

R E V I E W



# Prevention strategies for blood-borne viruses— in the Era of vaccines, direct acting antivirals and antiretroviral therapy

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## SUMMARY

Blood-borne viruses, such as hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and the facultative blood-borne hepatitis E virus, are considered a major public health problem given that they are accountable for millions of deaths each year. Treatment options, including effective vaccine design, development of antiviral strategies and the implementation of antiretroviral therapy have improved substantially over the last couple of years and contribute to successful treatment and prevention of these infectious diseases. In this review, we summarise the current knowledge and concepts in prevention of transmission of these blood-borne viruses.

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## OLD FOES AND NEW FACES: EPIDEMIOLOGY OF HIV, HBV, HCV, HEV

Exchange of blood and other body fluids between individuals bears the risk of acquiring blood-borne virus infections with often severe consequences.

Blood-borne virus infections are caused by HIV, HBV or HCV and are known for a high prevalence worldwide and significant associated morbidity and mortality [1]. Besides these ‘major three agents’, there is increasing concern regarding the prevalence of HEV, even if classically not defined as a true ‘blood-borne virus’ due to its transmission mainly via the faecal/oral route. Nevertheless, especially in the context of the safety of blood products, non-diagnosed HEV infection can pose a significant risk for immunosuppressed patients, patients with chronic liver disease and pregnant women [2].

With more than 34 million deaths so far, HIV infection continues to be a major global health problem. It was estimated that in 2014, 1.2 million people died from HIV-related causes globally with approximately 36.9 million people being chronically infected [3] (Figure 1 and Table 1). As the virus targets immune cells and specifically CD4<sup>+</sup> T cells,

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### Abbreviations used

ART, antiretroviral therapy; DAA, direct acting antivirals; GT, genotype; MTC, mother-to-child transmission; NNRTI, non-nucleosidic RT inhibitors; NRTI, nucleosidic RT inhibitor; NSP, needle/syringe programme; OST, opioid substitution therapy; PEG, pegylated; PEP, Post-exposure prophylaxis; PrEP, Pre-exposure prophylaxis; PWID, people who inject drugs; SVR, sustained virological response.

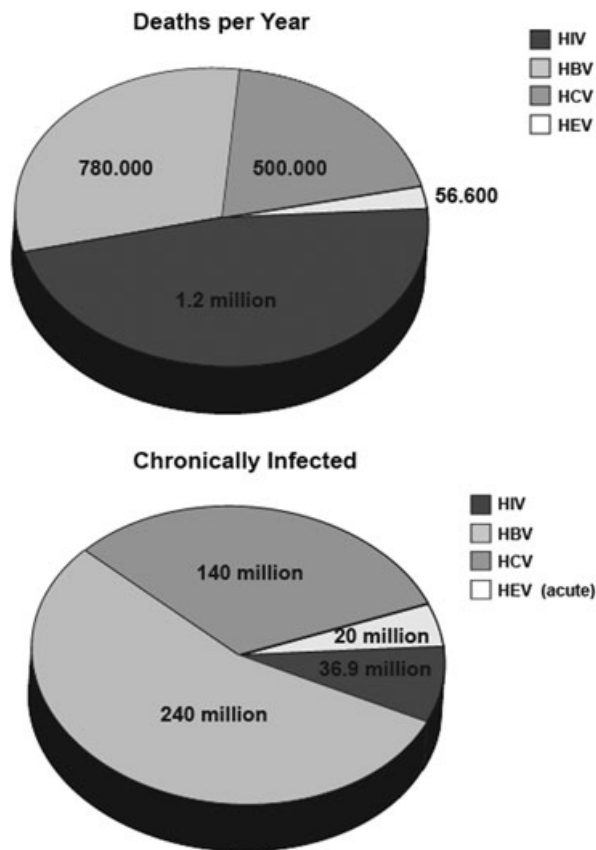


Figure 1. Blood-borne viruses and related deaths. Numbers are based on data released by the World Health Organisation updated July 2015 [3–6]

infected individuals become immunodeficient, which results in an increased susceptibility to infections and if untreated, HIV is almost universally fatal. In the most advanced stage, the infection progresses to AIDS, which leads to the development of certain cancers, high susceptibility to various opportunistic infections and other clinical manifestation [3].

