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Unusually high HIV infectiousness in an HIV-, HCV- and HSV-2-coinfected heterosexual man

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Summary

We report an HIV-HCV-HSV-2-coinfected man, who infected all of five sequential female sexual partners within seven years. HIV-RNA in semen was unusually high and exceeded that in plasma by one $\log_{10}$. Screening for sexually transmitted diseases remained negative with the exception of HSV-2-seropositivity. Recurrent asymptomatic genital herpes might explain the patient's increased HIV-RNA shedding in semen.

Key words: male-to-female transmission; HIV; HSV-2; herpes genitalis; seminal HIV load; phylogenetic analysis

Introduction

We report a case of an HIV-HCV-HSV-2-coinfected man with an unusually high HIV-RNA in semen ("supershedder"), who infected all of five sequential female sexual partners within seven years. We discuss the potential reasons for the unusually high infectiousness of this case.

Case

In 1989 the source patient acquired HIV-HCV-coinfection by needle-sharing (or unsafe sex) with an HIV-HCV-coinfected woman, who died of AIDS in 1996. CD4-count was 611/µl (30%) and HIV-RNA 5.16 log copies/ml when antiretroviral treatment was started in March 1997. Viral load was fully suppressed nine months later. As he felt healthy the patient stopped HIV-therapy in January 1998 and since then had refused any follow-up in his HIV clinic.

From 2000 to 2007 the index patient had five female steady sexual partners in sequence. He disclosed his HIV-status to none of them and even pretended to have negative HIV-tests. Hence, he never used condoms with his partners. In April 2006, the patient underwent vasectomy. In November 2006 he presented in a psychiatry clinic, where HIV was "re-diagnosed". His CD4-count was 550/µl (24%) and the clinical examination revealed candida stomatitis as well as porphyria cutanea tarda. In June 2008, HIV-RNA was 4.9 log copies/ml in plasma and 5.9 log copies/ml in semen.

Figure 1 summarises the time course of the five sequential female partnerships of the index patient (length of the sexual relation, negative and positive HIV-tests, occurrence of primary HIV-infection).

All women had regular (1–4×/week) unprotected vaginal sex with ejaculation with the source patient. Woman 1 also reported receptive anal sex with him.

Woman 1 and 2 were not diagnosed HIV-positive until several months after their last sexual contact with the index patient. In contrast, Woman 3, 4 and 5 presented with symptoms of acute HIV-infection in the third, seventh and second month respectively of their sexual relation with the source patient.

However, only Woman 4 was correctly diagnosed with primary HIV-infection. She presented with pharyngitis, lymphadenopathy, fever >38 °C and maculopapular exanthema. In addition, herpes genitalis and candida oesophagitis were suspected. Her HIV-antibody/antigen-test was positive and the initial HIV-immunoblot still negative while showing two bands four days later.

In Woman 3 fever up to 40 °C, non-itching exanthema, thrombocytopenia and elevated transaminases were initially attributed to CMV-infection (IgG negative, IgM positive) alone because of a negative HIV-antibody/antigen-test. However she already had 7.1 log copies/ml plasma HIV-RNA at that time, as discovered retrospectively.

Woman 5 presented with fever, conjunctivitis, dry cough, maculopapular rash, thrombocytopenia, elevated transaminases and LDH. She was initially diagnosed as

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measles, but HIV-RNA was already detectable in a retrospectively analysed sample from the time of her presentation.

Sequence analysis of the HIV-strains of the six individuals showed a high degree of sequence homology and phylogenetic relationship (fig. 1), confirming the hypothesis of five male-to-female transmissions from a common source.

Discussion

This case has infected all five of five female partners within seven years. With the exception of the first partner, all transmission events occurred within the first six months of the relationship. Vasectomy of the index patient in 2006 did not prevent HIV-transmission to his subsequent sexual partners (Woman 4 + 5), which is consistent with the literature [1].

Wawer et al. found a 22% overall transmission rate per partnership and a transmission rate of 8.7% within the first ten months of a sexual relationship with a chronically infected individual [2]. Based on these figures, the likelihood of the cumulative event of five subsequent infections in this case would equal 0.087^4 x 0.22, or 1 in 10 000. Thus, this man represents an extraordinary case of unusually high infectiousness.

One might speculate about possible reasons for this high infectiousness. In the light of seminal viral burden correlating with HIV-infectiousness [3], it is striking that the patient had a relatively high HIV-RNA in semen (5.9 log copies/ml), which exceeds that in blood by one log. Normally, seminal viral load measurements are approximately one log lower than in plasma [4, 5]. Consistent with other reports, Tachet et al. found a population of supershedders (HIV-RNA in semen one log higher than in blood) in less than 10% of chronically infected individuals without symptoms of urethritis [6].

This patient can clearly be defined as a supershedder and supports Tachet's speculation of a high infectiousness in such an individual [6]. The reasons for the high infectivity and/or supershedding are unknown. As Cohen et al. impressively showed, concomitant sexually transmitted diseases are a major cause of increased seminal HIV-RNA [7]. In sub-Saharan Africa, seminal viral load was eight times higher in HIV-seropositive men with urethritis than in seropositive men without urethritis (5.1 vs 4.2 log copies/ml, p = 0.035), despite similar CD4-counts and HIV-RNA in blood plasma. Other possible explanations for supershedders might be non-infectious inflammatory conditions.

