Treatment as prevention: can hepatitis C learn the lesson from HIV?

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Abstract: Long-term experience in the treatment of HIV-infected individuals has shown indirect benefits of early initiation on antiretroviral therapy, particularly in preventing HIV transmission. With the advent of direct-acting antivirals for the treatment of hepatitis C, the preventive strategy of treatment-as-prevention has become feasible. However, economic, clinical, ethical and public health issues arise from the concept of using therapeutic interventions only as prevention strategies.

Keywords: HIV, Hepatitis C, direct-acting antivirals, prevention, resistances

1. Introduction

After decades of use of highly-active antiretroviral therapy (HAART), long-term benefits besides suppressing HIV replication have been found. Early initiation of HAART has been associated with decreased mortality[1], increasing life expectancy both in low and high-income countries[2,3], as well as with a significant reduction in the incidence of opportunistic infections[4]. But arguably, one of the most encouraging indirect benefits of early initiation of HAART is the reduction of HIV transmission among serodiscordant couples[5]. The use of HAART in the context of treatment-as-prevention (TasP) might thus represent the most important paradigm change in HIV prevention for decades.

Hepatitis C (HCV) infection is experiencing a similar revolution with the development of direct-acting antivirals (DAA), resulting in highly efficacious regimens with very favourable safety profiles[6]. Furthermore, and unlike with interferon (IFN) based therapies, the efficacy and safety of DAA in HIV/HCV-coinfected patients is not significantly different from that observed in HCV-monoinfected patients[7]. Hence, although their natural histories are different, HIV and HCV share common transmission routes, and safe and efficacious therapies are available for both conditions, making

TasP a potentially feasible strategy for decreasing the incidence of HCV infection, especially in high-risk populations (Table 1).

2. Treatment as prevention for HIV infection

Since the advent of HAART in the mid 90s, the worldwide prevalence of HIV has escalated as a consequence of the increase in the number of patients on antiretroviral therapy[8] and the subsequent reduction of opportunistic infections and other AIDS-related deaths[4]. However, the incidence of HIV infection has not significantly changed in recent years, due to the increase in new HIV diagnoses in areas such as Eastern Europe, Middle East and Central Asia[8]. HIV prevention remains a major challenge, particularly since a significant proportion of HIV patients are unaware of their status[9].

An interim analysis of the HPTN-052 trial[10] showed that starting HAART in the HIV-infected partner in a serodiscordant couple reduced the risk of linked transmission by 96%. After a 5-year follow-up of the same cohort[5] the risk reduction was 93%, thus confirming the efficacy of TasP in serodiscordant couples in the long term. Similar results were found in trials in South Africa[11] and China[12].

In light of the available evidence, and regardless of other strategies for preventing HIV transmission such as pre-exposure prophylaxis (PrEP), TasP has shown a remarkable efficacy in reducing linked transmission of HIV.

3. DAA for the prevention of HCV transmission in PWID

The development of DAA for the treatment of HCV infection can be considered as the most significant milestone in the history of HCV since its discovery in 1989. Previous IFN-based therapies required lengthy treatments, with a high rate of adverse events, often leading to therapy discontinuation or persisting for long periods after therapy completion. The efficacy of such therapies was highly variable depending on HCV genotype[13], with particularly poor results for HIV/HCV-coinfected individuals[14]. Besides, IFN-based therapies were contraindicated in patients with decompensated cirrhosis. Altogether, these features restricted patient eligibility for antiviral therapy and made the concept of TasP for HCV infection unthinkable.

The development of DAA dramatically changed the landscape of HCV therapy, particularly in light of the efficacy and safety of all-oral treatments[15-17]. TasP thus became feasible, in a similar way to HIV infection.