The development of viral hepatitis is the shared hallmark of infections with HBV, HCV and HEV, even though the viruses differ substantially from each other. Viral hepatitis is often silent and symptomless, and it can take years until the development of significant liver disease, which then results in noticeable symptoms [7]. Infection with either HBV, HCV or HEV can lead to viral hepatitis, which results in liver fibrosis, cirrhosis and hepatocellular carcinoma rendering viral hepatitis in many countries as the leading cause of liver transplantations [8]. It is estimated that HBV causes approximately

780 000 deaths each year with globally 240 million people being chronically infected [4] (Figure 1 and Table 1). The risk for proceeding to a chronic infection varies according to the age of infection, with children being at the greatest risk. Approximately 90% of infants and 25–50% of children aged 1–5 years will remain chronically infected with HBV, whereas the majority of adults (95%) are able to eliminate viral infection [9].

Hepatitis C virus infections account for approximately 500 000 deaths worldwide each year. Once infected, approximately 75–85% of the individuals proceed to chronic infections leading to an estimated worldwide infection rate of 130–150 million people who are chronically infected [5] (Figure 1 and Table 1).

In comparison, HEV infections seem negligible with an annual 56 600 deaths and 20 million acute infections globally [6] (Figure 1 and Table 1). Furthermore, in contrast to HIV, HBV and HCV, infection is mainly asymptomatic and self-limiting, and progress to chronicity is rare. However, especially in immunosuppressed patients, pregnant women and patients with liver failure, HEV-related mortality is higher, and/or disease progression is more severe [10].

## KNOWING THE RISKS: TRANSMISSION ROUTES

Blood-borne viruses are transmitted as the name implies mainly by blood or by other body fluids containing infectious virus particles. Penetration through intact skin does not occur, and airborne transmission can also be excluded for HBV, HIV, HCV and HEV. The rate of viral transmission can vary depending on the virus type, viral load in the donor, volume of blood inoculated, route of infection and the immune status of the exposed individual. The main routes of transmission for blood-borne viruses include contaminated blood products, sharing injection equipment, sexual intercourse, mother-to-child (MTC) transmission and occupational exposure. HEV is an exception as it is mainly transmitted via the faecal–oral route with the most common transmission being faecal contamination of drinking water or eating uncooked meat [11]. However, blood–blood transmission is possible. In the last decades, transfusion transmitted infections by virus-contaminated blood products have decreased tremendously through the awareness of these pathogens and the introduction

**Table 1. Characteristics of blood-borne viruses**

Viral characteristic	HBV	HCV	HEV	HIV
Family	<i>Hepadnaviridae</i>	<i>Flaviviridae</i>	<i>Hepeviridae</i>	<i>Retroviridae</i>
Genome	DNA, partially ds	RNA, ss (+)	RNA, ss (+)	RNA, ss (+)
Genotypes	8	7	4	2
Replication site	GT A-H	GT 1-7	GT 1-4 <sup>1</sup>	HIV-1, HIV2
Transmission route	Liver	Liver	Liver	CD4+ T cells
	Blood and body fluids	Blood and body fluids	Water borne faecal–oral, food-borne	Blood and body fluids
<b>Public health<sup>2</sup></b>				
Chronically infected	240 million	140 million	few cases	36.9 million
New infections p.a.	4 million	2 million	20 million	2 million
Related deaths p.a.	780 000	500 000	56 600	1.2 million
<b>Clinical impact</b>				
Outcome of infection	Chronicity: 10% adults, 20–30% children <sup>3</sup> 95% neonates	Chronicity: 75–85%	Mostly self-limiting <sup>4</sup>	Chronicity: 100%
Clinical manifestation	Viral hepatitis	Viral hepatitis	Viral hepatitis	AIDS
Treatment	Antiviral therapy	Direct acting antivirals	Ribavirin	Antiretroviral therapy
Vaccine	Available	Not available	Available	Not available

<sup>1</sup>HEV1 and HEV2 restricted to humans.

<sup>2</sup>Numbers are based on data published from the World Health Organisation (WHO) and Averhoff *et al.*, CID.

<sup>3</sup>Age 1–5 years.

<sup>4</sup>Chronicity can develop in solid-organ transplant recipients.

of screening assays for HBV, HIV and HCV in most countries. However, in the case of HEV, blood products are not routinely tested for the presence of viral RNA, and so represent a potential risk of HEV transmission [12].

