High Clustering of Acute HCV Infections and High Rate of Associated STIs Among Parisian HIV-Positive Male Patients

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HIGHLIGHTS

- High clustering of acute HCV infections among parisian HIV-positive male patients
- High rate of associated sexually transmitted infections
- Call for a rapid treatment of not only chronic but also acute HCV infections
- Need of preventive behavioral interventions

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Abstract

Background

Increasing incidence of hepatitis C virus (HCV) infection in HIV-positive men having sex with men (MSM) has been described in recent years. We performed phylogenetic analyses of acute HCV infections to characterize the dynamics during the epidemic in Paris and evaluated associated sexually transmitted infections (STI).

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 intra-clade genetic distances <0.02 nucleotide substitutions per sites. STI 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 genotype 1a, 4d, 3a and 2k. At least 91.8% were HIV co-infected. HCV reinfection was evidenced for 24.7% of the patients and STIs for 20.0% of them. Twenty-two transmission chains were identified, including 52 acute Hepatitis C (11 pairs and 11 clusters from 3 to 7 patients).

Conclusions

These results revealed a strong clustering of acute HCV infections. Thus, rapid treatment of not only chronic but also acute infections is needed among this population to decrease HCV prevalence, in combination with preventive behavioral interventions.

Keywords: Hepatitis C; Coinfections, HIV; Sexually Transmitted Infections; Phylogeny; Homosexuality, Male.

INTRODUCTION

Emerging acute hepatitis C virus (HCV) infections among HIV-positive men having sex with men (MSM) have been described worldwide in recent years. For instance, rising incidence of HCV infections 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 (0.23/100 PY to 4.09/100 PY) [2]. This phenomenon has also been observed in cities such as Amsterdam [3], New York, or Sydney. Phylogenetic analyses revealed extensive networks of HCV transmission. And lastly, in Amsterdam, an expansion to non-HIV-infected MSM with high-risk behaviors and under Pre-Exposure Antiretroviral Prophylaxis (PrEP) was highlighted [4].

Furthermore, a high rate of reinfections among HIV-infected MSM was recently reported in an European study [5], 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 a high risk behavior towards contamination [8]. Indeed, many studies have shown that AHC are associated with recreational drug use and risky sexual behaviors (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 (called « le Marais ») among HIV-positive MSM in 2014-2016. We explored the phylogenetic clustering of these infections and characterized associated STIs, in order to better understand the dynamics of acute hepatitis C transmission in this area and support the need of efficient screening and management strategies in a high risk population.

METHODS

This retrospective, observational study enrolled 85 male patients from the geographical area « le Marais » of Paris, for whom an acute hepatitis C infection was diagnosed between May 2014 and April 2016 on virological results carried out by Virology departments of Pitié-Salpêtrière, Saint Antoine and Tenon hospitals, and by Cerballiance Laboratory. Highly likely acute hepatitis C was defined as a positive serology test and/or a positive HCV viral load (VL) associated with a negative HCV serology within the previous 12 months, or a positive HCV VL beyond 24 weeks of a successful treatment or spontaneous clearance with modification of HCV genotype (n=72). Possible acute hepatitis C was defined as a positive HCV VL with increase of alanine aminotransferase (ALT) ≥10 upper limit of normal (ULN) without any other etiology of hepatitis, or a positive HCV VL beyond 24 weeks of a 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 infections in the 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 retrospectively extracted from hospital electronic database or medical records and anonymized prior to analysis. This information included 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 ≤ 1 month before the acute HCV diagnosis (for syphilis: new diagnosis or reinfection defined as increase of Venereal Disease Research Laboratory (VDRL) titer by a factor ≥ 4). All subjects were informed by an information note and gave their consent to the study.

Polymerase sequences (NS5b, 334 nucleotides, amino acids 228 to 338) were obtained by Sanger Sequencing from the first HCV-positive sample, as described before (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]. Publically available consensus sequences (n=93 confirmed HCV genotypes/subtypes) and HCV sequences from local database (n=450, including 131 genotype 1a, 52 genotype 3a and 37 genotype 4d) were added to the dataset, after removing of the duplicates [14]. Clades with a branch probability≥0.80 and intra-clade genetic distances <0.02 nucleotide substitutions per sites were considered as representing transmission chains.

