

HIV

Increase in hepatitis C virus incidence in HIV-1-infected patients followed up since primary infection

J Ghosn, C Deveau, C Goujard, I Garrigue, N Saïchi, J Galimand, Z Nagy, C Rouzioux, L Meyer, M-L Chaix, for the French PRIMO Cohort Study Group (ANRS CO 06)



Sex Transm Infect 2006;**82**:458–460. doi: 10.1136/sti.2006.021493

See end of article for authors' affiliations

Correspondence to:
Dr Jade Ghosn,
Laboratoire de Virologie,
EA MRT 3620, Université
René Descartes Paris5,
CHU Necker-Enfants
Malades, 149 Rue de
Sèvres, 75015 Paris,
France; jade.ghosn@bct.
ap-hop-paris.fr

Accepted 16 August 2006
Published Online First
21 August 2006

Background: An increase in the incidence of sexually transmitted infections and hepatitis C virus (HCV) infections in HIV-infected men who have sex with men (MSM) has recently been reported.

Objective: To estimate HCV incidence and risk factors among HIV-1-infected patients followed up since primary HIV infection in the French PRIMO Cohort between 1996 and 2005.

Patients and methods: All patients with at least 18 months of follow-up were studied. HCV antibody tests were performed on baseline plasma samples and repeated on the latest available sample when negative at baseline.

Results: In total, 402 patients with a median follow-up of 36 (range 18–104) months were eligible. HCV seroconversion was observed in 6 patients (4 men and 2 women), corresponding to an HCV incidence rate of 4.3 per 1000 person-years. Incidence rates in men and women were 3.5 and 7.8 per 1000 person-years, respectively. The incidence rate was 1.2 per 1000 person-years before January 2003 and 8.3 per 1000 person-years after January 2003 ($p=0.06$). The classic risk factors for HCV infection were found in women (intravenous drug use, and body piercing), whereas the only identified risk factor for HCV acquisition was unsafe sex in the four men.

Conclusions: Increase in the incidence of acute HCV infection in recently HIV-infected patients confirms the shift in sexual behaviour in the recent years, especially in HIV-infected MSM. Repeated testing for HCV antibodies should be carried out in HCV-negative HIV-infected patients and specific recommendations about protected sex should be clearly provided.

The recent increase in sexually transmitted infections (STIs) among HIV-infected men who have sex with men (MSM) suggests a relapse in at-risk sexual behaviour in this population, and is a major public health issue. Since the beginning of the 21st century, marked increases in syphilis,¹ rectal and genital gonorrhoea,^{1,2} as well as anorectal lymphogranuloma venereum,^{3,4} have been reported in HIV-infected MSM from Europe and the US.

Along with the increasing reports on STI and HIV superinfection among HIV-infected MSM, many groups have reported an increasing incidence of acute hepatitis C virus (HCV) infections in patients who had no risk factor other than high-risk sexual practices.^{5–10}

In France, an increase in at-risk sexual behaviour was recorded since the late 1990s in HIV-1-infected patients presenting with (primary HIV infection) PHI and enrolled in the French PRIMO cohort.¹¹ We investigated the incidence of HCV infections in this specific population.

PATIENTS AND METHODS

Study population

Our study comprised patients presenting with primary HIV infection, enrolled in the multicentre prospective French ANRS PRIMO Cohort (ANRS CO 06).^{12,13} From 1996 to July 2005, 605 patients with PHI have been enrolled in the cohort, with a median follow-up of 30 (range 0–109) months.

Primary HIV infection (PHI) was identified as described previously.¹⁴

For all patients enrolled in the PRIMO Cohort, clinical visits were carried out and serum or plasma samples were stored at -80°C at inclusion, at 1, 3 and 6 months, and then every 6 months. HCV serology is a part of the tests performed

at baseline for all the patients included in the cohort. Our analysis was restricted to patients enrolled in the PRIMO Cohort who had at least 18 months of clinical and biological follow-up, with the cut-off date of 1 July 2005.

