Scoping document:

A review of viral hepatitis in injecting drug users and assessment of priorities for future activities

For World Health Organization, Geneva

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The following document was based on the terms of reference to provide scoping document which reviews the state of the art regarding viral hepatitis in injecting drug users and assesses priorities for future activities. Specifically:

- To review background documentation
- Prepare an overview of the epidemiological situation, global response and cost effectiveness
- Assess feasibility of implementing specific interventions and define priorities for development of specific guidance on HBV, HCV, HIV in IDUs.

Glossary

EVR	Early virologic response (> 2 log drop in HCV viral load 12 weeks into HCV treatment
HBcAb	Hepatitis B core antibody. Indicates previous exposure to hepatitis B
HBeAb	Hepatitis B e antibody. Indicates inactive disease, so called “e seroconversion”, though may not indicate clearance of HBV
HBeAg	Hepatitis B e antigen. Indicates active replication/active disease
HBsAb	Hepatitis B surface antibody. Indicates immunoprotection against hepatitis from either vaccination or previous exposure
HBsAg	Hepatitis B surface antigen. Indicates current infection with hepatitis B (a carrier)
HBV	Hepatitis B virus
HBV DNA	Hepatitis B DNA. Presence indicates active replication and disease. Magnitude of DNA is ‘viral load’
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCVAb	Hepatitis C antibody
HCVRNA	Hepatitis C ribonucleic acid. Magnitude of RNA is ‘viral load’
HIV	Human immunodeficiency virus
MMT	Methadone maintenance therapy
QALY	Quality adjusted life year
RVR	Rapid virologic response (negative HCV RNA at 4 weeks into treatment)
SVR	Sustained virologic response (HCV RNA negative 24 weeks after completion of treatment)
ETR	End of treatment response (negative HCV RNA at the end of treatment)

Contents

Introduction

Injecting drug use is major cause of both morbidity and mortality worldwide. It is estimated there are between 11 and 21.2 million IDUs globally in at least 148 countries(Mathers et al., 2008). Estimated prevalence by country is shown in figure 1 below.

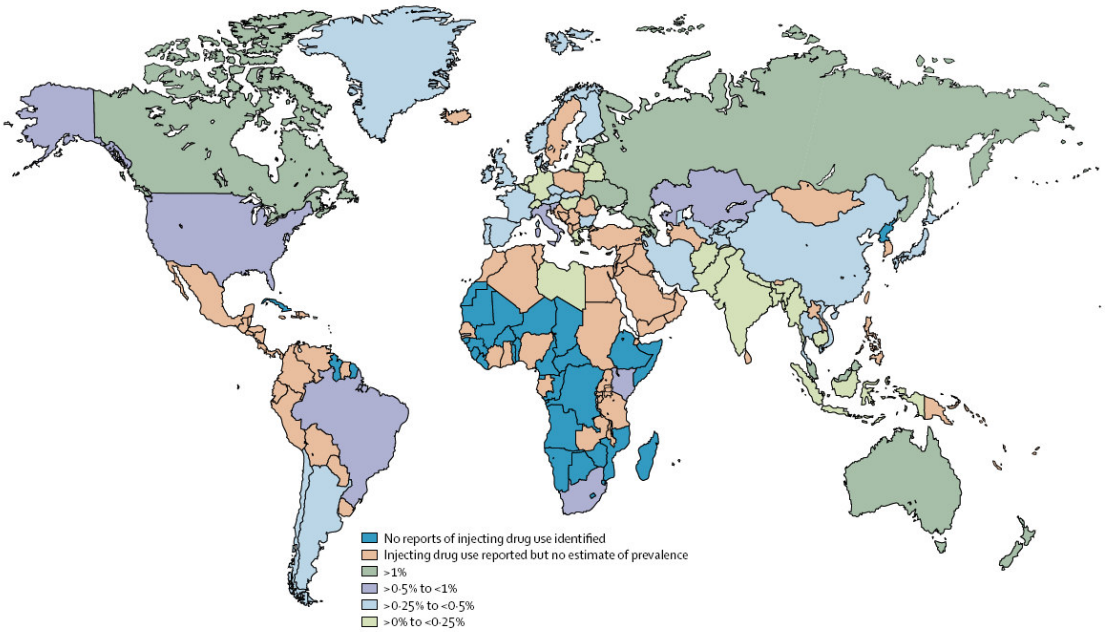

Figure 1 - Global prevalence of injecting drug use by country(Mathers et al., 2008)

Viral hepatitis B and C and related disease is common among IDUs. To date the urgency of preventing HIV among IDUs has overshowed the 'silent' epidemic of viral hepatitis. This paper examines the epidemiology of viral hepatitis and HIV coinfection among IDUs, the response options available for prevention and treatment and provides an overview of the cost effectiveness of these options. A summary of the current global response is given and priorities for the future discussed in the final section.

The relevance of viral hepatitis and related disease among IDUs is that IDUs are disproportionally affected by these two viruses, a result of shared modes of transmission. Hepatitis B and C can cause liver fibrosis, dysfunction and ultimately cirrhosis and hepatocellular carcinoma – all resulting in increased morbidity and mortality among those affected. Viral hepatitis can adversely affect treatment of HIV as a result of the direct hepatoxicity of antiretroviral agents, and in those treated for HIV, becomes a significant cause of illness. Despite this the provision and uptake of testing for viral hepatitis is generally poor among IDUs, and knowledge of the management of viral hepatitis inadequate among many injecting drug using populations worldwide. Both hepatitis B and C can be effectively treated and even cured; however treatment uptake is extremely low among IDUs. Hepatitis B is almost entirely preventable by vaccination; however vaccination rates among IDUs are also low worldwide, with some exceptions.

For hepatitis C, while prevention is difficult, treatment is effective in most cases. An understanding of the importance of genotype informs how long an individual should be treated. For example genotype 1 requires 48 weeks of treatment compared with 24 for genotypes 2 and 3. This is very relevant to cost effective analysis as medication used in the treatment for HCV is currently very expensive. This medication is on patient until at least 2015. There are no generic versions of the most effective treatment (pegylated interferon ribavirin combination therapy) available.

For hepatitis B, prevention is very effective while treatment less so. Genotypes are less relevant in HBV. An understanding of the disease process and the various biomarkers (such as HbsAg, HBeAg and HBVDNA) is important to inform accurate diagnosis, treatment and in some cases appropriate vaccination.

Lack of access to effective prevention and treatment for viral hepatitis C among IDUs follows a similar narrative to that of HIV. Like HIV, integrated and patient oriented treatment and prevention are effective in engaging and retaining IDUs. Service delivery must balance quality and coverage and thus crossdisciplinary and multisectorial engagement is needed in order to increase uptake of viral hepatitis prevention and treatment initiatives among IDUs worldwide.

Epidemiology

Hepatitis C

Global

It is estimated that 170 million individuals are living with hepatitis C globally, the majority in developing countries. There are a number of reasons for this including unsterile medical injections, transfusions, cultural practices where blood is potentially exchanged between individuals and injecting drug use. The prevalence by country in 2005 is shown below:

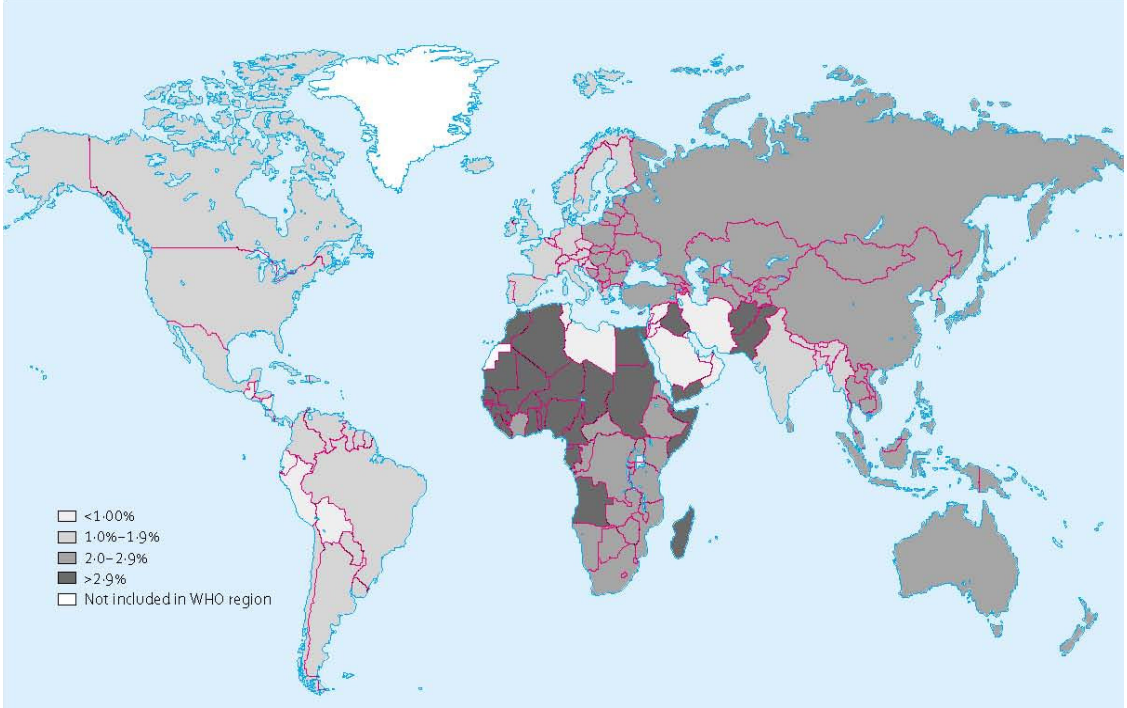

Figure 2 - Hepatitis C prevalence by country(Shepard et al., 2005)

Although injecting drug use is a very common way to obtain hepatitis C, the proportion of hepatitis C cases attributable to injecting drug use is lower in developing countries than developed countries. Despite this, the incidence of hepatitis C among IDUs appears to be higher in developing/transitional countries(Hagan et al., 2008), a result of the time to HCV infection in IDUs has lengthened in developed nations. The epidemiology of hepatitis C among IDUs in selected countries is detailed below. Summary figures for the prevalence of Hep C among IDUs in selected countries and prisons is shown in table 2.

Table 1 - Prevalence of HCV among community IDUs and prisoners in selected countries(Cook and Kanaef, 2008)

Country or territory	Adult HCV prevalence among people who inject drugs	**HCV prevalence among prisoners**
Bahrain	81%	-
Brazil	39.5–69.6%	-
Czech Republic	21–59%	18–78%
Estonia	90%	82–97.4%
Germany	75%	80% (prisoners with a of history of injecting, Berlin)
India	92%	-
Indonesia	60–98%	-
Iran	35%	18.7%
Japan	55.1–60%	-
Kazakhstan	65.7%	-
Mauritius	95%	-
New Zealand	70%	80% (prisoners with a history of injecting)
Pakistan	89%	-
Saudi Arabia	69%	-
Sweden	83.8%	-
Thailand	90%	-
Ukraine	70–90%	-
United Kingdom	41%	30–44% (prisoners with a history of injecting)
United States	50–80%	30–40%

Prisons consistently have a very high proportion of inmates who are living with hepatitis C(Macalino et al., 2004) and shown in table 1 above, Although most is attributed to injecting drug use, non-IDUs in closed settings have a substantially higher prevalence of hepatitis C than the general population.

Within IDU populations, the sharing of contaminated injecting equipment such as needles and syringes is the most common mechanism of acquisition. The sharing of other equipment such as spoons and filters has also been associated with the transmission of HCV though this is less common(Hagan et al., 2001). Hepatitis C is more easily transmissible than HIV, and therefore the prevalence of HCV in an IDU population is often much higher than the HIV prevalence. Hepatitis C is difficult to transmit by unprotected sexual intercourse(Vandelli et al., 2004), though recent studies suggest that traumatic sexual practices and HIV coinfection may be conducive to HCV transmission(Gambotti et al., 2005, Browne et al., 2004, Terrault, 2005). A recent study from the Netherlands highlighted that sexual transmission of HCV is occurring among HIV positive no injecting but substance using MSM engaging in traumatic sexual practices(Urbanus et al., 2009).

Although this review concerns itself with injecting drug use, studies of HCV in drug users who do not inject indicates an increased risk of HCV. A synthesis of available higher quality data in 2007 regarding HCV among non-IDUs found a range in prevalence of 2 – 35% across 35 studies globally(Scheinmann et al., 2007). In addition it is not uncommon for non-IDUs to transition to injecting.

The epidemiology of HCV HIV coinfection is less well understood. It is estimated there are 4 – 5 million individuals with HIV HCV coinfection worldwide(Alter, 2006). Generally speaking, coinfection, by the nature of the shared transmission routes, is transmitted by injecting drug use, however the transmission can also occur sexually. Thus coinfection is very common in HIV positive injecting drug using populations. Hepatitis C is more difficult to clear spontaneously in the presence of HIV, therefore HIV positive IDUs with exposure to HCV are much more likely to develop chronic hepatitis C than their HIV negative counterparts. In the number of countries in Asia, the prevalence of HIV HCV coinfection among HIV positive IDU is > 95% (parts of China, Thailand, Vietnam)(Walsh et al., 2007). By contrast in countries where HIV is mainly sexually transmitted, HCV HIV coinfection is less common – but not among IDUs where it is still very high – such as countries like India where the main mode of transmission is still sexual.(Alter, 2006).

HCV genotypes

Globally, there is a wide distribution of HCV genotypes, with almost all countries having infections from more than one genotype. Nevertheless different genotypes predominate in different areas around the world. This has important implications for the cost and effectiveness of treatment.

In Europe, genotype 1 is the most common followed by 3a, although 2c is the most common in Southern Italy. Scattered genotype 4 infections occur in southern Europe. Genotype 5a has been identified in France. Immigration and the shift to injecting drug use are changing the epidemiology of HCV in Europe resulting in a greater proportion of 1a, 3a and 4 as well as other genotypes(Esteban et al., 2008).

Asia has a wide variety of HCV genotypes, with most countries having most genotypes. Of particular note is that genotype 1 is widespread, Genotype 2 is common in Japan, 3 is common in Australia, New Zealand and Thailand, 5 in the South Pacific and 6 in Hong Kong(McCaughan, 2000).

While most HCV genotypes occur in the Middle East, the most common genotype within Middle Eastern Arab countries is genotype 4. Genotypes 1 and 3 are the most common in Iran, with genotype 1 the most prevalent in Israel and Turkey(Ramia and Eid-Fares, 2006).

The major genotype in North America is 1. In the USA it has been reported prevalence of genotype one is 73%, genotype two 15%, genotype three 7% while the others are relatively uncommon(Alter et al., 1999).

Overall, genotype 1 is the most prevalent HCV genotype in the Caribbean and in South and Central America. Genotypes 2 and 4 are more common in the Caribbean than in the rest of Latin America. There are differences in the distribution of genotypes within and between countries in the region. In addition, some strains of genotype 1 have diverse origins(Cristina, 2005, Dehesa-Violante and Nunez-Nateras, 2007)

Hepatitis B

Many studies considered in this section on HBV epidemiology, particularly those working with IDUs, only reported hepatitis B infection – not differentiating between HBsAg, HBeAg and HBcAb, let alone HBV DNA viraemia - prevalence within the studies thus leading to difficulty in interpretation and comparison between studies.

Global

Worldwide, two billion people have been infected with hepatitis B virus (HBV), 360 million have chronic infection, and 600,000 die each year from HBV-related liver disease or hepatocellular carcinoma(Shepard et al., 2006). Approximately 60 percent of the world's population lives in areas where HBV infection is highly endemic - much of Asia and Africa, although there are exceptions such as Taiwan and Gambia which have managed through comprehensive vaccination programs to reduce the prevalence of chronic HBV infection.

The main mode of HBV transmission varies between countries depending on the endemicity of the virus. In highly endemic settings, perinatal and horizontal routes are responsible for most disease transmission, and 70–90 percent of the adult population has serologic evidence of prior infection. Countries with intermediate endemicity have a mix of perinatal, horizontal, health-care-related, sexual, and other forms of transmission. In countries with low endemicity, most new infections occur among young adults and are acquired sexually or through injecting drug use(Custer et al., 2004, Shepard et al., 2006). It is estimated in the US that drug users comprise 17% of all new cases of hepatitis B(CDC, 2002a) and that 12% of all HBV cases are in individuals with a history of injecting(Weinbaum et al., 2008), while in Europe 40 – 70% of all diagnosed cases occur in IDUs(EMCDDA, 2003).

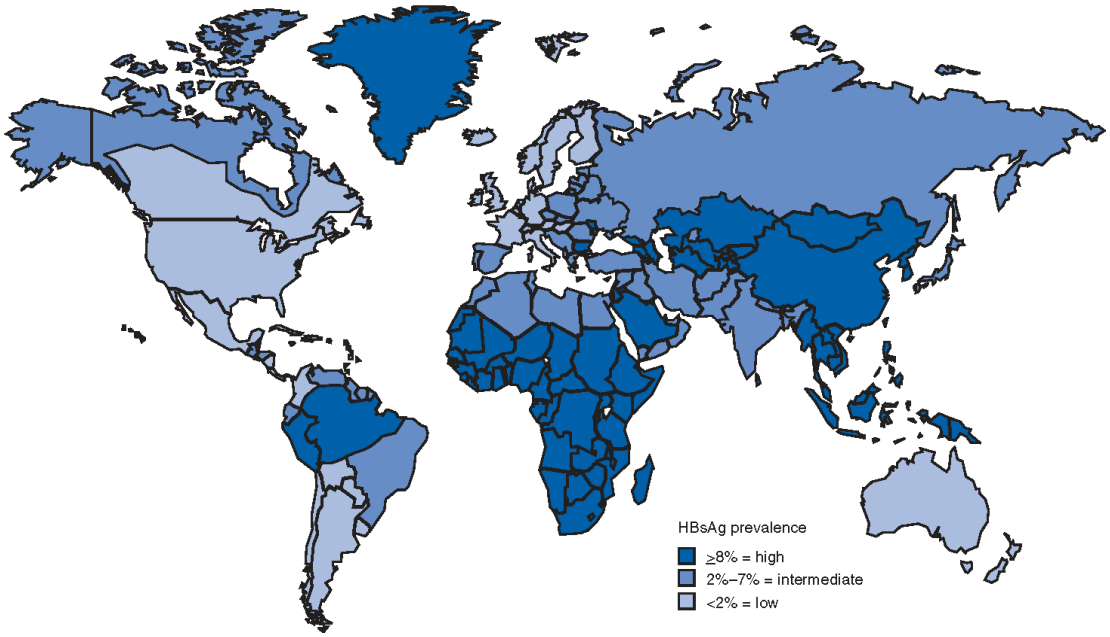

Figure 3 - Global prevalence of chronic hepatitis B based on available data 2006(Weinbaum et al., 2008)

The prevalence of HBV in HIV positive individuals varies widely. In essence it is higher in area where vertical and perinatal transmission is high and low in areas where exposure to HBV is limited to adulthood. This is because although the rate of chronic infection in adults with HIV exposed to HBV, it is much lower than the risk of chronicity in early childhood. For example the prevalence of HBV infection among people living with HIV ranges from 5 to 10% in the United States to 20 - 30% in Asia and parts of sub-Saharan Africa(Koziel and Peters, 2007).

