Prevalence of Human T-Cell Leukemia/Lymphoma Virus (HTLV) Type II Infection Among High-Risk Individuals: Type-Specific Identification of HTLVs by Polymerase Chain Reaction


The extent of human T-cell leukemia/lymphoma virus type II (HTLV-II) infection and its rate of spread have been difficult to determine owing to the serological cross-reactivity between HTLV-I and HTLV-II. The present study overcame this problem by directly detecting type-specific proviral sequences by means of the polymerase chain reaction (PCR) and liquid hybridization. Screening was performed on a cohort of primarily white intravenous drug abusers (IVDAs), and individuals of other behaviorally defined risk groups from the New York City area. Eleven percent (19 of 169) of the individuals in these high-risk groups were determined by PCR to have HTLV-II proviral infections. One of these patients displayed an exfoliative erythrodermatitis. Thirteen of the 19 subjects were positive in an HTLV-II enzyme-linked immunosorbent assay (ELISA). The remaining six individuals, although negative in the HTLV-II ELISA, were confirmed as HTLV-II positive by analyzing their DNA with a second HTLV-II-specific primer detector system. Four additional individuals were reactive in the HTLV-II ELISA but were PCR-negative for HTLV-II. PCR analysis for HTLV-I revealed that all four were positive for that virus. Thirty-seven percent (seven of 19) of the HTLV-II PCR-positive subjects were also PCR-positive for HTLV-I, and 84% (16 of 19) of the HTLV-II positive individuals were infected with human immunodeficiency virus (HIV-1). Six individuals were triply infected with HTLV-I, HTLV-II, and HIV-1.

The human T-cell leukemia/lymphoma virus (HTLV) family includes HTLV-I, HTLV-II, simian T-cell leukemia virus (STLV-I), bovine leukemia virus (BLV), and perhaps the recently described HTLV-V. This group of mammalian oncogenic retroviruses is distinguished by a reverse transcriptase with a preference for Mg++; possession of a virally encoded gene located 3' to env referred to as tax (pX/or/tat/chj), and a long latent period between infection and onset of symptomatic disease. The cognate protein product of the tax gene, TAX, from HTLV-I, HTLV-II, and BLV is involved in a positive transcriptional regulatory loop with the proviral long terminal repeat and certain cellular genes. The lymphoproliferative effects associated with these viruses are thought to be due to this transcriptional loop. Epidemiological considerations indicate that this process is probably only an initial event in a multistep oncogenic pathway. The mechanism whereby TAX expression up-regulates the interleukin-2 receptor (IL-2R) gene has been recently elucidated. Tax induces expression of the NF-kappa beta transcription factor, which in turn binds to a 12 basepair fragment of the IL-2R enhancer, resulting in an increased rate of transcriptional initiation. These viruses also produce a 27 kilodalton protein, REX, encoded in an overlapping reading frame with TAX. REX has been identified in cell lines infected with HTLV-I and HTLV-II and is probably involved in a negative feedback loop with TAX for regulating proviral gene expression, and can replace human immunodeficiency virus (HIV-1) Rev in functional assays.

HTLV-I is associated with a spectrum of lymphoproliferative disorders from benign polyclonal lymphocytoses to adult T-cell leukemia/lymphoma, and the chronic progressive neuropathy, tropical spastic paraparesis (now referred to as HTLV-I associated myelopathy [HAM]). HAM is often confused clinically with multiple sclerosis (MS) and there is some evidence that a related virus may be associated with some cases of MS, but this relationship is not universally accepted. HTLV-II has been isolated from two cases of atypical hairy-cell leukemia and also from a case of CD8+ lymphoma associated with profound neutropenia and other hematopoietic disorders. The etiological role of this virus in these or other diseases has not been fully established, but the preponderance of evidence indicates that HTLV-II, like HTLV-I, is probably associated with multiple maladies of varying severity.

Results of previous serological analyses have indicated that HTLV-II is prevalent among the same behaviorally defined groups as HTLV-I and HIV-1. In the present study we attempted to confirm and extend these findings using both serological assays and the polymerase chain reaction (PCR).

METHODS

Patient selection. One hundred sixty-nine subjects from the New York City area, predominately Staten Island, were chosen for human retroviral screening based on behavioral practices. All patients gave informed consent before testing. Ninety-three percent

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of the 157 subjects had histories of intravenous drug abuse (IVDA); most were being treated at an inpatient detoxification unit, but some were seen at a methadone maintenance clinic. One of the IVDAs listed homosexual activity as a second risk factor. Four subjects gave homosexual activity as their only risk, six subjects gave heterosexual contact with risk group members as their only risk factor, and two subjects were transfusion recipients, one of whom had additionally suffered three needle-sticks from retroviral risk group members over the last 10 years.

