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MINIREVIEWS

Hepatitis C virus/human T lymphotropic virus 1/2 co-infection: Regional burden and virological outcomes in people who inject drugs

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Abstract

This review analyses current data concerning co-infection with hepatitis C virus (HCV) and human T lymphotropic virus (HTLV)-1/2 in people who inject drugs (PWID), with a particular focus on disease burden and global implications for virological outcome. In addition, the available treatment options for HTLV-1/2 are summarized and the ongoing and likely future research challenges are discussed. The data in this review was obtained from 34 articles on HCV/HTLV-1/2 co-infection in PWID retrieved from the PubMed literature database and published between 1997 and 2015. Despite unavailable estimates of the burden of HCV/HTLV-1/2 co-infection in general, the epidemiologic constellation of HTLV-1/2 shows high incidence in PWID with history of migration, incarceration, and other blood-borne infectious diseases such as HCV or human immunodeficiency virus. The most recent research data strongly suggest that HTLV-1 co-infection can influence HCV viral load, HCV sustained virological response to α-interferon treatment, and HCV-related liver disease progression. In short, outcome of HCV infection is worse in the context of HTLV-1 co-infection, yet more studies are needed to gain accurate estimations of the burden of HCV/HTLV-1/2 co-infections. Moreover, in the current era of new direct-acting antiviral treatments for HCV and proven HTLV-1/2 treatment options, prospective clinical and treatment studies should be carried out, with particular focus on the PWID patient population, with the aim of improving virological outcomes.

Key words: Hepatitis C virus; Human T lymphotropic virus; Hepatitis C virus/human T lymphotropic virus-1/2 co-infection; People who inject drugs; Human T lymphotropic virus-1/2 screening among people who inject drugs; Co-infection treatment

Core tip: People who inject drugs (PWID) are at higher risk of infection with blood-borne viruses and even co-

infections. Co-infections with human immunodeficiency virus and human T lymphotropic virus (HTLV)-1/2 are common, and well-studied, among PWID; however, the rise of HTLV-1/2 co-infections with hepatitis C virus (HCV) has gained much research attention and studies have shown that the former influences the chronic disease course of the latter. This review summarizes the data from 34 articles on HCV/HTLV-1/2 co-infection in the PWID patient population, including current treatment options and impact on virological outcome.

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HEPATITIS C VIRUS AND HUMAN T LYMPHOTROPIC VIRUS-TYPES 1/2 CO-INFECTION BURDEN

The rate of hepatitis C virus (HCV) infection has reached the level of a global epidemic, with an estimated burden of 2.8% seroprevalence (anti-HCV antibody) in over 185 million individuals from both developed and developing nations[1]. In Europe and the United States, however, HCV transmission occurs mainly through intravenous drug use[2,3]. While this practice facilitates spread of blood-borne viruses, including the human immunodeficiency virus (HIV) as well as the hepatitis B virus, it allows transmission of HCV much more efficiently, as evidenced by the higher incidence rates of HCV in people who inject drugs (PWID) *vs* those with HIV[3]. Specifically, the 2011 estimate of global PWID seroprevalence for HCV was 67.0%[4]. PWID are a select population subgroup with extremely high seroprevalences of HCV; as such, they represent a primary driving force of the current HCV epidemic in high-resource settings, accounting for the majority of new (80%) and existing (60%) cases reportedly[5]. Yet, the high proportion of undiagnosed asymptomatic HCV carriers has precluded obtainment of an accurate estimate of chronic hepatitis C burden.

Human T lymphotropic virus (HTLV)-1 is an oncogenic retrovirus with a similar worldwide incidence. Although its founder effect remains unresolved, HTLV-1 shows high endemicity in Southwestern Japan, sub-Saharan Africa, South America, the Caribbean basin, the Middle East, and Australo-Melanesia[6]. The worldwide prevalence estimate of 20 million infected people is based on a serological screening from nearly 30 years ago, and an accurate estimate of the current global burden is unavailable[7]. The main transmission routes are contaminated blood products, sexual intercourse, and vertical transmission. In Europe, most HTLV-1 carriers are descendants of immigrants originally from regions with high endemicity and often with an HIV co-infection[6,7]. However, as reported for Spain, Italy and Ireland, PWID represent an especially affected population for HTLV-1 infection, even though HTLV-2 is much more prevalent[6]. In contrast, clinical onset of associated chronic illnesses, such as cancer [adult T-cell leukaemia/lymphoma (ATLL)] and neurological disorders [myelopathy and tropical spastic paraparesis (HAM/TSP)], has been reported in only 5%-10% of HTLV-1 carriers[8-10].