The patient, however, denied symptoms of STDs (sexually transmitted diseases) including genital ulcers in the past. Syphilis serology, chlamydial and gonococcal PCR in urine were negative. Finally, leucocyturia (66/µl) and specific HSV-2-seropositivity (HSV-1 negative) pointed to recurrent asymptomatic genital herpes. Unfor-

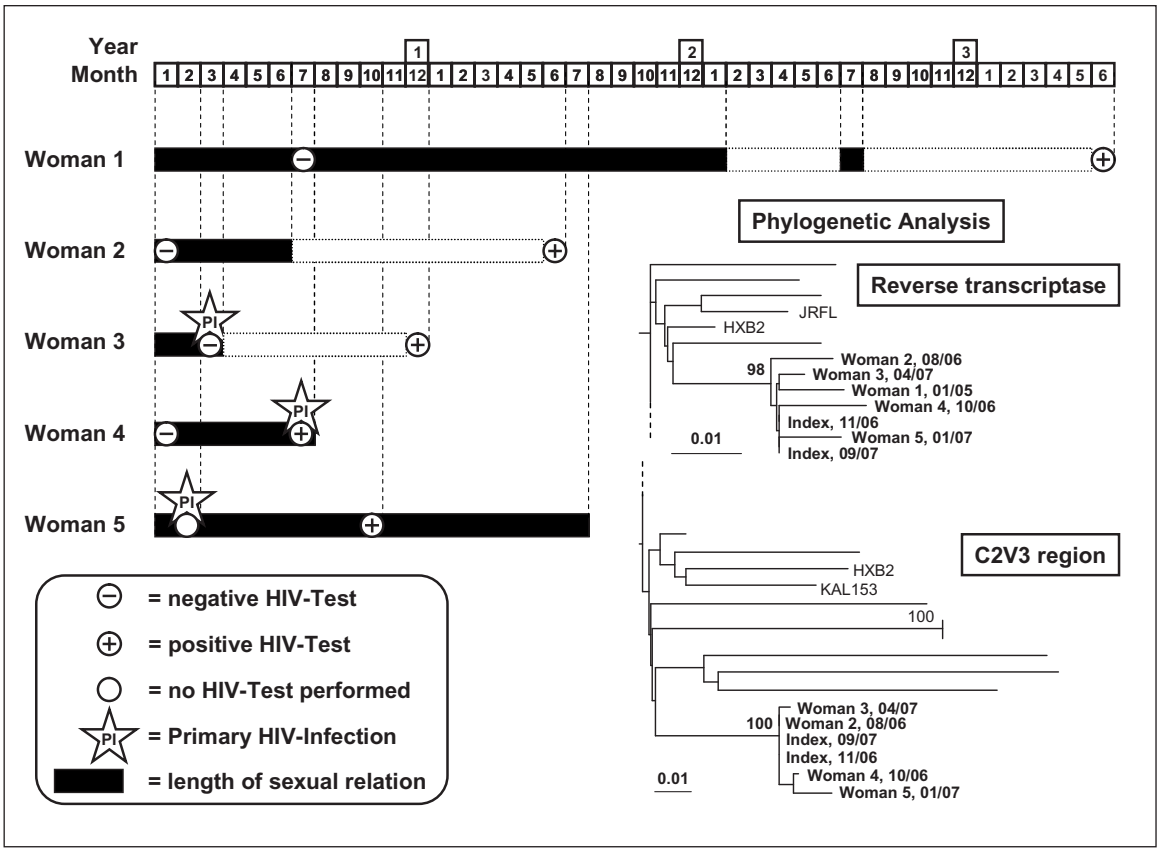

Figure 1

Time course of the five sexual relations of the index patient and phylogenetic relationship of the HIV-strains. Phylogenetic analyses were performed by maximum-likelihood tree produced with PhyML, using the General Time-Reversible model (nucleotide substitution), from a multiple alignment made with Muscle. Bootstrap values above 98/100 were considered significant. JRFL, HXB2 and KAL153 are standard viral strains for reference. C2V3 refers to the sequenced domain of the viral envelope.

tunately, after HIV-RNA-determination no semen was left for HSV-2-DNA-detection.

Causality of HSV-2 for the high infectiousness and HIV-supershedding cannot be proven. However, we found no other explanation in this case and increasing evidence supports the hypothesised link [8]. Butler et al. correlated HIV transmission risk with HSV-2-serostatus in MSM (men who have sex with men). HSV-2-serostatus was associated with HIV transmission only when the HIV-infected source partner was HSV-2-seropositive and the HIV-exposed partner was not (OR 16, p <0.03). Thus, HSV-2-infection increased the risk of transmission but not acquisition of HIV.

A "mucosal synergy" between HSV-2 and HIV has been described with HIV-infection impairing HSV-2 mucosal immune control and increased HSV-2 genital reactivation resulting in enhanced HIV-shedding [9, 10]. Acyclovir was not effective in reducing HIV-1 acquisition in HSV-2 seropositive women and MSM [11, 12], but, as demonstrated by Dunne et al. and others, acyclovir and valacyclovir, respectively, significantly reduced rectal and plasma HIV-1-levels in HIV-1/HSV-2-coinfected men [13] and genital and plasma HIV-1-levels in dually infected women [14, 15]. Proof-of-concept trials whether HSV suppression can prevent HIV-1 transmission are in progress.

In 1989 Clumeck et al. published a similar cluster of HIV infection in Belgium. 19 previous women sexual partners of a HIV-infected man were identified [16]. 11 (56%) of the tested partners were seropositive. Interestingly, the index case presented by Clumeck also had HSV-2 infection (Clumeck, personal communication). Concerning the cause of this high rate of transmission several factors were discussed. For example, high disseminator patient, highly virulent HIV strain, and presence of genital herpes). In our case, transmission rate was even higher.

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