Due to the different routes of transmission, TasP faces different challenges depending on the risk group involved. In many countries, injection drug use (IDU) accounts for the majority of new cases of HCV infection[18]. Hence, people who inject drugs (PWID) are arguably the population who theoretically might benefit the most from TasP. Several mathematical models and studies have assessed the effects of this strategy in active IDU. An early mathematical model[19] showed that the efficacy and efficiency of TasP was highly dependent on HCV prevalence among PWID. In low prevalence scenarios, a modest increase in the number of PWID treated might have a moderate impact on the reduction of HCV incidence. However, in areas with higher HCV prevalence among PWID, a much higher number of PWID would need to be treated in order to achieve a significant decrease in HCV incidence. Of note, this mathematical model did not assess the impact of risk compensation, which has been found to play a major role in the efficacy of other prevention strategies in HIV[20,21], as confirmed by recent studies in patients receiving PrEP[22]. Another important aspect this mathematical model does not consider is the rate of reinfection, which might significantly decrease the efficacy of TasP among HCV-infected PWID.

Another mathematical model[23] identified PWID as a target population for TasP in order to reduce new cases of HCV infection and prevent liver-related morbidity and mortality. Considering several scenarios differing in the degree of intervention, from merely pharmacological, to escalation on to linkage to care, diagnosis and enhancing adherence, this study found that pharmacological interventions alone achieved very modest results. Interestingly, the model that provides the best results implied a significant escalation in behavioural interventions. The authors identified some caveats when interpreting the results. Firstly, the effect of risk compensation and/or reinfection was not completely assessed, making results valid only assuming certain rates of reinfection or persisting risk behaviours. On the other hand, ?medication costs would make the optimal model difficult to implement and sustain with the current costs of drugs and the increased need for medical and other support measures.

In light of the scarce evidence available to date, wholly based on mathematical models, and while waiting for real-world data, DAA could be potentially used for prevention. However, mathematical models concur in the significant impact of

persisting risk behaviours and subsequent reinfections, as well as cost and ethical implications.

4. Treatment as prevention of sexually-transmitted HCV

In recent years, outbreaks of sexually-transmitted HCV have been reported, particularly among men who have sex with men (MSM)[24]. Traditionally HCV has been considered a blood-borne virus (BBV), leaving other risk groups aside from regular screening for HCV. That has resulted in a significant increase in the incidence of sexually-transmitted HCV, particularly among MSM[25]. This public health issue is even more concerning among HIV infected MSM, in whom a 20-fold increase in incidence has been reported over the last two decades[26]. Though sexual transmission is significantly less efficient than parenteral transmission, some studies have reported seroconversion rates of up to 1.9 cases/100 person-years[26]. Behavioural factors such as inconsistent condom use[27], non-injectable illicit drug use[28] or traumatic sexual intercourse[29] have been associated with higher HCV seroconversion rates.

Data about TasP in MSM is still scarce. A mathematical model based on HCV transmission among the UK HIV-positive MSM population[30] showed that significant reductions in HCV prevalence might be obtained by a scale-up of 80% in DAA treatment in HIV/HCV-positive individuals within the first year of diagnosis, regardless of the degree of liver fibrosis. However, behavioural interventions might enhance the efficacy of TasP, further reducing transmission risk by an additional 20%. This model also revealed the significant impact of reinfection on the efficacy of TasP as well as on the sustainability of the proposed interventions. Another study[31], revealed that stabilising high-risk behaviour in conjunction with enhancing access to DAA can significantly reduce HCV transmission among HIV-infected MSM individuals. Of note, this study was consistent with other models in finding risk compensation as a key factor for the success of TasP for HCV prevention. In this line, some authors[32] also suggest that an increase in reinfection rates can be expected as a consequence of the increased uptake of DAA and their lack of side effects, creating an environment of lack of concern about reinfection, similarly to what has been observed in HIV transmission. So far, further real-world data is necessary to assess the efficacy of DAA for TasP as a prevention strategy for sexually-transmitted HCV. Currently, the few mathematical models available are based on HIV-infected populations, and the need for evidence

on HIV-negative individuals remains unmet. With the evidence available, the efficacy of TasP for preventing sexually-transmitted HCV would require a significant increase in the number of patients treated, with an associated increase in costs that many healthcare systems would not be able to sustain. Besides, behavioural interventions might be necessary to maximise the efficacy of TasP and reduce the number of reinfections and development of resistance.