HCV serological and amplification testing

For all patients, inclusion plasma samples were prospectively tested for anti-HCV antibodies (Ortho HCV 3.0 enzyme linked immunosorbent assay test, Ortho Diagnosis System, Raritan, New Jersey, USA). For patients with negative anti-HCV antibodies at inclusion in the PRIMO cohort, the latest available frozen plasma sample was tested for HCV serology. When this latest sample was positive for HCV antibodies, HCV serology was retrospectively performed on stored frozen plasma samples from previous visits to determine the timing of HCV infection more precisely. Qualitative detection of HCV RNA (HCV Cobas Monitor V.2.0, Roche Diagnosis System, Meylan, France; lower limit of quantification 50 IU/ml) was performed on all samples positive for anti-HCV antibodies, and genotyping (Innolipa HCV II, Bayer Diagnostics, Emeryville, California, USA) in samples with detectable HCV RNA.

RESULTS

Characteristics of patients at baseline

In all, 402 of 605 patients were eligible for this study as they had at least 18 months of follow-up in the cohort at the time of the analysis. Their median age was 34 (range 15–72) years,

Abbreviations: HCV, hepatitis C virus; IVDU, intravenous drug use; MSM, men who have sex with men; PHI, primary HIV infection; STI, sexually transmitted infection

Table 1 Characteristics of patients at baseline (n = 402)

| | |
|--------------------------|-----------------|
| Men | 327/402 (81.3%) |
| HIV risk factor | |
| Homosexual intercourse | 252/327 (77.1%) |
| Heterosexual intercourse | 44/327 (13.5%) |
| IVDU or blood exposure | 5/327 (1.5%) |
| Other | 8/327 (8%) |
| Women | 75/402 (18.7%) |
| HIV risk factor | |
| Heterosexual intercourse | 72/75 (96%) |
| Other | 3/75 (4%) |
| Positive HCV antibodies | 23/402 (5.7%) |
| Women | 4/23 |
| Men | 19/23 |
| Detectable HCV RNA | 10/23 |
| HCV genotype 1 | 9/10 |
| HCV genotype 2 | 1/10 |

HCV, hepatitis C virus; IVDU, intravenous drug use.

and 18.7% (n = 75) were women. Table 1 summarises their characteristics.

Anti-HCV antibodies were detected in 23 (5.7%) patients at inclusion—that is, soon after PHI. These patients (4 women and 19 men) did not significantly differ (p = NS) from the remaining 379 HCV-negative patients, except for risk factor for HIV infection. The proportion of patients with blood exposure (occupational, or intravenous drug use (IVDU)) was significantly higher among the HCV-positive patients (17.4%, 4/23; two patients infected from occupational exposure and two IVDU) than among HCV-negative patients (0.3%, 1/379; infected from occupational exposure, p < 0.001). Conversely, the proportion of homosexual men was significantly lower among HCV-positive patients (47.8%) than among HCV-negative patients (63.9%, p < 0.001). In addition, among all MSM, the proportion of patients with positive anti-HCV antibodies at the time of PHI was 4.3%.

HCV RNA was detectable in 10 of the 23 (45%) patients with positive HCV antibodies, with HCV genotype 1 in nine patients (MSM, n = 2; IVDU n = 4; heterosexual, n = 1; occupational exposure, n = 1; unknown, = 1), and genotype 2a/2c in one patient (occupational exposure).

Longitudinal follow-up

The median follow-up time of the 379 HCV-uninfected patients was 36 (range 18–104) months, providing a follow-up period of 1405 person-years. HCV seroconversion was observed in six patients (4 men) between 1996 and 2005, corresponding to an HCV incidence rate of 4.3 per 1000 person-years. Incidence rates in men and women were 3.5 and 7.8 per 1000 person-years, respectively (p = NS). All but one seroconversion occurred since 2003, yielding to an incidence rate of 1.2 per 1000 person-years before January 2003 and 8.3 per 1000 person-years since 2003 (p = 0.06).

In four of six patients, the classic risk factors for HCV infection (IVDU, blood transfusion, recent invasive medical procedures, a history of acupuncture, tattooing or, body piercing) were inquired into, but were not found.

