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Short Communication

High clustering of acute HCV infections and high rate of associated STIs among Parisian HIV-positive male patients

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ABSTRACT

Background: Increasing incidence of hepatitis C virus (HCV) infection in human immunodeficiency virus (HIV)-positive men having sex with men (MSM) has been described in recent years. Phylogenetic analyses of acute HCV infections were undertaken to characterize the dynamics during the epidemic in Paris, and associated sexually transmitted infections (STIs) were evaluated.
Methods: Sanger sequencing of polymerase gene was performed. Maximum likelihood phylogenies were reconstructed using FastTree 2.1 under a GTR+CAT model. Transmission chains were defined as clades with a branch probability ≥0.80 and intraclade genetic distances <0.02 nucleotide substitutions per sites. STIs detected ≤1 month before HCV diagnosis were considered.
Results: Among the 85 studied patients, at least 81.2% were MSM. Respectively, 47.6%, 39.0%, 11.0% and 2.4% were infected with genotypes 1a, 4d, 3a and 2k. At least 91.8% were co-infected with HIV. HCV re-infection was evidenced for 24.7% of patients and STIs for 20.0% of patients. Twenty-two transmission chains were identified, including 52 acute hepatitis C (11 pairs and 11 clusters from three to seven patients).

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Conclusions: These results revealed strong clustering of acute HCV infections. Thus, rapid treatment of both chronic and acute infections is needed among this population to decrease the prevalence of HCV, in combination with preventive behavioural interventions.

1. Introduction

Emerging acute hepatitis C virus (HCV) infections among human immunodeficiency virus (HIV)-positive men having sex with men (MSM) have been described worldwide in recent years. For instance, increasing incidence of HCV infection in HIV-infected MSM patients has been estimated by European data network CASCADE to range from 0.09–0.22 per 100 person-years (PY) in 1990 to 2.34–5.11 per 100 PY in 2007 [1]. In the Swiss cohort of patients living with HIV, the incidence of HCV infection among MSM patients increased by a factor of 18 between 1998 and 2011 (from 0.23/100 PY to 4.09/100 PY) [2]. This phenomenon has also been observed in cities such as Amsterdam [3], New York and Sydney. Phylogenetic analyses revealed extensive networks of HCV transmission. Also, in Amsterdam, expansion to non-HIV-infected MSM with high-risk behaviours and under pre-exposure antiretroviral prophylaxis was highlighted [4].

Furthermore, a high rate of re-infection among HIV-infected MSM has been reported recently in an European study [5], and in the UK [6] and the Netherlands [7]. In France, the annual incidence of HCV was estimated at 3.42% in 2015 among the subgroup of MSM presenting high-risk behaviour towards contamination [8]. Indeed, many studies have shown that acute HCV infection is associated with recreational drug use and risky sexual behaviours (e.g. unprotected anal intercourse, bleeding during sex, 'fisting') [3,9], and links between past history of associated sexually transmitted infections (STIs) and HCV seroconversion have been identified [2].

In this context, many acute HCV infections were diagnosed in a restricted geographical area of central Paris ('le Marais') among HIV-positive MSM in 2014–2016. The phylogenetic clustering of these infections was explored and associated STIs were characterized in order to better understand the dynamics of acute HCV transmission in this area, and support the need for efficient screening and management strategies in a high-risk population.

2. Methods

This retrospective, observational study enrolled 85 male patients from le Marais who had been diagnosed with acute HCV infection between May 2014 and April 2016 based on virological results from the Virology Departments of Pitié-Salpêtrière, Saint Antoine and Tenon Hospitals, and Cerballiance Laboratory. Highly likely acute hepatitis C was defined as a positive HCV serology test and/or a positive HCV viral load (VL) associated with a negative HCV serology test within the previous 12 months, or a positive HCV VL beyond 24 weeks of successful treatment or spontaneous clearance with modification of HCV genotype (n=72). Possible acute hepatitis C was defined as a positive HCV VL with increased alanine aminotransferase (ALT) $\geq$10 upper limit of normal without any other aetiology of hepatitis, or a positive HCV VL beyond 24 weeks of successful treatment or spontaneous clearance without modification of HCV genotype (n=13). Highly likely acute and possible acute hepatitis C were treated as acute HCV infection in this study, without distinction. No contact tracing was performed.