Serological assays. Serum antiretroviral antibodies were detected using viral protein ELISAs for HTLV-I, HTLV-II, and HIV-1 and a recombinant TAX protein ELISA for HTLV-I.24-25 Some sera that reacted positively in the ELISAs were further examined by HTLV-I and -II Western blots and HTLV-II radioimmunoprecipitation assays (RIPAs). HIV-1 and HTLV-I viral protein ELISA kits were purchased from Cellular Products Inc (Buffalo) and used according to the manufacturer's specifications. HTLV-I TAX protein ELISAs were performed at Triton Biosciences Inc (Alameda, CA) as previously described.24-25 HTLV-II ELISAs were prepared and run as previously described,12 except that HTLV-II viral proteins purified from the cell line MOLT12 were substituted for HTLV-I viral proteins, and anti-bovine serum albumin (BSA) reactivity was determined for each serum sample and subtracted from the anti-HTLV-II absorbance to obtain the final result. The criterion used for establishing the cutoff value for positives in the HTLV-I TAX ELISA, and the HTLV-I and HIV-1 viral protein ELISAs was an optical density reading of greater than five standard deviations above the mean of the normals run on that test. This convention resulted in sensitivities and specificities of greater than 99% in these assays23 (Pozzessere et al, in preparation). We therefore used this formula for the HTLV-II ELISA as well. This worked out to be approximately 0.400 absorbance units (AU) for the HTLV-I viral protein ELISA, 0.500 AU for the HTLV-I TAX ELISA, and 0.250 AU for the HTLV-II ELISA. The HTLV-II value is lower because we subtracted the anti-BSA (used as a blocking agent) value from the anti-HTLV-II value. The HIV-1 ELISA cutoff was used was established by Cellular Products (Buffalo, NY).

RIPAs were run as previously described,12 except that identical cultures were simultaneously labeled with 35S Met and 35S Cys and then combined to make the lysate. MO-T and HUT-78 cell lines were used as positive and negative antigenic sources, respectively. HTLV-I western blot strips were provided by Cellular Products Inc and used according to the manufacturer's instructions. HTLV-II western blot strips were prepared and handled in a similar manner.

Polymerase chain reaction. The methodology used was as previously described26 with the following modifications. All amplifications were for 30 cycles and all reaction products were assayed by liquid hybridization, followed by electrophoresis on 8% polyacrylamide gels and then autoradiography. Positive and negative DNA controls were run for each amplification; reagent controls included all reaction compounds with the exception of template DNA. Initial patient surveys were conducted using three sets of primer pairs in a single reaction and then assaying for all reaction products simultaneously. All DNAs giving a positive hybridization result for any of the three retroviruses were re-examined for each of the three viral types individually. Therefore, all virus positive findings were confirmed by at least one complete repeat amplification and hybridization procedure. Many DNA samples testing positive for a given virus were further examined by amplification with a second and sometimes a third primer pair that was specific for the virus detected. The primary screening of most patients was done by amplifying their DNA simultaneously in a single tube with SK58/59, which is specific for HTLV-II pol; SK68/69, which is specific for HIV env; and SG231/238, which is specific for HTLV-I pol.18,27,28 Liquid hybridization was carried out simultaneously with the respective end-labeled detectors SK60, SK70, and SG232. Other primer pairs and detectors used included SK38/39 with SK19 for HIV-1 gag13,29 SK110/111 with SK188 for HTLV-II pol, SK110/111 with SK112 for HTLV-I pol, SK110/111 with SK115 for HTLV-I and -II pol28, SK43/44 with SK45 for HTLV-I and -II tax, SK34/55 with SK36 for HTLV-I pol10; SG221/227 with SG229 for HTLV-I env, and SG166/296 with SG242 for HTLV-I gag.18

