu L, Balistreri W, Gonzalez-Peralta RP, Haber B, et al. Pathology of chronic hepatitis C in children: liver biopsy findings in the Peds-C trial. Hepatology. 2008;47(3):836–43. https://doi.org/10.1002/hep.22094.
22. Gonzalez-Peralta RP, Langham MR Jr, Andres JM, Mohan P, Colombani PM, Alford MK, et al. Hepatocellular carcinoma in 2 young adolescents with chronic hepatitis C. J Pediatr Gastroenterol Nutr. 2009;48(5):630–5. https://doi.org/10.1097/MPG.0b013e318170af04.
23. European Paediatric Hepatitis C Virus Network. A significant sex—but not elective cesarean section—effect on mother-to-child transmission of hepatitis C virus infection. J Infect Dis. 2005;192(11):1872–9. https://doi.org/10.1086/497695.
24. European Paediatric Hepatitis C Virus Network. Effects of mode of delivery and infant feeding on the risk of mother-to-child transmission of hepatitis C virus. BJOG. 2001;108(4):371–7.
25. Gibb DM, Goodall RL, Dunn DT, Healy M, Neave P, Cafferkey M, et al. Mother-to-child transmission of hepatitis C virus: evidence for preventable peripartum transmission. Lancet. 2000;356(9233):904–7.
26. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461(7262):399–401. https://doi.org/10.1038/nature08309.
27. Ruiz-Extremera A, Munoz-Gamez JA, Salmeron-Ruiz MA, de Rueda PM, Quiles-Perez R, Gila-Medina A, et al. Genetic variation in interleukin 28B with respect to vertical transmission of hepatitis C virus and spontaneous clearance in HCV-infected children. Hepatology. 2011;53(6):1830–8. https://doi.org/10.1002/hep.24298.
28. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461(7265):798–801. https://doi.org/10.1038/nature08463.
29. Hashem M, Jhaveri R, Saleh DA, Sharaf S, El-Mougy F, Abdelsalam L, et al. Spontaneous viral load decline and subsequent clearance of chronic hepatitis C virus in postpartum women correlates with favorable interleukin-28B gene allele. Clin Infect Dis. 2017;65(6):999–1005. https://doi.org/10.1093/cid/cix445.
30. Dickover RE, Dillon M, Leung KM, Krogstad P, Plaeger S, Kwok S, et al. Early prognostic indicators in primary perinatal human immunodeficiency virus type 1 infection: importance of viral RNA and the timing of transmission on long-term outcome. J Infect Dis. 1998;178(2):375–87.
31. Frederick T, Mascola L, Eller A, O'Neil L, Byers B. Progression of human immunodeficiency virus disease among infants and children infected perinatally with human immunodeficiency virus or through neonatal blood transfusion. Los Angeles County Pediatric AIDS Consortium and the Los Angeles County-University of Southern California Medical Center and the University of Southern California School of Medicine. Pediatr Infect Dis J. 1994;13(12):1091–7.
32. Diaz C, Hanson C, Cooper ER, Read JS, Watson J, Mendez HA, et al. Disease progression in a cohort of infants with vertically acquired HIV infection observed from birth: the women and infants transmission study (WITS). J Acquir Immune Defic Syndr Hum Retrovirol. 1998;18(3):221–8.
33. Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group protocol 076 study group. N Engl J Med. 1994;331(18):1173–80. https://doi.org/10.1056/NEJM199411033311801.
34. Achievements in public health. Reduction in perinatal transmission of HIV infection—United States, 1985–2005. MMWR Morb Mortal Wkly Rep. 2006;55(21):592–7.
35. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. N Engl J Med. 1975;292(15):771–4. https://doi.org/10.1056/NEJM197504102921503.
36. Beasley RP, Hwang LY, Lee GC, Lan CC, Roan CH, Huang FY, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet. 1983;2(8359):1099–102.
37. Schillie S, Walker T, Veselsky S, Crowley S, Dusek C, Lazaroff J, et al. Outcomes of infants born to women infected with hepatitis B. Pediatrics. 2015;135(5):e1141–7. https://doi.org/10.1542/peds.2014-3213
38. Xu WM, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. J Viral Hepat. 2009;16(2):94–103. https://doi.org/10.1111/j.1365-2893.2008.01056.x.