Patients were followed by the Departments of Infectious Diseases of the Pitié-Salpêtrière, Saint Antoine and Tenon Hospitals or outside the hospitals by their referring doctors (Paris, France). Clinical information was extracted retrospectively from hospital electronic databases or medical records, and anonymized prior to analysis. This information included the age of the participants, reported sexual orientation, HIV status, time of last negative HCV test (when applicable), HCV and HIV VL at sampling (when applicable), previous HCV genotype (when applicable), ALT, and STIs detected $\leq$1 month before diagnosis of acute hepatitis C (for syphilis: new diagnosis or re-infection defined as increase in Venereal Disease Research Laboratory titre by a factor $\geq$4). All subjects gave their informed consent to participate in the study.

Polymerase sequences (NS5b, 334 nucleotides, amino acids 228–338) were obtained by Sanger sequencing from the first HCV-positive sample, as described previously (Genbank accession numbers: MH378080–MH378160) [10]. Subtype determination was performed using the Geno2pheno[HCV] tool [11].

Maximum likelihood phylogenies were reconstructed using FastTree 2.1.7 [12], under the general time reversible model of nucleotide substitution (GTR+CAT with 20 rate categories), and branch supports were estimated by Shimodaira-Hasegawa-like test [13]. Publicly available consensus sequences (n=93 confirmed HCV genotypes/subtypes) and HCV sequences from local databases (n=450, including 131 genotype 1a, 52 genotype 3a and 37 genotype 4d) were added to the dataset after removal of duplicates [14]. Clades with a branch probability $\geq$0.80 and intraclade genetic distances $<$0.02 nucleotide substitutions per sites were considered to represent transmission chains.

3. Results

Patients were mainly MSM (81.2%, n=69; sexual orientation unknown for 16 participants), with a median age of 41.3 years [interquartile range (IQR) 35–46 years]. Median HCV VL at sampling was 5.5 $\log_{10}$IU/mL (IQR 4.4–6.3 $\log_{10}$IU/mL), median ALT was 320 IU/L (IQR 113–581 IU/L) and 24.7% of the 85 HCV infections were re-infections (n=21). Patients were infected with HCV genotype 1a (47.6%), 4d (39.0%), 3a (11.0%) and 2k (2.4%; three viruses not amplified), and at least 91.8% of patients were co-infected with HIV (n=78; HIV status unknown for two participants). No acute HIV infection was reported. Among the co-infected patients, nine had a detectable HIV VL, from 20 to 13 251 copies/mL (IQR 29–364), in a context of low-level viraemia (n=3), blips (n=2), recent treatment initiation (n=1), absence of antiretroviral treatment (n=1), treatment non-compliance (n=1) and resistance to the received treatment (n=1, lost to follow-up; Tenofovir resistance mutations: M41L, D67N, T215F; Emtricitabine: M184V; Raltegravir: N155H).

Acute HCV infections were found in 22 transmission chains [52/81 acute HCV sequenced (64.2%); one short sequence of genotype 3a excluded], of which 13 were re-infections, divided into 11 pairs and 11 clusters from three to seven patients (Fig. 1).

In detail, 27/39 acute genotype 1a hepatitis C, 5/8 acute genotype 3a hepatitis C and 20/32 acute genotype 4d hepatitis C infections were detected among the 10 (five pairs and five clusters from three to six patients), one (one cluster of seven patients) and 11 (six pairs and five clusters from three to five patients) transmission chains identified by genotype, respectively. Nine transmission chains were composed of acute HCV infections alone (four pairs and five clusters from three to six patients, including four

