Management of HIV and hepatitis C virus infections in resource-limited settings

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Purpose of review

To provide an update on the epidemiology and management of HIV and hepatitis C virus (HCV) in resource-limited settings (RLSs).

Recent findings

The global prevalence of HIV is 33.3 million people of whom 22.5 million live in sub-Saharan Africa. Hepatitis C affects 170 million people globally with majority of the infected persons living in sub-Saharan Africa and other RLSs. Transmission of these viruses varies greatly even within the RLSs. In the RLSs in Europe, Asia and Central/South America, most transmissions occur through injection drug use, whereas in Africa use of needles for medical treatment and blood transfusion may be the main modes of transmission. However, generally there is a rise in injection drug use even in RLSs.

Summary

Hepatitis C and HIV are common infections and are more prevalent in RLSs, but there are regional differences in transmission even in RLSs. Treatment is difficult in some of the RLSs and prevention by screening donor blood as well and use of sterile instruments in treatment of patients will be important in curbing transmission in some of these settings.

Keywords

epidemiology, hepatitis C virus, HIV, resource-limited setting, treatment

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Introduction

This overview gives an update on the management of HIV and hepatitis C virus (HCV) in resource-limited settings (RLSs), giving the epidemiological aspects based on research findings, especially those published over the last 2 years on transmission and treatment. This review describes studies that have reported HCV and HIV and those studies that were conducted predominantly in an HIV-infected population. This article also reviews the natural history of HIV and HCV infections with a focus on the RLSs and discusses prevention strategies. Described in this review are studies that took place in low and middle income countries such as sub-Saharan Africa, Latin America, the Caribbean, east, south and south-east Asia, some countries in Europe and central Asia as well as north Africa and the Middle East.

Epidemiology of hepatitis C virus and HIV

Worldwide, HCV is one of the leading causes of chronic liver disease, including cirrhosis and hepatocellular carcinoma (HCC); worldwide, more than 170 million persons are infected with HCV [1]. The African continent bears one of the highest burdens of infection in RLSs, although the prevalence varies considerably by country from 1 to 2% in Eastern Africa to greater than 10% in Egypt [2••,3]. In comparison, HIV is also most prevalent in RLSs with highest prevalence in sub-Saharan Africa, where up to 22.5 million of the estimated 33.3 million global HIV-infected patients reside [4••]. Worldwide, an estimated one-third of all HIV-infected patients are also infected with HCV. The rates of coinfection vary with modes of HIV acquisition. In areas where HIV is acquired mainly through injection drug use, coinfection rate may be seen in up to 90% of cases [5••].

Both HIV and HCV have similar modes of transmission. However, there are differences in the ways that each virus is usually transmitted in the RLSs and in the resource-rich countries of the world. Table 1 shows the distribution of these virus infections in some RLSs.

In Europe and China (Table 1a), prevalence rates of HCV and HCV/HIV coinfections described in studies conducted among injection drug users show prevalence rates of more than 60% [7,8,14] for HCV and lower rates of 8.7% among commercial sex workers [11•]. In China, a national survey of HIV-infected drug users revealed that 97% had HIV/HCV coinfection [10••]. A systematic

review and meta-analysis of hepatitis B/C and HIV in sub-Saharan Africa demonstrated a wide variation in rates of coinfection, with HCV/HIV coinfections rates under 5% registered in most of the countries [24].

As is evident in Table 1b, in Africa the reported studies are mainly conducted among HIV-infected patients and HCV prevalence is generally lower than 3%, except among prisoners in Nigeria where a prevalence of HCV of up to 12.3% was reported. In that study, the HIV prevalence was up to 18%. A Cameroonian study among HIV patients also showed a coinfection rate of up to 12.4% [15–23]. In HIV-infected men who have sex with other men, the HCV prevalence is typically under 10% [5••]. There are also differences in the distribution of HIV and HCV in RLSs. In Egypt, where prevalence rate of HCV is very high, HIV prevalence is quite low (<0.1%). In comprison, in countries like Botswana with HIV prevalence rates of 24.8%, HCV is uncommon [4••,25]. This trend is also seen in some other places. In Croatia, HIV prevalence is low even among injection drug users, but HCV prevalence is quite high dependent upon the region of the country [26]. This observed difference is because of the differences in transmission patterns of HCV and HIV.