Injection drug use is a clear risk factor for the acquisition and transmission of HIV, HCV and HBV. Virus cross-transmissions may occur at various stages during the drug preparation process like sharing syringes and drug preparation equipment such as cookers, filters, water and water containers [13]. It is estimated worldwide that about 3 million people who inject drugs (PWID) are HIV-positive [14], 10 million HCV-positive and about 1.2 million living with HBV [15].

The risk for sexual transmission of HCV is low, while an increased risk is linked to co-infection with HIV, increasing number of sexual partners and men who have sex with men. In contrast, unprotected intercourse is one of the most common routes of infection worldwide for HBV and HIV. In case of HIV, the

majority of transmissions occur through heterosexual contacts; however, depending on the country, the pattern of sexual HIV transmission varies. Risk factors for HIV and HBV sexual transmission are repeated intercourse with an infected person, the type of sexual contact and the amount of virus present in the blood or secretions of the infected partner.

Also, MTC transmission of HIV and HBV is a major transmission route and can occur during childbirth or breastfeeding. The risk of HIV transmission to the infant is about 25% at the delivery and up to an estimated 40% due to prolonged (18–24 months) breastfeeding in untreated HIV infection and in the absence of interventions [16]. For HCV, MTC infection was reported in only about 5–10% of deliveries [17]. The role of breastfeeding for perinatal HCV transmission is thought to be negligible, even though some studies have reported HCV RNA in breast milk and colostrum samples from infected women [18]. In case of HBV, viral DNA can be

detected in the breastmilk [19], but several studies suggest that breastfeeding does not add risk to MTC [20]. Furthermore, all infants born to HBV-infected mothers should receive hepatitis B immune globulin and the first dose of hepatitis B vaccine within 12 h after birth.

Other body fluids like tears, saliva and sweat could additionally harbour the risk of transmitting blood-borne viruses. HIV as well as HCV RNA has been detected in different body fluids, including saliva; nevertheless, direct transmission via this route has never been shown [21,22]. This is in contrast to HBV, where viral DNA has been detected in tears, saliva and sweat of infected patients, and virus isolated from tear specimens of a patient have been shown to be infective *in vivo*, indicating a potential risk that body fluids can serve as a vehicle for HBV transmission [23]. Occupational exposure to blood-borne viruses also poses a serious risk for instance to health care workers, and although safety precautions have been introduced, occupational modes of transmission will continue to occur. These include percutaneous or mucosal exposure to blood or body fluids of

infected individuals as well as needlestick or other sharp injuries with transmission risks of approximately 30% for HBV, 2% for HCV and 0.3% for HIV [24–26].

## REDUCING THE SPREAD: PREVENTION OF INFECTION

### Primary prevention

Primary prevention seeks to prevent the onset of a viral infection by reducing risk factors in non-infected people. It involves interventions that are applied before there is any evidence of infection or disease. Examples include an increased awareness, safety of blood products, hygiene and disinfection, reduction of viral exposure, as well as prophylaxis and induction of immunity in uninfected people by vaccination (Figure 2) [8].

### Raising awareness

Successful prevention strategies of viral infections require a high level of awareness of the infected individuals as well as a detailed knowledge among