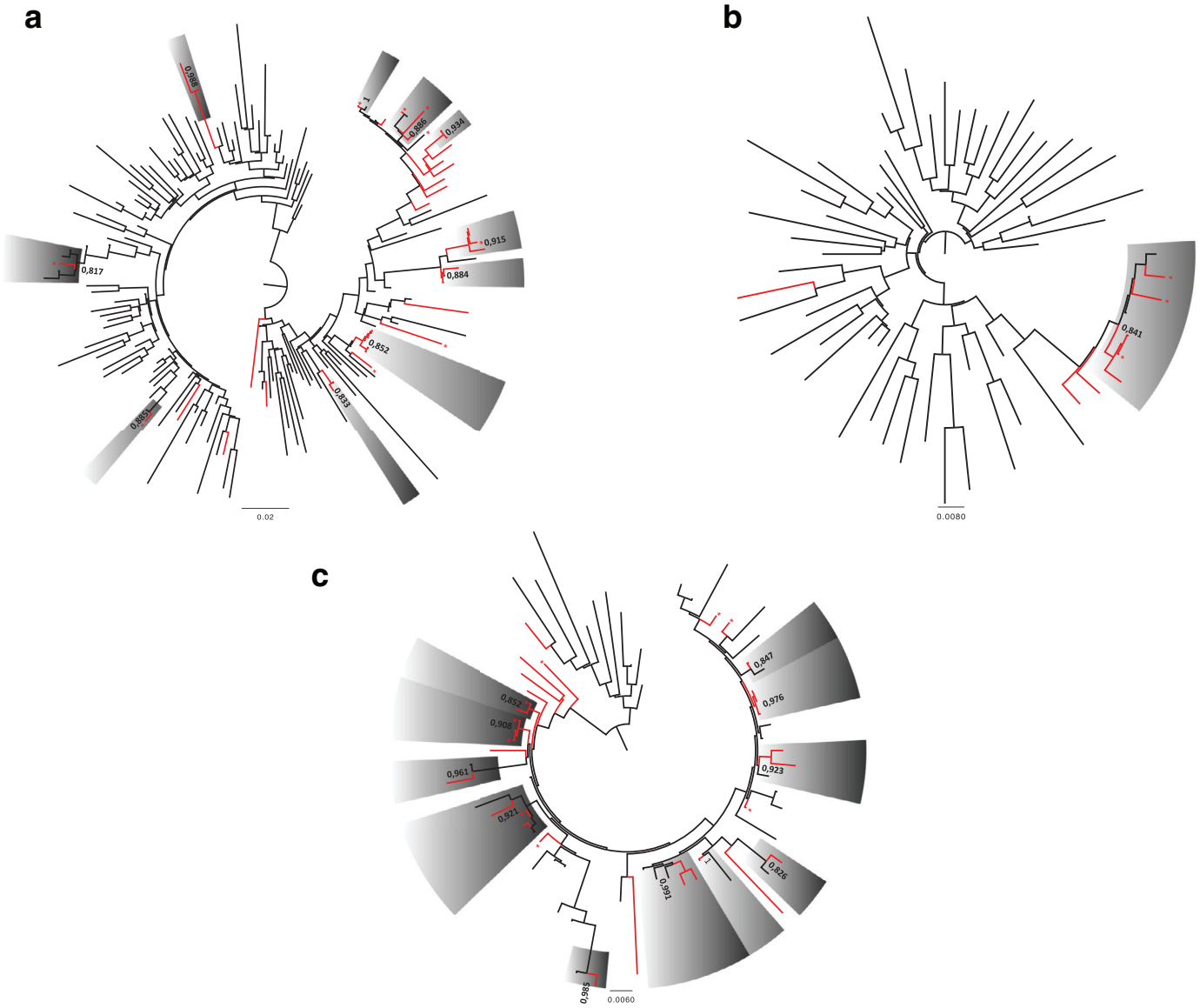

Fig. 1. Phylogenetic tree of hepatitis C virus (HCV) subtype 1a (a), subtype 3a (b) and subtype 4d (c). Grey halos represent the men-having-sex-with-men-specific clusters containing acute hepatitis C (red branches). HCV re-infections are indicated by *.

re-infections in one pair and two clusters), whereas 13 transmission chains were mixed with acute and chronic HCV infections from the background controls (seven pairs and six clusters from three to seven patients, including nine re-infections in two pairs and four clusters and 18 controls). Three re-infections were part of the genotype 3a cluster of seven patients. The rate of re-infection did not differ between the linked cases and the unlinked cases (P=0.868).