RESULTS

Patients were mainly MSM (at least 81.2%, n=69; 16 sexual orientations unknown), with a median age of 41.3 years (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 reinfections (n=21). Patients were infected with HCV genotype 1a (47.6%), 4d (39.0%), 3a (11.0%) and 2k (2.4%; 3 viruses not amplified) and at least 91.8% of them were co-infected with HIV (n=78; 2 HIV status unknown). No acute HIV infection was reported. Among the co-infected patients, 9 had a detectable HIV VL, from 20 to 13251 copies/mL (IQR:29-364), in a context of low level viremia (n=3), blips (n=2), recent treatment initiation (n=1), absence of ART treatment (n=1), treatment non-compliance (n=1), and resistance to the received treatment (n=1, loss to follow-up; Tenofovir resistance mutations: M41L, D67N, T215F, Emtricitabine: M184V and Raltegravir: N155H).

Acute HCV infections were found in twenty-two transmission chains, (52/81 acute Hepatitis C viruses sequenced (64.2%; 1 short sequence of genotype 3a excluded), of which 13 reinfections), divided in 11 pairs and 11 clusters from 3 to 7 patients (**Figure 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 (5 pairs and 5 clusters from 3 to 6 patient), 1 (1 cluster of 7 patients) and 11 (6 pairs and 5 clusters from 3 to 5 patients) transmission chains identified by genotype, respectively. Nine transmission chains were composed of acute HCV infections only (4 pairs and 5 clusters from 3 to 6 patients, including 4 reinfections in 1 pair and 2 clusters) whereas 13 were mixed with acute and chronic HCV infections from the background controls (7 pairs and 6 clusters from 3 to 7 patients, including 9 reinfections in 2 pairs and 4 clusters and 18 controls). Three reinfections

were part of the genotype 3a cluster of 7 patients. The rate of reinfection was not different between the linked cases and the unlinked ones (p= 0.868).

STIs were detected in 17 patients (20%) ≤1 month before the acute HCV diagnosis (8 *Treponema pallidum*, 5 *Neisseria gonorrhoeae*, 7 *Chlamydia trachomatis*, and 1 *Giardia intestinalis*). It must be noted that 56.2% of the STIs were detected among patients included in a HCV chain of transmission (n= 9/16, 1 non amplified), without any statistical significant difference with patients not included in a chain of transmission (p= 0.507). Two patients exhibited the same STIs among a cluster of 5 patients (*Neisseria gonorrhoeae* and *Chlamydia trachomatis*) and 2 among a cluster of 4 patients (*Neisseria gonorrhoeae)*.

In addition, prevalence of STIs was not higher among reinfections than in first HCV infections (p=0.615).

DISCUSSION

A large number of acute HCV infections has been diagnosed among HIV-infected MSM patients in Paris during the period 2014-2016 and, in this study, 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 reinfections. This is in line with recent report by Ingiliz *et al.* who showed that among 8 European centers from Austria, France, Germany, and the UK, the highest incidence of HCV reinfections was in Paris (21.8/100PY, 95% CI 11.3–41.8) [5]. These results raise concerns about the transmission of drug resistant viruses, as previously described [15].

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

In this study, most of the patients were co-infected with HIV, which might has a critical role in HCV transmission. Indeed, it has been shown that HIV increases HCV plasma VL compared to mono-infected patients [16], and causes defects in the gastrointestinal immune system [17]. Lastly, HIV-serosorting practice to avoid condom use had been supposed to also have enhanced HCV infection or other STIs within HIV-infected men. With PrEP, the spread of HCV infections might change from HIV-positive to HIV-negative patients, as already 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 behavior.

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 very rarely described in MSM cluster, contributing to the controversy about the importance of HCV contamination by injecting drug.

Our study presents some limitations: chains of transmission are certainly non-exhaustive, as it is usually the case in phylogenetic studies. Indeed, in the present study, acute HCV infection diagnosis was realized on virological results during HIV usual monitoring or in the event of symptoms. Moreover, number of reinfections might be underestimated as reinfections with the same genotype were not detected. In addition, even if the results were in accordance to previous reports, most patients were HIV-positive, a group generally more closely monitored than HIV-negative MSM before the spread of PrEP in France, potentially representing another recruitment bias of acute HCV infections. Nevertheless, 3 major hospitals and one of the main private laboratory of the area under consideration have participated to the study and conclusions of the study are meaningful. Moreover, it has been recently showed by modeling data that HCV eradication in Europe will be based in large parts on control of infections in the subgroup of MSM engaging in high risk behavior towards contamination, for whom high treatment coverage will be needed [8,20].