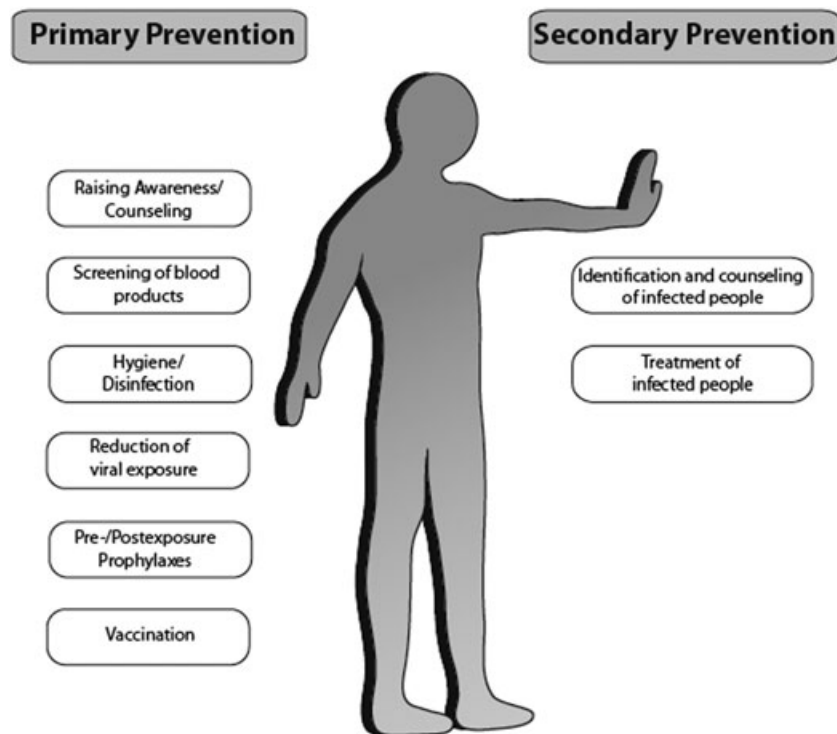


Figure 2. Primary and secondary prevention strategies for blood-borne viral infections. Prevention strategies that help reduce transmission of blood-borne viral infections

healthcare professionals and society [7]. Public campaigns including world hepatitis day, which is commemorated every year on the 28th of July and world AIDS day, commemorated on the 1st of December, are helping to raise awareness in the community. Many healthcare professionals lack basic knowledge about risk factors or screening recommendations associated with viral hepatitis or AIDS [27,28]. Extensive and reiterated education of medical personnel is a prerequisite, and raising awareness of opportunities for prevention, care and treatment is a major goal to help reduce occupational transmission. Updated guidelines are available provided by different organisations including the World Health Organisation or the Centers for Disease Control and Prevention (CDC)/European CDC as well as national guidelines.

#### *Screening of blood products*

In the last decades, there have been significant reductions in the risk of transfusion-transmitted blood-borne infections because of the implementation of routine screening procedures of blood products. Nucleic acid amplification testing has been successfully established for the detection of HIV, HBV and HCV resulting in a reduction of transmission [29]. However, there is increasing concern regarding the transmission risk of HEV by transfusion and ongoing debates whether routine HEV screening for blood donors should be implemented [12]. Recent studies from different European countries reported a low prevalence of HEV RNA in blood donors [10], but due to pooling procedures, the risk can increase substantially to a rate of up to 10% HEV RNA positivity in pooled plasma [30]. To date, screening of blood products for HEV has not been standardised, and also due to poor sensitivity and specificity of anti-HEV assays, it is estimated that the risk for transfusion-mediated transmission of HEV is far higher than for other blood-borne viruses including HIV [12].

#### *Hygiene/disinfection*

Simple measures regarding hygiene and disinfection of possible contamination sources can help reduce viral transmission. To prevent occupational transmission, prevention strategies involve implementation of standard barrier precautions including gloves, gowns and protective eye wear as well as minimal manual manipulation of sharp instruments (e.g. by not recapping needles) as well as

disposal of sharp material into suitable containers [1,31]. Furthermore, appropriate disinfection practices should be employed to facilitate a contamination-free environment. This involves sterilisation of medical and dental equipment as well as surface disinfection of contaminated areas. Next to nosocomial environments, the usage of sterile equipment in tattoo and piercing studios is of utmost importance, and a non-sterile environment, for example, upon tattooing and piercing in prisons, homes and other potentially non-sterile setting, can facilitate viral transmission [32].

#### *Reduction of viral exposure*

Sexual transmission poses a major risk factor, and prevention strategies have been implemented to reduce viral spread. Behavioural interventions including condom use have been shown to successfully reduce the incidence of HIV infections [33] and are also effective measures to prevent transmission of HBV and HCV. Furthermore, medical male circumcision has been shown to effectively reduce transmission of HIV by the sexual route [34], and new intervention strategies including vaginal and rectal microbiocides are being developed to further reduce transmission [35].

Injection drug use is one of the most efficient transmission routes for blood-borne infections in the developed world, and sharing of contaminated needles and preparation equipment have been associated with viral transmission [36]. The introduction of harm reduction interventions like needle/syringe programmes (NSP) and opiate substitution therapy contributes to prevention of viral transmission. NSP have been initiated in several countries worldwide, and sterile needles have been made available for drug users at low or no costs. Opioid substitution therapy also provides an ideal context for viral screening to efficiently contribute to reducing transmission risks [37], and together with NSP and antiretroviral therapy (ART), it efficiently helps to reduce viral transmission [38].