Although intravenous drug use is generally on the rise, a meta-analysis of global injection drug use found limited data from many countries in Africa, Middle East and Latin America [27]. In most of these regions, HIV is spread mainly by heterosexual intercourse. In areas such as Iran, China and Vietnam, intravenous drug use represents the major route of transmission of HCV infection in the HIV-infected populations [28–31].

HCV is not efficiently transmitted sexually, although there remains the possibility that HIV may potentiate HCV sexual transmission, as it does with perinatal HCV transmission. Sexual transmission has been reported in the West among men who have sex with men [32], but such a phenomenon has not yet been reported in RLSs. Perinatal transmission of HCV from HIV/HCV coinfected mothers is increased as compared with that which occurs in HCV monoinfection [33]. In Egypt, the risk of infection has also been shown to be associated with infection among family members, although this was reported to be of limited importance [34].

In some of the RLSs, the most likely route of HCV transmission is through blood transfusion and use of infected sharp unsterile objects including re-use of needles used in the treatment of various medical conditions. In fact, some other reports from Africa seem to trace the origin of HCV and HIV to parenteral treatment of tropical diseases including malaria and trypanosomiasis [35••,36]. The transmission of HCV genotype 4 in Egypt is also traced to parenteral treatment of schistosomiasis [37].

Key points

- Injection drug use is generally on the rise in the resource-limited settings (RLSs).
- Introduction of qualitative nucleic acid testing in blood banks in RLSs will reduce the transmission of hepatitis C virus (HCV).
- In RLSs, where HCV treatment is not affordable, effective and earlier ART may be the most effective way of limiting liver fibrosis.
- More studies are required on interactions between HCV and HIV in RLSs.

Many countries have implemented testing for HCV, HIV, HBV and syphilis in their national blood transfusion services. In a study carried out in the Democratic Republic of Congo before implementation of testing for HCV, 10 of 127 multiply transfused sickle cell disease patients had been infected with HCV through blood transfusion [38]. Some countries have not yet implemented this donor blood testing service [39] and high additional costs for testing for HCV in such settings could be the explanation for failure to implement this strategy.

Other factors in RLSs that might not have been studied in detail include tattooing, and various forms of scarifications (both therapeutic and cosmetic) that tend to be a common practice in some communities in sub-Saharan Africa.

Diagnostic challenges for hepatitis C virus in sub-Saharan Africa

Most sub-Saharan African countries utilize rapid test kits for the detection of HCV antibodies [19,21,22]. This testing method has been demonstrated to show high rates of false-positive results [40–44]. Similar testing methods have been employed in some blood banks with sensitivities lower than enzyme-linked assays (EIAs) [45], leading to the possibility of continued viral transmission by blood transfusion. Because EIA has also shown false-positive reactions in some of these settings [41], the use of qualitative nucleic acid testing would be the most appropriate in the blood bank settings.

Implications for these false reactions are many and lead to escalated prevalence rates of infection in sub-Saharan Africa. In individual patients the positive test will cause anxiety, especially in those countries where treatment of HCV is complicated by high costs of confirming infection using nucleic acid testing, genotyping and treatment. Most national blood transfusion services utilize similar rapid tests or EIA for screening donor blood. This

Table 1 Prevalence of hepatitis C virus, hepatitis C virus/HIV in resource-limited settings in Europe, China and Africa