HBV genotypes

Globally almost all regions have more than one HBV genotype circulating. An individual can be infected with more than one genotype at the same time. Where this occurs re-assortment can occur and recombinant versions of genotypes can develop. Recombinant HBV genotypes, occur in a number of countries. The distribution of hepatitis B genotypes is complex and represented in the figure below:

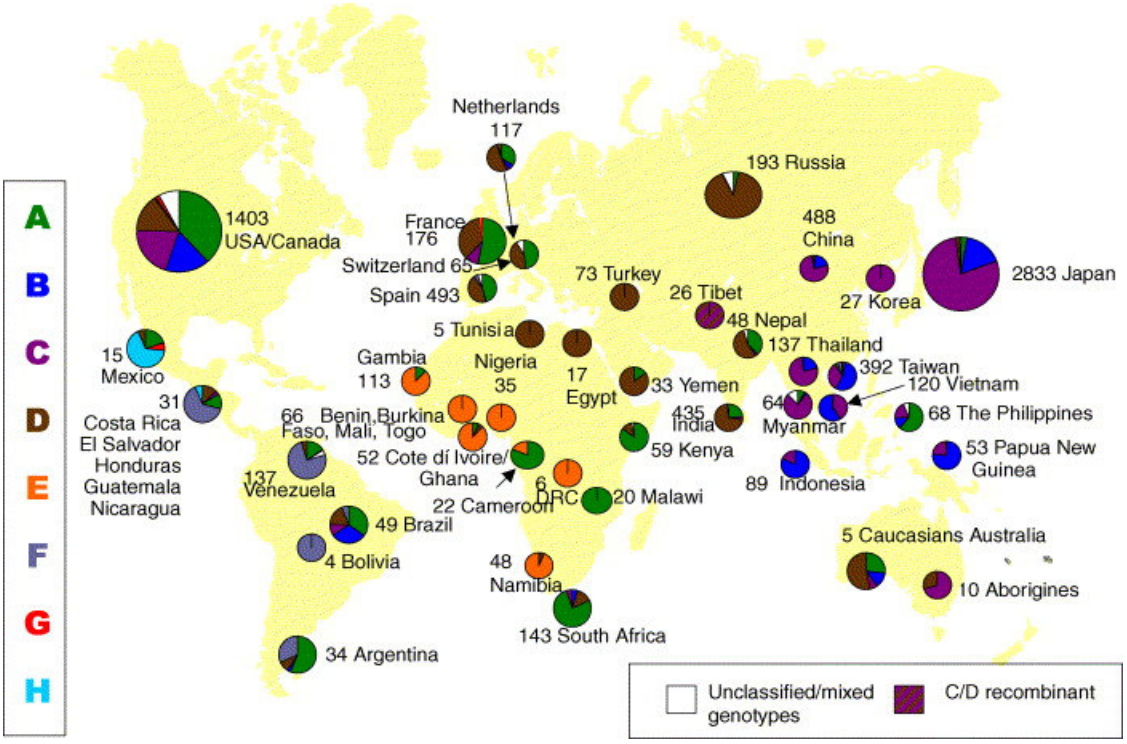

Figure 4 - Global distribution of hepatitis B genotypes(Kramvis et al., 2005)

There is some association of genotype and mode of transmission. Genotypes B and C are generally transmitted via perinatal transmission, genotype A is associated with sexual or parenteral routes whereas all routes may be involved in the transmission of genotype D(Chu et al., 2003). Genotype G is mainly confined to USA and Europe (Bhat et al., 1990) and has been associated predominantly with MSM transmission. Nevertheless, studies on the influence of genotype and mode of transmission are limited in their relevance due to other factors such as geography and ethnicity.

Regional epidemiology of HCV and HBV

In general, high HBV population prevalence refers to HBsAg > 8%, intermediate 2-7% and low < 2%.

Europe

The epidemiology of hepatitis C infection in Europe is explained by unsafe parenteral injections, invasive medical and surgical procedures and transfusion of blood products last century, followed by increasing injecting drug use and rapid spread of HCV among this population. In Northern Europe HCV was mainly transmitted by injecting drug use thus the population prevalence is only between 0.1 and 1%. The population prevalence of HCV in Western Europe is higher (0.2 – 1.2%) and higher still in Southern Europe at between 2.5% and 3.5% consisting of a high prevalence in older persons through iatrogenic spread and high prevalence among the young with a history of injecting drug use(Esteban et al., 2008).

European countries are generally countries of low HBV endemicity though there is variation. The prevalence of HBsAg in Italy is now < 1% but was 3% in the 1980's, a result of unsafe medical injections and other practices followed by a comprehensive immunisation program(Da Villa and Sepe, 1999). The prevalence of hepatitis B among IDUs in Europe varies widely. Less information is available about HBV HIV coinfection in IDUs.

Table 2 - Epidemiology of viral hepatitis and HIV coinfection in Western Europe

Europe – Western Europe	HCV IDUs*	HCV HIV IDUs	HBV Population	HBV IDUs**	HBV HIV IDUs
Andorra			Low		
Austria	26 -33%		Low	18% (HBcAb)	
Belgium	14 - 80%		Low	25 53% (HBcAb) 0 – 2.6% (HBsAg)	
Denmark	87%		Low	37% (HbcAb) 60% new HBV cases linked to IDUs in Funen(Christensen et al., 2001)	
Finland	38 - 52%		Low		
France	43 – 72%	92% of IDU with HIV have HCV(Larsen et al., 2008)	Low		8% of IDU with HIV have HBV(Larsen et al., 2008)
Germany	66 – 97%		Low	53% (HBcAb)	
Greece	11 – 68%		Intermediate	15 – 29% (HBsAb) 2 – 4% (HBsAg)	
Iceland			Low		
Ireland	72 – 81%		Low		
Italy	42 – 90%	13%(Quaglio et al., 2003) 50% of IDU with HIV have HCV(Quaglio et al., 2003)	Low	37% (HbcAb)	
Luxembourg	37%		Low	18 -36% (HBcAb)	
Malta			Low		
Monaco			Low		
Netherlands	47%		Low	31% (HBcAb)	
Norway	68 – 79%(Oslo)		Low	45% (HBcAb) 0.5% (HBsAg)	
Portugal	63% (Lisbon)		Intermediate	16 -28% (HBcAb) 3 – 7% (HBsAg)	
San Marino			Low		
Spain	60 -85%	11 – 95%	Intermediate	23% (HBcAb)	
Sweden			Low		
Switzerland	91%	91%	Low		
United Kingdom	21 – 59% (London); 2 – 64% (other sites)		Low	6 -27% (HBcAb)	

*(Aceijas and Rhodes, 2007) unless otherwise cited
**(EMCDDA, 2009) unless otherwise cited

There is limited information about the prevalence of hepatitis C in Eastern Europe. Nevertheless data that is available indicates higher prevalence than other parts of Europe, and very high among risk groups including IDUs(Naoumov, 1999). The reported prevalence of HCV in selected countries in Eastern Europe is shown in the table below. Most studies of HIV positive IDUs in Eastern Europe found the prevalence of HCV HIV coinfection to be greater than 80%(Cook and Kanaef, 2008).

In comparison with Western Europe, the prevalence of HBV in the general population and IDUs is higher.

Table 3 - Epidemiology of viral hepatitis and HIV coinfection in Eastern Europe and the Baltics

Europe – Eastern Europe & the Baltics					
	HCV IDUs*	HCV HIV IDUs	HBV Population	HBV IDUs**	HBV HIV IDUs
Albania			Intermediate		
Belarus	51%	71% of HIV positive IDUs(Eremin et al., 2004)	Intermediate		24% (HBsAg) of HIV positive IDUs(Eremin et al., 2004)
Bosnia and Herzegovina			Intermediate		
Bulgaria	60-95%		High	12% (HBsAg)	
Croatia		58%	Intermediate	24% (HBcAb) 0.5% (HBsAg)	
Cyprus			Intermediate		
Czech Republic	18.1-37%		Intermediate		
Estonia	34%(Wiessing and Nardone, 2006) 90% (Cook and Kanaef, 2008)		Intermediate		
Georgia	>50% (Cook and Kanaef, 2008)		High	7% (HBsAg) 40% (HBcAb)(Tsertsvadze et al., 2000) 55% (unclear which markers)(Shapatava et al., 2006)	
Hungary	10.4-30.4%		Low	0.4% (HbsAg)	
Israel	54%		Intermediate		
Latvia	83%		Intermediate		
Lithuania	>50% (Cook and Kanaef, 2008) 79-95.9%		Intermediate	3 – 9% (HBsAg)	
Montenegro			Intermediate		
Poland	>41.8 - 90%(Aceijas and Rhodes, 2007)	90%	Intermediate	24 – 67% (HBcAb) 1 – 9% (HBsAg)	
Moldova			High		
Romania	40% - up to 70% in Bucharest(Aceijas and Rhodes, 2007)		Intermediate	12% (HBsAg)	
Russian Federation	68% (Moscow), other sites up to 95%		Intermediate		
Serbia			Intermediate		
Slovakia	>40%(Aceijas and Rhodes, 2007)		Intermediate	6% (HBcAb)	
Slovenia		61.5%	Intermediate	4% (HBcAb)	
The former Yugoslav Republic of Macedonia			Intermediate		
Turkey			Intermediate		

Ukraine	70 – 90% (Cook and Kanaef, 2008) 51.7-62.7%	Intermediate	48% (unclear which marker)(Gore et al., 2007) 11% (HBsAg), 43% (HBcAb)(Sergeyeva et al., 2002)	11% (HBsAg) 62% (HBcAb)(Sergeyeva et al., 2002)

*(Aceijas and Rhodes, 2007) unless otherwise cited
**(EMCDDA, 2009) unless otherwise cited

Central Asia

The prevalence of HCV in IDUs in Central Asia is less well studied, though presumed high. Most studies of HIV positive IDUs in Central Asia have found the prevalence of HCV HIV coinfection to be greater than 80%(Cook and Kanaef, 2008).

Little is known about HBV and HBV HIV coinfection in Eastern Europe

Table 4 - Epidemiology of viral hepatitis and HIV coinfection in Central Asia

Europe – Central Asia					
	HCV IDUs*	HCV HIV IDUs	HBV Population	HBV IDUs	HBV HIV IDUs
Azerbaijan	>50% (Cook and Kanaef, 2008)		High		
Armenia			High		
Kazakhstan			High		
Kyrgyzstan	47%(Kyrgyz National HIV/AIDS Center, 2006)		High		
Tajikistan			High		
Turkmenistan	75%		High	80% HBsAg (Godinho et al., 2004)	
Uzbekistan			High		

*(Aceijas and Rhodes, 2007) unless otherwise cited

South and Eastern Asia, Australasia

The prevalence of Hepatitis C in Asia and Australasia varies between countries. The prevalence of blood borne viruses including hepatitis C across Asia can be explained by unsterile medical injections(Kermode, 2004, Simonsen et al., 1999) contaminated transfusions(Duraisamy et al., 1993, Darmadi et al., 1996, Luksamijarulkul et al., 2002) traditional cultural practices(Darmadi et al., 1996) and more recently, injecting drug use(Aceijas et al., 2004). Iatrogenic transmission still occurs in some countries though injecting drug use is increasingly responsible for transmission(Kao and Chen, 2000). The population prevalence ranges from 1.4% in Australia to 5.6% of the population northwestern Thailand. Hepatitis C is very common among IDUs in Asia and almost universal in those coinfected with HIV(Walsh et al., 2007, Garten et al., 2005). HCV HIV coinfection is a major issue in Asia given there are estimated 735 000 HIV positive IDUs in the region, and possibly up to 1.4 million(Mathers et al., 2008) – virtually all coinfected with HCV.

Hepatitis B is endemic in most of Asia, with some notable exceptions. The prevalence among IDUs is high accordingly. Few studies have examined the prevalence of HBV HIV coinfection in IDUs.

Table 5 - Epidemiology of viral hepatitis and HIV coinfection in the South East Asian region

Asia – South East Asia Region	HCV IDUs*	HCV HIV IDUs	HBV Population	HBV IDUs	HBV HIV IDUs
Bangladesh	25% (national) 66.5% (Azim et al., 2002)		Intermediate		
Bhutan			Intermediate		
Democratic People's Republic of Korea			High		
India	92% (national); 26 – 93% (individual sites)		Intermediate	30% (unclear which marker)(Sweat et al., 2000)	
Indonesia	60 – 98%	10 – 40%	High		
Maldives					
Myanmar			High		
Nepal			Intermediate		
Sri Lanka			Intermediate		
Thailand	90%	5 – 98%(Paungtubtim et al., 2004)	High		
TimorLeste			High		

*(Aceijas and Rhodes, 2007) unless otherwise cited

Table 6 - Epidemiology of viral hepatitis and HIV coinfection in the Western Pacific Region

Asia – Western Pacific Region	HCV IDUs*	HCV HIV IDUs	HBV Population	HBV IDUs	HBV HIV IDUs
Australia			Low	50% of new infections attributable to IDU(NCHECR, 2008)	
Brunei Darussalam			High		
Cambodia			High		
China	85% (Hong Kong) (Lee et al., 2008) 72% (Southern China) (Garten et al., 2004) 61.4% (pooled nationwide prevalence)(Xia et al., 2008)	99%(Zhang et al., 2002) 95%(Garten et al., 2005)	High		
Cook Islands					
Fiji					
Japan	55 – 60%		Intermediate		
Kiribati					

Lao People's Democratic Republic			High		
Malaysia			High		
Marshall Islands					
Micronesia (Federated States of)					
Mongolia			High		
Nauru					
New Zealand			Low		
Niue					
Palau					
Papua New Guinea			High		
Philippines			High		
Republic of Korea			High		
Samoa					
Singapore			Intermediate		
Solomon Islands					
Tonga					
Tuvalu					
Vanuatu					
Viet Nam	10 – 81%	99%(Quan et al., 2004)	High		

*(Aceijas and Rhodes, 2007) unless otherwise cited

Middle East

The prevalence of hepatitis C in the Middle East varies significantly. The country with the highest population prevalence of hepatitis C (globally) is Egypt at 15 – 20%, a consequence of unsterile injections during schistosomiasis programs from the 1960s to 1987(Frank et al., 2000, Shepard et al., 2005) while other countries report a much lower prevalence. Apart from Iran, little data is available regarding viral hepatitis in IDUs.

Middle East has an intermediate level of HBV endemicity while much of Africa has high endemicity of HBV. There are an estimated 50 million chronic carriers in Sub Saharan Africa alone with the population prevalence of HBsAg between 9 – 20%(Kiire, 1996). Unlike Asia, it appears that transmission is perinatal and in early childhood rather than vertical(Hoffmann and Thio, 2007). Studies among IDUs are scarce.

Table 7 - Epiedemiology of viral hepatitis and HIV in the Middle East

MENA- Middle East					
	HCV IDUs*	HCV HIV IDUs	HBV Population	HBV IDUs	HBV HIV IDUs
Afghanistan			Intermediate		
Bahrain			Intermediate		

Iran (Islamic Republic of)	59 – 80% 74%(Alavi and Etemadi, 2007)	87%	Intermediate	50% have evidence of past or present infection. 13% HBsAg (Rahimi-Movaghar et al., 2009).	
Iraq			Intermediate		
Jordan			Intermediate		
Kuwait			Intermediate		
Lebanon	5%		Intermediate		
Oman			Intermediate		
Pakistan			Intermediate		
Qatar			Intermediate		
Saudi Arabia			High		
Syrian Arab Republic	61%(Othman and Monem, 2002)		Intermediate		
United Arab Emirates			Intermediate		
Yemen			Intermediate		

*(Aceijas and Rhodes, 2007) unless otherwise cited

Africa

The population prevalence of hepatitis C prevalence in Africa varies by country but is generally high(Coursaget et al., 1990, Madhava et al., 2002). It is presumed the mechanism of transmission is iatrogenic and coincided with the introduction of HIV across Africa(Gisselquist et al., 2002, Drucker et al., 2001).

The prevalence of HBV is also high across much of Africa.

Little is known about the prevalence of HCV and HBV among IDUs in Africa.

Table 8 - Epidemiology of viral hepatitis and HIV coinfection in North Africa

MENA- North Africa					
	HCV IDUs	HCV HIV IDUs	HBV Population	HBV IDUs	HBV HIV IDUs
Djibouti			High		
Egypt	63%(Tsertsvadze et al., 2000)		Intermediate	62% (HBcAb)(Tsertsvadze et al., 2000)	
Libyan Arab Jamahiriya			Intermediate		
Morocco			Intermediate		
Somalia			High		
Sudan			High		
Tunisia			Intermediate		

Table 9 - Epidemiology of viral hepatitis and HIV in Africa

Africa					
	HCV IDUs	HCV HIV IDUs	HBV Population	HBV IDUs	HBV HIV IDUs
Algeria			High		
Angola			High		
Benin			High		
Botswana			High		
Burkina Faso			High		
Burundi			High		
Cameroon			High		
Cape Verde			High		
Central African Republic			High		
Chad			High		
Comoros			High		
Congo			High		
Côte d'Ivoire			High		
Democratic Republic of the Congo			High		
Equatorial Guinea			High		
Eritrea			High		
Ethiopia			High		
Gabon			High		
Gambia			High		
Ghana			High		
Guinea			High		
GuineaBissau			High		
Kenya	42%(Odek-Ogunde et al., 2004) – was 73% among the 15 women IDUs		High		
Lesotho			High		
Liberia			High		
Madagascar			High		
Malawi			High		
Mali			High		
Mauritania			High		
Mauritius			High		
Mozambique			High		
Namibia			High		
Niger			High		
Nigeria			High		
Rwanda			High		
Sao Tome and Principe			High		
Senegal			High		
Seychelles			High		
Sierra Leone			High		
South Africa			High		
Swaziland			High		
Togo			High		
Uganda			High		

United Republic of Tanzania		High			
Zambia		High			
Zimbabwe		High			

North America

The prevalence of chronic HCV is approximately 1.3% in the USA (Armstrong et al., 2006) and 0.7% in Canada. Over 60% of new infections in Canada are attributable to injecting drug use(PHAC, 2009), a similar proportion in the USA(CDC, 2002b).

The prevalence of HBV in the USA is low and decreasing though remains higher in some immigrant groups and indigenous communities(McQuillan et al., 1999, Franks et al., 1989, Schreeder et al., 1983). Although sexual activity is the most common mode of transmission, around 12% of all cases of HBV in USA occur in individuals with a history of injecting drug use. Similarly in Canada, 34% of cases of acute hepatitis B occur in IDUs(Zhang et al., 2001).

Table 10 - Epidemiology of viral hepatitis and HIV coinfection in North America

Americas - North					
	HCV IDUs	HCV HIV IDUs	HBV Population	HBV IDUs	HBV HIV IDUs
United States of America	65%(1994-6); 35%(1997-9 and 2002-4) (Amon et al., 2008).		Low	22% (unclear which marker)(Garfein et al., 2002) 2 – 11% (HBsAg)(Weinbaum et al., 2008)	7%(Weinbaum et al., 2008)
Canada	46 – 90%(Aceijas and Rhodes, 2007)		Low		

Latin America

The population prevalence of hepatitis C in Latin America varies by country but is generally less than 1%. Most HCV in Latin America is as a consequence of contaminated blood products, though there are areas where IDU is any important risk factor such as the northern states of Mexico and major urban areas.

The prevalence of HCV among IDUs is high in Latin America. It is also elevated in non-injecting cocaine users in Brazil and Argentina. Studies of HCV in HIV positive IDUs have shown very high proportions of coinfection.

Most of Central and South America is considered a region of low HBV endemicity although there are some exceptions. It is estimated that 400 000 new cases of hepatitis B occur in Latin America annually (Torres and Machado, 1994, Dehesa-Violante and Nunez-Nateras, 2007). The prevalence among IDUs is less well known though there are some studies from major Latin American cities illustrated in the table below.