RESULTS

The HTLV-I and HTLV-II retroviruses share approximately 65% sequence homology, the specific genes share 55% to 85% homology. Therefore, the sequences of the cognate proteins are similar, which results in the difficulty in distinguishing them serologically. Indeed the homologous nucleic acid sequences can be exploited for generic screening analyses by enzymatically amplifying and then detecting sequences that are common to both species, such as with the tax gene primers SK43/44 and their cognate detector sequence SK45.27 The PCR technology is precisely suited, however, for discerning small differences in nucleotide sequences. This is due to the fact that amplification and detection require the proper base pairing of three different oligonucleotides to the target DNA, any one of which will produce a negative result if it does not hybridize. The choice of oligonucleotide primers that support the specific amplification of either HTLV-I or -II, but not both, allows for unambiguous determination of the identity of the infectious agent in each case. This type-specificity has allowed for facile determination of patients who are simultaneously infected with two or more retroviruses. We have previously exploited this ability of PCR by the construction of primers and probes that make it possible to amplify and detect either HTLV-I or HTLV-II independently of the other, as, for example, with SK54/56 and SK58/60, respectively.27 These two primer-detector systems have repeatedly proved to be type-specific when used to analyze prototype samples. An alternative strategy is to amplify for both viruses simultaneously with a generic primer pair, SK110/111, which will support amplification of either HTLV-I or -II sequences and then assay the amplified target DNA with specific HTLV-I (SK112) or HTLV-II (SK188) probes.29 DNA amplified in this system can also be screened generically with SK115, which will detect HTLV-I and -II.

In this study we initially screened individual DNA samples simultaneously for HTLV-I and -II and HIV-1 by amplifying the target DNAs simultaneously for all three viruses. All HTLV-II PCR-positive samples that were non-reactive in the HTLV-II ELISA were reamplified with an additional primer pair (SK110/111) and the amplified DNA was assayed with two detectors (SK188 and SK115). This is an important control due to the risk of carryover of specific high copy number amplified DNAs to negative samples when a given primer pair is used extensively in one laboratory.30 Since this case represents the first use of new primers in our laboratory it is almost certain that the positive amplification results represent HTLV-II proviral DNA and not artifactual findings.

We analyzed plasma and DNA from peripheral blood...
mononuclear cells from 169 risk group members for evidence of retroviral infection(s). The majority of the subjects (157) were IVDAs, eight of whom were diagnosed with AIDS. This cohort consisted of 103 whites, 68 male and 35 female; 31 Hispanics, 20 male and 11 female; and 23 blacks, 19 male and four female. The remaining 12 subjects consisted of: four white homosexual males; two transfusion recipients, both white females; and six who had had heterosexual contact with risk group members—one white male, and five females (four white and one Hispanic). PCR analyses of these individuals identified 18 of 157 (11%) of the IVDAs and one of 12 (8%) of the other risk group individuals as containing HTLV-II proviral sequences (Fig 1, Table 1). One of the patients displayed an exfoliative erythrodermatitis, the remainder showed no symptoms attributable to HTLV-II infection. The sole non-IVDA HTLV-II PCR+ individual had risk factors of transfusion and work related needle sticks from retroviral risk group members. Fourteen percent of the whites, 17% of the blacks, and 3% of the Hispanic IVDAs were HTLV-II PCR+. Sera from 13 of these 19 HTLV-II PCR+ individuals were reactive in an HTLV-II viral protein ELISA (Table 1). The remaining six patients were HTLV-II PCR+ only; however, two of these had HTLV-II ELISA results considerably above the mean of the normals but below our cutoff (Table 2). Four additional patients whose DNA did not support HTLV-II specific gene amplifi-

Table 1. PCR and EIA Results of Epidemiological Screen for Human Retroviruses HTLV-II, HTLV-I, and HIV-1

<table>
<thead>
<tr>
<th></th>
<th>PCR+</th>
<th>EIA+</th>
<th>PCR+/EIA+</th>
<th>PCR+/EIA-</th>
<th>EIA+/PCR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTLV-II diagnostic tests</td>
<td>19/169 (11%)</td>
<td>17/169 (10%)</td>
<td>13/169 (7%)</td>
<td>6/19 (32%)</td>
<td>4/17*</td>
</tr>
<tr>
<td>HTLV-I diagnostic tests</td>
<td>15/169 (9%)</td>
<td>17/169 (10%)</td>
<td>10/169 (6%)</td>
<td>5/16 (31%)</td>
<td>7/17†</td>
</tr>
<tr>
<td>HIV-1 diagnostic tests</td>
<td>56/166 (33%)</td>
<td>65/143 (45%)</td>
<td>48/143 (32%)</td>
<td>3/55 (2%)</td>
<td>19/65 (11%)</td>
</tr>
<tr>
<td>HTLV-I diagnostic tests on HTLV-II PCR+ subjects</td>
<td>7/19 (37%)</td>
<td>11/19 (65%)</td>
<td>5/19 (26%)</td>
<td>2/7 (29%)</td>
<td>0/11</td>
</tr>
<tr>
<td>HIV-1 diagnostic tests on HTLV-II PCR+ subjects</td>
<td>4/6 (67%)</td>
<td>6/7 (86%)</td>
<td>4/6 (67%)</td>
<td>0/6</td>
<td>1/6 (17%)</td>
</tr>
<tr>
<td>HIV-1 diagnostic tests on HTLV-II PCR+ subjects</td>
<td>11/18 (61%)</td>
<td>16/19 (84%)</td>
<td>11/18 (61%)</td>
<td>0/18</td>
<td>4/18 (22%)</td>
</tr>
<tr>
<td>HIV-1 diagnostic tests on HTLV-II PCR+ subjects</td>
<td>7/15 (47%)</td>
<td>8/11 (73%)</td>
<td>4/10 (40%)</td>
<td>0/10</td>
<td>3/10 (30%)</td>
</tr>
</tbody>
</table>