Patients A and B were women (A: HCV genotype 3; B: HCV genotype 1a). Both had a history of body piercing during the period around HCV seroconversion. Patient B reported inconstant condom use and intravenous drug use in the few months before HCV seroconversion with her steady partner who was an IVDU who became HIV infected in 2002 and was diagnosed HCV infected in 2003.

The other four cases of HCV seroconversion occurred in men (C, E, F: HCV genotype 4d; D: HCV genotype 1). All four patients reported highly at-risk sexual behaviour with unprotected anal sex with men. At the time of HCV seroconversion, syphilis was concomitantly diagnosed in two of them (C and E). A history of syphilis (in patients D

and E) and *Chlamydia trachomatis* prostatitis (D) was also recorded.

DISCUSSION

Evidence is now available that HCV may be transmitted via the sexual route. Indeed, HCV is detectable in semen,^{15, 16} and male-to-female sexual transmission has been clearly documented.¹⁷ We observed an HCV incidence rate of 4.3 per 1000 person-years in a cohort of HIV-infected patients comprising <1% of injecting drug users and where most people became HIV infected through the sexual route. We also showed that HCV seroconversion occurred not only in HIV-infected MSM but also in HIV-infected women. In France, the incidence rate of HCV infection in the general population has been estimated at a much lower level, 0.076 per 1000 person-years.¹⁸ The same trend was also found in Switzerland, where the incidence of acute HCV ranged from 0 to 0.04 cases per 1000 person-years in the general population (<http://www.bag.admin.ch/infreprting/gso1/index.htm>), but it reached 7 per 1000 person-years among HIV-infected MSM between 1988 and 2004.¹⁰ The incidence rate of HCV transmission was also evaluated among a large sample of non-HIV-infected, heterosexual, monogamous HCV-serodifferent couples followed for 10 years in Italy, and reached only 0.37 per 1000 person-years.¹⁹ In our study, we also found that the proportion of MSM with positive anti-HCV antibodies at the time of PHI was low (4.3%), suggesting that, even among MSM with at-risk sexual behaviour (given that they acquired HIV), HCV prevalence was low before the acquisition of HIV infection. This is in keeping with other published data, suggesting that HCV sexual transmission may be enhanced by HIV coinfection,²⁰ past or current syphilis or gonorrhoea,^{20–22} herpes simplex type 2 infection²³ and at-risk sexual behaviour with multiple casual partners,^{23–25} anal intercourse^{17, 26} and traumatic sexual practices.⁸

HCV RNA is more often detected in semen of HIV–HCV-coinfected men than is HCV-monoinfected patients,¹⁶ and HIV-infected men have markedly higher seminal lymphocytes than HIV-uninfected men,²⁷ which could yield a higher viral burden of HCV in the semen of HIV–HCV-coinfected men than in HCV-monoinfected men. In addition, the concomitant presence of another STI, with genital erosive lesions, may facilitate HCV infection.²¹ In two of the four men who seroconverted for HCV, the concomitant diagnosis of syphilis may suggest that HCV was transmitted when a chancre was present. Finally, high-risk sexual practices with bleeding during sex may facilitate transmission of blood-borne infections such as HCV.⁸

Interestingly, the only identified risk factor in men was at-risk sexual behaviour, whereas the classic risk factors for HCV acquisition were found in both women. In addition, even if we considered that patient B might have acquired HCV through heterosexual intercourse with her HCV-infected partner, the incidence of heterosexual transmission of HCV in our cohort would be close to that reported by Vandelli *et al*,¹⁹ suggesting that the increase in HCV incidence is fuelled by the sexual route only in a specific group of MSM engaging in highly at-risk sexual behaviour. Moreover, patients C, E and F were infected with HCV genotype 4d in 2003 and 2004, concomitantly with other reports of acute HCV infections with a cluster of HCV genotype 4d in the same geographical area,⁹ suggesting the sexual spread of this genotype in HIV-infected MSM in Paris.