#### *Post-exposure prophylaxis*

In case of a high chance of getting infected, for example, by accidental blood contact with infected body fluids or to prevent viral transmission from infected mothers to newborns, measurements for HBV and HIV are available to assess the risk for viral transmission [39,40]. Post-exposure prophylaxis

(PEP) refers to immediate treatment with antiviral drugs following exposure to a pathogen in order to prevent infection. In the case of HIV, PEP should be initiated as early as possible and no later than 48–72 h. It is recommended after any high risk—usually sexual, occupational or associated with intravenous drug use—exposure [41,42]. Given the possibility of side effects such as drug induced liver injury, PEP should not be initiated if the risk of infection is deemed very low given the nature of the exposure [43]. Similarly, in the event of high-risk exposure of an unvaccinated individual to HBV and in newborns to HBsAg positive mothers, PEP should be initiated using combined active/passive vaccination [44]. Newborns to HBsAg positive mothers should receive PEP irrespective of the mother's HBeAg status: the usual dose being 30–100 IU anti-HBs per kilogramme bodyweight. No PEP protocols or recommendations exist for HCV or HEV.

#### *Pre-exposure prophylaxis*

Pre-exposure prophylaxis (PrEP) refers to the concept of administering antiviral drugs to individuals prior to anticipated exposures. PrEP has been shown to reduce the risk of acquisition of HIV infection in individuals at high risk and is recommended by the CDC [45]. No PrEP protocols are established or recommended for HBV, HCV or HEV infection.

#### *Vaccination*

Effective immune protection in the community contributes greatly to the prevention and eradication of viral infections. A safe and effective vaccine against HBV has been available since 1982, and nowadays, vaccination against HBV has been successfully implemented with 47 European countries having adopted universal HBV vaccination programmes [46,47]. HBV vaccination leads to appearance of anti-HBs: generally levels >100 U/l are considered to represent a good response, while levels >10 U/l are still protective. In individuals at risk from HBV infection, antibody levels should be rechecked after 10 years. Introduction of the vaccine has contributed to a 96% decline in the incidence of acute hepatitis B in children and adolescents [48].

For HEV, there is currently no global vaccine available even though in 2011, the first vaccine to prevent HEV infection (HEV239 vaccine) was

registered in China [2]. It has to be seen whether this will soon be available also in other countries. Up to now, there is no effective prophylactic vaccine available for HCV or HIV infections. Several vaccine candidates for HCV are in phase I/II clinical trials, but their clinical usefulness remains to be demonstrated [49,50]. Similarly, HIV vaccine research has been ongoing for several years, but an effective and safe preparation has thus far remained elusive [51,52].

#### **Secondary prevention**

Secondary prevention strategies aim to identify infected people and to provide appropriate medical management to reduce the risk of chronic diseases (Figure 2) [8]. These strategies include identification as well as treatment of infected people.

#### *Identification and counselling of infected people*

A major impediment to the potential of antiviral therapy to prevent transmission is the high number of undiagnosed infections [53,54]. It has been estimated that 45–85% of HCV-infected individuals in the USA are unaware of their infection [55]. Thus, it is important to suspect and test for blood-borne infections in individuals at risk or showing suggestive symptoms. Screening services are crucial for a comprehensive strategy to reduce and eliminate blood-borne viral infections [56]. These services aim to identify individuals who are unaware of their infection status and provide them with counselling and education thereby allowing the infected persons to make behavioural changes and to take steps that prevent transmission to uninfected individuals. Early diagnosis of an infectious disease offers the best chance for a successful medical treatment and the prevention of viral spread [57]. Next to the implementation of screening strategies, notification and counselling of blood donors who have been tested positive after blood donation provide ample opportunity to identify unaware infected people and to facilitate medical support.

#### *Treatment of infected people*

Powerful antiviral drugs with a defined molecular target exist for all pathogens discussed here with the exception of HEV. Antiviral therapy prevents transmission events either by reducing the number of infected individuals in the population (HCV) or

by reducing viral load and thus the risk of person-to-person spread (HBV, HIV).

All oral antivirals approved against HBV infection inhibit the HBV RT [58]. Taken as a single pill per day, all of them block production of new viral particles, which in turn reduces viral load and prevents the progression of liver disease. However, HBV antivirals do not clear covalently closed circular DNA from the nuclei of infected cells and thus cannot cure infection [59]. Hence, antiviral therapy for HBV must be taken long term in most cases.