5. Risk of reinfection

Arguably, costs are a major barrier for accessing DAA therapies in many countries, either due to being low-income? countries or due to high HCV prevalence[33]. There is no doubt that DAA are superior to the previous IFN-based therapies, even in genotypes 2 and 3, in which the response to IFN-based treatments was already very good[34]. However, therapy costs limit the cost- of these new treatments[35] and pose an ethical dilemma on which populations should be prioritised for treatment. International guidelines[36, 37] concur in recommending that all HCV-infected patients should be treated with oral agents, with the exception of those with short life expectancy due to liver disease, in which antiviral therapy is not recommended. Such broad recommendations pose a significant challenge for doctors, who ultimately have to make the best use of the available resources and maximise the numbers of cured patients.

PWID have been described as an ideal population for TasP[38]. Higher rates of HCV prevalence make, in theory, interventions among this population more likely to be effective. However, data shows that treating active injecting individuals regardless of their degree of liver disease may be an inefficient intervention. Firstly, studies have shown that the leading cause of mortality among PWID who achieve SVR after antiviral treatment are related to the persistent use of drugs, rather than liver cancer[39]. Hence, even though scaling up the access of PWID to DAA might potentially reduce HCV prevalence among this population, IDU remains the most significant preventable cause of morbidity and mortality among PWID, and should be addressed as part of the care pathway for this population.

Another important factor to be considered is the risk of reinfection (Figure 1), which has been found to play a major role in the efficacy of TasP both for PWID and MSM. Whereas evidence supports the efficacy of DAA therapies in PWID, reinfection

accounted for the majority of late relapses in some registration clinical trials, particularly among patients on opiate replacement therapy[40]. A study on a mixed cohort of HIV/HCV-coinfected and HCV-monoinfected individuals treated for HCV infection[41] found a reinfection rate of 7.4 cases/100 persons-year. However, in patients who reported active injection drug use after therapy, that rate was twice as high (15.5/100 persons-year). Active IDU after therapy was also strongly associated with reinfection. Of note, the time to reinfection was highly variable among patients. This is a significant limitation for TasP, since the period of time in which cured active PWID are at reduced risk of transmission is unpredictable. Another study involving a population of PWID who had not used drugs 6 months prior to therapy and who had achieved SVR after treatment[32] found a reinfection rate of 11%, which was as high as 27% in patients who relapsed IDU after therapy. Finally, some studies have shown that reinfection risk among active PWID increases over time after achieving SVR, due to a lack of frequent testing and support[42].

Reinfection rates among HCV-positive MSM have been found to be higher than among PWID[43], with rates of reinfection of up to 24.6% and, most concerning, with a significant proportion of patients presenting with second reinfections. Overall, the incidence of reinfection among MSM is estimated to be over 7 cases/100 p-y[32] (Figure 2). Though overall, PWID remain as the population with highest HCV prevalence, in the near future sexually-transmitted HCV will be of further relevance in public health terms.

6. Public health and ethical issues

Reinfection poses a significant public health risk. Many studies have shown the frequent development of resistant-associated variants (RAV) in patients failing therapy. This is particularly concerning in patients infected with HCV genotype 3, in which the use of NS5a inhibitors remains essential[44]. The development of RAVs against NS5a inhibitors tends to confer cross-resistance with all the currently available drugs of this class, and these RAVs might be present even 5 years after their emergence[45]. Hence, a scaling up of DAA therapies for patients at high risk of reinfection might be followed by an increase in the prevalence of RAV, which may compromise the efficacy of antiviral therapies. This is particularly likely to happen if risk compensation increases and behavioural interventions are not implemented in

order to reduce risk behaviour. Mathematical models concur that risk compensation would not just compromise the theoretical efficacy of TasP, but would be also jeopardise the efficacy of DAA in general.

Reinfection after DAA therapy would also cause an ethical dilemma, bearing in mind the high prices of these treatments. DAA costs are causing an accessibility issue in developing countries[46], but also a sustainability issue for public healthcare systems in the Western World[47]. Guidelines remark that all HCV patients are eligible unless their life expectancy due to liver disease is poor, and that prioritization should be made on the basis of the severity of liver disease[36, 37]. However, due to economic constraints the access to DAA is limited, and might raise the dilemma on whether re-infected patients due to risk behaviours should be treated more than once before some other patients who are not engaged in such activities are treated for the first time[48].