Table 11 - Epidemiology of viral hepatitis and HIV coinfection in Latin America

Americas - Central					
	HCV IDUs*	HCV HIV IDUs	HBV Population	HBV IDUs	HBV HIV IDUs
Belize			Low		
Costa Rica			Low		
El Salvador			Low		
Guatemala			Intermediate		
Honduras			Intermediate		
Mexico			Low		
Nicaragua			Low		
Panama			Low		
Americas - South					
Argentina	35 – 79%	77 – 83%(Weissenbacher et al., 2003)		42% (unclear which marker)(Weissenbacher et al., 2003)	86% of HIV positive have evidence ofHBV (unclear which marker)(Weissenbacher et al., 2003)
Bolivia			Low		
Brazil	40 -70%	3 – 85% (Segurado et al., 2004)	Intermediate	56% (HBcAb) 7% (HBsAg) (Oliveira et al., 1999) 2% (HBsAg)(Caiaffa et al., 2002)	
Chile			Low		
Colombia	2%		Low		
Dominica					
Ecuador			Intermediate		
Guyana			Intermediate		
Paraguay			Low		
Peru			High		
Suriname			Intermediate		
Uruguay	22%		Low		
Venezuela (Bolivarian Republic of)			Intermediate		
Americas – Caribbean					
Antigua and Barbuda					
Bahamas					
Barbados					
Cuba					
Dominican Republic			Intermediate		
Grenada					
Haiti			Intermediate		
Jamaica					
Saint Kitts and Nevis					
Saint Lucia					
Saint Vincent and the Grenadines					

Trinidad and Tobago

*(Aceijas and Rhodes, 2007) unless otherwise cited

Important clinical issues

Hepatitis C

There are 3 key issues which are particularly relevant in the management of hepatitis C which aid to understand the burden of hepatitis C related disease and its treatment among IDUs.

The most important clinical issue from the patient's point of view is a correct diagnosis. Unfortunately HCVAb is still widely used as confirmation of hepatitis C. Acute infection is spontaneously cleared in around 14 – 26%(Lauer and Walker, 2001) although some studies suggest up to 50% will clear(Kamal, 2008). As a consequence, without HCV RNA testing, the diagnosis of chronic hepatitis C cannot be confirmed. Unfortunately this test is more inexpensive than the less accurate HCVAb. There is no relationship between the genotype of hepatitis C infection and the likelihood to clear spontaneously.

The second important issue is the long time lag between initial infection and progression to liver disease from the chronic hepatitis state. Around 5 – 20% of individuals with chronic hepatitis C will develop cirrhosis at 20 – 25 years after initial infection. Excessive alcohol use can strongly influence progression. Those with cirrhosis are 30% likely to develop end stage liver disease after 10 years. The risk of hepatocellular carcinoma in those with cirrhosis is 1 – 2% per year(Strader et al., 2004).

Knowing the genotype is also important from a treatment as well as cost effectiveness point of view. Genotypes 2 and respond well to treatment. In HCV monoinfection, current recommendations are for 24 weeks pegylated interferon and ribavirin combination therapy resulting in an sustained virologic response (SVR) (negative HCV RNA 24 weeks post treatment) of 76 - 84%. Genotype 1 requires 48 weeks of combination therapy with expected SVR of 42-46%(Strader et al., 2004). Regardless of genotype, the treatment of acute hepatitis C is much more effective with an expected SVR of over 90%(Kamal, 2008), though this is somewhat diminished in HCV HIV coinfection.

For HCV HIV coinfection, the important issues for IDUs are (1) that individuals are much less likely to clear HCV spontaneously if they are already living with HIV; (2)HIV coinfection can accelerate HCV related liver disease; (3) a number of antiretroviral medications are associated with hepatitis steatosis (such a some NRTIs) or are hepatotoxic and this is exacerbated by HCV (e.g. nevirapine); and (4) HCV treatment is less effective in the presence of HIV coinfection(Koziel and Peters, 2007). Thus the burden of HCV among HIV coinfection IDUs is higher and options for reducing this burden more limited.

Hepatitis B

Hepatitis B is a DNA virus which infects and replicates within hepatocytes (liver cells) though it causes little or no damage to the cells. Liver damage is caused by the immune response to the virus and so chronic infection results in greater hepatic dysfunction from a chronic immune response. In infancy and early childhood (< 2 years old) acute infection is usually asymptomatic but much more likely to result in chronic infection but at a slower rate of about 2% per year(Kato et al., 2000). HIV infected individuals are less likely to lose DNA, are more likely to experience reactivation of HBV and

may experience occult HBV infection. Occult infection is the absence of HBsAg but with detectable HBV DNA(Mphahlele et al., 2006, Colin et al., 1999).

Evidence from the HAART era has suggested that HBV does not appear to alter the course of HIV, although the risk of hepatoxicity from ARVs is increased 3 – 5 fold(Hoffmann and Thio, 2007). There is some evidence of increased viral resistance in HBV HIV coinfected individuals, which could be a result of the increased likelihood of treatment interruptions necessary from liver disease flares. HIV co-infection influences the course and natural history of HBV infection by impairing the quantity and quality of the innate and adaptive immune response. The rates of spontaneous resolution after acute infection and spontaneous HBeAg and HBsAg seroconversions are decreased, and levels of HBV replication are increased in HIV-infected patients resulting in higher viral loads. There is more rapid progression of liver fibrosis and a higher rate of cirrhosis and decompensation (but not hepatocellular carcinoma). The risk of HBV-associated end-stage liver disease and liver-related mortality may be increased by HIV co-infection(Koziel and Peters, 2007).

Implications of HBV clinical progression for IDUs

There are several issues that are particularly important to IDUs. Firstly, given that adult hepatitis B acquisition rarely results in chronic infection, the prevalence of chronic hepatitis B in IDU populations depends on the population prevalence of hepatitis given that the majority of chronic infections will be secondary to perinatal transmission. Secondly, the prevalence of HIV among IDUs will influence the prevalence of chronic hepatitis B as those living with HIV will more likely develop either adult acquired chronic hepatitis B or reactivation following HIV seroconversion. Finally, the prevalence of immunoprotection to HBV is high among IDUs in most studies given that IDU are more at risk of HBV exposure through sharing injecting equipment or sexual transmission but are likely to clear this adulthood exposure spontaneously(Lopez-Zetina et al., 2001, Torbenson et al., 2004, Walsh et al., 2004). This latter issue means that many IDUs may not need vaccination.

Response options

The public health management of HCV and HBV in IDUs can be divided into prevention initiatives and treatment initiatives.

Prevention

There no available vaccine for hepatitis C and therefore the prevention is limited to reducing transmission risk. An HBV vaccine has been available since 1981. It is cheap, effective and forms the mainstay of the prevention response to HBV.

Transmission routes of HCV and HBV determine the necessary prevention intervention. Apart from in the context of HCV HIV coinfection, the transmission of HCV is limited to blood to blood such as the use of non-sterile injecting equipment and contaminated blood. Sexual transmission can occur in HCV HIV coinfection, but is very limited in HCV monoinfection. For HBV, transmission is efficient via sexual activity as well as blood to blood contact so prevention initiatives need to recognise this. Despite this, it is active immunization which has the greatest efficacy in preventing HBV infection.

Vaccination

HCV

There is no vaccine available for hepatitis C. Development has been complicated by the high mutation rate of the virus during infection and the lack of a robust tissue culture system until recently. Phase 1 and 2 studies are currently being conducted for therapeutic and prophylactic vaccines, though an effective vaccine candidate has yet to emerge.

HBV

The hepatitis B vaccine is safe, effective and relatively cheap. It became commercially available in 1981. It is available in monovalent as well as combination forms with other vaccines. It produces an adequate immune response to protect against infection in close to 100% of children and around 95% of adults lasting at least 10 years, decaying exponentially(Zanetti et al., 2008). Immnosuppressed individuals may require higher doses in order to achieve an immune response. Revaccination results in a response in >95% of individuals, the degree of which is proportional to the magnitude of the initial response(Fitzsimons et al., 2005). Long term protection in immunized infants is unclear though is thought to last at least 12 years if not longer and is highly efficacious in prevention childhood chronic infection(Kao and Chen, 2005). Booster following childhood immunization may be required after 15 – 20 years of age, as result of declining HBsAb concentration despite preservation of the anamnesic response and apparent immunoprotection(Zanetti et al., 2005). The standard schedule for infants and unvaccinated adults is 0,1 and 6 months with infants to HbsAg mother given an additional booster, although rapid or accelerated schedules such as the Barcelona protocol (0, 7, 21 days and 1 year) may confer a similar immune response.

Vaccination is less immunogenic in HIV infected individuals with seroconversion occurring in less than half of recipients of a complete course. Higher CD4 counts, lower viral loads and being on HAART increase the chance of an immune response to vaccination(Koziel and Peters, 2007, Landrum et al., 2009).

Most countries have both targeted and population wide vaccination programs. Target groups are health care workers, haemodialysis patients, blood product repeated recipients, and other risk groups such as injecting drug users, sexual partners of viraemic individuals, prisoners and travellers to endemic areas. Population wide vaccination begins at birth according to country specific schedules and the HbsAg status of the mother. By 2007 163 had incorporated HBV vaccination into their national schedule(Lavanchy, 2008).

Although there has been debate about the immunogenicity of HBV vaccine in IDUs, there appears to be little difference between the rates of protection in IDUs compared with the general population(Baral et al., 2007), meaning that the vaccine works as effectively when administered to IDUs.

Adherence to schedule may be a complicating factor for IDUs with convenience of access being a key determinant (Campbell et al., 2007). Significantly there are opportunities to vaccinate IDUs which may be lost because of poor access or reluctance to opportunistically vaccinate (Kuo et al., 2004). Rapid (0, 7, 21 days and 1 year) and accelerated schedules (0, 1, 2 months) are adequately immunogenic and may boost adherence (Harries et al., 1991, Jilg et al., 1989). Nevertheless, even partial immunisation confers some immunoprotection (Hall, 1993) supporting the case for opportunistic vaccination.

Blood product screening and reducing blood product use.

HCV

Key aspects of preventing the transmission of hepatitis C through blood products include screening and/or testing of blood donors, screening donated blood for HCV RNA and not pooling donated blood. The use of autologous blood in predictable transfusions (such as major elective surgery) and reducing the use of blood products is an important component of this response.

HBV

Similarly to hepatitis C, screening and/or testing of blood donors is paramount addition to the screening of blood and not pooling collected blood where possible.

Sterile needles and syringes

HCV

Sterile, single use needles, syringes and cannulation equipment prevents transmission associated with the reuse of medical equipment (including tattooing). These are universal in the developed world though cost has reduced uptake in the developing world, in particular Asia and Africa. It is estimated there are over 12 billion injections are administered worldwide annually, almost half in developing countries where almost 40% are unsafe. Many are for antibiotics or vitamins that could be administered with equal effect orally. This results in more than 2 million annual HCV infections(Kermode, 2004, Kane et al., 1999, Simonsen et al., 1999).

Injecting drug use typically results in early acquisition of hepatitis C infection (Maher, 2007, Hagan et al., 2007). Sterile injecting equipment (including tourniquets and spoons) is the mainstay of preventing transmission in this group. Ease of access to needles and syringes is paramount, particularly in high risk settings such as street drug markets and closed settings.

A recent study modeling HCV transmission and NSP coverage in London concluded that very high NSP coverage is necessary to reduce HCV seroprevalence among IDUs who are long term injectors – much higher than for HIV prevention. For example the number of sharing episodes per IDU needs to be reduced from current 16 per month to only 1 – 2 per month if the HCV seroprevalence is to be reduced to < 10% in IDUs injecting < 8 years. More modest reductions in sharing frequency are required to reduce the seroprevalence among recent injectors emphasizing the importance of early engagement of individuals who have recently commenced injecting(Vickerman et al., 2007).

HBV

Similar to HCV, HBV is transmitted by reused medical injection equipment and the sharing of injecting equipment by substance users. Attendance by IDUs at NSP programs has been shown to be effective in reducing HBV acquisition compared with non-attendance(Hagan et al., 1995). Single use needles and syringes are very important in reducing transmission however vaccination of key risk groups such as injecting drugs users is equally important.

Behaviour modification and condoms

HCV

Key aspects of behavioural modification are the use of universal precautions for health care workers and engendering the acceptability of not sharing injecting equipment among drug users. Preventing or delaying transition to injecting drug use is crucial to preventing acquisition.

HC V can be sexually transmitted during traumatic sex in the context of HIV coinfection(Browne et al., 2004, Terrault, 2005) thus the correct use of condoms and knowledge of mechanisms to prevent sexual transmission is important among MSM who are IDUs.

HBV

Similar to HCV, engendering the use of universal precautions and single use injection equipment by medical professionals is important. Behavioural interventions resulting in reduced sharing of injecting equipment.

As HBV is efficacy transmitted sexually, barrier protection such as condoms is recommended. This is particularly important for 'high risk' populations such as IDUs, MSM and sex workers. Despite this, vaccination is the most important intervention for at-risk populations.

Post exposure prophylaxis

HCV

Although PEP is available for HBV in the form of HBIG and for HIV in the form of dual to triple antiretroviral therapy taken for 1 month from the event, at this stage post exposure prophylaxis regimens for HCV are not available. There has been only very limited investigation on the efficacy this approach.

HBV

Passive immunoglobulin is administered in the case of acute exposure to HBV where there is no history of vaccination or immune response to vaccination (such as in an immunosuppressed individual). It is typically given in combination with vaccination. Protection is immediate and persists for 3 – 6 months. It is also recommended in the prevention of mother to child transmission at birth

in HBsAg positive mothers if given immediately after birth(CDC, 2005) as it results in a reduction in the risk of vertical transmission compared with vaccine alone by almost 50%(Lee et al., 2006b, Lee et al., 2006a).

PMTCT

HCV

Hepatitis C is not effectively transmitted in the perinatal period with a transmission rate of 2 – 4%, although in HIV co infection this is 2 – 4 fold higher. There are no current interventions which are effective in reducing this transmission. Caesarean section does not reduce transmission(Hadzic, 2001, Jain et al., 2007). It should be noted that ribavirin is contraindicated in pregnancy as it is teratogenic. explain

HBV

Transmission of HBV can occur in-utero but most commonly occurs during delivery or perinatally. Transmission is prevented by administration of HBV vaccine within the first 12 – 24 hours of life, and in HBsAg positive mothers, adjuvant treatment of the neonate with HBiG. Combined active and passive immunization is more effective than administering either one alone, boosting efficacy from around 75% to up to 95%(Tada et al., 1986, Ranger-Rogez and Denis, 2004). Prevention of transmission necessitates diagnosis of chronic hepatitis B infection in the mother, although in areas of high endemicity combined vaccination should be given anyway(WHO, 2001).

Opioid substitution therapy

HCV

OST is the most effective treatment for opioid dependence available. Opioid injectors form a large proportion of all IDUs worldwide. OST is less effective at reducing HCV transmission in opioid dependent IDUs compared to HIV transmission. The impact is greatest among those on long term continuous therapy(Palmateer et al., 2008).

HBV

The effectiveness of OST in preventing HBV transmission in IDUs has not been assessed however given the multiple routes of transmission presumably it would have only partial efficacy.

Treatment

HCV

The efficacy of HCV treatment has improved substantially in recent years; chronic HCV treatment with combination pegylated interferon and ribavirin for between 24 and 48 weeks results in a sustained virological response of between 50 and 80%, depending on genotype(Pawlotsky, 2006, Strader et al., 2004) and acute HCV of over 90%(Jaeckel et al., 2001, Craxi and Licata, 2006, Licata et al., 2003). Recent developments of small molecule treatments in combination with pegylated interferon result in higher rates of SVR – up to 75% in genotype 1, although side effects area significant issue(McHutchison et al., 2009, Zeuzem, 2008). Hepatitis C treatment is generally only available in develop countries. It is currently very expensive at between USD$6000 - $20000 per course. In addition the side effect profile is significant and requires intensive monitoring. The attainment of rapid virological response (RVR) – a negative RNA at 4 weeks after initiation – can mean a reduction in duration of treatment to 12-16 weeks in genotype 2/3 and 24 weeks in

genotype 1 without loss of effectiveness, and thus is cost saving(Poordad et al., 2008). Although treatment of acute hepatitis C is more effective, the main barrier to treating newly acquired HCV is that only a small proportion of HCV infections are identified as being newly acquired due to the asymptomatic nature of the infection and the lack of repeat HCV testing allowing of the at-risk population. Any discussion of Hep c treatment should also include how adherence among substance using populations can be improved and how access can be improved given the high prevalence of mental health and depression issues. The need for coordination with HIV, TB and mental health services in Hep B and C treatment should be emphasised.

There is an increasing body of evidence suggesting that substance dependant injecting drug users living with hepatitis C can achieve favourable antiviral treatment outcomes when engaged in comprehensive substance use treatment and supportive HCV treatment program which also aggressively address mental health issues during treatment(Backmund et al., 2001, Sylvestre et al., 2004b, Sylvestre, 2002, Wong et al., 2004, Grebely et al., 2007). These are also known as integrated models of care.

Treatment of HCV in HIV coinfection

Treatment of HCV HIV is pegylated interferon ribavirin combination therapy for 48 weeks regardless of genotype. Response rates are generally much lower than in HCV monoinfection. Sustained virologic response rates are between 14% and 44% for genotypes 1 or 4 and 44% to 73% for genotypes 2 or 3(Carrat et al., 2004, Laguno et al., 2004, Torriani et al., 2004, Chung et al., 2004). Others have achieved higher SVRs in this population (Laguno et al., 2009).

Novel HCV treatments

New treatments have concentrated on augmenting current treatments, such as the creation of albuferon α by fusing interferon α with human albumin, developing ribavirin analogues and investigation of selective inhibitors of HCV replication – the protease and polymerase inhibitors, as well as immune modulators. Currently the ribavirin analog taribavirin/viramidine and telapevir (VX-950) are the only drugs in phase 3 trials. A number of potential candidates have had their development halted, a consequence of adverse events. Immunomodulators and RNA interference techniques are still in the early phases of development.

Key protease inhibitors which have shown promise are telaprevir and boceprevir. The use of telaprevir in a 12 week triple therapy followed by completion of 24 weeks with pegylated interferon ribavirin achieved an SVR of between 61 and 67%(Hezode et al., 2009, McHutchison et al., 2009). The use of boceprevir for 44 weeks of triple therapy after 4 weeks lead with of pegylated interferon ribavirin combination therapy achieved SVR in 75% of patients(Kwo et al., 2009). Polymerase inhibitors having shown promise are the nucleoside analogs R1626 and R7128. Currently the INFORM-1 trial is investigating the non-peg regimen of the protease inhibitor ITMN191 (also known as R7227) and R1626 in combination.

Thus HCV treatment is moving towards shortened, combination therapy with the increasing use of protease and polymerase inhibitors to augment response. Currently pegylated interferon remains the mainstay of therapy, resulting in continued high costs.

HBV

Hepatitis B treatment is widely available and effective. It should also be noted that many individuals with chronic hepatitis B will eventually lose HBeAg over time (usually several decades). In summary pegylated interferon is the most effective but less well tolerated and most expensive of the treatments available. Despite this oral agents can achieve similar levels of efficacy if given for long enough. Lamivudine is well tolerated, very effective, is the cheapest but subject to resistance. Tenofovir is a promising agent being oral, well tolerated, effective and not subject to resistance.

Treatment outcomes can be biochemical (normalization of ALT), virological (absence of HBV DNA), serological (so called 'e' antigen seroconversion) or histological (improvement or stabilization of METAVIR score). Relapse can occur during the first 12 months post treatment. A sustained treatment response is persistence of outcome variable at 12 months post completion of treatment.

