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HIV-1 cDNA in Semen

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Abstract

Episomal 2-long terminal repeat (LTR) HIV-1 cDNA, a by-product of HIV-1 infection, is used in clinical trials as a marker for ongoing viral replication. It would be useful to employ 2-LTR cDNA to monitor cryptic HIV-1 infection in the genital tract of men on antiretroviral therapy (ART) to predict the evolution of sexually transmissible drug-resistant HIV-1, but studies thus far have failed to detect this marker in semen.

Keywords: Hungary; Peginterferon alfa-2a/Ribavirin; Predictive value; PROPHESYS; Real-world; Virologic response

Introduction

The global AIDS epidemic is primarily attributed to the sexual transmission of Human Immunodeficiency Virus type-1 (HIV-1), a retrovirus that infects CD4+ T cells and macrophages and causes severe immunosuppression in most untreated infected individuals. In HIV-1-infected men, sexual transmission rates are high during acute infection and late-stage disease when HIV-1 viral loads are elevated in both semen and peripheral blood [1, 2].

Materials And Methods

Semen processing

The semen samples used in this study were archived from previously published studies [1, 6]. Positive control samples used for validation of 2-LTR cDNA detection/quantification were from ART-naïve men with evidence of seminal HIV-1 viremia (Group I). HIV-1 proviral DNA in the cellular fraction had been assessed by quantitative PCR; infectious HIV-1 was detected in seminal plasma and cellular fractions by p24 assay following up to 21 days of coculture with phytohaemagglutinin A (PHA)-stimulated peripheral blood mononuclear cells (PBMC) [1].

The PCR products were also analyzed by agarose gel electrophoresis, Southern blot and DNA sequencing. Fifteen microliters of PCR product were separated on a 1% agarose gel and transferred to a Hybond N+ membrane (Schleicher & Schuell, Keene, NH); Southern blot was performed using the 29-base biotinylated probe. After a high-stringency wash, streptavidin-HRP conjugate and its substrate in Luminol/enhancer solution (Pierce, Rockford, IL) were added to the membrane. The image was acquired with Fluorchem SP (Alpha Innotech, San Leandro, CA). Direct sequencing of the PCR product was performed by the Dana-Farber/Harvard Cancer Center core facility.

Results

Many semen samples with indicators of HIV-1 infection were negative in the 2-LTR cDNA assay. Of the four negative Group I samples, all were from ART-naïve men with seminal HIV-1 proviral DNA (inclusion criteria for Group I); one was culture-positive for HIV-1, and 2 were CMV DNA+. Of the 20 2-LTR cDNA-negative Group II baseline samples, one was leukocytospermic, 4 had >100 copies of HIV-1 proviral DNA, 5 contained >1,000 copies of cell-free HIV-1 RNA and 6 were CMV DNA-positive. Of the 40 2-LTR cDNA-negative post-indinavir semen samples, four were leukocytospermic, 12 had proviral HIV-1 DNA, and 5 were from men with seminal CMV DNA.

Discussion

The highest copy numbers of 2-LTR cDNA in this study were detected in semen of a man failing indinavir therapy who later developed unique PI resistance mutations in semen. Data from this study suggest that seminal 2-LTR cDNA may provide a useful marker to predict the evolution of sexually transmissible HIV-1 drug resistance mutations in men on ART. Since the number of HIV-1-infected cells in semen is restricted by small sample size, steps must be taken to maximize HIV-1 DNA extraction. In the only other published study to investigate 2-LTR cDNA in semen, Nunnari et al.

All of the 2-LTR cDNA+ semen samples contained HIV-1 proviral DNA, and all but two were positive for HIV-1 RNA or infectious virions. Five out of 7 of the 2-LTR cDNA+ semen samples were also positive for seminal CMV DNA, but this association was not statistically significant because CMV infection was common overall (4/8 men in Group I and 9/22 men in Group II were positive for seminal CMV).

Two men on dual nucleoside analog treatment had 2-LTR cDNA in semen; one of these individuals failed subsequent indinavir therapy and continued to have high levels of HIV-1 RNA and 2-LTR cDNA in semen, although peripheral viral load was undetectable. These data provide further evidence that HIV-1 replication can occur in the genital tract of men on ART, potentially leading to the evolution of drug resistance mutations in semen that cannot be monitored in peripheral blood. On the other hand, none of 40 post-indinavir semen samples from men controlling HIV-1 RNA levels in blood and semen was positive for 2-LTR cDNA, suggesting that cryptic HIV-1 replication in the genital tract (without the appearance of HIV-1 RNA in blood or semen) may be uncommon in men on effective ART [6].

Conclusion

This study, which shows that HIV-1 2-LTR c-DNA is detectable in semen cells, provides evidence that HIV-1 infection occurs in the genital tract.

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