We showed that acquisition of HCV infection seems to be more frequent in HIV-infected people followed up in the French PRIMO cohort (especially in MSM) than in non-HIV heterosexual people, and the incidence of HCV has increased in this cohort since 2003, concomitantly with other reports of increasing STI incidence among HIV-infected MSM, thus

confirming the shift in the sexual behaviour of this population between the late 1990s and the beginning of the 21st century,¹¹ with a recent lower adherence to safer sex. As the treatment of chronic HCV infection is less potent in HIV-HCV-coinfected patients than in HCV-monoinfected patients,^{28, 29} early identification of acute HCV infection is important as treatment during the acute phase may represent a window for HCV eradication.³⁰ Thus, repeated screening for HCV antibodies in HCV-negative HIV-infected patients (not only MSM) with sexual activity should be recommended and routinely set. HIV-infected patients should be aware of the ongoing HCV spread, and specific recommendations regarding protected sex (condom use and gloves for at-risk practices) should be clearly provided for the prevention of STI and blood-borne diseases.

ACKNOWLEDGEMENTS

We thank all the patients and the participating doctors.

.....

Authors' affiliations

J Ghosn, J Galimand, C Rouzioux, M-L Chaix, Laboratoire de Virologie, Université René Descartes Paris 5, CHU Necker-Enfants Malades, Paris, France

C Deveau, N Saïchi, Z Nagy, L Meyer, Epidemiology, Demography and Social Sciences, INSERM, National Institute of Health and Medical Research, Le Kremlin-Bicêtre, France; University Paris-Sud 11, Faculté de Médecine, Le Kremlin-Bicêtre, France; AP-HP, Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

C Goujard, Service de Médecine Interne et INSERM E109, CHU Bicêtre, Le Kremlin-Bicêtre, France

I Garrigue, Laboratoire de Virologie, CHU Pellegrin, Bordeaux, France

Funding: This study was supported by a scholarship from Sidaction-Ensemble Contre le Sida (JG) and funded by the French National Agency for Research on AIDS.

Competing interests: None declared.

Part of this study was presented at the 13th Conference on Retroviruses and Opportunistic Infections, Denver, Colorado, USA, February 2006.

Contributors: JG: clinical coordination, study design, paper writing; CD: coordination of the PRIMO Cohort, sample monitoring, statistical analysis; CG: referent physician of the PRIMO Cohort study, study design, paper writing; IG: virology assessments; NS and ZN: study monitoring of the PRIMO Cohort; J Galimand: virology assessments; CR: referent virologist of the PRIMO Cohort, study design, paper writing; LM: principal investigator of the PRIMO Cohort, study design, statistical analysis, paper writing; M-LC: principal investigator, study design, virological validation, paper writing.

REFERENCES

- Dupin N, Jdid R, N'Guyen YT, et al. Syphilis and gonorrhoea in Paris: the return. *AIDS* 2001;**15**:814-15.
- Fenton KA, Rogers PA, Simms I, et al. Increasing gonorrhoea reports—not only in London. *Lancet* 2000;**355**:1907.
- Bauwens JE, Orlander H, Gomez MP, et al. Epidemic lymphogranuloma venereum during epidemics of crack cocaine use and HIV infection in the Bahamas. *Sex Transm Dis* 2002;**29**:253-9.
- Den Hollander JG, Ossewaarde JM, de Marie S. Anorectal ulcer in HIV patients, don't forget lymphogranuloma venereum! *AIDS* 2004;**18**:1484-5.
- Ghosn J, Pierre-Francois S, Thibault V, et al. Acute hepatitis C in HIV-infected men who have sex with men. *HIV Med* 2004;**5**:303-6.