	Country	Author	HCV infection (%)	HIV infection (%)	HCV/HIV coinfection (%)	Population studied	Design
(a) Region							
Europe	Croatia	Cavlek *et al.* [6]	51.3			IDU	CS
	Russia	Gyarmathy *et al.* [7]	96	44		IDU	CS
	Slovenia	Platt *et al.* [8]	63.4	8.1		IDU	CS
Asia	China	Seme *et al.* [9]			10.7	HIV patients	CS
		Shang *et al.* [10••]			97	HIV IDU	CS (National survey)
		Yang *et al.* [11•]	8.7	1.5		Commercial sex male clients	CS
		Yan *et al.* [12]			41.83	HIV patients	CS
		Zhou *et al.* [13]			9.6	HIV children	CS
		Bao and Liu [14]	66.97 (IDUs), 18.3 (non-IDUs	12.55 (IDUs), 1.05 (non-IDUs)		Drug users	Systemic review
(b) Region							
Africa	Cameroon	Laurent *et al.* [15]			12.4	HIV infected	CS
	Gambia	Mboto *et al.* [16]	2.1	6.7	0.6	Referral to HIV testing	CS
		Mboto *et al.* [17]	1.6	6.7		Referral for HIV testing	CS
		Jobarteh *et al.* [18]			0.9	HIV patients	CS
	Nigeria	Onakewhor and Okonofua [19]			3.3	HIV infected	CS
		Akinbami *et al.* [20]			14.7	HIV infected	CS
		Balogun *et al.* [21]	5	3		Pregnant mothers	CS
		Duru *et al.* [22]	12.3	18		Prisoners	CS
		Adoga *et al.* [23]			2.3	HIV infected	CS

The data included here are from studies that described HIV and HCV coinfection or were conducted only in the HIV population. Only studies in 2009–2011 are included. CS, cross-sectional study; HCV, hepatitis C virus.

practice leads to wastage in such areas where donor blood is already scarce.

Natural history of hepatitis C virus in HIV infection

The clinically asymptomatic nature of HCV infection from the beginning of infection makes natural history studies difficult. The precise time of acquisition of infection is not usually known with certainty [46]. In RLSs, diagnosis is commonly made when patients present with complications of infection such as cirrhosis and HCC.

Acute infection with HCV in patients who are infected with HIV does occur and is being reported with increasing frequency [32]. Following acute infection, progression to chronicity occurs more commonly among HIV-infected patients ranging from 70–85% in HCV monoinfected patients to 90% among those with HIV coinfection especially in the setting of advanced immune suppression [5••,47].

A recent-meta analysis on natural history of HCV infection has shown progression of liver disease to cirrhosis among patients who acquired infection through injection drug use to be 8.1 per 100 person-years. The risk of progression was higher among the men and those taking alcohol [48].

Effect of HIV/hepatitis C virus coinfection on liver disease

Controversy still exists on the effect of HCV on HIV disease progression. However, infection with HIV has obvious effects on the progression of liver disease caused by HCV infection. The immune suppression induced by HIV increases HCV virus loads, and thus leads to more rapid progression of liver disease and development of cirrhosis and HCC [49].