In conclusion, our results highlight the need for frequent screening of STIs and HCV among HIV-positive MSM. HCV-screening by PCR could be considered to reduce the diagnostic window period. Moreover, the high clustering of acute HCV infections calls for a rapid treatment of not only chronic but also acute HCV infections among this population. Preventive behavioral interventions are also urgently required.

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Declarations

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Ethical Approval: Not required

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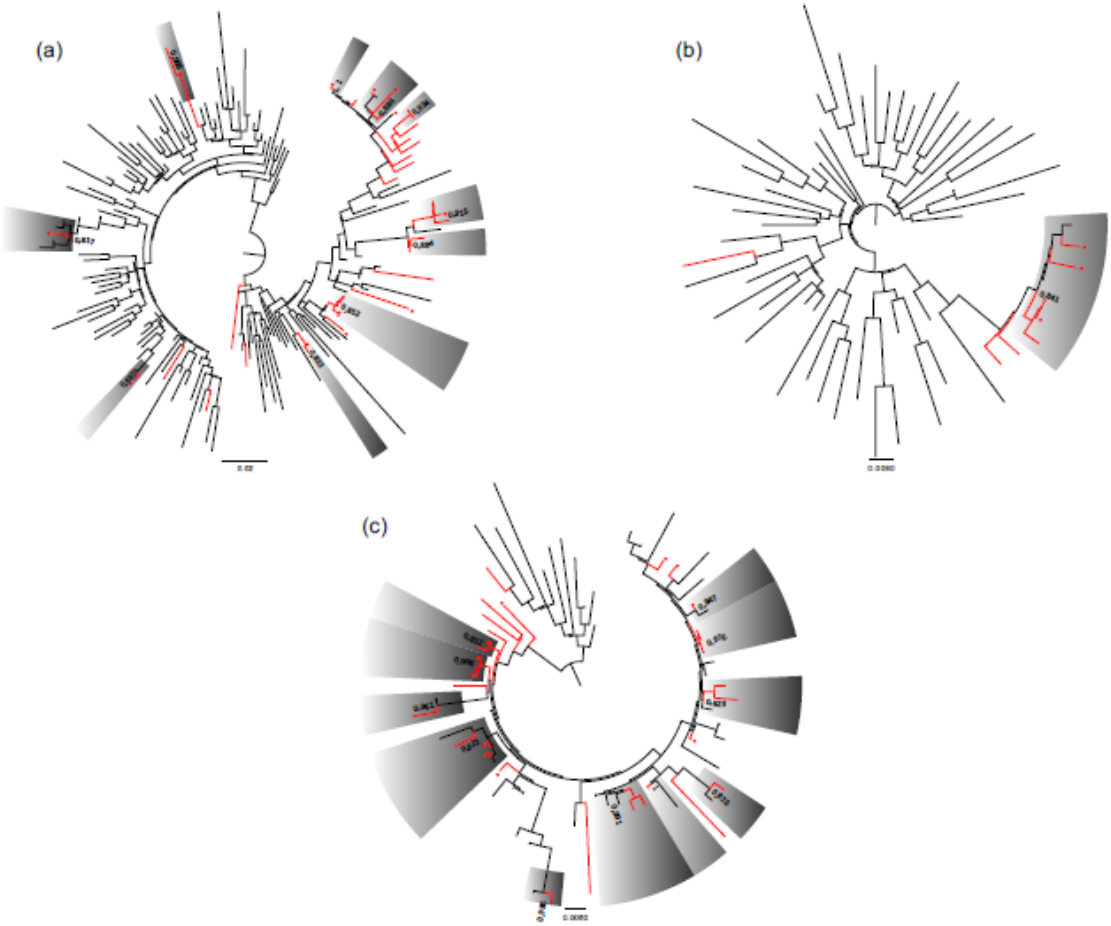

Figure 1. Phylogenetic tree of HCV subtype 1a (a), subtype 3a (b) and subtype 4d (c). Grey halos represent the men having sex with men-specific clusters containing acute hepatitis C (red branches). HCV reinfections are indicated by a mark (*).