Arguably, DAA costs are at the core of all the ethical dilemmas arising from TasP in active PWID, bearing in mind that in countries with high HCV prevalence, including those in the Western world, public healthcare systems are already under economic pressure, and maximising the outcomes of interventions is essential for their sustainability. Economic implications, public health (RAV development), and ethical considerations (equality in the access to DAA) all pose a major dilemma for clinicians.

7. Conclusions

With the development of DAA, the landscape of HCV therapy has dramatically changed, offering new therapeutic strategies. Due to current costs, prioritising the access to such therapies to the populations with a higher need of HCV eradication remains essential. Besides therapeutic implications, DAA make TasP feasible, unlike IFN-based treatments. Unlike HIV, in which ART is currently a life-long treatment, thus extending the effects of TasP on the long-term. The high variability in time to reinfection in populations engaged in high-risk behaviours makes difficult to assess the period of time in which individuals in these populations are not at risk of transmitting HCV.

So far, real-world evidence regarding the efficacy of TasP in HCV infection remains scarce, and estimations are based on mathematical models. From the data available, two main messages emerge. Firstly, that the economic feasibility of TasP is hardly achievable with current costs. And secondly, that pharmacological interventions alone

are not enough to significantly curb HCV transmission, since risk compensation is a limiting factor for its efficacy. Hence, until further real-world evidence is available, TasP for HCV transmission has to be looked at carefully and behavioural interventions developed in order to maximise the effects of DAA therapies.

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Figure 1. Reinfection rates in active PWID after achieving SVR