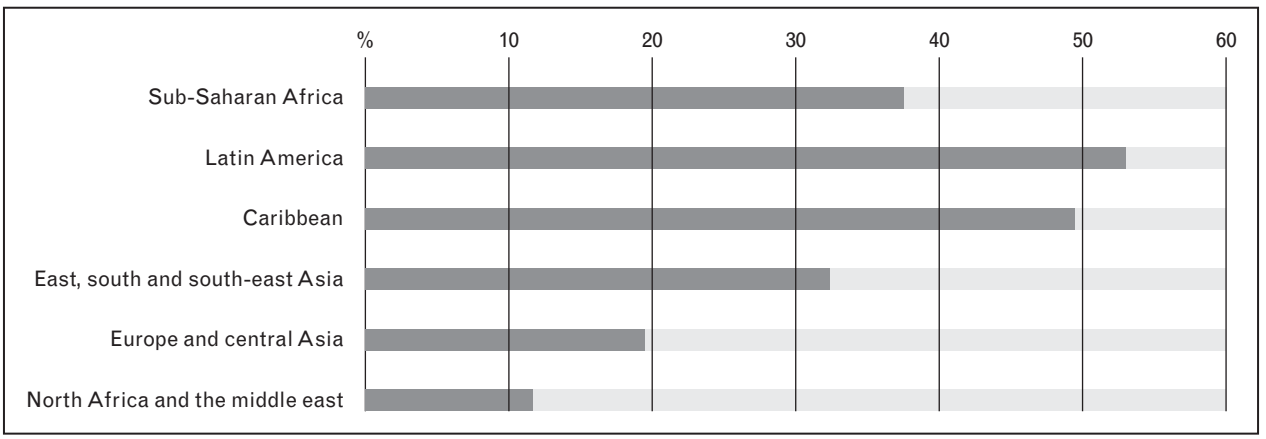
An increase in the development of cirrhosis and HCC among the HCV and HIV coinfected patients has been demonstrated in resource-rich countries [48]. Even among patients with compensated cirrhosis, decompensation may occur more rapidly especially at lower CD4 cell count of or less 300 cells/μl and lack of treatment for HCV [50]. In countries with high HIV prevalence, most patients present with advance HIV and low CD4 cell count. Until recently in most sub-Saharan African countries, treatment was only initiated at a CD4 cell count less than 200 cells/μl. In most of these cases, information on HCV status of the patients is not available. However, the frequency of HCC is high in Asia and Africa. Apart from HCV, this high frequency could be explained by other factors such as viral hepatitis B, alcohol consumption and aflatoxin which are highly prevalent in some of the RLSs [51]. In a Puerto Rican study of Latinos, the median cumulative risk for cirrhosis was higher among patients who had HIV/HCV coinfection compared with HCV monoinfection [52]. There is a need for systematic studies on interactions of HIV and these factors in RLSs.

Highly active antiretroviral therapy and HCV infection

By 2009, the WHO reported highly active antiretroviral therapy (HAART) coverage in RLSs, varying from just over 10% in north Africa and Middle East to over 50% in Latin America as shown in Fig. 1 [4••].

The effect of HAART on liver disease is double edged. Studies have demonstrated protective effects of HAART in fibrosis progression in patients with HCV infection

Figure 1 Access to highly active antiretroviral therapy by 2010



Latin America had more than 50% highly active antiretroviral therapy (HAART) coverage. Data from the UNAIDS Report on the Global AIDS Epidemic, 2010 [4••].

[53,54]. Although the short-term and mid-term effects of HAART are beneficial, the balance on the liver lies in between this positive impact and hepatotoxicity. Drug-induced liver injury (DILI) following HAART is more common in HIV/HCV coinfection and may be associated with an increased risk for liver disease-related morbidity and mortality. The risk for DILI in the coinfected patients is particularly high among patients with advanced liver disease [55,56]. Eradication of HCV infection may decrease the likelihood of antiretroviral-associated DILI.

The goal of therapy for HCV in HIV infection is similar to the treatment of HCV monoinfection. Success of treatment is defined as sustained virologic response (SVR), which is undetectable HCV viral load 6 months after completion of therapy. In the ARICOT study, which evaluated baseline factors prognostic of sustained virological response in patients with HIV/HCV coinfection, the use of an HIV protease inhibitor or non-nucleoside reverse transcriptase inhibitor (NNRTI) for HIV treatment was among the factors that were associated with a high SVR ($P = 0.034$) [57]. The relatively poor response to nucleoside reverse transcriptase inhibitors (NRTIs) may be attributed to the toxicity of these drugs, particularly the mitochondrial toxicity attributed to didanosine with or without stavudine, zidovudine (AZT)-associated anemia and probably the decreased viral response associated with abacavir/lamivudine as compared to a tenofovir/lamivudine or emtricitabine based HAART regimen [58]. A combination of pegylated interferon and ribavarin with didanosine/stavudine is therefore contraindicated. Although the situation is changing in most of the RLSs, the HAART combination that was used more commonly contained stavudine. Zidovudine is still being used in most combinations in RLSs, yet co-administration of AZT with ribavirin is associated with higher anemia rates. It may be wise to avoid these regimens in HCV/HIV coinfected patients.