Interferon results in DNA loss in up to 40% of individuals treated and sustained HbeAg loss in around a third (Gluud and Gluud, 2009). Pegylated interferon increases this substantially (Shamliyan et al., 2009, Hui et al., 2005). In HBV treatment, longer duration of therapy results in a greater proportion of individuals achieving a successful outcome so 1 – 2 year of therapy is recommended. Although effective, as discussed above, interferon has a significant side effect profile, is expensive, and in HBV treatment there is not necessary a fixed time end point for treatment which can add to cost.

Lamivudine is a nucleoside reverse transcriptase inhibitor with antiviral effects. Lamivudine is effective in achieving loss of DNA or HBeAg after 1 year of therapy of 32% and 44% respectively with histological improvement in over 50% of individuals (Dienstag et al., 1999). Up to 50% of individuals will lose HBeAg after 5 years of therapy(Dienstag, 2008). The relapse rate of lamivudine is high at 54%(van Nunen et al., 2003). Treatment duration is determined by loss of DNA or HBeAg. Treatment is continued for at least 6 – 12 months after this occurs to prevent relapse. It is an oral medication, is relatively cheap and has fewer side effects compared with interferon. On the downside, long term lamivudine therapy results in resistance mostly commonly from the YMDD mutation. Incidence of YMDD mutants rises from 15–32% in the first year to 67–69% by the fifth year of treatment(Lai et al., 2003).

Adefovir dipivoxil is a nucleotide analogue with antiviral activity. It is effective in achieving loss of HBV DNA in around 13-21% of individuals after 1 year of treatment, HBeAg loss in 12% at 1 year and up to 43% at 3 years. High rates of ALT normalization and histological improvement are also seen. Resistance is rare. It is more expensive that lamvudine though cheaper than pegylated interferon(Dienstag, 2008).

Tenofovir is a HBV polymerase inhibitor which also acts as a nucleotide analogue reverse transcriptase inhibitor in HIV. It is effective in achieving loss of HBV DNA in 80% of individuals and loss of HBsAg in 21% of individuals at 1 year. Around 75% of individuals experience an improvement in histology. It I well tolerated with little if any resistance. It is more expensive that lamvudine though cheaper than pegylated interferon(Dienstag, 2008).

Other newer agents such as entecavir and telbivudine are also available and have similar efficacy to to other oral medication. Entecavir results in undetectable DNA at 1 year of 67%, loss of HBeAg at 1 year of 21% and 39% after 3 years of treatment. It is well tolerated, resistance rare but is more expensive than other oral agents, though cheaper than pegylated interferon. Telbuvudine results in

loss of DNA in 60% at 1 year, loss of HBeAg in 22% at 1 year and 30% at 2 years. It is well tolerated, moderately expensive but unfortunately subject to the development of resistance(Dienstag, 2008).

Little data is available about combination therapy, though adding pegylated interferon to lamivudine does not increase effectiveness (Marcellin et al., 2004, Lau et al., 2005). There may be a role for dual therapy in individuals with severe or progressive liver disease who have developed resistance during mono-therapy(Dienstag, 2008).

Hepatitis B treatment in HBV HIV coinfection

Individuals with HBV HIV coinfection may require pre HIV treatment antiviral therapy for HBV in order to prevent immune reconstitution hepatitis associated with the commencement of antiretroviral therapy. HIV therapy in individuals coinfected with HBV should contain 1 if not 2 anti HBV agents (e.g. lamivudine and tenofovir). HIV HBV coinfection generally requires lifelong therapy for both. Clearance of HBV DNA or loss of HBeAg is much less common in HBV HIV coinfection. In individuals with HBV but where HIV therapy is not yet indicated, HBV should consist of an agent with only HBV activity (e.g. entecavir) in order prevent any chance of HIV resistance. At this stage pegylated interferon does not have a role in HBV HIV co infection(Koziel and Peters, 2007).Prisons

HCV

A high proportion of inmates in the world's prison have hepatitis C. The incidence of transmission in prisons is high(Crofts et al., 1995, Champion et al., 2004, Jurgens et al., 2009). OST, NSP, HCV testing and treatment are options that could potentially reduce transmission together with initiatives to prevent iatrogenic transmission and unprotected male to male sex. For those individuals incarcerated for longer than 6 – 12 months, treatment can be offered. This controlled environment may be conducive in some cases to completing antiviral therapy compared with community based treatment, given the obstacles to accessing and completing treatment in the general community.

HBV

Prison is an effective site for vaccination given the population is easily accessible. A full vaccine schedule can be completed in individuals incarcerated for longer periods.

Sexual activity is common during incarceration. For example, despite laws prohibiting sex between adult residents of correctional systems in most States in the USA, an estimated 2 - 30% of inmates have sex while incarcerated(Weinbaum et al., 2003). Although vaccination against HBV is important, condoms and education should be provided.

Integrated models of care

There are multiple issues feeding into the prevention and treatment of viral hepatitis among IDUs. In particular, high rates of problematic substance use and psychiatric comorbidity necessitate interdisciplinary approaches including collocation of services, codispensing of medication and fluency in more than one medical, mental health or psychosocial discipline for health care providers. Integrated models of care are based on a patient or client based need. Thus at integrated model of care for hepatitis B and C prevention and treatment would include the capacity to assess and treat substance dependence and psychiatric disease as well as providing vaccination, treatment and social welfare services or referral capacity. This is particularly the case for HIV coinfection. This kind of service tailored to the needs of IDUs is not always feasible, nor possible, though the concept of

building multidisciplinary capacity in health professionals working with IDUs should be a key component of any response to viral hepatitis among IDUs.

Cost effectiveness of individual options

Hepatitis C

There are substantial costs to the individual and society associated with hepatitis C. These include the cost of testing (diagnosing) and treatment, the health burden associated with the clinical management of chronic hepatitis C and its complications including hospitalisation, and indirect costs such as the loss of productive capacity from impaired physical and mental health. In general the former (direct costs) are reducing over time and thus become outdated reasonably quickly, while the latter (indirect) are intrinsically difficult to measure.

Prevention

A 2001 paper estimating the cost of HCV and cost effectiveness of its prevention found that prevention of each case of HCV released AUD$6000 - $19000, depending indirect costs were included. This was based on standard interferon as the only antiviral treatment option and that around 30% of individuals with chronic hepatitis C would seek antiviral treatment(Shiell and Law, 2001).

For injecting drug users only needle syringe programs and to a limited extent OST have been shown to be effective for primary prevention(Wright and Tompkins, 2006), thus the discussion of cost effectiveness is limited to these options.

The Australian Government's review of the effectiveness of NSPs in 2003 was an ecological study including modelling examining the impact of NSP in Australia. Although. The main cost saving related to averted treatment costs for HIV and HCV. A lifetime saving in the cost of treatment of HIV and HCV was AUD$3398 million if discounted at 3% annually. The cost savings related to HIV were much higher than HCV which were estimated at AUD$239 million. The primary difference in averted treatment costs between HIV and HCV were the delay in the necessity for HCV treatment and the smaller proportion of individuals progressing to severe illness in HCV compared with HIV. A total gain of 170 279 QALYs were also calculated due to avoiding HCV and HIV(DHAA, 2003). This report is currently being updated and should be available later in 2009. An American study in 2001 estimated the cost per averted hepatitis C infection from NSPs exceeding USD$250000 given the high transmissibility of hepatitis C(Pollack, 2001).

The cost effectiveness of OST to prevent hepatitis C among IDUs has not been assessed. MMT was cost effective in a 2000 study for preventing HIV transmission in substance using populations costing USD$8200 per QALY gained in high-prevalence communities and USD$10,900 per QALY gained in the low-prevalence communities. Leaving aside the benefits of MMT preventing HIV transmission, MMT costed between $14,100 and $15,200 per QALY gained(Zaric et al., 2000). It is likely given the reduced efficacy of MMT in preventing HCV compared with HIV transmission that the cost per QALY gained would be higher in HCV prevention.

Treatment

Current pegylated interferon-ribavirin combination therapy has been demonstrated to be cost effective as an intervention given the direct and indirect costs associated with chronic hepatitis C infection and its complications. The cost per QALY gained is less for genotypes 2 and 3 compared with genotype 1 due to the length and subsequent higher cost of treating genotype one and HCV HIV coinfection. Studies vary widely in their estimate of each QALY gained(Salomon et al., 2003, Siebert et al., 2003, Gerkens et al., 2007, Lidgren et al., 2007, Bernfort et al., 2006, Buti et al., 2003, Sullivan et al., 2004a, Annemans et al., 2004, Sullivan et al., 2004b). In 2007 Health Canada conducted a detailed economic analysis of HCV treatment concluding that PEG IFN, although more expensive than standard IFN, was more effective. The cost per QALY is reduced when disease progression is higher and in younger individuals, thus is most expensive for those with the least progression who are older(Brady et al., 2007). Others have demonstrated that even treating individuals with persistantly normal liver function is cost effective(Hornberger et al., 2006) apart from older (> 65) patients with genotype 1 disease(Grieve et al., 2006). Cost utility analysis has also showed that total lifetime costs are reduced when pegylated interferon ribavirin combination therapy is used appropriately(Yeh et al., 2007), although a high SVR (probably >70%) is needed in genotype 1 for treatment to be cheaper than no treatment if treatment is greater than 24 weeks(Lin et al., 2006).

Specifically for injecting drug users, there are few studies that have looked at the cost effectiveness of treatment. A New Zealand study looked at the cost effectiveness of standard interferon-ribavirin or pegylated interferon-ribavirin treatment for IDUs following stabilisation with methadone maintenance. They found similar cost effectiveness for both regimens which compared favourably to the cost effectiveness of methadone maintenance itself. Cost effectiveness was improved if individuals were stabilised on MMT earlier in their injecting drug using career. (Sheerin et al., 2004). An analysis by the European Monitoring Centre for Drugs and Drug Addiction found hepatitis C treatment among IDUs was cost effective, particularly in younger, genotype 2 and 3 IDUs. This is illustrated in the table below:

Table 12 – Cost effectiveness of Combination therapy with standard interferon versus natural history (no antiviral treatment) for HCV in IDUs(Wong et al., 2004)

	Gain in years of life (years)	Gains in QALYs	Incremental cost-effectiveness (USD per discounted QALY gained)
Age 40	1.0	1.2	8 600
Age 50	0.4	0.6	17 300
Age 60	0.2	0.3	38 800
Male	1.4	1.6	6 500
Female	2.4	2.6	3 800
Not genotype 2 or 3	1.1	1.2	10 700
Genotype 2 or 3	2.4	2.7	2 400
Moderate hepatitis	1.9	2.3	5 100
Compensated cirrhosis	1.2	1.1	7 500
Never relapsed **to injecting during treatment**	2.9	3.4	1 500
Abstinent from injecting drug use for > 5 years at time of antiviral treatment	2.3	2.6	3 100

Studies of cost effectiveness of HCV in non substance using populations are relevant in that injecting drug users tend to be younger, and often have little progression of their fibrosis during their years injecting thus increasing the potential cost effectiveness of treatment as an intervention. The implications for developing countries are substantially different as (1) pegylated interferon ribavirin is often not available and (2) the costs of health care are often much lower (3) appropriate health care is not always available or accessible.

The use of RVR as a mechanism to shorten treatment for hepatitis C was reviewed in a 2007 paper from Japan. In their hypothetical cohort of patients defined as being 45 years old, male, with chronic hepatitis C, and without cirrhosis or HCC treated with either standard or shortened duration (G1 24 weeks, G2/3 12 weeks) of therapy depending on whether RVR was achieved and followed for 30 years. In RVR based protocol vs standard protocol, genotype 1 patients gained 0.33 QALYs but reduced lifetime cost by €5993, while genotype 2 or 3 patients gained 0.02 QALYs but reduced lifetime cost by €2851. Others have suggested that using the RVR protocol to shorten treatment in genotype 1 can result in overall cost savings of 27% in genotype 1 compared with the standard protocol(Wong et al., 2007), just as the current 12 week EVR protocol is cost saving.

The cost effectiveness of PEG IFN/ ribavirin HCV treatment in prisons was modelled in a 2008 paper. The proposed middle aged prison cohort was similar to that of the US prison population. Treatment was with or without prior liver biopsy. It was found that treatment was cost-effective in prisoners of all age ranges and genotypes when liver biopsy was not a prerequisite to starting antiviral therapy. It was not cost effective in genotype 1 patients with no fibrosis. In prisoners between 40 and 49 years of age, treatment saved USD$41,321 and increased QALYs by 0.75. For prisoners between 50 and 59 years of age, treatment decreased costs by USD$33,445 and increased QALYs by 0.69. In prisoners between 60 and 69 years of age, treatment produced $11,637 in savings and a gain of 0.5 in QALYs(Tan et al., 2008).

The high cost of hepatitis C treatment relates to the high cost of interferon. Pegylated interferon is currently on patent. Schering Plough's patent on pegylated interferon α2b expires in 2015, while Roche's patent on pegylated interferon α2a expires in 2017. After this time it would be expected that the price of pegylated interferon would drop substantially as generic production increases.

Hepatitis B

Prevention

At a population level, hepatitis B vaccination has been demonstrated to be cost effective and even cost saving, particularly as the cost of the vaccine itself as reduced in recent years(Da Villa and Sepe, 1999). This is particularly the case in countries of high endemicity and in developing countries with intermediate endemnicity(Aggarwal et al., 2003, Tu et al., 2009).

Disregarding those who have acquired hepatitis B in the perinatal period, the prevalence of exposure to hepatitis B (HBcAb positive) is high. Vaccination should occur early in the course of injecting drug use or even before this to achieve greater cost effectiveness. There is debate in high exposure populations as to whether HBV serostatus should be known before the vaccination to prevent doses being given unnecessarily. It appears the most cost effective mechanism is giving the first dose of vaccination and determining serostatus then completing a rapid or accelerated course to increase

adherence(Hu et al., 2008). Small incentive payments to IDUs to increase completion rates have also demonstrated cost effectiveness (Seal et al., 2003).

There has been little examination of the cost effectiveness of NSPs for hepatitis B prevention. Although it is effective in preventing injection related transmission, given HBV can be sexually transmitted as well NSP only confers partial protection against acquisition. This reduces the potential cost effectiveness of NSP as an intervention to prevent transmission.

Although condoms are effective at preventing non HIV STI transmission, including hepatitis B, little work has been conducted on the cost effectiveness of condoms for preventing HBV infection in drug users.

The cost effectiveness of post exposure prophylaxis for HBV among IDUs has not been examined.

Treatment

The cost effectiveness of hepatitis B treatment has been examined in non-IDU populations. Given that hepatitis B treatment requires adherence to long term therapy, its integration with substance use treatment or other supportive care may boost effectiveness and therefore cost effectiveness. Similar to hepatitis C cost evaluations, it is difficult to compare studies between countries and across time spans due to reductions in costs of medications over time and currency fluctuations. A 2007 review found that for HBeAg positive infection lamivudine was the most cost effective treatment, pegylated interferon was more cost effective than interferon and more cost effective than adefovir monotherapy. Lamivudine monotherapy plus adefovir salvage was more cost effective than the interferons. Pegylated interferon is the most cost effective treatment for HBeAg negative disease(Rajendra and Wong, 2007). A 2009 paper modelled the cost effectiveness of current HBV treatments available (aside from the interferons). The figure below illustrates the cost and QALYs gained in HbeAg positive patients. Of the treatment options was the most cost effective option due to its greater efficacy, despite its higher cost. Lamivudine is also reasonably cost effect compared with other treatments. The cost in HBeAg negative hepatitis B is higher per QALY gained(Buti et al., 2009).

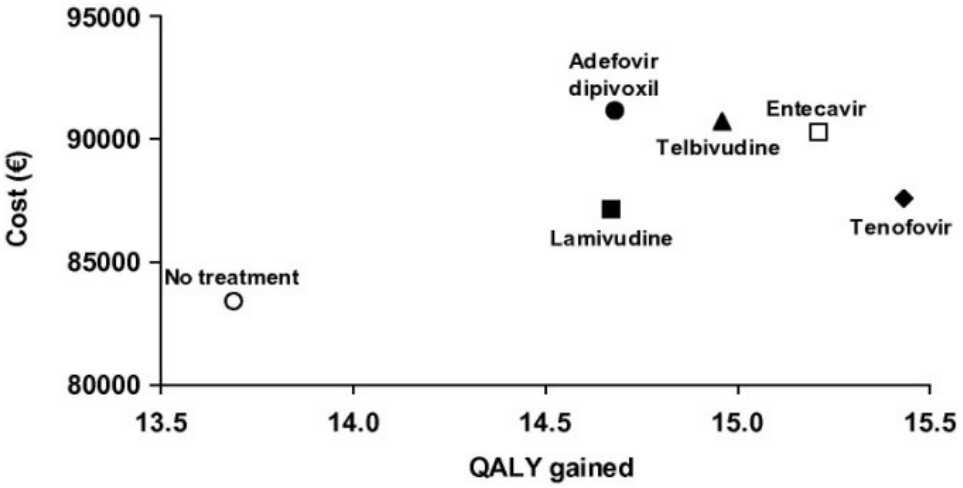

Figure 5 - Lifetime costs (€, 2008 values) and QALY gained in HBeAg-positive patients(Buti et al., 2009).

Feasibility of individual options

There have been few papers discussing the feasibility of implementing the various options discussed above in the peer reviewed literature in developed countries and even less in developing countries. Most studies have looked specifically at the effectiveness as well as the cost and acceptability of the options.

Hepatitis C

Despite the wide variety of options described above and implementation of many of these in various countries, the prevalence of hepatitis C remains high among injecting drug users worldwide. Unlike HIV, there are few effective mechanisms to prevent transmission (Mateu-Gelabert et al., 2007, Maher et al., 2007, Wright and Tompkins, 2006). Nevertheless, when compared with developing/transitional countries, time initial HCV infection in developed countries appears to be lengthening which may indicate some success in prevention(Hagan et al., 2008).

The most acute need in implementing comprehensive treatment and prevention of hepatitis C is the need for technical capacity. Ultimately it is local health services that are responsible for implementing health policy. A 2002 study surveyed 612 local health districts across 42 states in USA and found that 71 – 91% of local health services required technical assistance relating to HCV education, counselling and testing(Fraser et al., 2002). Although there is little data, the level of technical capacity required in developing countries appears significantly higher.

Scaling up implementation and coverage of NSPs is crucial, and is occurring as result of the response to HIV. While many countries have implemented NSPs, coverage levels are still well below the recommended targets for even for HIV. In addition only 11 countries provide NSPs in closed settings – there remain 'moral' and legal hurdles in most jurisdictions to date. Early engagement of IDUs with access to sterile injecting equipment is crucial, thus programs should focus on recruiting new injectors early in their careers.

The availability of OST is increasing worldwide. Recently Asia has embraced OST and programs are now available in most countries in that region. To date OST remains isolated to only a few centres in these countries. OST is less commonly available in closed settings. Unfortunately OST is not effective in non-opioid dependence, thus its use is limited in regions where injecting is predominantly non-opioid such as Latin America.

The sexual transmission of HCV in the context of HIV coinfection and traumatic sexual practices is an area already identified as priority in MSM populations. Behavioural and condom based interventions are possible within MSM IDUs at risk – particularly those coinfected with HIV.

Testing and treatment are key areas where significant progress is and can be made. Widespread HCV testing is still not available, particularly in developing countries. In addition injecting drug users with HIV are not always screened for HCV prior to HIV treatment. When HCV testing does occur, it is often limited to HCV Ab detection rather than HCV RNA, often because of the higher cost. Ideally, the first line test would be HCV RNA in order to accurately diagnose those living with HCV rather than just having had exposure to the virus.