Numerous direct acting antivirals (DAAs) for HCV infection have reached the market starting in 2011 [60]. All HCV antivirals inhibit one of three molecular targets: the NS3/4A protease, the NS5A RNA binding protein and the NS5B RNA-dependent RNA polymerase [60]. The polymerase inhibitor class can be further divided into nucleoside analogues targeting the NS5B active site and non-nucleoside analogues [61]. Current treatment protocols combine two or more of these agents sometimes together with the non-specific antiviral ribavirin (see succeeding discussion) for an 8- to 24-week course with the intent to permanently cure infection [62,63]. The exact choice of drugs and treatment duration depends on viral genotype, severity of liver disease and sometimes other factors such as co-morbidities, co-medications, sex or pre-treatment viral load. In almost all cases, viral load drops rapidly to undetectable levels when treatment is initiated. Undetectable HCV RNA 12 weeks after end of therapy is referred to as sustained virological response (SVR) and seen as equivalent to cure. This is achieved in over 90% of individuals treated [64]. Post-SVR individuals are clearly non-infectious. It is likely that individuals with undetectable HCV RNA are already non-infectious prior to reaching SVR, but this has not been formally shown.

Beyond antiviral drugs, both HBV and HCV also respond to treatment with IFN- $\alpha$  [65]. It is usually applied as weekly subcutaneous injections of a pegylated form (PEG) and exerts a non-specific antiviral effect through stimulation of cellular antiviral defences. In chronic HBV infection, PEG-IFN- $\alpha$  is administered for 48 weeks instead of or in addition to antivirals [66]. In a minority of cases, it achieves a lasting attenuation of viral replication or even long-term immune control so that further antiviral treatment is not required. In the case of HCV, PEG was used in combination with ribavirin and later also different DAA, but it has now been

all but replaced by oral DAA combination therapy that achieves higher SVR rates with fewer side effects [64,66]. No specific antivirals exist for HEV infection. However, ribavirin monotherapy has been shown to often cure chronic infection in immunosuppressed individuals and is sometimes also used in severe forms of acute HEV infection [67]. No data exist on the effect of ribavirin treatment on HEV transmission.

Since the introduction of zidovudine in 1987, ART has evolved to highly potent combination ART that now allows infected individuals with access to good healthcare to live a lifespan very comparable with that of uninfected individuals [68,69]. However, as in HBV, treatment is suppressive and not curative and thus must be taken lifelong. Four classes of HIV antivirals are currently employed as part of first-line combinations: nucleosidic inhibitors of the HIV RT (NRTI) form the backbone of many regimens [70]. Several HIV NRTI are also active against HBV; most notably, tenofovir is widely used in both HBV and HIV infection. Other classes of first line agents are non-nucleosidic RT inhibitors (NNRTI), protease inhibitors and integrase inhibitors [71]. Agents with different mechanism of action such as fusion inhibitors and blockers of the CCR5 co-receptor are available as second line agents [72]. Additionally, other antiretroviral drugs are currently in the drug pipeline including monoclonal antibodies, maturation inhibitors and attachment inhibitors [73]. Furthermore, the new long-acting injectable antiretrovirals as well as the new boosting agent cobicistat have the potential to improve therapy [74,75]. Treatment usually combines two NRTI with a third first-line agent from a different class [41,42]. Several fixed dose combinations allow administration of state-of-the-art combination therapy as a single pill taken once daily. Choice of initial combination is based on co-morbidities, co-medications, viral resistance profile, anticipated side effects and convenience of administration. Given the many options and assuming that medications are taken regularly, it is now possible to suppress viral replication for life in almost all patients. Thus, the recommendations have been evolving towards early initiation of ART rather than waiting until the CD4 cell count drops below some threshold or even symptoms of immunodeficiency appear as clinical trials, for example, START have shown clear benefits of starting treatment earlier [76,77]. Following

initiation of ART in most cases, viral load steadily declines eventually falling below the limit corresponding to markedly reduced risk of transmission of infection to others, which has been supported by the HPTN 052 study that showed both personal and public health benefits of HIV treatment as prevention [78].

## CONCLUSION

There are several key challenges ahead to efficiently prevent transmission of blood-borne pathogens. It is necessary to raise awareness and discuss risks associated with blood-borne viruses. Global screening and detection systems need to be implemented and general treatment guidelines

mediated, which are also available in low-income countries. Vaccines for both HCV and HIV still remain elusive. In the case of HBV and HIV, avenues towards curative rather than suppressive treatments need to be explored and in the case of HEV, specific antiviral drugs are lacking.

## CONFLICT OF INTEREST

TVH Speaker's Fees from BMS, Johnson & Johnson and Roche.

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