In RLSs where HCV treatment is not affordable, effective and earlier HAART may be the most effective way of limiting liver fibrosis.

The impact of CD4 cell count on SVR is still questionable. In a bid to assess the effect of baseline CD4 cell count on the efficacy and safety of peginterferon plus ribavirin in patients with HIV/HCV coinfection, Opravil *et al.* [59] reported that the above regimen could be effective and well tolerated by individuals with stable HIV and that with this drug combination, response tended to increase with higher CD4 counts in patients with HCV genotype1. The response rates recorded in this study were 13, 19 or 32% among patients with a CD4 cell count less than 200, 200–350 or greater than 350 cells/μl, respectively. These findings (on CD4 and treatment success) were, however, not reproduced in a multicenter French study [60]. A Brazilian study showed that during treatment with HAART, immunological recovery may be thwarted but morbidity and mortality due to AIDS defining illness may not be affected by this treatment [61].

Challenges in management of hepatitis C virus/HIV in resource-limited settings

Aside from the reliability issues of rapid test methods of HCV in sub-Saharan Africa and drug toxicities among HIV/HCV-infected patients, resource-limited countries have their unique issues dealing with coinfection, where they exist.

There is wide distribution of HCV throughout the world. (Global distribution of HCV genotypes, WHO 2009). In most RLSs, non-2,3 HCV genotypes predominate, except in some West African countries where genotype 2 predominates. This distribution of the more difficult-to-treat genotypes in RLSs further complicates the treatment of HCV infection.

Cost of treatment for HCV is enormous. Most of the countries do not have health insurance services to take care of treatment of HCV. Consequently, while HIV is being treated in these countries, in some of the RLSs, especially those in Africa, testing and treatment for HCV is not routinely performed. This situation is also complicated by shortage of adequately trained health professionals who are able to recognize side-effects and monitor response. Treatment of HIV among drug users in Central and Eastern Europe and Central Asia have been complicated by lack of personnel and institutions and high cost of antiretroviral drugs [62].

Above all, few research studies have been done in most of the RLSs on HCV and HIV coinfection. Most national programs have concentrated on HIV, tuberculosis and malaria. Despite HCV being an opportunistic infection, this virus is not specifically recognized in most of these countries.

Prevention and control of hepatitis C virus

Currently, there is no active vaccine for the prevention of HCV transmission. In regions where IDU is not prominent, most likely transmission will be through blood transfusion and use of unsafe injections in treatment of medical conditions. Provision of simple qualitative test methods in national blood bank services would significantly reduce the transmission of HCV in these countries. Safe injection practices need to be encouraged. Fortunately, the WHO introduced the Safe Injection

Global Network (SIGN), which covers all resource-rich and RLSs WHO members' states. This introduction has had an impact in some of the countries that are applying the recommended methods for medical injection.

Conclusion

There is still limited information on HIV/HCV coinfection in some RLSs, especially those in sub-Saharan Africa. Injection drug use is generally on the rise and screening of donor blood for HCV infection is not optimal in some of these RLSs. Safe injections for the treatment of various medical conditions may not be universally practiced in some countries, leading to continued spread of HCV and HIV. Where proper diagnosis of HCV and HIV has been made, treatment is still complicated by high costs of medications and investigations. Reversal of transmission pattern by improving factors leading to transmission both among injection drug users and the general population will limit the transmission of HCV and HIV in these settings. This change will reduce the need for complicated treatment programs required in these patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 569–570).

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