Currently the uptake of hepatitis C treatment is low, particularly among IDUs. It is also virtually entirely limited to the developed world. Integrated treatment models for IDU have been demonstrated in a number of settings, some even being peer based(Norman et al., 2008, Sylvestre and Zweben, 2007, Sylvestre et al., 2004a). Specialised HCV treatment clinics for IDUs are not feasible in many locations. Nevertheless, increasing the capacity of services working with IDU to test and collaborate with specialised treatment services is possible. Prisons should be a key component of this response given the benefits of easy access and a relatively stable environment for the treatment, which can be difficult.

The key components of addressing hepatitis C prevention and treatment among injecting drug users are:

- Preventing transition to injecting from non-injecting drug use - great. That means that any Hep C strategy should focus on drug users rather than IDU
- Comprehensive needle and syringe programs (including access to and distribution of injecting paraphernalia)
- Building capacity and knowledge among services working with IDUs to increase HCV education and counselling service provision, particularly those who are providing HIV treatment and care services
- Addressing sexual transmission among HIV coinfected MSM
- reducing the stigma associated with hepatitis C and service access
- providing pregnant women living with HCV with antenatal counselling
- Increasing the availability of OST, particularly earlier in a drug users career (pre-IDU/non-IDU)
- Incorporating the testing and/or treatment of hepatitis C into services working with IDUs
- Incorporating the testing and/or treatment of hepatitis C into prisons

Hepatitis B

As discussed above, despite HBV being almost completely preventable with adequate vaccination vaccine uptake among IDUs is low in the developed world with little data is available from developing nations. A 2005 review of viral hepatitis vaccination among drug users(Quaglio et al., 2006) suggested a number of factors contributing to this:

- economic and social barriers, such as homelessness, poverty, unemployment, lack of health insurance or lack of public health infrastructure that reduce access to medical care for DUs
- the absence of targeted healthcare programs to provide hepatitis B vaccination for this risk group
- the low number of health workers with the required training and experience to carry out vaccination among DUs. Family practitioners may have a key role, because they often know the patient and their social circumstances. However, they may not have the necessary time (or compensation) to offer vaccination and they frequently see this as a public health task;
- the lack of awareness among DUs about the risk of hepatitis
- many healthcare workers have negative attitudes toward DUs, assuming that these patients are “incurable” and “unmotivated

Prisons are a potential site for contacting IDUs and ensuring a higher rate of vaccine completion. One study in the UK modeled that assuming a current 5% coverage of HBV vaccination in prison, increasing 10% each year to reach 50% coverage over 4 years, would reduce the incidence of HBV in IDUs by almost 80% within 12 years, and the HBV prevalence of exposure (HBsAg and/or HbcAb 3 fold over the same period(Sutton et al., 2006). Indeed universal prison vaccination can result in greater acceptability and uptake in community IDU populations(Hutchinson et al., 2004).

The feasibility of NSPs is discussed above in the hepatitis C section.

Condoms are feasible as an intervention for hepatitis B in IDUs and are widely available as a consequence of HIV prevention programs. The use of condoms to prevent HBV transmission among IDUs should include involvement of partners where possible.

Although there has been substantial work carried out on the effectiveness, feasibility and acceptability of HIV and hepatitis C treatment among IDUs, there is a dearth of literature about the treatment of hepatitis B among IDUs. Given that the vast majority of adult acute onset hepatitis B among IDUs will resolve without chronic sequelae, there is little need for long term antiviral treatment among this population. Rather, the focus should be vaccination and thus prevention as well as facilitating diagnosis and management of acute hepatitis B.

IDUs with chronic hepatitis B almost always have acquired it early in life. The principles of management are therefore similar to that of non-drug using patients. Spontaneous seroconversion will continue to occur throughout the individual's drug using career. The question is therefore when treatment should occur in order to give the best outcome as well as how to minimise the burden of transmissible hepatitis B within injecting drug using populations. The available literature does not currently answer this question. Presumably the principles that apply to effective hepatitis Cand HIV treatment in IDUs also apply to hepatitis B treatment. Specifically that treatment should be accessible, affordable, appropriate, have a peer based component, be associated with other services including substance use treatment and be able to continue unaffected during periods of incarceration.

Specifically regarding the treatment of HBV HIV coinfection among IDUs, an appreciation of the importance of supporting adherence, providing access to substance use treatment such as OST in conjunction with therapy and commencing treatment using a HBV active ARV prior to initiation of HIV treatment should be considered. The latter is used to prevent immune reconstitution hepatitis, particularly in IDUs presenting late in the course of their HIV disease. The feasibility of appropriately managing hepatitis B treatment in HBV HIV coinfected IDUs rests with appropriate testing, technical capacity for treating hepatitis B and adequate preparation of the patient prior to treatment at facilities offering HIV treatment for IDUs.

Current response

Hepatitis C

Global

The global response to hepatitis C has been effective in preventing transmission in the general population in recently years primarily through the screening of blood products and the use of sterile medical equipment. It has been relatively ineffective at preventing transmission in IDUs. Affordable HCV treatment is available, but almost exclusively in developed nations. The proportion of those accessing treatment is low – even in developed countries

Considering prevention in the general population, the availability of testing from 1989 resulted in blood product screening as well as an increase in the use of sterile medical equipment, two important vectors in the hepatitis C epidemic. The screening of blood products for hepatitis C was first introduced in the late 1980's in Australia, Europe and USA, but now is common in many countries. In those countries which have initiated screening, the number of new cases of hepatitis C has dropped dramatically and has shifted the epidemic almost exclusively to IDUs. Unfortunately non sterile medical injections continue to occur in the developing world(Kermode, 2004).

The most important prevention responses for IDU are NSP and OST so discussion in the section will focus on these interventions. The efficacy of NSP and OST is discussed in the response options section.

A report on harm reduction policies and practices worldwide in 2009 found there were 84 countries and territories worldwide that supported harm reduction explicitly in national policy documents (74 countries), and/or through the implementation or tolerance of harm reduction interventions NSP and OST. Seventy seven countries had community based NSP while only 10 had NSP projects in prisons. Sixty five countries had OST while 37 had OST prisons. Only 8 had drug consumption rooms(Cook, 2009). In 2008 it was estimated 950 000 were currently receiving OST(Cook and Kanaef, 2008).

A 2008 review of the global state of harm reduction found the policy response specifically focusing on HCV in IDUs less impressive. Only Australia, Brazil and some Western European countries had policies and harm reduction initiatives specifically focusing on IDU and hepatitis C referral for testing and treatment, although sporadic programs exist in other countries. In Sub-Saharan Africa and much of Asia and Eastern Europe, the response was nascent and governments and civil society were just beginning to form a response. In these areas HCV testing and particularly treatment remained largely unavailable to IDUs. The main treatment barriers identified for IDUs were poor access, cost and exclusion criteria(Cook and Kanaef, 2008). Exclusion criteria includes drug use status as a contraindication.

Regional

Governments' and civil societies response to initiating harm reduction services for IDUs including OST and NSP has been comprehensively reviewed in the Cook *et al.* document of 2008 which is publically available here. The following relates only other aspects of the response to HCV.

Europe continues to lead in progress towards greater access to HCV testing and treatment for IDUs. Most countries in the EU provide access at this stage. Despite this, stigma remains an impediment to access in a number of countries. France, the Netherlands, Sweden and the UK have national strategies for HCV prevention and treatment. Although HCV is subsidised or free in many countries, cost remains a barrier in some(Cook and Kanaef, 2008).

In Eastern Europe and Central Asia HCV testing is available to IDUs in at least 10 countries - Armenia, Bosnia and Herzegovina, Bulgaria, Croatia, the Czech Republic, Georgia, Kosovo, Moldova, Romania and Slovenia. In addition, there is testing, but very limited access, in Estonia, Hungary, Lithuania, Poland, Russia and Slovakia. Low threshold testing is not available for IDUs in Ukraine and Belarus. Hepatitis C treatment is available to a limited extent in the region but exclusionary criteria prevent IDUs from enrolling or require abstinence before treatment. For example in Belarus, Bulgaria, the Czech Republic, Estonia, Hungary, Lithuania, Romania and Slovakia active injecting drug use is a contraindication for HCV treatment. In the Czech Republic, Hungary, Romania, Slovakia and Slovenia, people receiving OST have improved access to HCV treatment though at the discretion of the doctor though abstinence for at least 6 months is still recommended in some of these countries. In 2006 in Bulgaria half of the 300 patients reported to be on treatment were on OST and a similar proportion in the Czech Republic in 2005(Gore et al., 2007). Slovenia and Slovakia offer HCV treatment in prisons. Belarus and Russia there are efforts to enrol HCV HIV coinfected individuals in HCV treatment programs, though in the region only Bulgaria, the Czech Republic, Estonia, Lithuania and Romania have guidelines on the management of HCV HIV coinfection(Cook and Kanaef, 2008, Gore et al., 2007). There is limited reported awareness in the health sector about HCV treatment in the region. Cost is a major prohibitive factor, particularly for people living with HIV. In The main stated barrier to treatment in Eastern Europe are negative attitudes by medical staff to IDUs, cost, a lack of 'slots' for patients in programs and limited geographical reach of treatment services(Gore et al., 2007).

In Asia there is limited information on the availability of hepatitis C related services for IDUs. Blood screening for HCV infection has been initiated in Bangladesh, Bhutan, India, Indonesia, Japan, Republic of Korea, the Maldives, Myanmar, Nepal, Sri Lanka and Thailand. Relative to the response to HIV, the response has been extremely limited(Cook and Kanaef, 2008). Both Australia and New Zealand have hepatitis C strategies. Targeted prevention, testing and treatment for injecting drug users is available. Stigma remains an issue (Hopwood and Treloar, 2007). Treatment is available in prisons in at least 2 states of Australia. Treatment in Australia is covered under the universal Government health care scheme. Despite this, less than 1% of people living with HCV have been treated(Matthews et al., 2005, NCHECR, 2008). The main reasons are a lack of knowledge of the availability of treatment among people living with hepatitis C and health professionals, stigma associated with hepatitis C and the long time lag between initial infection and significant liver disease in hepatitis C reducing the perceived urgency to seek treatment.

There is very limited information available about HCV testing and treatment for IDUs in The Middle East, North Africa and Sub Saharan Africa. It is known that HCV testing for IDUs is available in Iran and Oman and that treatment is also available in Iran. Testing and treatment is available in South Africa. The degree to which IDUs access these services is not known(Cook and Kanaef, 2008).

In 2002 the National Institutes of Health in the USA amended the recommendation that IDU be excluded from HCV treatment thus opening the way for greater access nationwide. There are now an increasing number of settings which provide access to HCV testing and treatment in the community and closed settings (Birkhead et al., 2007, Sylvestre and Zweben, 2007, Klein et al., 2007, Maru et al., 2008). The availability of interventions varies significantly between and within states and localities. Unfortunately the cost of hepatitis C therapy in the US is prohibitive without adequate insurance and only a limited number of IDUs have access via Government, NGO or research programs. In addition there remain substantial barriers towards accessing treatment for IDUs in the mainstream health system(Edlin et al., 2005). In Canada access to testing and treatment is available and increasing, though the number of IDU actually receiving this is low(CAS, 2007).

In Latin America there are no programs seeking to actively engage IDUs in HCV testing and treatment Brazil has a national HCV treatment program, which does provide limited access to IDUs. There are no targeted HCV prevention, treatment or care programs available in the Caribbean.

Hepatitis B

Global

The global response to HBV has concentrated on widespread population based vaccination, improved screening of blood products and prevention of transmission in medical facilities.

Currently transmission of HBV via blood products has been virtually eliminated in developed and many developing nations through screening of donors and blood products. Transmission via medical procedures including injections is rare in developed nations but continues in developing countries. The incidence of HBV transmission to healthcare workers has reduced significantly worldwide since the adoption of HBV vaccination programs for health workers and standard infection control (universal) precautions.

The global expansion of HBV immunization has resulted in a decline in acute cases of hepatitis B, a reduction in the proportion of deaths attributable to cirrhosis of the liver or HCC and falling seroprevalence of HBsAg in vaccinated populations(Namgyal, 2003). In 1992 the World Health Assembly passed resolution 45.17 that called for member states, *"…to integrate cost-effective new vaccines, such as hepatitis B vaccine, into national immunization programmes in countries where it is feasible…"*. The aim was for all member countries to integrate hepatitis B vaccination into their schedules by 1997. The development of Global Alliance for Vaccines and Immunization resulted increased support specifically to less developed member states in order to ensure the 1997 would eventually be met. By 2000 116 countries had policies and by 2007 171 countries had implemented population based HBV vaccination programs. Coverage targets with the 3-dose hepatitis B vaccination is 90% by 2010. In 2006 the global coverage rate of 3rd dose HBV immunisation in infants was 60%.

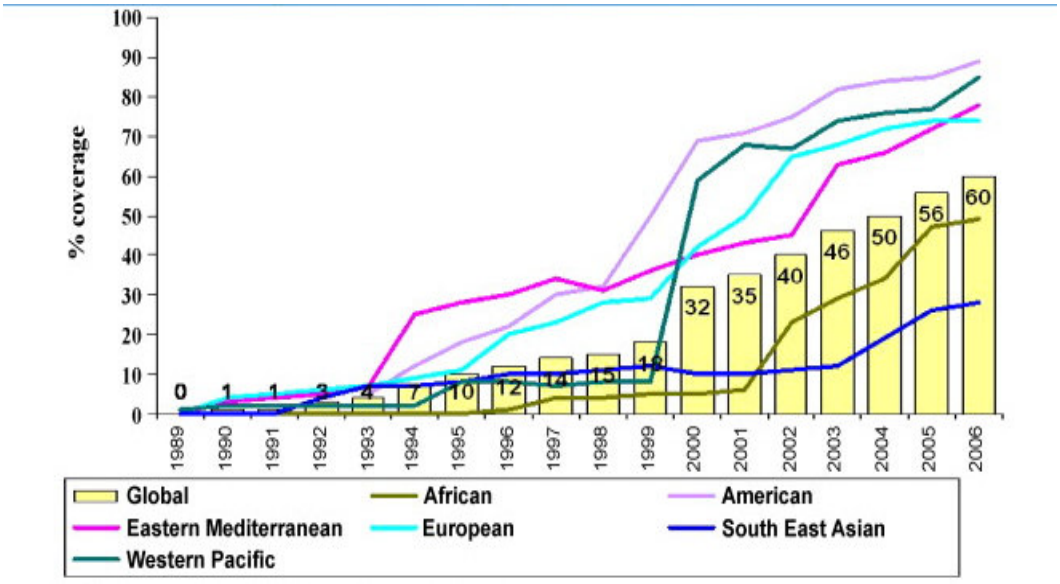

Figure 6 - Global coverage of 3rd HBV dose in infants 1989 - 2006(Zanetti et al., 2008)

Little global policy movement has focused on injecting drug users. The 2004 WHO position statement states that "*Catch-up strategies targeted at older age groups or groups with risk factors for acquiring HBV infection should be considered as a supplement to routine infant vaccination in countries of intermediate or low hepatitis B endemicity."* Further *"In countries of high endemicity* [HBsAg > 8%]*, large-scale routine vaccination of infants rapidly reduces the transmission of HBV. In these circumstances, catch-up vaccination of older children and adults has relatively little impact on chronic disease because most of them have already been infected."*(WHO, 2004). The relevance to IDUs is that vaccination for this group is recommended in low prevalence (mostly developed) nations but not necessarily high prevalence (mostly developing) nations. Many developed countries currently recommend hepatitis B vaccination for IDUs and have implemented programs to reduce sexual and injecting transmission risk, including in prisons and other high risk settings such as safe injection rooms and NSPs.

Regional

The relevance of population wide vaccination programs against HBV is that it is the most effective way to prevent infection in the general community thus influencing the proportion of IDUs who begin their injecting career already having chronic hepatitis B.

From a population perspective, significant gains in reducing the prevalence of HBV have been made in a number of countries worldwide, even in countries which previously had high rates of chronic HBV prevalence. Despite this, there is a significant lag between in implementation of widespread vaccination programs and a reduction in the population prevalence of HBsAg and many countries particularly in Africa, South East Asia and Latin America have not experienced the same success as the cases outlined below.

In the USA from 1990 to 2001, the overall incidence of acute hepatitis B declined by 66%, from 8.1 to 2.8 cases per 100,000. Among children 0–11 years old there was an 89% decline, from 1.1 to 0.12

per 100,000(Fitzsimons et al., 2005). In Italy, following the implementation of a vaccine program, the prevalence of chronic hepatitis B fell from 3.4% to 0.9% between 1985 and 1996(Da Villa, 2000). In Bulgaria infant immunisation commenced in 1991 reduce the incidence of HBV in that age from 22-30/100 000 to 5.6/100 000(Gatcheva et al., 1995). In the Gambia, the prevalence of HBsAg in children decreased from 10 to 0.6% following the introduction of the universal infant vaccination(Viviani et al., 1999, Whittle et al., 1995). In Malaysia following the 1990 introduction of universal infant vaccination, HBsAg reduced from 1.6% to 0.3% between 1997 and 2003 among 7 – 12 year old children(Ng et al., 2005).

Taiwan is probably the best example of the transition from endemicity sporadic cases. Prior to the 1980's around 90% of Taiwan's population had had exposure to HBV with 15-20% of these having chronic hepatitis B the prevalence of HBV in Taiwan was between 15-20%(Sung, 1984, Beasley et al., 1982, Chen et al., 1978). A nationwide hepatitis B vaccination program was launched in July 1984. During the first 2 years only newborns of HBsAg positive mothers were vaccinated. This was extended to all newborns in 1986, catch up for other children and health care workers in 1987, and all primary school children in 1988. The prevalence of HBsAg in children under the age of 5 reduced from 9.3% in 1984 to 2% in 1989. The prevalence of HBsAg among individuals less than 15 years old was 0.7 percent in 1999 compared to 7%among 15–20 years of age. The incidence of hepatocellular carcinoma in children 6–9 years of age declined from 0.52 for those born in 1974–1984 to 0.13 for those born in 1984–1986(Chien et al., 2006).

Most developed countries actively encourage vaccination of IDUs as they are considered a high risk group. Nevertheless only 10 – 25% of drug users in the US and Europe report being offered vaccination against HBV(Quaglio et al., 2006) and studies consistently report vaccination rates of less than 30%(Maher, 2008). There is very limited information available about the prevalence of vaccination among IDUs in the developing world.

In Eastern Europe HBV vaccination is available free to drug users in Slovakia, Belarus, the Czech Republic, Bucharest in Romania, and for a fee in Bulgaria and Estonia. Other countries in this region not provide low threshold HBV vaccination for drug users. Condoms are available in almost all countries in the region and to some degree in prisons(Gore et al., 2007).

Conclusion and recommendations

Response priorities for HCV

Priority for response in reducing the burden of HCV among IDUs differ somewhat from those of the general population. For example in developing countries, reducing indications for the use of blood products is a key component of the population response. This is less relevant to IDUs. In many ways most interventions are available across the world. Unfortunately the availability of these interventions does not necessarily correspond to the epidemiology of the epidemic.