Abbreviations: PCR, polymerase chain reaction; EIA, enzyme linked immunosorbent assay.

*All four of these individuals' DNAs were HTLV-I PCR+ and therefore are presumed to be cross reactive in the HTLV-II EIA.
†All seven of these individuals' DNAs were HTLV-II PCR+ and therefore are presumed to be cross reactive in the HTLV-I EIA.
PREVALENCE OF HTLV-II

Table 2. Retroviral Reactivities of HTLV-II PCR-Positive Patients

<table>
<thead>
<tr>
<th>Patient Code No.</th>
<th>Risk Factors</th>
<th>HTLV-II EIA*</th>
<th>PCR (60)</th>
<th>PCR (188)</th>
<th>PCR (115)</th>
<th>HTLV-I EIA</th>
<th>TAX EIA</th>
<th>PCR (56)</th>
<th>PCR (19 + 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5488</td>
<td>IVDA WM</td>
<td>1,899(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1,853(+)</td>
<td>309(-)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15361</td>
<td>IVDA WM</td>
<td>277(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>110(-)</td>
<td>553(+)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>15489</td>
<td>IVDA WM</td>
<td>1,054(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>618(-)</td>
<td>661(+)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>16589</td>
<td>IVDA WF</td>
<td>891(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1,558(+)</td>
<td>209(-)</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>16541</td>
<td>IVDA WM</td>
<td>576(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>518(+)</td>
<td>790(+)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>16432</td>
<td>IVDA WM</td>
<td>700(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>726(-)</td>
<td>238(-)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16453</td>
<td>IVDA WF</td>
<td>1,029(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1,012(+)</td>
<td>214(-)</td>
<td>-</td>
<td>-</td>
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<tr>
<td>16490</td>
<td>IVDA BM</td>
<td>780(+)</td>
<td>-§</td>
<td>+</td>
<td>+</td>
<td>596(+)</td>
<td>232(-)</td>
<td>+</td>
<td>+</td>
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<tr>
<td>16497</td>
<td>IVDA BM</td>
<td>1,271(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>377(-)</td>
<td>383(-)</td>
<td>+</td>
<td>+</td>
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<tr>
<td>16498</td>
<td>IVDA BM</td>
<td>961(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>498(+)</td>
<td>183(-)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>17242</td>
<td>IVDA WF</td>
<td>700(-)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>405(-)</td>
<td>1,292(+)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17304</td>
<td>IVDA WM</td>
<td>1,138(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>969(+)</td>
<td>1,007(+)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>17654</td>
<td>IVDA BM</td>
<td>3,000(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>3,000(+)</td>
<td>306(-)</td>
<td>+</td>
<td>+</td>
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<tr>
<td>16163</td>
<td>IVDA HM</td>
<td>170(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>178(-)</td>
<td>219(-)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>16168</td>
<td>IVDA WM</td>
<td>45(-)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>56(-)</td>
<td>223(-)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>16501</td>
<td>IVDA WM</td>
<td>35(-)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>65(-)</td>
<td>831(+)</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>16503</td>
<td>IVDA WM</td>
<td>196(-)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>880(+)</td>
<td>247(-)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>16546</td>
<td>IVDA WM</td>
<td>0(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>112(-)</td>
<td>189(-)</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>18319</td>
<td>NS TR WF</td>
<td>70(+)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>79(-)</td>
<td>127(-)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: IVDA, intravenous drug abuser; NS, needlestick; TR, transfused; W, white; H, hispanic; B, black; M, male; F, female.
*All numerical results are O.D. x 1.000.
†All PCR results are listed by detector probe number, see methods for region amplified.
‡PCR with SK 70 only.
§PCR + with HTLV-I and II generic tax primer detector system SK43-45.