39. Celen MK, Mert D, Ay M, Dal T, Kaya S, Yildirim N, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. World J Gastroenterol. 2013;19(48):9377–82. https://doi.org/10.3748/wjg.v19.i48.9377.
40. Pan CQ, Duan Z, Dai E, Zhang S, Han G, Wang Y, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. N Engl J Med. 2016;374(24):2324–34. https://doi.org/10.1056/NEJMoa1508660.
41. Chen HL, Lee CN, Chang CH, Ni YH, Shyu MK, Chen SM, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology. 2015;62(2):375–86. https://doi.org/10.1002/hep.27837.
42. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63(1):261–83. https://doi.org/10.1002/hep.28156.
43. Lawitz E, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial. Lancet. 2014;383(9916):515–23. https://doi.org/10.1016/S0140-6736(13)62121-2.
44. Wilson-Mitchell K, Rummens JA. Perinatal outcomes of uninsured immigrant, refugee and migrant mothers and newborns living in Toronto, Canada. Int J Environ Res Public Health. 2013;10(6):2198–213. https://doi.org/10.3390/ijerph10062198.
45. Wilson-Mitchell K. Increasing access to prenatal care: disease prevention and sound business practice. Health Care Women Int. 2014;35(2):120–6. https://doi.org/10.1080/07399332.2013.810221.
46. Ly KN, Jiles RB, Teshale EH, Foster MA, Pesano RL, Holmberg SD. Hepatitis C virus infection among reproductive-aged women and children in the United States, 2006 to 2014. Ann Intern Med. 2017;166(11):775–82. https://doi.org/10.7326/M16-2350.
47. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. Ann Intern Med. 2012;156(4):271–8. https://doi.org/10.7326/0003-4819-156-4-201202210-00004.
48. Aghemo A, Prati GM, Rumi MG, Soffredini R, D'Ambrosio R, Orsi E, et al. Sustained virological response prevents the development of insulin resistance in patients with chronic hepatitis C. Hepatology. 2012;56(5):1681–7. https://doi.org/10.1002/hep.25867.
49. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014;370(20):1879–88. https://doi.org/10.1056/NEJMoa1402355.
50. Yehia BR, Schranz AJ, Umscheid CA, Lo Re V III. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. PLoS One. 2014;9(7):e101554. https://doi.org/10.1371/journal.pone.0101554.
51. Kuncio DE, Newbern EC, Johnson CC, Viner KM. Failure to test and identify perinatally infected children born to hepatitis C virus-infected women. Clin Infect Dis. 2016;62(8):980–5. https://doi.org/10.1093/cid/ciw026.
52. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology. 2010;138(2):513–21, 21 e1–6. https://doi.org/10.1053/j.gastro.2009.09.067.
53. Asrani SK, Davis GL. Impact of birth cohort screening for hepatitis C. Curr Gastroenterol Rep. 2014;16(4):381. https://doi.org/10.1007/s11894-014-0381-5.
54. Bonner JE, Barritt AS 4th, Fried MW, Evon DM. Time to rethink antiviral treatment for hepatitis C in patients with coexisting mental health/substance abuse issues. Dig Dis Sci. 2012;57(6):1469–74. https://doi.org/10.1007/s10620-012-2141-4.
55. Chahal HS, Marseille EA, Tice JA, Pearson SD, Ollendorf DA, Fox RK, et al. Cost-effectiveness of early treatment of hepatitis C virus genotype 1 by stage of liver fibrosis in a US treatment-naive population. JAMA Intern Med. 2016;176(1):65–73. https://doi.org/10.1001/jamainternmed.2015.6011.
56. Nuno Solinis R, Arratibel Ugarte P, Rojo A, Sanchez Gonzalez Y. Value of treating all stages of chronic hepatitis C: a comprehensive review of clinical and economic evidence. Infect Dis Ther. 2016;5(4):491–508. https://doi.org/10.1007/s40121-016-0134-x.
57. McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. J Manag Care Pharm. 2011;17(7):531–46. https://doi.org/10.18553/jmcp.2011.17.7.531.
58. Gordon SC, Pockros PJ, Terrault NA, Hoop RS, Buikema A, Nerenz D, et al. Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection. Hepatology. 2012;56(5):1651–60. https://doi.org/10.1002/hep.25842.
59. Reau NS, Jensen DM. Sticker shock and the price of new therapies for hepatitis C: is it worth it? Hepatology. 2014;59(4):1246–9. https://doi.org/10.1002/hep.27039.