In developed countries:

- A clear focus on reducing transmission in closed settings including:
    - increasing knowledge of hepatitis C among prisoners and staff and education about preventing transmission
    - increasing the coverage of OST
    - Increasing the coverage of NSPs and evaluating effectiveness
    - Increasing the availability of HCV treatment during incarceration
- Focusing on non-IDU and early IDU to reduce transmission
    - interventions to prevent or delay transition to injection
    - early engagement with NSP following initiation to injecting
    - early commencement of OST even in non injecting opioid dependent individuals
- Increasing the availability and reducing barriers to treatment for IDUs including
    - IDU is not a contraindication for treatment
    - increasing capacity of HCV treatment services to work with IDU
    - increasing links between services working with IDUs and HCV treatment services
    - providing integrated models of care and treatment
    - facilitating peer networks to promote HCV treatment
    - Advocating for a reduction in the cost of pegylated interferon to increase treatment uptake
- In HCV HIV coinfection
    - ensuring all IDUs are screened for HCV prior to initiating HIV treatment and are monitored for hepatotoxicity during HIV treatment
    - exploring the feasibility of HCV treatment in HIV coinfected individuals.

In developing/transitional countries:

- Continuing to advocate for NSPs including pharmacy based provision of NS to increase coverage
- Continuing to advocate for increasing coverage of OST
- Continuing to advocate for closed setting harm reduction projects
- Increasing awareness and building capacity in services working with IDUs in HCV knowledge, including prevention, testing and treatment
- Developing projects to delay or prevention transition to injection

- Increasing the availability of HCV testing, particularly in conjunction with HIV treatment programs working with IDUs
- Developing HCV treatment demonstration projects

Response priorities for HBV

Many priorities outlined for hepatitis C also apply to hepatitis B.

The main priorities for preventing and responding to the burden of hepatitis B among injecting drug users are:

- Increasing the prevalence of vaccination for hepatitis B through:
  - opportunistic vaccination
  - increasing the ability of services frequented by IDUs to provide vaccination such as drug treatment services and NSPs
  - building awareness of the importance of vaccination among drug using populations
  - focusing on vaccination early in a drug users career
  - using rapid and accelerated schedules
  - universal vaccination in prisons
  - Increasing awareness of hepatitis B vaccination within developing countries
  - ensuring pregnant IDUs living with hepatitis B, particularly in developing countries, have access to vaccination for their newborn in accordance with their national schedule
  - Ensuring country vaccination programs highlight drug users and IDUs as priority groups for vaccination
- Increasing awareness of the multiple routes of transmission of hepatitis B in IDUs and service provision agencies working with IDUs
- Increasing the use of condoms in IDUs not just for STI and HIV prevention, but also hepatitis B
- Developing models of care for the treatment of HBeAg positive drug users with liver dysfunction in conjunction with substance use services – including within closed settings – and importantly in countries of high endemicity.
- Using lamivudine or tenofovir as first line therapy in IDUs noting 3TC currently is part of standard 1st line ART
- Evaluating the effectiveness and cost effectiveness of hepatitis B treatment for IDUs.
- Ensuring that all IDU commencing on ART are screened for hepatitis B and have it appropriately managed to prevent immune reconstitution hepatitis B.
- Ensuring HBV HIV coinfected individuals on HIV treatment are on a regimen with at least 1 ARV with activity against HBV.

References

ACEIJAS, C. & RHODES, T. 2007. Global estimates of prevalence of HCV infection among injecting drug users. *Int J Drug Policy,* 18**,** 352-8.

ACEIJAS, C., STIMSON, G. V., HICKMAN, M. & RHODES, T. 2004. Global overview of injecting drug use and HIV infection among injecting drug users. *Aids,* 18**,** 2295-303.

AGGARWAL, R., GHOSHAL, U. C. & NAIK, S. R. 2003. Assessment of cost-effectiveness of universal hepatitis B immunization in a low-income country with intermediate endemicity using a Markov model. *J Hepatol,* 38**,** 215-22.

ALAVI, S. M. & ETEMADI, A. 2007. HIV/HBV, HIV/HCV and HIV/HTLV-1 co infection among injecting drug user patients Hospitalized at the infectious disease ward of a training hospital in Iran. *Pakitan Journal of Medical Science,* 23**,** 510-513.

ALTER, M. J. 2006. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol,* 44**,** S6-9.

ALTER, M. J., KRUSZON-MORAN, D., NAINAN, O. V., MCQUILLAN, G. M., GAO, F., MOYER, L. A., KASLOW, R. A. & MARGOLIS, H. S. 1999. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med,* 341**,** 556-62.

AMON, JOSEPH J., GARFEIN, RICHARD S., AHDIEH-GRANT, L., ARMSTRONG, GREGORY L., OUELLET, LAWRENCE J., LATKA, MARY H., VLAHOV, D., STRATHDEE, STEFFANIE A., HUDSON, SHARON M., KERNDT, P., JARLAIS, DON D. & WILLIAMS, IAN T. 2008. Prevalence of Hepatitis C Virus Infection among Injection Drug Users in the United States, 1994–2004. *Clinical Infectious Diseases,* 46**,** 1852-1858.

ANNEMANS, L., WARIE, H., NECHELPUT, M. & PERAUX, B. 2004. A health economic model to assess the long term effects and cost-effectiveness of PEG IFN alpha-2a in hepatitis C virus infected patients. *Acta Gastroenterol Belg,* 67**,** 1-8.

ARMSTRONG, G. L., WASLEY, A., SIMARD, E. P., MCQUILLAN, G. M., KUHNERT, W. L. & ALTER, M. J. 2006. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med,* 144**,** 705-14.

AZIM, T., BOGAERTS, J., YIRRELL, D. L., BANERJEA, A. C., SARKER, M. S., AHMED, G., AMIN, M. M., RAHMAN, A. S. & HUSSAIN, A. M. 2002. Injecting drug users in Bangladesh: prevalence of syphilis, hepatitis, HIV and HIV subtypes. *Aids,* 16**,** 121-3.

BACKMUND, M., MEYER, K., VON ZIELONKA, M. & EICHENLAUB, D. 2001. Treatment of hepatitis C infection in injection drug users. *Hepatology,* 34**,** 188-93.

BARAL, S., SHERMAN, S. G., MILLSON, P. & BEYRER, C. 2007. Vaccine immunogenicity in injecting drug users: a systematic review. *Lancet Infect Dis,* 7**,** 667-74.

BEASLEY, R. P., HWANG, L. Y., LIN, C. C., LEU, M. L., STEVENS, C. E., SZMUNESS, W. & CHEN, K. P. 1982. Incidence of hepatitis B virus infections in preschool children in Taiwan. *J Infect Dis,* 146**,** 198-204.

BERNFORT, L., SENNFALT, K. & REICHARD, O. 2006. Cost-effectiveness of peginterferon alfa-2b in combination with ribavirin as initial treatment for chronic hepatitis C in Sweden. *Scand J Infect Dis,* 38**,** 497-505.

BHAT, R. A., ULRICH, P. P. & VYAS, G. N. 1990. Molecular characterization of a new variant of hepatitis B virus in a persistently infected homosexual man. *Hepatology,* 11**,** 271-6.

BIRKHEAD, G. S., KLEIN, S. J., CANDELAS, A. R., O'CONNELL, D. A., ROTHMAN, J. R., FELDMAN, I. S., TSUI, D. S., COTRONEO, R. A. & FLANIGAN, C. A. 2007. Integrating multiple programme and policy approaches to hepatitis C prevention and care for injection drug users: a comprehensive approach. *Int J Drug Policy,* 18**,** 417-25.

BRADY, B., SIEBERT, U., SROCZYNSKI, G., MURPHY, G., HUSEREAU, D., SHERMAN, M., WONG, W. & MENSINKAI, S. 2007. Pegylated interferon combined with ribavirin for chronic hepatitis C virus infection: an economic evaluation [Technology report no 82]. Ottawa: Canadian Agency for Drugs and Technologies in Health.

BROWNE, R., ASBOE, D., GILLEECE, Y., ATKINS, M., MANDALIA, S., GAZZARD, B. & NELSON, M. 2004. Increased numbers of acute hepatitis C infections in HIV positive homosexual men; is sexual transmission feeding the increase? *Sex Transm Infect,* 80**,** 326-7.

BUTI, M., BROSA, M., CASADO, M. A., RUEDA, M. & ESTEBAN, R. 2009. Modeling the cost-effectiveness of different oral antiviral therapies in patients with chronic hepatitis B. *J Hepatol*.

BUTI, M., MEDINA, M., CASADO, M. A., WONG, J. B., FOSBROOK, L. & ESTEBAN, R. 2003. A cost-effectiveness analysis of peginterferon alfa-2b plus ribavirin for the treatment of naive patients with chronic hepatitis C. *Aliment Pharmacol Ther,* 17**,** 687-94.

CAIAFFA, W. T., PROIETTI, F. A., REIS, A. C., GANDOLFI, D. & DONEDA, D. 2002. Seroprevalences of HIV, HCV, HBV and HTLVI/II among Injecting Drug Users (IDU) from Northeast to South in Brazil - The AjUDE-Brasil II Project. *14th International Conference on AIDS.* Barcelona, Spain.

CAMPBELL, J. V., GARFEIN, R. S., THIEDE, H., HAGAN, H., OUELLET, L. J., GOLUB, E. T., HUDSON, S. M., OMPAD, D. C. & WEINBAUM, C. 2007. Convenience is the key to hepatitis A and B vaccination uptake among young adult injection drug users. *Drug Alcohol Depend,* 91 Suppl 1**,** S64-72.

CARRAT, F., BANI-SADR, F., POL, S., ROSENTHAL, E., LUNEL-FABIANI, F., BENZEKRI, A., MORAND, P., GOUJARD, C., PIALOUX, G., PIROTH, L., SALMON-CERON, D., DEGOTT, C., CACOUB, P. & PERRONNE, C. 2004. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *Jama,* 292**,** 2839-48.

CAS 2007. Responding to the Epidemic: Recommendations for a Canadian Hepatitis C Strategy. Canadian AIDS Society.

CDC 2002a. Viral hepatitis and injecting drug users. *Centers for Diseases Control and Prevention. MMWR Morb Mortal Wkly Rep*.

CDC 2002b. Viral hepatitis and injection drug users. Fact sheet. Atlanta: Centre for Disease Control.

CDC 2005. A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States. *Morbidity and Mortality Weekly Report,* 54**,** 1-23.

CHAMPION, J. K., TAYLOR, A., HUTCHINSON, S., CAMERON, S., MCMENAMIN, J., MITCHELL, A. & GOLDBERG, D. 2004. Incidence of Hepatitis C Virus Infection and Associated Risk Factors among Scottish Prison Inmates: A Cohort Study. *Am. J. Epidemiol.,* 159**,** 514-519.

CHEN, D. S., SUNG, J. L. & LAI, M. Y. 1978. A seroepidemiologic study of hepatitis B virus infection in Taiwan. *Taiwan Yi Xue Hui Za Zhi,* 77**,** 908-18.

CHIEN, Y. C., JAN, C. F., KUO, H. S. & CHEN, C. J. 2006. Nationwide hepatitis B vaccination program in Taiwan: effectiveness in the 20 years after it was launched. *Epidemiol Rev,* 28**,** 126-35.

CHRISTENSEN, P. B., KRARUP, H. B., NIESTERS, H. G., NORDER, H., SCHAFFALITZKY DE MUCKADELL, O. B., JEUNE, B. & GEORGSEN, J. 2001. Outbreak of Hepatitis B among injecting drug users in Denmark. *J Clin Virol,* 22**,** 133-41.

CHU, C. J., KEEFFE, E. B., HAN, S. H., PERRILLO, R. P., MIN, A. D., SOLDEVILA-PICO, C., CAREY, W., BROWN, R. S., JR., LUKETIC, V. A., TERRAULT, N. & LOK, A. S. 2003. Hepatitis B virus genotypes in the United States: results of a nationwide study. *Gastroenterology,* 125**,** 444-51.

CHUNG, R. T., ANDERSEN, J., VOLBERDING, P., ROBBINS, G. K., LIU, T., SHERMAN, K. E., PETERS, M. G., KOZIEL, M. J., BHAN, A. K., ALSTON, B., COLQUHOUN, D., NEVIN, T., HARB, G. & VAN DER HORST, C. 2004. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med,* 351**,** 451-9.

COLIN, J. F., CAZALS-HATEM, D., LORIOT, M. A., MARTINOT-PEIGNOUX, M., PHAM, B. N., AUPERIN, A., DEGOTT, C., BENHAMOU, J. P., ERLINGER, S., VALLA, D. & MARCELLIN, P. 1999. Influence of human immunodeficiency virus infection on chronic hepatitis B in homosexual men. *Hepatology,* 29**,** 1306-10.

COOK, C. 2009. Harm Reduction Policy and Practice Worldwide. London: International Harm Reduction Association March 2009.

COOK, C. & KANAEF, N. 2008. Global state of harm reduction 2008: Mapping the response to drug-related HIV and hepatitis C epidemics. London: International Harm Reduction Association.

COURSAGET, P., BOURDIL, C., KASTALLY, R., YVONNET, B., RAMPANARIVO, Z., CHIRON, J. P., BAO, O., DIOP-MAR, I., PERRIN, J. & NTAREME, F. 1990. Prevalence of hepatitis C virus infection in Africa: anti-HCV antibodies in the general population and in patients suffering from cirrhosis or primary liver cancer. *Res Virol,* 141**,** 449-54.

CRAXI, A. & LICATA, A. 2006. Acute hepatitis C: in search of the optimal approach to cure. *Hepatology,* 43**,** 221-4.

CRISTINA, J. 2005. Genetic diversity and evolution of hepatitis C virus in the Latin American region. *J Clin Virol,* 34 Suppl 2**,** S1-7.

CROFTS, N., STEWART, T., HEARNE, P., PING, X. Y., BRESCHKIN, A. M. & LOCARNINI, S. A. 1995. Spread of bloodborne viruses among Australian prison entrants. *Bmj,* 310**,** 285-288.

CUSTER, B., SULLIVAN, S. D., HAZLET, T. K., ILOEJE, U., VEENSTRA, D. L. & KOWDLEY, K. V. 2004. Global epidemiology of hepatitis B virus. *J Clin Gastroenterol,* 38**,** S158-68.

DA VILLA, G. 2000. Rationale for the infant and adolescent vaccination programmes in Italy. *Vaccine,* 18 Suppl 1**,** S31-4.

DA VILLA, G. & SEPE, A. 1999. Immunization programme against hepatitis B virus infection in Italy: cost-effectiveness. *Vaccine,* 17**,** 1734-8.

DARMADI, S., SOETJIPTO, HANDAJANI, R., LUSIDA, M. I., SOEMARTO, SAKUGAWA, H., ISHIDO, S. & HOTTA, H. 1996. Hepatitis C virus infection-associated markers in sera from blood donors in Surabaya, Indonesia. *Microbiol Immunol,* 40**,** 401-5.

DEHESA-VIOLANTE, M. & NUNEZ-NATERAS, R. 2007. Epidemiology of hepatitis virus B and C. *Arch Med Res,* 38**,** 606-11.

DHAA 2003. Return on investment in needle and syringe programs in Australia. Canberra: Department of Health and Aging.

DIENSTAG, J. L. 2008. Hepatitis B virus infection. *N Engl J Med,* 359**,** 1486-500.

DIENSTAG, J. L., SCHIFF, E. R., WRIGHT, T. L., PERRILLO, R. P., HANN, H. W., GOODMAN, Z., CROWTHER, L., CONDREAY, L. D., WOESSNER, M., RUBIN, M. & BROWN, N. A. 1999. Lamivudine as initial treatment for chronic hepatitis B in the United States. *N Engl J Med,* 341**,** 1256-63.

DRUCKER, E., ALCABES, P. G. & MARX, P. A. 2001. The injection century: massive unsterile injections and the emergence of human pathogens. *The Lancet,* 358**,** 1989-1992.

DURAISAMY, G., ZURIDAH, H. & ARIFFIN, M. Y. 1993. Prevalence of hepatitis C virus antibodies in blood donors in Malaysia. *Med J Malaysia,* 48**,** 313-6.

EDLIN, B. R., KRESINA, T. F., RAYMOND, D. B., CARDEN, M. R., GOUREVITCH, M. N., RICH, J. D., CHEEVER, L. W. & CARGILL, V. A. 2005. Overcoming barriers to prevention, care, and treatment of hepatitis C in illicit drug users. *Clin Infect Dis,* 40 Suppl 5**,** S276-85.

EMCDDA 2003. The state of the drugs problem in the European Union and Norway. Annual report 2003. Lisbon: European Monitoring Centre for Drugs and Drug Addiction.

EMCDDA 2009. Statistical bulletin 2008. Lisbon: European Monitoring Centre for Drugs and Drug Addiction.

EREMIN, V. F., GASICH, E. L., BLASHKEVICH, N. V. & BARISENKO, Z. I. 2004. Hepatitis B, C among HIV infected IDUs in Belarus. *15th International Conference on AIDS.* Bangkok, Thailand.

ESTEBAN, J. I., SAULEDA, S. & QUER, J. 2008. The changing epidemiology of hepatitis C virus infection in Europe. *J Hepatol,* 48**,** 148-62.

FITZSIMONS, D., FRANCOIS, G., HALL, A., MCMAHON, B., MEHEUS, A., ZANETTI, A., DUVAL, B., JILG, W., BOCHER, W. O., LU, S. N., AKARCA, U., LAVANCHY, D., GOLDSTEIN, S., BANATVALA, J. & DAMME, P. V. 2005. Long-term efficacy of hepatitis B vaccine, booster policy, and impact of hepatitis B virus mutants. *Vaccine,* 23**,** 4158-66.

FRANK, C., MOHAMED, M. K., STRICKLAND, G. T., LAVANCHY, D., ARTHUR, R. R., MAGDER, L. S., EL KHOBY, T., ABDEL-WAHAB, Y., ALY OHN, E. S., ANWAR, W. & SALLAM, I. 2000. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet,* 355**,** 887-91.

FRANKS, A., BERG, C., KANE, M., BROWNE, B., SIKES, R., ELSEA, W. & BURTON, A. 1989. Hepatitis B virus infection among children born in the United States to Southeast Asian refugees. *N Engl J Med,* 321**,** 1301-1305.

FRASER, M. R., BUFFINGTON, J., LIPSON, L. & MEIT, M. 2002. Hepatitis C prevention programs: assessment of local health department capacity. *J Public Health Manag Pract,* 8**,** 46-9.

GAMBOTTI, L., BATISSE, D., COLIN-DE-VERDIERE, N., DELAROQUE-ASTAGNEAU, E., DESENCLOS, J. C., DOMINGUEZ, S., DUPONT, C., DUVAL, X., GERVAIS, A., GHOSN, J., LARSEN, C., POL, S., SERPAGGI, J., SIMON, A., VALANTIN, M. A. & VELTER, A. 2005. Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001-2004. *Euro Surveill,* 10**,** 115-7.

GARFEIN, R. S., VALVERDE, R., SWARTZENDRUBER, A., JARLAIS, D. C., KERNDT, P., MORSE, E., OUELLET, L., STRATHDEE, S. A., VLAHOV, D., WILLIAMS, I. T. & MONTERROSO, E. R. 2002. Differences in correlates of HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections among young, street-recruited injection drug users (IDUs) in United States metropolitan areas. *14th International Conference on AIDS.* Barcelona, Spain.

GARTEN, R. J., LAI, S., ZHANG, J., LIU, W., CHEN, J., VLAHOV, D. & YU, X. F. 2004. Rapid transmission of hepatitis C virus among young injecting heroin users in Southern China. *Int J Epidemiol,* 33**,** 182-8.

GARTEN, R. J., ZHANG, J., LAI, S., LIU, W., CHEN, J. & YU, X. F. 2005. Coinfection with HIV and hepatitis C virus among injection drug users in southern China. *Clin Infect Dis,* 41 Suppl 1**,** S18-24.

GATCHEVA, N., VLADIMIROVA, N. & KOURTCHATOVA, A. 1995. Implementing universal vaccination programmes: Bulgaria. *Vaccine,* 13 Suppl 1**,** S82-3.