HTLV-II was present in all four of these patients was positive indicating that the HTLV-II ELISA positive results were due to serological cross-reactivity with HTLV-I antigens. The plasma from all adult T-cell leukemia/lymphoma and HTLV-I associated myelopathy patients analyzed in the HTLV-II ELISA also gave strong positive signals, which confirm earlier reports of serological cross-reactivity and explain the false positive results obtained with our HTLV-II ELISA with HTLV-I PCR positive individuals. Sixteen of the 19 HTLV-II PCR positive individuals (84%) were also HIV positive by ELISA/Western blot and/or gene amplification (Table 2), but only one of the patients had acquired immunodeficiency virus (AIDS). HTLV-I and -II Western blot analysis of the sera from two of the HTLV-II PCR positive patients showed significant cross-reactivity with HTLV-I antigens. Both of these individuals' sera identified multiple gag and env peptides from both HTLV-II and -I antigen preparations (Fig 2A, B). Sera from these patients also recognized and immunoprecipitated the p37 HTLV-II TAX protein (Fig 2C).

**DISCUSSION**

The results of this study clearly indicate that HTLV-II is present in both white and black parenteral drug abusers and suggest that health care workers may be at risk of infection by needle sticks and that HTLV-II can be transmitted by transfusion (Table 2). Future studies will be needed to ascertain whether the prevalence of this virus is increasing in these populations, but it is likely to be the case based on the epidemiology of the other human retroviruses. Our data on the percentage of IVDAs infected with HTLV-I and HIV-1 is very similar (9% and 9% and 41%) to that reported by Robert-Guroff et al., but is somewhat lower for HTLV-II (11% and 18%). We did not find among our population a higher incidence of HTLV-II infection in blacks than whites as reported by Robert-Guroff et al. Whereas, the people from a region endemic for HTLV-II have not been identified it does not appear from this study to be co-endemic with HTLV-I as we found a similar or lower percentage of HTLV-II among blacks, four of 23 (17%), and Hispanics, one of 31 (3%), than we did among whites of European extraction, 14 of 103 (14%). This contrasts with HTLV-I where 100% of the HTLV-I associated myelopathy patients that we characterized, also from the New York City area, were black. From the present study, it appears that this virus has recently been introduced into both black and white IVDA populations from an outside source still to be elucidated.

Analyses of the PCR and ELISA data for HTLV-I and -II and HIV-1 (Tables 1 and 2) reveal that for the oncogenic retroviruses gene amplification is a more sensitive screening modality than ELISA. ELISAs for HTLV-II and -I missed 32% and 31%, respectively, of the PCR+ individuals. In contrast there were no bonafide HTLV-I or -II ELISA positives that were PCR−, but approximately two thirds of the HTLV-II positives cross-reacted in the HTLV-I ELISA and vice versa; however, 37% of the HTLV-II infected subjects in this study were also HTLV-I infected. PCR as conducted in this survey for HIV-1, however, even with two primer pairs, missed 29% of the Western blot confirmed HIV-1 seropositive individuals. Ongoing studies in our laboratory indicate that this sensitivity can be increased by using...
more target DNA (>1 μg) and also by including a reverse transcriptase step before PCR so as to be able to detect HIV-1 viral or mRNA as well as proviral DNA.31 The differences in the sensitivities of these tests with the various viral isolates may be due to the fact that HIV-1 is transcriptionally more active producing antigen against which antibody will be synthesized earlier in infection than the oncornaviruses. Epidemiological studies indicate that many individuals living in areas endemic for HTLV-1 who become infected during early childhood do not seroconvert until their third or fourth decade.1 This suggests that this virus may be quiescent for extended periods of time before becoming activated and producing virions. We have, however, previously demonstrated in HTLV-I infected (PCR+) ELISA negative, asymptomatic IVDAs that a substantial percentage of such individuals have significant anti-HTLV-I anti-
bodies only to TAX, which is a nuclear protein and not packaged in the mature virion. This finding in subjects who have been recently infected suggests preferential TAX expression early in HTLV-I infection. Due to the mitogenic effect of the TAX proteins of HTLV-I and -II, it is possible that even in asymptomatic seronegative individuals there is a relative polyclonal increase in the number of infected peripheral blood cells (without concomitant viral production), compared with HIV-1, which is cytopathic, making it easier to detect them by PCR. The variability of HIV-1 is also greater compared with HIV-1, which is cytotoxic, making it easier to detect evidence of the virus by either means.

Because of the high level of dual and triple retroviral infections in this cohort such individuals should prove valuable in helping to determine whether or not coinfection with one or both of the oncogenic viruses speeds the development of HIV-associated syndromes or vice versa.13

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