STIs were detected in 17 patients (20%) ≤1 month before diagnosis of acute hepatitis C (eight *Treponema pallidum*, five *Neisseria gonorrhoeae*, seven *Chlamydia trachomatis* and one *Giardia intestinalis*). It must be noted that 56.2% of the STIs were detected among patients included in an HCV transmission chain (n=9/16, one non-amplified), with no significant difference from patients not included in a transmission chain (P=0.507). Two patients exhibited the same STIs among a cluster of five patients (*N. gonorrhoeae* and *C. trachomatis*) and two among a cluster of four patients (*N. gonorrhoeae*). In addition, the prevalence of STIs was not higher among re-infections than among first HCV infections (P=0.615).

4. Discussion

A large number of acute HCV infections were diagnosed among HIV-infected MSM patients in Paris between 2014 and 2016, and this study found that many of them were part of a transmission chain, revealing a strong infection dynamic among this local population, as also suggested by the high number of re-infections. This is in line with a recent report by Ingiliz *et al.,* who showed that among eight European centres from Austria, France, Germany and the UK, the highest incidence of HCV re-infection was in Paris (21.8/100 PY, 95% confidence interval 11.3–41.8) [5]. These results raise concerns about the transmission of drug-resistant viruses, as described previously [15].

In addition, in this study, STIs were detected in 20% of the cases, which was very high given the strict time criterion (≤1 month before diagnosis of acute hepatitis C). These results corroborated a global rise in sexual risk behaviour that has been described since the early 2000s. Furthermore, it is well known that STIs could facilitate permucosal infectious agent transmission through mucosal damage, increasing the infectiousness of a low inoculum.

In this study, most patients were co-infected with HIV, which may play a critical role in HCV transmission. Indeed, it has been shown that HIV increases HCV plasma VL compared with mono-infected patients [16], and causes defects in the gastrointestinal immune system [17]. Lastly, the practice of HIV serosorting (i.e. choosing sexual partners based on their HIV status) in order to avoid the use of condoms may have enhanced HCV infection or other STIs within HIV-infected men. With pre-exposure prophylaxis, the spread of HCV might change from HIV-positive to HIV-negative patients, as described in Amsterdam [4]. In this study, surprisingly, 11.5% of HIV-infected patients had a detectable HIV VL. The median VL was relatively low, but it reached up to 13 251 copies/mL in a context of high-risk behaviour.

As expected, the most represented genotypes were 1a and 4d; the latter has been emerging for several years among MSM [18,19]. One genotype 3a cluster was detected in this study. Genotype 3a, which is highly prevalent among European injecting drug users, was previously described very rarely in MSM clusters, contributing to the controversy about the importance of HCV contamination by injecting drug users.

This study has some limitations. Chains of transmission are certainly non-exhaustive, as is usually the case in phylogenetic studies. Indeed, in the present study, diagnosis of acute HCV infection was based on virological results during HIV monitoring or in the event of symptoms. Moreover, the number of re-infections might be underestimated as re-infections with the same genotype were not detected. In addition, even if the results were in accordance with previous reports, most patients were HIV-positive, and this group is generally monitored more closely than HIV-negative MSM before the spread of pre-exposure prophylaxis in France, potentially representing another recruitment bias of acute HCV infections. Nevertheless, three major hospitals and one main private laboratory in the area under consideration participated in the study and the conclusions are meaningful. Moreover, it has been shown by modelling data that HCV eradication in Europe will be based in large part on the control of infection in the subgroup of MSM engaging in high-risk behaviour towards contamination, for whom high treatment coverage will be needed [8,20].

In conclusion, these results highlight the need for frequent screening of STIs and HCV among HIV-positive MSM. HCV screening by polymerase chain reaction could be considered to reduce the diagnostic window. Moreover, the high clustering of acute HCV infections calls for rapid treatment of both chronic and acute HCV infections among this population. Preventive behavioural interventions are also required urgently.

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Competing interests

None declared.

Ethical approval

Not required.

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