GERKENS, S., NECHELPUT, M., ANNEMANS, L., PERAUX, B., MOUCHART, M., BEGUIN, C. & HORSMANS, Y. 2007. A health economic model to assess the cost-effectiveness of PEG IFN alpha-2a and ribavirin in patients with mild chronic hepatitis C. *J Viral Hepat,* 14**,** 523-36.

GISSELQUIST, D., ROTHENBERG, R., POTTERAT, J. & DRUCKER, E. 2002. HIV infections in sub-Saharan Africa not explained by sexual or vertical transmission. *Int J STD AIDS,* 13**,** 657-66.

GLUUD, L. L. & GLUUD, C. 2009. Meta-analyses on viral hepatitis. *Infect Dis Clin North Am,* 23**,** 315-30.

GODINHO, J., NOVOTNY, T., TADESSE, H. & VINOKUR, A. 2004. HIV/AIDS and tuberculosis in Central Asia. Washington DC: World bank.

GORE, C., LIKATAVICIUS, G., LAZARUS, J. & SWAN, T. 2007. Hepatitis among injecting drug users in the new EU member states and neighbouring countries: situation, guidelines and recommendations. Vilnius: Central and Eastern European Harm Reduction network.

GREBELY, J., GENOWAY, K., KHARA, M., DUNCAN, F., VILJOEN, M., ELLIOTT, D., RAFFA, J. D., DEVLAMING, S. & CONWAY, B. 2007. Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection. *Int J Drug Policy,* 18**,** 437-43.

GRIEVE, R., ROBERTS, J., WRIGHT, M., SWEETING, M., DEANGELIS, D., ROSENBERG, W., BASSENDINE, M., MAIN, J. & THOMAS, H. 2006. Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. *Gut,* 55**,** 1332-8.

HADZIC, N. 2001. Hepatitis C in pregnancy. *Arch Dis Child Fetal Neonatal Ed,* 84**,** F201-4.

HAGAN, H., DES JARLAIS, D. C., STERN, R., LELUTIU-WEINBERGER, C., SCHEINMANN, R., STRAUSS, S. & FLOM, P. L. 2007. HCV Synthesis Project: Preliminary analyses of HCV prevalence in relation to age and duration of injection. *International Journal of Drug Policy,* 18**,** 341-351.

HAGAN, H., JARLAIS, D. C., FRIEDMAN, S. R., PURCHASE, D. & ALTER, M. J. 1995. Reduced risk of hepatitis B and hepatitis C among injection drug users in the Tacoma syringe exchange program. *Am J Public Health,* 85**,** 1531-7.

HAGAN, H., POUGET, E. R., DES JARLAIS, D. C. & LELUTIU-WEINBERGER, C. 2008. Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place. *Am J Epidemiol,* 168**,** 1099-109.

HAGAN, H., THIEDE, H., WEISS, N. S., HOPKINS, S. G., DUCHIN, J. S. & ALEXANDER, E. R. 2001. Sharing of drug preparation equipment as a risk factor for hepatitis C. *Am J Public Health,* 91**,** 42-6.

HALL, A. J. 1993. Hepatitis B vaccination: protection for how long and against what? *Bmj,* 307**,** 276-7.

HARRIES, A. D., CLARK, M., BEECHING, N. J., LAVELLE, J. & MUTTON, K. J. 1991. Early anti-HBs antibody response to accelerated and to conventional hepatitis B vaccination regimens in healthy persons. *J Infect,* 23**,** 251-4.

HEZODE, C., FORESTIER, N., DUSHEIKO, G., FERENCI, P., POL, S., GOESER, T., BRONOWICKI, J. P., BOURLIERE, M., GHARAKHANIAN, S., BENGTSSON, L., MCNAIR, L., GEORGE, S., KIEFFER, T., KWONG, A., KAUFFMAN, R. S., ALAM, J., PAWLOTSKY, J. M. & ZEUZEM, S. 2009. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *N Engl J Med,* 360**,** 1839-50.

HOFFMANN, C. J. & THIO, C. L. 2007. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. *Lancet Infect Dis,* 7**,** 402-9.

HOPWOOD, M. & TRELOAR, C. 2007. The drugs that dare not speak their name: Injecting and other illicit drug use during treatment for hepatitis C infection. *Int J Drug Policy,* 18**,** 374-80.

HORNBERGER, J., FARCI, P., PRATI, D., ZEUZEM, S., GREEN, J. & PATEL, K. K. 2006. The economics of treating chronic hepatitis C patients with peginterferon alpha-2a (40 kDa) plus ribavirin presenting with persistently normal aminotransferase. *J Viral Hepat,* 13**,** 377-86.

HU, Y., GRAU, L. E., SCOTT, G., SEAL, K. H., MARSHALL, P. A., SINGER, M. & HEIMER, R. 2008. Economic evaluation of delivering hepatitis B vaccine to injection drug users. *Am J Prev Med,* 35**,** 25-32.

HUI, A. Y., CHAN, H. L., CHEUNG, A. Y., COOKSLEY, G. & SUNG, J. J. 2005. Systematic review: treatment of chronic hepatitis B virus infection by pegylated interferon. *Aliment Pharmacol Ther,* 22**,** 519-28.

HUTCHINSON, S. J., WADD, S., TAYLOR, A., BIRD, S. M., MITCHELL, A., MORRISON, D. S., AHMED, S. & GOLDBERG, D. J. 2004. Sudden rise in uptake of hepatitis B vaccination among injecting drug users associated with a universal vaccine programme in prisons. *Vaccine,* 23**,** 210-214.

JAECKEL, E., CORNBERG, M., WEDEMEYER, H., SANTANTONIO, T., MAYER, J., ZANKEL, M., PASTORE, G., DIETRICH, M., TRAUTWEIN, C. & MANNS, M. P. 2001. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med,* 345**,** 1452-7.

JAIN, S., GOHARKHAY, N., SAADE, G., HANKINS, G. D. & ANDERSON, G. D. 2007. Hepatitis C in pregnancy. *Am J Perinatol,* 24**,** 251-6.

JILG, W., SCHMIDT, M. & DEINHARDT, F. 1989. Vaccination against hepatitis B: comparison of three different vaccination schedules. *J Infect Dis,* 160**,** 766-9.

JURGENS, R., BALL, A. & VERSTER, A. 2009. Interventions to reduce HIV transmission related to injecting drug use in prison. *Lancet Infect Dis,* 9**,** 57-66.

KAMAL, S. M. 2008. Acute hepatitis C: a systematic review. *Am J Gastroenterol,* 103**,** 1283-97; quiz 1298.

KANE, A., LLOYD, J., ZAFFRAN, M., SIMONSEN, L. & KANE, M. 1999. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. *Bull World Health Organ,* 77**,** 801-7.

KAO, J. H. & CHEN, D. S. 2000. Transmission of hepatitis C virus in Asia: past and present perspectives. *J Gastroenterol Hepatol,* 15 Suppl**,** E91-6.

KAO, J. H. & CHEN, D. S. 2005. Hepatitis B vaccination: to boost or not to boost? *Lancet,* 366**,** 1337-8.

KATO, Y., NAKAO, K., HAMASAKI, K., KATO, H., NAKATA, K., KUSUMOTO, Y. & EGUCHI, K. 2000. Spontaneous loss of hepatitis B surface antigen in chronic carriers, based on a long-term follow-up study in Goto Islands, Japan. *J Gastroenterol,* 35**,** 201-5.

KERMODE, M. 2004. Unsafe injections in low-income country health settings: need for injection safety promotion to prevent the spread of blood-borne viruses. *Health Promot Int,* 19**,** 95-103.

KIIRE, C. F. 1996. The epidemiology and prophylaxis of hepatitis B in sub-Saharan Africa: a view from tropical and subtropical Africa. *Gut,* 38 Suppl 2**,** S5-12.

KLEIN, S. J., WRIGHT, L. N., BIRKHEAD, G. S., MOJICA, B. A., KLOPF, L. C., KLEIN, L. A., TANNER, E. L., FELDMAN, I. S. & FRALEY, E. J. 2007. Promoting HCV treatment completion for prison inmates: New York State's hepatitis C continuity program. *Public Health Rep,* 122 Suppl 2**,** 83-8.

KOZIEL, M. J. & PETERS, M. G. 2007. Viral hepatitis in HIV infection. *N Engl J Med,* 356**,** 1445-54.

KRAMVIS, A., KEW, M. & FRANCOIS, G. 2005. Hepatitis B virus genotypes. *Vaccine,* 23**,** 2409-23.

KUO, I., SHERMAN, S. G., THOMAS, D. L. & STRATHDEE, S. A. 2004. Hepatitis B virus infection and vaccination among young injection and non-injection drug users: missed opportunities to prevent infection. *Drug Alcohol Depend,* 73**,** 69-78.

KWO, P., LAWITZ, E. J., MCCONE, J., SCHIFF, E. R., VIERLING, J. M., POUND, D., DAVIS, M., GALATI, J. S., GORDON, S. C., RAVENDHRAN, N., ROSSARO, L., ANDERSON, F. H., JACOBSON, I. M., RUBIN, R., KOURY, K., PEDICONE, L., CHAUDHRI, L. & ALBRECHT J. K. Year. HCV SPRINT-1: Final Results SVR 24 NS3 Protease Inhibitor Boceprevir plus PegIFN alpha-2b/Ribavirin HCV 1: Treatment Naïve Patients *In:* European Association for the study of the Liver (EASL), 2009 Copenhagen, April 2009.

KYRGYZ NATIONAL HIV/AIDS CENTER 2006. HIV sentinel surveillance. Bishkek.

LAGUNO, M., CIFUENTES, C., MURILLAS, J., VELOSO, S., LARROUSSE, M., PAYERAS, A., BONET, L., VIDAL, F., MILINKOVIC, A., BASSA, A., VILLALONGA, C., PEREZ, I., TURAL, C., MARTINEZ-REBOLLAR, M., CALVO, M., BLANCO, J. L., MARTINEZ, E., SANCHEZ-TAPIAS, J. M., GATELL, J. M. & MALLOLAS, J. 2009. Randomized trial comparing pegylated interferon alpha-2b versus pegylated interferon alpha-2a, both plus ribavirin, to treat chronic hepatitis C in human immunodeficiency virus patients. *Hepatology,* 49**,** 22-31.

LAGUNO, M., MURILLAS, J., BLANCO, J. L., MARTINEZ, E., MIQUEL, R., SANCHEZ-TAPIAS, J. M., BARGALLO, X., GARCIA-CRIADO, A., DE LAZZARI, E., LARROUSSE, M., LEON, A., LONCA, M., MILINKOVIC, A., GATELL, J. M. & MALLOLAS, J. 2004. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV/HCV co-infected patients. *Aids,* 18**,** F27-36.

LAI, C. L., RATZIU, V., YUEN, M. F. & POYNARD, T. 2003. Viral hepatitis B. *Lancet,* 362**,** 2089-94.

LANDRUM, M. L., HUPPLER HULLSIEK, K., GANESAN, A., WEINTROB, A. C., CRUM-CIANFLONE, N. F., BARTHEL, R. V., PEEL, S. & AGAN, B. K. 2009. Hepatitis B vaccine responses in a large U.S. military cohort of HIV-infected individuals: another benefit of HAART in those with preserved CD4 count. *Vaccine,* 27**,** 4731-8.

LARSEN, C., PIALOUX, G., SALMON, D., ANTONA, D., LE STRAT, Y., PIROTH, L., POL, S., ROSENTHAL, E., NEAU, D., SEMAILLE, C. & DELAROCQUE ASTAGNEAU, E. 2008. Prevalence of hepatitis C and hepatitis B infection in the HIV-infected population of France, 2004. *Euro Surveill,* 13.

LAU, G. K., PIRATVISUTH, T., LUO, K. X., MARCELLIN, P., THONGSAWAT, S., COOKSLEY, G., GANE, E., FRIED, M. W., CHOW, W. C., PAIK, S. W., CHANG, W. Y., BERG, T., FLISIAK, R., MCCLOUD, P. & PLUCK, N. 2005. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med,* 352**,** 2682-95.

LAUER, G. M. & WALKER, B. D. 2001. Hepatitis C virus infection. *N Engl J Med,* 345**,** 41-52.

LAVANCHY, D. 2008. Chronic viral hepatitis as a public health issue in the world. *Best Practice & Research Clinical Gastroenterology,* 22**,** 991-1008.

LEE, C., GONG, Y., BROK, J., BOXALL, E. H. & GLUUD, C. 2006a. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. *Bmj,* 332**,** 328-36.

LEE, C., GONG, Y., BROK, J., BOXALL, E. H. & GLUUD, C. 2006b. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. *Cochrane Database Syst Rev***,** CD004790.

LEE, K. C., LIM, W. W. & LEE, S. S. 2008. High prevalence of HCV in a cohort of injectors on methadone substitution treatment. *J Clin Virol,* 41**,** 297-300.

LICATA, A., DI BONA, D., SCHEPIS, F., SHAHIED, L., CRAXI, A. & CAMMA, C. 2003. When and how to treat acute hepatitis C? *J Hepatol,* 39**,** 1056-62.

LIDGREN, M., HOLLANDER, A., WEILAND, O. & JONSSON, B. 2007. Productivity improvements in hepatitis C treatment: impact on efficacy, cost, cost-effectiveness and quality of life. *Scand J Gastroenterol,* 42**,** 867-77.

LIN, W. A., TARN, Y. H. & TANG, S. L. 2006. Cost-utility analysis of different peg-interferon alpha-2b plus ribavirin treatment strategies as initial therapy for naive Chinese patients with chronic hepatitis C. *Aliment Pharmacol Ther,* 24**,** 1483-93.

LOPEZ-ZETINA, J., KERNDT, P., FORD, W., WOERHLE, T. & WEBER, M. 2001. Prevalence of HIV and hepatitis B and self-reported injection risk behavior during detention among street-recruited injection drug users in Los Angeles County, 1994-1996. *Addiction,* 96**,** 589-95.

LUKSAMIJARULKUL, P., THAMMATA, N. & TILOKLURS, M. 2002. Seroprevalence of hepatitis B, hepatitis C and human immunodeficiency virus among blood donors, Phitsanulok Regional Blood Center, Thailand. *Southeast Asian J Trop Med Public Health,* 33**,** 272-9.

MACALINO, G. E., VLAHOV, D., SANFORD-COLBY, S., PATEL, S., SABIN, K., SALAS, C. & RICH, J. D. 2004. Prevalence and incidence of HIV, hepatitis B virus, and hepatitis C virus infections among males in Rhode Island prisons. *Am J Public Health,* 94**,** 1218-23.

MADHAVA, V., BURGESS, C. & DRUCKER, E. 2002. Epidemiology of chronic hepatitis C virus infection in sub-Saharan Africa. *Lancet Infect Dis,* 2**,** 293-302.

MAHER, J. J. 2007. Alcoholic steatohepatitis: management and prognosis. *Curr Gastroenterol Rep,* 9**,** 39-46.

MAHER, L. 2008. Hepatitis B vaccination and injecting drug use: narrowing the efficacy-effectiveness gap. *Int J Drug Policy,* 19**,** 425-8.

MAHER, L., LI, J., JALALUDIN, B., CHANT, K. G. & KALDOR, J. M. 2007. High hepatitis C incidence in new injecting drug users: a policy failure? *Aust N Z J Public Health,* 31**,** 30-5.

MARCELLIN, P., LAU, G. K., BONINO, F., FARCI, P., HADZIYANNIS, S., JIN, R., LU, Z. M., PIRATVISUTH, T., GERMANIDIS, G., YURDAYDIN, C., DIAGO, M., GUREL, S., LAI, M. Y., BUTTON, P. & PLUCK, N. 2004. Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med,* 351**,** 1206-17.

MARU, D. S., BRUCE, R. D., BASU, S. & ALTICE, F. L. 2008. Clinical outcomes of hepatitis C treatment in a prison setting: feasibility and effectiveness for challenging treatment populations. *Clin Infect Dis,* 47**,** 952-61.

MATEU-GELABERT, P., TRELOAR, C., CALATAYUD, V. A., SANDOVAL, M., ZURIAN, J. C., MAHER, L., RHODES, T. & FRIEDMAN, S. R. 2007. How can hepatitis C be prevented in the long term? *Int J Drug Policy,* 18**,** 338-40.

MATHERS, B. M., DEGENHARDT, L., PHILLIPS, B., WIESSING, L., HICKMAN, M., STRATHDEE, S. A., WODAK, A., PANDA, S., TYNDALL, M., TOUFIK, A. & MATTICK, R. P. 2008. Global epidemiology of injecting drug use and HIV among people who inject drugs: a systematic review. *Lancet,* 372**,** 1733-45.

MATTHEWS, G., KRONBORG, I. J. & DORE, G. J. 2005. Treatment for hepatitis C virus infection among current injection drug users in Australia. *Clin Infect Dis,* 40 Suppl 5**,** S325-9.

MCCAUGHAN, G. W. 2000. Asian perspectives on viral hepatitis: hepatitis C virus infection. *J Gastroenterol Hepatol,* 15 Suppl**,** G90-3.

MCHUTCHISON, J. G., EVERSON, G. T., GORDON, S. C., JACOBSON, I. M., SULKOWSKI, M., KAUFFMAN, R., MCNAIR, L., ALAM, J. & MUIR, A. J. 2009. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *N Engl J Med,* 360**,** 1827-38.

MCQUILLAN, G. M., COLEMAN, P. J., KRUSZON-MORAN, D., MOYER, L. A., LAMBERT, S. B. & MARGOLIS, H. S. 1999. Prevalence of hepatitis B virus infection in the United States: the National Health and Nutrition Examination Surveys, 1976 through 1994. *Am J Public Health,* 89**,** 14-18.

MPHAHLELE, M. J., LUKHWARENI, A., BURNETT, R. J., MOROPENG, L. M. & NGOBENI, J. M. 2006. High risk of occult hepatitis B virus infection in HIV-positive patients from South Africa. *J Clin Virol,* 35**,** 14-20.

NAMGYAL, P. 2003. Impact of hepatitis B immunization, Europe and worldwide. *Journal of Hepatology,* 39**,** 77-82.

NAOUMOV, N. V. 1999. Hepatitis C virus infection in Eastern Europe. *J Hepatol,* 31 Suppl 1**,** 84-7.

NCHECR 2008. HIV/AIDS, viral hepatitis and sexually transmissible infections in Australia Annual Surveillance Report. National Centre in HIV Epidemiology and Clinical Research, The University of New South Wales, Sydney, NSW.

NG, K. P., SAW, T. L., BAKI, A., ROZAINAH, K., PANG, K. W. & RAMANATHAN, M. 2005. Impact of the Expanded Program of Immunization against hepatitis B infection in school children in Malaysia. *Med Microbiol Immunol,* 194**,** 163-8.

NORMAN, J., WALSH, N. M., MUGAVIN, J., STOOVE, M. A., KELSALL, J., AUSTIN, K. & LINTZERIS, N. 2008. The acceptability and feasibility of peer worker support role in community based HCV treatment for injecting drug users. *Harm Reduct J,* 5**,** 8.

ODEK-OGUNDE, M., OKOTH, F. A., LORE, W. & OWITI, F. R. Year. Seroprevalence of HIV, HBC and HCV in injecting drug users in Nairobi, Kenya: World Health Organization drug injecting study phase II findings. . *In:* XV international AIDS conference., 2004 Bangkok.

OLIVEIRA, M. L., BASTOS, F. I., TELLES, P. R., YOSHIDA, C. F., SCHATZMAYR, H. G., PAETZOLD, U., PAULI, G. & SCHREIER, E. 1999. Prevalence and risk factors for HBV, HCV and HDV infections among injecting drug users from Rio de Janeiro, Brazil. *Braz J Med Biol Res,* 32**,** 1107-14.

