High risk of reacquisition of hepatitis C virus infection in people with HIV with continued risk behavior

Hugo Soudeyns[a,b,c,d]

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A significant proportion of people with HIV (PWH) worldwide are also infected with hepatitis C virus (HCV) [1], which is associated with serious comorbid consequences [2]. Multiple combinations of orally administered direct acting antiviral agents (DAAs) are highly effective at curing HCV infection, even in PWH [3,4]. Unfortunately, people who clear or were cured of HCV infection can become reinfected [5]. This is primarily based on the fact that primary infection does not lead to the development of protective immunity against the virus [6]. Studies on chimpanzees experimentally infected with HCV showed that cell-mediated immune responses mediated by $CD4^+$ and $CD8^+$ T lymphocytes and directed against HCV played an important, but incomplete role in resistance to reinfection [7–9]. This could be due in part to the well documented expression of so-called co-inhibitory receptors, including PD-1 and TIM-3, at the surface of HCV-specific $CD4^+$ and $CD8^+$ T cells, leading to T-cell exhaustion and loss of T-cell effector function [10,11]. DAA treatment was recently associated with decreased expression of co-inhibitory receptors TIM-3 and PD-1 in $CD4^+$ and $CD8^+$ T cells from DAA-treated HCV-infected persons [12], although this effect was not seen in persons with advanced liver disease. Unfortunately, these basic questions, which also directly impact the field of HCV vaccine development, have not yet been convincingly resolved in hepatitis C.

The overall epidemiology of HCV infection has changed in recent years with the increasing availability, and affordability, of highly-effective DAA treatment leading to HCV clearance in the large majority of cases, a remarkable public health achievement. In the case of the actual risk of HCV reinfection following DAA-mediated clearance of the virus, one issue that has recently stood out is so-called 'risk compensation'. Risk compensation is defined as 'increases in risky behavior sparked by decreases in perceived risk' [13,14], in this case, the comparatively wide availability of highly effective treatment, at least in high-income settings, including the 'treatment as prevention effect'. As a result, the proportion of incident HCV cases due to reinfection following DAA-related clearance is rising. This is a major concern in specific risk groups, including PWH, people who inject drugs (PWID), and persons involved in condomless anal sex (CAS) [15], as reinfection represents a serious obstacle to HCV microelimination programs/strategies in these populations.

In this issue of *AIDS*, Kris Hage and coworkers report the results of a study carried out on participants to an international cohort of PWH (International Collaboration on Hepatitis C Elimination in HIV Cohorts – InCHEHC) from six high income countries (11 prospective cohorts; Australia; Canada; France; The Netherlands; Spain; and Switzerland) [16,17]. Study participants ($n = 1477$) acquired HCV infection and successfully achieved sustained virological response (SVR) following 12 weeks of treatment with DAAs.

[a]Centre de recherche Azrieli du Centre hopitalier universitaire (CHU) Sainte-Justine, Montreal, [b]Department of Microbiology, Infectiology and Immunology, [c]Department of Pediatrics, Faculty of Medicine, Université de Montréal, Montreal, QC, Canada, and [d]Pathology Advanced Translational Research Unit (PATRU), Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA, USA.

Correspondence to Hugo Soudeyns, PhD, Unité d'immunopathologie virale, Centre de recherche Azrieli du CHU Sainte-Justine, 3175 Côte Sainte-Catherine, Room 7961, Montreal, QC, Canada H3T 1C5.
Tel: +1 514 345 4931 x3907; fax: +1 514 345 4794; e-mail: hugo.soudeyns.hsj@ssss.gouv.qc.ca
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Self-reported longitudinal patterns of behavioral risks after successful DAA treatment were examined using group-based trajectory models (GBTM), a statistical modelling strategy that has been in use for many years in varied circumstances, including the use of seat belts in cars [18]. The authors defined patterns of behavioral risks as four distinct and somewhat self-explanatory behavioral trajectories: 'consistently low', 'moderate increasing', 'high decreasing', and 'consistently high'. Sensitivity analyses were conducted on subgroups of participants, including MSM ($n = 378$) and PWID ($n = 487$). The main strength of the study lies in its six-countries international multicentric design and its comparatively large number of participants, a clearly remarkable achievement by the leadership of the InCHEHC Study Group and the large number of its contributors. This enabled Hage *et al.* to examine and compare trajectories in subgroups that would otherwise have contained too few participants had the study been conducted in a single site or single cohort.

Main findings were that 30 cases of HCV reinfection occurred in the participants included in the study (0.74 per 100 persons-years). Incidence rate was lower than what was observed in a previous study [19], probably due in part to differences in inclusion criteria, that is, clearance following DAA treatment vs. all participants who cleared, and at least two visits with behavioral data instead of one. Overall, there were little changes in patterns of risk behavior associated with drug use or CAS over the follow-up period – there was only a modest decline in risk behaviors following DAA treatment. Incidence rate of HCV reinfection was highest in participants with the highest degree of risk behavior ('consistently high') (1.28 cases per 100 persons-years), this trajectory accounting for ~50% of all trajectories recorded in study participants. The majority of these individuals continued to engage in high-risk behavior for HCV acquisition, including injection drug use and CAS with casual partners. These participants include the youngest cohort participants; those who were most recently diagnosed with HIV infection; and those who were the least likely to be virologically suppressed in terms of undetectable HIV-1 viral load [16]. Overall, there was only a modest decline in risk behaviors following DAA treatment, and the majority of study participants admitted that they continued to engage in risk behaviors for HCV acquisition. This is indicative of limited behavioral changes and modification in risk behaviors in the majority of individuals – a sobering finding in light of the recently demonstrated importance of reinfections in key populations in the incidence rate of new HCV infections worldwide since the introduction of DAAs [20–25]. At the same time, these results clearly highlight a subgroup of participants towards whom the potentially most effective prevention practices and strategies should be targeted.

This manuscript carries a sobering but essential message: in most cases, at the present time, risk behaviors do not change significantly following DAA-mediated clearance of HCV infection in PWH, possibly contributing to the maintenance of incident rates of HCV infection in settings where effective treatment is readily or almost readily available. These findings should motivate public health authorities to rethink how strategies to prevent HCV reinfection are deployed and implemented among key populations, including regular, nonjudgemental HCV testing in persons who cleared HCV infection following DAA treatment but are still involved in risk behaviors.

Based on current knowledge in the field, lack of prior immunity and reinfection are an inescapable biological property of HCV and related viruses, leading to their widespread distribution across multiple vertebrate species [26,27]. To limit the potential for forward transmission, horizontal or vertical, reinitiation of DAA treatment should be implemented in a wholly unprejudiced fashion in those persons who reacquire HCV infection, irrespective of how and why reinfection occurs or whether it occurs repeatedly: primary prevention; treatment; retesting; and retreatment. This is not a question of pointing fingers but one of sound public health policy.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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