Similar to HTLV-1, HTLV-2 can be transmitted intravenously, sexually, or vertically. In the United States and Europe, needle sharing is a major route of HTLV-2 transmission among the PWID population[11-13]. Moreover, study of a cohort of PWID in the United States revealed significant associations between HTLV-2 infection and increased rates of pneumonia, acute bronchitis, urinary tract infection, and myelopathy[14], and the authors noted that the observed high correlation of HTLV-2 infection with HCV infection was suggestive of injection practices as a major route of transmission.

Studies of retroviral transmission carried out in various developing countries have identified incarceration as a risk factor, especially for HCV, suggesting that incarceration may be a surrogate marker for risky behaviour in general, such as needle sharing and unprotected sex[14]. In addition, our previous case report of HTLV in Eastern European countries indicated that the criminalization of drug use and lack of harm reduction strategies in prisons may also serve to increase risk for sexual and parental transmission[15].

Finally, the contribution of health care-associated infection (or "nosocomial") as a source of HCV and retrovirus transmission among migrant population originally coming from limited resources settings has been largely undervalued to date, with little research available[16]. The limited data reported has shown nosocomial rates ranging from as low as 5% and all the way up to 19%[16].

In conclusion, the epidemiological constellation of HCV/HTLV-1/2 co-infection is found within regions with high rates of PWID and history of other risk factors (Figure 1).

CLINICAL AND THERAPEUTIC IMPLICATIONS OF HCV/HTLV-1/2 CO-INFECTION

In order to gain a comprehensive overview of the current available knowledge on the clinical and therapeutic implications of HCV/HTLV-1/2 co-infection, we searched the PubMed (www.pubmed.gov) literature database for all articles affiliated with the terms "HTLV HCV", "HCV and HTLV coinfection", "HTLV burden", "HTLV treatment", and "HTLV migrants". Exclusion of articles published before January 1, 1990 left a total of 34 studies for review.

Clinical implications of HCV/HTLV-1/2 co-infection

A large-scale survey of residents of Iki Island in Japan, an endemic region for HTLV-1 infection, conducted by

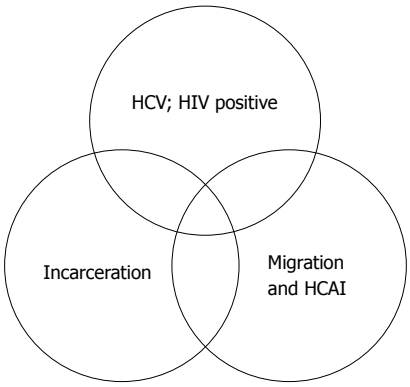

Figure 1 Global risk factors for co-infection with hepatitis C virus and human T lymphotropic virus-1/2 in people who inject drugs. Adapted from Roger and Castro, 2014[15]. In this model, each circle represents a risk factor of hepatitis C virus (HCV)/human T lymphotropic virus-1/2 co-infection in people who inject drugs in the context of global migration patterns and increased health care-associated infections (HCAI; also known as "nosocomial" or "hospital-based" infections) in settings with limited resources, incarceration (particularly in countries that lack harm-reduction programs for incarcerated populations), and in the background of human immunodeficiency virus (HIV) or HCV infection.

Kishihara *et al*[17] showed that individuals with HCV/HTLV-1 co-infection had a lower rate of natural clearance of HCV RNA and of sustained virological response to interferon (IFN) treatment than their counterparts with HCV infection alone; moreover, the co-infected population showed significantly higher HCV viremia ($P < 0.05$). Other Japanese studies of HCV/HTLV-1 co-infection in PWID showed associations with liver disease (6-fold increased risk)[18] and liver cancer mortality (2.6-fold increased risk)[19], leading to the hypothesis of an HTLV-1–induced immune modulation and inflammatory cytokine dysregulation that could affect HCV persistence and progression to liver disease[20,21]. In contrast to the Japanese findings, however, two Brazilian studies[22,23] of HCV/HTLV-1 co-infection provide epidemiological and immunological evidence of a higher rate of spontaneous clearance of HCV in patients with HIV/HTLV-1 co-infection as compared to patients harbouring only an HIV/HCV co-infection or an HCV mono-infection. The differences between HCV and HTLV-1 interaction outcomes in these two settings may be due to host genetic factors (*e.g.,* HLA genotypes), study design, or other unmeasured parameters of the study populations. Studies of the molecular underpinnings of the HCV and HTLV-1 interaction outcomes have shown that HTLV-1-infected T cells, together with viral gene expression and cellular signalling mechanisms, can trigger a strong virus-specific immune response and increased proinflammatory cytokine production[24,25]. Moreover, the cellular immune response has been implicated in the control of HTLV-1 infection as well as in the development of related inflammatory alterations in patients[26]. The cellular immune response involves $CD4^+$ T cells differentiating towards the Th1, Th2 and Th17 lineages, producing a variety of proinflammatory cytokines, chemokines, adhesion molecules and proinflammatory enzymes, which contribute to chronic inflammatory conditions and include reactive oxygen species (ROS), tumour necrosis factor alpha (TNFα), interleukins (IL1, 6, 8 and 18), nuclear factor-kappa B (NF-κB), hypoxia-inducible factor (HIF), IFNγ, and cyclooxygenase (COX)[27,28]. Moreover, contributions of different HTLV-1 oncogenic pathways related to viral proteins have been recently described recently[29]. Additionally, a study of 199 HTLV-1 infected subjects by Treviño *et al*[30] showed that the risk of developing TSP was 10-times higher among HTLV-1 carriers who harboured the IL B-28 CT and TT alleles than their counterparts who harboured the CC allele. The same study also showed an association between the CT polymorphism and increased HTLV-1 viral loads, and that the CC allele is found more frequently among asymptomatic carriers of HTLV-1 (62%). Collectively, these data strongly suggest that HTLV-1 co-infection plays a role in HCV viremia and evolution, attainment of HCV sustained virological response to α-interferon treatment, and HCV-related liver disease progression. Briefly, the current evidence supports postulation of worsening of HCV infection in the context of HTLV-1 co-infection.