- Browne R, Asboe D, Gilleece Y, et al. Increased numbers of acute hepatitis C infections in HIV positive homosexual men; is sexual transmission feeding the increase? *Sex Transm Infect* 2004;**80**:326-7.
- Gambotti L, Batisse D, Colin-de-Verdiere N, et al. Acute hepatitis C infection in HIV positive men who have sex with men in Paris, France, 2001-2004. *Euro Surveill* 2005;**10**:115-17.
- Gotz HM, van Doornum G, Niesters HG, et al. A cluster of acute hepatitis C virus infection among men who have sex with men—results from contact tracing and public health implications. *AIDS* 2005;**19**:969-74.
- Serpogaj J, Chaix M, Batisse D, et al. Sexually transmitted acute infection with a clustered genotype 4 hepatitis C virus in HIV-infected men and inefficacy of early antiviral therapy. *AIDS* 2006;**20**:233-40.
- Rauch A, Rickenbach M, Weber R, et al. Unsafe sex and increased incidence of hepatitis C virus infection among HIV-infected men who have sex with men: the Swiss HIV Cohort Study. *Clin Infect Dis* 2005;**41**:395-402.
- Desquilbet L, Deveau C, Goujard C, et al. Increase in at-risk sexual behaviour among HIV-1-infected patients followed in the French PRIMO cohort. *AIDS* 2002;**16**:2329-33.
- Ghosn J, Pellegrin I, Goujard C, et al. HIV-1 resistant strains acquired at the time of primary infection massively fuel the cellular reservoir and persist for lengthy periods of time. *AIDS* 2006;**20**:159-70.
- Chaix ML, Descamps D, Harzic M, et al. Stable prevalence of genotypic drug resistance mutations but increase in non-B virus among patients with primary HIV-1 infection in France. *AIDS* 2003;**17**:2635-43.
- Desquilbet L, Goujard C, Rouzioux C, et al. Does transient HAART during primary HIV-1 infection lower the virological set-point? *AIDS* 2004;**18**:2361-9.
- Leruez-Ville M, Kunstmann JM, De Almeida M, et al. Detection of hepatitis C virus in the semen of infected men. *Lancet* 2000;**356**:42-3.
- Briat A, Duloust E, Galimand J, et al. Hepatitis C virus in the semen of men coinfecting with HIV-1: prevalence and origin. *AIDS* 2005;**19**:1827-35.
- Halfon P, Riflet H, Renou C, et al. Molecular evidence of male-to-female sexual transmission of hepatitis C virus after vaginal and anal intercourse. *J Clin Microbiol* 2001;**39**:1204-6.
- Conférence de consensus. Traitement de l'hépatite C. *Gastroenterol Clin Biol* 2002;**26**:B303-11.
- Vandelli C, Renzo F, Romano L, et al. Lack of evidence of sexual transmission of hepatitis C among monogamous couples: results of a 10-year prospective follow-up study. *Am J Gastroenterol* 2004;**99**:855-9.
- Mittal A. High frequency of antibodies to syphilis and HIV in hepatitis C virus positive blood donors may reflect its sexual transmission in this region. *Sex Transm Infect* 2003;**79**:170-1.
- Marx MA, Murugavel KG, Tarwater PM, et al. Association of hepatitis C virus infection with sexual exposure in southern India. *Clin Infect Dis* 2003;**37**:514-20.
- Bodsworth NJ, Cunningham P, Kaldor J, et al. Hepatitis C virus infection in a large cohort of homosexually active men: independent associations with HIV-1 infection and injecting drug use but not sexual behaviour. *Genitourin Med* 1996;**72**:118-22.
- Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999;**341**:556-62.
- Mele A, Stroffolini T, Tosti ME, et al. Heterosexual transmission of hepatitis C in Italy. *J Med Virol* 1999;**57**:111-13.
- Feldman JG, Minkoff H, Landesman S, et al. Heterosexual transmission of hepatitis C, hepatitis B, and HIV-1 in a sample of inner city women. *Sex Transm Dis* 2000;**27**:338-42.
- Balasekaran R, Bulterys M, Jamal MM, et al. A case-control study of risk factors for sporadic hepatitis C virus infection in the southwestern United States. *Am J Gastroenterol* 1999;**94**:1341-6.
- Ghosn J, Viard JP, Katlama C, et al. Evidence of genotypic resistance diversity of archived and circulating viral strains in blood and semen of pre-treated HIV-infected men. *AIDS* 2004;**18**:447-57.
- Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA* 2004;**292**:2839-48.
- Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004;**351**:438-50.
- Vogel M, Bieniek B, Jessen H, et al. Treatment of acute hepatitis C infection in HIV-infected patients: a retrospective analysis of eleven cases. *J Viral Hepat* 2005;**12**:207-11.