OTHMAN, B. M. & MONEM, F. S. 2002. Prevalence of hepatitis C virus antibodies among intravenous drug abusers and prostitutes in Damascus, Syria. *Saudi Med J,* 23**,** 393-5.

PALMATEER, N., KIMBER, J., HICKMAN, H., HUTCHINSON, S., RHODES, T. & GOLDBERG, D. 2008. Evidence for the effectiveness of harm reduction interventions in preventing Hepatitis C transmission among injecting drug users: a review of reviews. Report for the Prevention Working Groups of the Advisory Council on the Misuse of Drugs and the Hepatitis C Action Plan for Scotland. Scotland.

PAUNGTUBTIM, W., THAISRI, H., VONGSHEREE, S., SAWANPANYALERT, P., ROJANAWIWAT, A., SRI-NGAM, P., JAISUE, R., CHADBANCHACHAI, C., KONGPROMSOOK, W. & LERWITWORAPONG, J. Year. High incidence and prevalence of hepatitis C virus infection among Bangkok inmates, Thailand. *In:* Proceedings of the XVth International AIDS Conference, 2004 Bangkok.

PAWLOTSKY, J. M. 2006. Therapy of hepatitis C: from empiricism to eradication. *Hepatology,* 43**,** S207-20.

PHAC 2009. Epidemiology of Acute Hepatitis C Infection in Canada: Results from the Enhanced Hepatitis Strain Surveillance System (EHSSS). Ottawa: Centre for Communicable Disease and Infection Control, Public Health Agency of Canada.

POLLACK, H. A. 2001. Cost-effectiveness of Harm Reduction in Preventing Hepatitis C among Injection Drug Users. *Med Decis Making,* 21**,** 357-367.

POORDAD, F., REDDY, K. R. & MARTIN, P. 2008. Rapid virologic response: a new milestone in the management of chronic hepatitis C. *Clin Infect Dis,* 46**,** 78-84.

QUAGLIO, G., LUGOBONI, F., MEZZELANI, P., DES JARLAIS, D. C. & LECHI, A. 2006. Hepatitis vaccination among drug users. *Vaccine,* 24**,** 2702-9.

QUAGLIO, G., LUGOBONI, F., PAJUSCO, B., SARTI, M., TALAMINI, G., LECHI, A., MEZZELANI, P. & DES JARLAIS, D. C. 2003. Factors associated with hepatitis C virus infection in injection and noninjection drug users in Italy. *Clin Infect Dis,* 37**,** 33-40.

QUAN, V. M., GO, V. F., BERGENSTROM, A., GIANG, P. N. V. & NAM, L. V. Year. Prevalence of antibody to hepatitis C virus and associated risks among injection drug users in Northern Vietnam. *In:* Proceedings of the XVth International AIDS Conference, 2004.

RAHIMI-MOVAGHAR, A., RAZAGHI, E. M., SAHIMI-IZADIAN, E. & AMIN-ESMAEILI, M. 2009. HIV, hepatitis C virus, and hepatitis B virus co-infections among injecting drug users in Tehran, Iran. *Int J Infect Dis*.

RAJENDRA, A. & WONG, J. B. 2007. Economics of chronic hepatitis B and hepatitis C. *J Hepatol,* 47**,** 608-17.

RAMIA, S. & EID-FARES, J. 2006. Distribution of hepatitis C virus genotypes in the Middle East. *Int J Infect Dis,* 10**,** 272-7.

RANGER-ROGEZ, S. & DENIS, F. 2004. Hepatitis B mother--to--child transmission. *Expert Rev Anti Infect Ther,* 2**,** 133-45.

SALOMON, J. A., WEINSTEIN, M. C., HAMMITT, J. K. & GOLDIE, S. J. 2003. Cost-effectiveness of treatment for chronic hepatitis C infection in an evolving patient population. *Jama,* 290**,** 228-37.

SCHEINMANN, R., HAGAN, H., LELUTIU-WEINBERGER, C., STERN, R., DES JARLAIS, D. C., FLOM, P. L. & STRAUSS, S. 2007. Non-injection drug use and Hepatitis C Virus: a systematic review. *Drug Alcohol Depend,* 89**,** 1-12.

SCHREEDER, M. T., BENDER, T. R., MCMAHON, B. J., MOSER, M. R., MURPHY, B. L., SHELLER, M. J., HEYWARD, W. L., HALL, D. B. & MAYNARD, J. E. 1983. Prevalence of hepatitis B in selected Alaskan Eskimo villages. *Am J Epidemiol,* 118**,** 543-9.

SEAL, K. H., KRAL, A. H., LORVICK, J., MCNEES, A., GEE, L. & EDLIN, B. R. 2003. A randomized controlled trial of monetary incentives vs. outreach to enhance adherence to the hepatitis B vaccine series among injection drug users. *Drug Alcohol Depend,* 71**,** 127-31.

SEGURADO, A. C., BRAGA, P., ETZEL, A. & CARDOSO, M. R. 2004. Hepatitis C virus coinfection in a cohort of HIV-infected individuals from Santos, Brazil: seroprevalence and associated factors. *AIDS Patient Care STDS,* 18**,** 135-43.

SERGEYEVA, T. A., MAXIMENOK, O. V., KISLYKH, O. M. & GURAL, A. L. 2002. Viral hepatitis B and C at HIV-infected in Ukraine: seroprevalence of markers. *14th International Conference on AIDS.* Barcelona, Spain.

SHAMLIYAN, T. A., MACDONALD, R., SHAUKAT, A., TAYLOR, B. C., YUAN, J. M., JOHNSON, J. R., TACKLIND, J., RUTKS, I., KANE, R. L. & WILT, T. J. 2009. Antiviral therapy for adults with chronic hepatitis B: a systematic review for a National Institutes of Health Consensus Development Conference. *Ann Intern Med,* 150**,** 111-24.

SHAPATAVA, E., NELSON, K. E., TSERTSVADZE, T. & RIO, C. D. 2006. Risk behaviors and HIV, hepatitis B, and hepatitis C seroprevalence among injection drug users in Georgia. *Drug and Alcohol Dependence,* 82**,** S35-S38.

SHEERIN, I. G., GREEN, F. T. & SELLMAN, J. D. 2004. What is the cost-effectiveness of hepatitis C treatment for injecting drug users on methadone maintenance in New Zealand? *Drug and Alcohol Review,* 23**,** 261-272.

SHEPARD, C. W., FINELLI, L. & ALTER, M. J. 2005. Global epidemiology of hepatitis C virus infection. *Lancet Infect Dis,* 5**,** 558-67.

SHEPARD, C. W., SIMARD, E. P., FINELLI, L., FIORE, A. E. & BELL, B. P. 2006. Hepatitis B virus infection: epidemiology and vaccination. *Epidemiol Rev,* 28**,** 112-25.

SHIELL, A. & LAW, M. G. 2001. The cost of hepatitis C and the cost-effectiveness of its prevention. *Health Policy,* 58**,** 121-131.

SIEBERT, U., SROCZYNSKI, G., ROSSOL, S., WASEM, J., RAVENS-SIEBERER, U., KURTH, B. M., MANNS, M. P., MCHUTCHISON, J. G. & WONG, J. B. 2003. Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut,* 52**,** 425-32.

SIMONSEN, L., KANE, A., LLOYD, J., ZAFFRAN, M. & KANE, M. 1999. Unsafe injections in the developing world and transmission of bloodborne pathogens: a review. *Bull World Health Organ,* 77**,** 789-800.

STRADER, D., WRIGHT, T., THOMAS, D. & SEEFF, L. 2004. Diagnosis, management, and treatment of hepatitis C. *Hepatology,* 39**,** 1147-1171.

SULLIVAN, S. D., CRAXI, A., ALBERTI, A., GIULIANI, G., DE CARLI, C., WINTFELD, N., PATEL, K. K. & GREEN, J. 2004a. Cost effectiveness of peginterferon alpha-2a plus ribavirin versus interferon alpha-2b plus ribavirin as initial therapy for treatment-naive chronic hepatitis C. *Pharmacoeconomics,* 22**,** 257-65.

SULLIVAN, S. D., JENSEN, D. M., BERNSTEIN, D. E., HASSANEIN, T. I., FOSTER, G. R., LEE, S. S., CHEINQUER, H., CRAXI, A., COOKSLEY, G., KLASKALA, W., PETTIT, K., PATEL, K. K. & GREEN, J. 2004b. Cost-effectiveness of combination peginterferon alpha-2a and ribavirin compared with interferon alpha-2b and ribavirin in patients with chronic hepatitis C. *Am J Gastroenterol,* 99**,** 1490-6.

SUNG, J. L. 1984. Hepatitis B virus infection and its sequelae in Taiwan. *Gastroenterol Jpn,* 19**,** 363-6.

SUTTON, A. J., GAY, N. J. & EDMUNDS, W. J. 2006. Modelling the impact of prison vaccination on hepatitis B transmission within the injecting drug user population of England and Wales. *Vaccine,* 24**,** 2377-2386.

SWEAT, M., SAMSON, L., SARIN, E., DORABJEE, J., BRAHMBHATT, H. & STRATHDEE, S. 2000. Risk factors for HIV-1, hepatitis B, hepatitis C, and syphilis infection among buprenorphine injectors in New Delhi, India. *13th International Conference on AIDS.* Durban, South Africa.

SYLVESTRE, D., LOFTIS, J., HAUSER, P., GENSER, S., CESARI, H., BOREK, N., KRESINA, T., SEEFF, L. & FRANCIS, H. 2004a. Co-occurring hepatitis C, substance use, and psychiatric illness: Treatment issues and developing integrated models of care. *Journal of Urban Health,* 81**,** 719-734.

SYLVESTRE, D. L. 2002. Treating hepatitis C in methadone maintenance patients: an interim analysis. *Drug Alcohol Depend,* 67**,** 117-23.

SYLVESTRE, D. L., LOFTIS, J. M., HAUSER, P., GENSER, S., CESARI, H., BOREK, N., KRESINA, T. F., SEEFF, L. & FRANCIS, H. 2004b. Co-occurring Hepatitis C, substance use, and psychiatric illness: treatment issues and developing integrated models of care. *J Urban Health,* 81**,** 719-34.

SYLVESTRE, D. L. & ZWEBEN, J. E. 2007. Integrating HCV services for drug users: a model to improve engagement and outcomes. *Int J Drug Policy,* 18**,** 406-10.

TADA, H., YANAGIDA, M., MISHINA, J., SATO, N., AIHARA, S., BABA, K. & MAYUMI, M. 1986. Combined Passive and Active Immunization for Preventing Perinatal Transmission of Hepatitis B Virus Carrier State. *Pediatrics International,* 28**,** 306-311.

TAN, J. A., JOSEPH, T. A. & SAAB, S. 2008. Treating hepatitis C in the prison population is cost-saving. *Hepatology,* 48**,** 1387-95.

TERRAULT, N. A. 2005. Sex and hepatitis C. *Am J Gastroenterol,* 100**,** 825-6.

TORBENSON, M., KANNANGAI, R., ASTEMBORSKI, J., STRATHDEE, S. A., VLAHOV, D. & THOMAS, D. L. 2004. High prevalence of occult hepatitis B in Baltimore injection drug users. *Hepatology,* 39**,** 51-7.

TORRES, J. R. & MACHADO, I. V. 1994. Special aspects of hepatitis B virus and delta virus infection in Latin America. *Infect Dis Clin North Am,* 8**,** 13-27.

TORRIANI, F. J., RODRIGUEZ-TORRES, M., ROCKSTROH, J. K., LISSEN, E., GONZALEZ-GARCIA, J., LAZZARIN, A., CAROSI, G., SASADEUSZ, J., KATLAMA, C., MONTANER, J., SETTE, H., JR., PASSE, S., DE PAMPHILIS, J., DUFF, F., SCHRENK, U. M. & DIETERICH, D. T. 2004. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med,* 351**,** 438-50.

TSERTSVADZE, T., NELSON, K., GVETADZE, R., SHARTAVA, T., GHVABERIDZE, M. & BADRIDZE, N. 2000. HIV and Hepatitis B and C in Georgian injecting drug users. *13th International Conference on AIDS.* Durban, South Africa.

TU, H. A., WOERDENBAG, H. J., KANE, S., RIEWPAIBOON, A., VAN HULST, M. & POSTMA, M. J. 2009. Economic evaluations of hepatitis B vaccination for developing countries. *Expert Rev Vaccines,* 8**,** 907-20.

URBANUS, A. T., VAN DE LAAR, T. J., STOLTE, I. G., SCHINKEL, J., HEIJMAN, T., COUTINHO, R. A. & PRINS, M. 2009. Hepatitis C virus infections among HIV-infected men who have sex with men: an expanding epidemic. *Aids,* 23**,** F1-7.

VAN NUNEN, A. B., HANSEN, B. E., SUH, D. J., LOHR, H. F., CHEMELLO, L., FONTAINE, H., HEATHCOTE, J., SONG, B. C., JANSSEN, H. L., DE MAN, R. A. & SCHALM, S. W. 2003. Durability of HBeAg seroconversion following antiviral therapy for chronic hepatitis B: relation to type of therapy and pretreatment serum hepatitis B virus DNA and alanine aminotransferase. *Gut,* 52**,** 420-4.

VANDELLI, C., RENZO, F., ROMANO, L., TISMINETZKY, S., DE PALMA, M., STROFFOLINI, T., VENTURA, E. & ZANETTI, A. 2004. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. *Am J Gastroenterol,* 99**,** 855-9.

VICKERMAN, P., HICKMAN, M. & JUDD, A. 2007. Modelling the impact on Hepatitis C transmission of reducing syringe sharing: London case study. *Int J Epidemiol,* 36**,** 396-405.

VIVIANI, S., JACK, A., HALL, A. J., MAINE, N., MENDY, M., MONTESANO, R. & WHITTLE, H. C. 1999. Hepatitis B vaccination in infancy in The Gambia: protection against carriage at 9 years of age. *Vaccine,* 17**,** 2946-50.

WALSH, N., HIGGS, P. & CROFTS, N. 2007. Recognition of hepatitis C virus coinfection in HIV-positive injecting drug users in Asia. *J Acquir Immune Defic Syndr,* 45**,** 363-5.

WALSH, N., HIGGS, P. & NGUYEN, O.,

HELLARD, M., 2004. HBV HCV co/superinfection in Vietnamese Australian injecting drug users. 4th Australasian conference on Hepatitis C, 31 August – 2 September 2004; Canberra.

WEINBAUM, C., LYERLA, R. & MARGOLIS, H. S. 2003. Prevention and control of infections with hepatitis viruses in correctional settings. Centers for Disease Control and Prevention. *MMWR Recomm Rep,* 52**,** 1-36; quiz CE1-4.

WEINBAUM, C. M., WILLIAMS, I., MAST, E. E., WANG, S. A., FINELLI, L., WASLEY, A., NEITZEL, S. M. & WARD, J. W. 2008. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep,* 57**,** 1-20.

WEISSENBACHER, M., ROSSI, D., RADULICH, G., SOSA-ESTANI, S., VILA, M., VIVAS, E., AVILA, M. M., CUCHI, P., REY, J. & PERALTA, L. M. 2003. High seroprevalence of bloodborne viruses among street-recruited injection drug users from Buenos Aires, Argentina. *Clin Infect Dis,* 37 Suppl 5**,** S348-52.

WHITTLE, H. C., MAINE, N., PILKINGTON, J., MENDY, M., FORTUIN, M., BUNN, J., ALLISON, L., HOWARD, C. & HALL, A. 1995. Long-term efficacy of continuing hepatitis B vaccination in infancy in two Gambian villages. *Lancet,* 345**,** 1089-92.

WHO 2001. Introduction of hepatitis B vaccine into childhood immunization services: Management guidelines, including information for health workers and parents. Geneva: Department of vaccines and biologicals, World Health Organization.

WHO 2004. Hepatitis B vaccines: World Health Organization position paper. *Weekly epidemiological record,* 28**,** 255-263.

WIESSING, L. & NARDONE, A. 2006. Ongoing HIV and viral hepatitis infections in IDUs across the EU, 2001-2005. *Euro Surveill,* 11**,** E061123 2.

WONG, J., SYLVESTRE, D. & SIEBERT, U. 2004. Cost-effectiveness of treatment of HCV in injecting drug users. *In:* JAGER, J., LIMBURG, W., KRETZSCHMAR, M., POSTMA, M. & WIESSING, L. (eds.) *Hepatitis C and injecting drug use: impact, costs and policy options.* Lisbon: European Monitoring Centre for Drugs and Drug Addiction.

WONG, J. B., ZEUZEM, S., MANNS, M. P., HARVEY, J. & ALBRECHT, J. K. 2007. Clinical and economic implications of a 4-week viral negative response to peginterferon alfa-2b plus ribavirin for chronic hepatitis C and genotype 1 with low viral load. *56th Annual Meeting of the American-Association-for-the-Study-of-Liver-Diseases, San Francisco, CA, USA; November 11 -15, 2005.*

WRIGHT, N. M. & TOMPKINS, C. N. 2006. A review of the evidence for the effectiveness of primary prevention interventions for hepatitis C among injecting drug users. *Harm Reduct J,* 3**,** 27.

XIA, X., LUO, J., BAI, J. & YU, R. 2008. Epidemiology of hepatitis C virus infection among injection drug users in China: systematic review and meta-analysis. *Public Health,* 122**,** 990-1003.

YEH, W. S., ARMSTRONG, E. P., SKREPNEK, G. H. & MALONE, D. C. 2007. Peginterferon alfa-2a versus peginterferon alfa-2b as initial treatment of hepatitis C virus infection: a cost-utility analysis from the perspective of the Veterans Affairs Health Care System. *Pharmacotherapy,* 27**,** 813-24.

ZANETTI, A. R., MARIANO, A., ROMANO, L., D'AMELIO, R., CHIRONNA, M., COPPOLA, R. C., CUCCIA, M., MANGIONE, R., MARRONE, F., NEGRONE, F. S., PARLATO, A., ZAMPARO, E., ZOTTI, C., STROFFOLINI, T. & MELE, A. 2005. Long-term immunogenicity of hepatitis B vaccination and policy for booster: an Italian multicentre study. *Lancet,* 366**,** 1379-84.

ZANETTI, A. R., VAN DAMME, P. & SHOUVAL, D. 2008. The global impact of vaccination against hepatitis B: a historical overview. *Vaccine,* 26**,** 6266-73.

ZARIC, G. S., BARNETT, P. G. & BRANDEAU, M. L. 2000. HIV transmission and the cost-effectiveness of methadone maintenance. *Am J Public Health,* 90**,** 1100-11.

ZEUZEM, S. 2008. Telaprevir, peginterferon alfa-2a, and ribavirin for 28 days in chronic hepatitis C patients. *J Hepatol,* 49**,** 157-9.

ZHANG, C., YANG, R., XIA, X., QIN, S., DAI, J., ZHANG, Z., PENG, Z., WEI, T., LIU, H., PU, D., LUO, J., TAKEBE, Y. & BEN, K. 2002. High prevalence of HIV-1 and hepatitis C virus coinfection among injection drug users in the southeastern region of Yunnan, China. *J Acquir Immune Defic Syndr,* 29**,** 191-6.

ZHANG, J., ZOU, S. & GIULIVI, A. 2001. Viral Hepatitis and Emerging Bloodborne Pathogens in Canada: Hepatitis B in Canada. Canadian Communicable Disease Report. Ottawa: Public Health Agency of Canada.