Treatment implications of HCV/HTLV-1/2 co-infection

HTLV-1/2 asymptomatic carriers do not require treatment. However, for HTLV-1/2 carriers who experience clinical onset of ATLL or HAM/TSP the current treatment options are limited and those available have a suboptimal range of efficacy. A meta-analysis of ATLL antiviral therapies showed that α-IFN and zidovudine (AZT) combination can induce complete remission and produce a high (82%) 5-year survival rate in ATLL patients[31]. Another ATLL therapeutic approach, specifically the α-interferon, arsenic and AZT combination, was evaluated in a later study of 16 patients and showed induction of a beneficial cytokine modulation response with a shift from the pre-treatment Treg/Th2 phenotype to the Th1 phenotype post-treatment[32]. Thus, this triple drug combination may be a useful treatment approach to restore an immuno-competent microenvironment, which will enhance the eradication of ATL cells and the prevention of opportunistic infections. Yet another study evaluated the combination of valproate (VPA) and AZT in patients with advanced HAM/TSP and found that the treatment may control viral replication through inhibition of the virus reverse-transcriptase and/or its associated molecular machinery[33]. The same strategy has been evaluated in non-human primates (*Papio papio*) naturally infected with the simian T cell lymphotropic virus type 1 (STLV-1; the equivalent of HTLV-1 which also causes simian ATLL). The animals were asymptomatic carriers and treatment with AZT/VPA induced a reduction of viral load which relapsed after treatment interruption[34]. A study of the HIV integrase inhibitor drug, raltegravir, as treatment for HTLV-1 (evaluating 5 carriers, including 2 with HAM and 3 asymptomatic) showed achievement of a transitory viral load reduction during the 24 wk of treatment but with no main clinical improvement[35]. Finally, Abad-Fernández

Table 1 Key features of hepatitis C virus and human T lymphotropic virus-1/2 co-infection

HTLV-1/2 infections are found in HCV co-infected PWID worldwide, as a consequence of unsafe injection practices
HTLV-1 infection induces chronic inflammation and oncogenic cellular changes
HTLV-1 co-infection of chronic hepatitis C carriers can increase HCV viral load, accelerate liver disease progression, and favour onset of liver cancer
Evidence suggests that HTLV-1/2 clinical presentations can be linked to higher viral loads in contrast to asymptomatic HTLV-1/2 carriers
Available treatment data shows that HTLV-1/2 viral load can be suppressed but not eradicated

HTLV: Human T lymphotropic virus; HCV: Hepatitis C virus; PWID: People who inject drugs.

et al[36] reported the only study to date in our collected articles from the PubMed literature to assess the evolution of HTLV co-infection (including with HIV, HTLV-2 and HCV) among patients who received treatment for HCV and showed reduction of HTLV-2 viral load in response to the α-IFN and ribavirin combination treatment.

DISCUSSION AND FUTURE PROSPECTS

The main features of HCV/HTLV-1/2 co-infection, based on evidence reported in the current literature, are summarized in Table 1. Briefly, they highlight the role of PWID as a core affected population and the negative immune modulation effect of HTLV-1 co-infection in patients with chronic hepatitis C. At the same time, HCV/HTLV-1/2 co-infection remains an unresolved clinical challenge; prospective studies looking at the HTLV-1/2 infection outcome in subjects receiving new direct-acting antiviral treatments targeting the HCV infection will likely provide further insights towards improvement.

The features listed in Table 1 are a source of new research questions to be addressed. In addition, they should challenge the clinical field to reflect on the pertinence of adding HTLV-1/2 screening for PWID patients and particularly in relation to caring for migrant populations from high endemic areas in different worldwide settings.

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