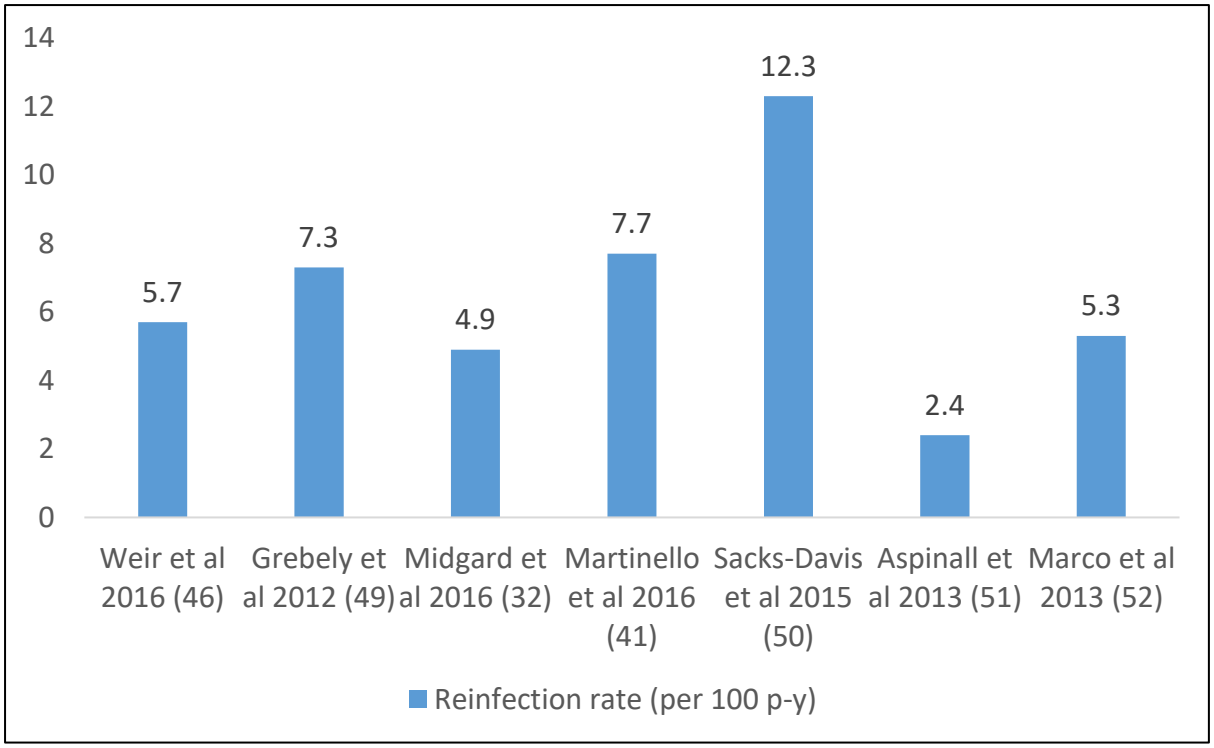

Figure 2. Reinfection rates in MSM after achieving SVR

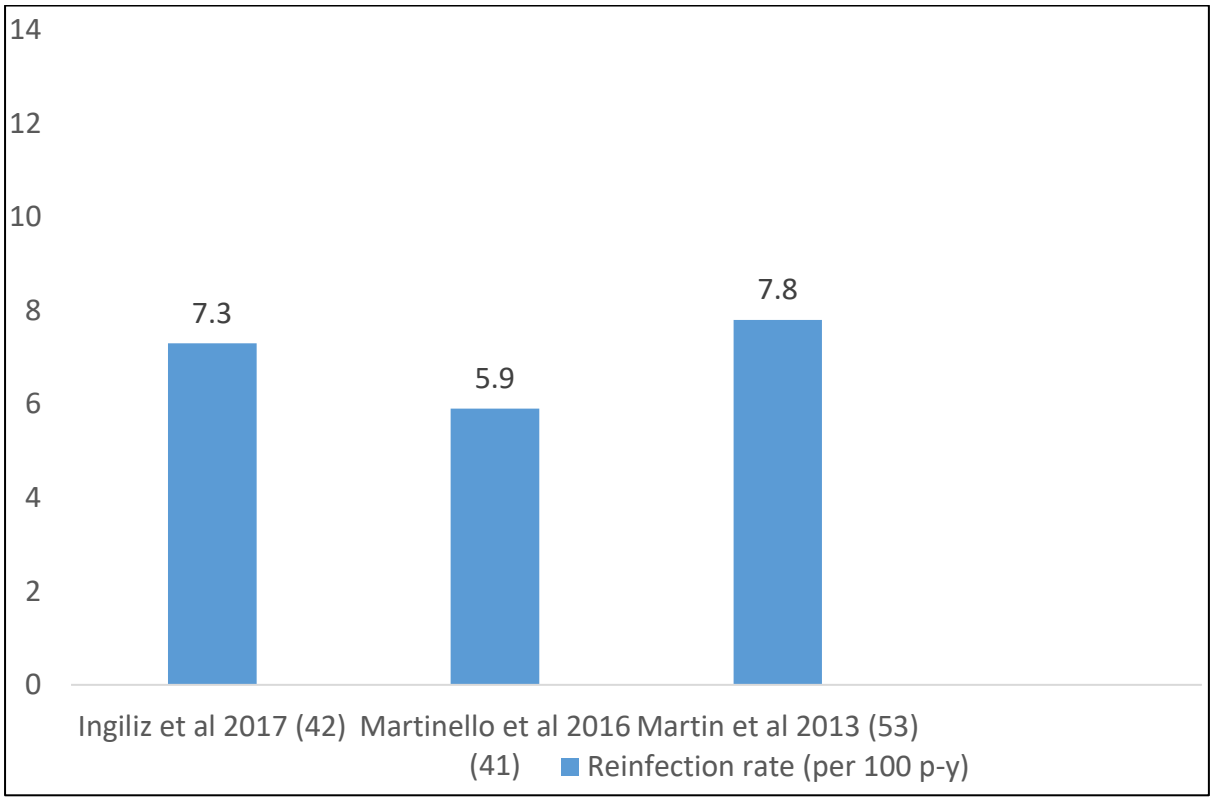

Table 1. Comparison in factors involved in TasP in HIV and HCV

TasP Element	HIV	HCV
Target populations	Serodiscordant couples HIV- positive pregnant women MSM	PWID MSM
Intervention	HAART	DAA
Intervention duration	Lifelong	Often 12 weeks (range 8-24)
Intervention efficacy	80-90%	95-100%
Intervention adverse effects leading to discontinuation	<5%	0-2%
Ideal adjunct risk modification	Safe sex promotion and condom use	Services to prevent drug/alcohol use

DAA: direct acting antivirals, HAART: highly active antiretroviral therapy, MSM: men who have sex with men, PWID: people who inject drugs, TasP: treatment as prevention