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Author(s): Renu B. Lal, Renan A. Gongora-Biachi, Diance Pardi, William M. Switzer, Ira Goldman, Altaf A. Lal

Source: *The Journal of Infectious Diseases*, Vol. 168, No. 3 (Sep., 1993), pp. 586-591

Published by: [The University of Chicago Press](#)

Stable URL: <http://www.jstor.org/stable/30113422>

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## Evidence for Mother-to-Child Transmission of Human T Lymphotropic Virus Type II

Renu B. Lal, Renan A. Gongora-Biachi, Diane Pardi,  
William M. Switzer, Ira Goldman, and Altaf A. Lal

*Retrovirus Diseases Branch, Division of Viral and Rickettsial Diseases,  
and Malaria Branch, Division of Parasitic Diseases, National Center for  
Infectious Diseases, Centers for Disease Control and Prevention, Atlanta,  
Georgia; Centro de Investigaciones Regionales, Merida, Mexico*

Serologic analysis of the children of 2 married human T lymphotropic virus type II (HTLV-II)-infected prostitutes demonstrated antibodies to HTLV-II in an 8-year-old boy whose only recognizable risk for HTLV-II infection was breast-feeding during his first 4 years of life. Limited sequence analysis of isolates infecting the mother and child demonstrated 100% identical sequences in the long terminal repeat (LTR<sup>65-297</sup>; 236 bp), *pol*<sup>4762-4919</sup> (157 bp), and *env*<sup>5523-6003</sup> (480 bp) regions (both isolates were subtype a), suggesting mother-to-child transmission. In contrast, isolates obtained from 2 other prostitutes from the same geographic region had sequences different from those of the first woman and her child, and the second and third women were infected with HTLV-II subtype b. Although vertical transmission of HTLV-II in this 8-year-old child cannot be conclusively ascertained, the probability is overwhelming that infection occurred through breast-feeding for an extended period of time.

Human T lymphotropic virus (HTLV) types I and II are lymphoproliferative viruses that share extensive structural and functional homologies. HTLV-I has been etiologically associated with adult T cell leukemia and HTLV-I-associated myelopathy (HAM) and is endemic in southwestern Japan, the Caribbean, and some parts of Africa [1, 2]. While the etiologic role of HTLV-II in lymphoproliferative diseases has yet to be defined [2], it has been isolated from 2 patients with hairy cell leukemia [3, 4], a patient with myelopathy similar to HAM [5], and more recently from a patient with large granular lymphocytic leukemia [6]. Infection with HTLV-II appears to be endemic among American and European intravenous drug users (IVDUs) [1, 7] as well as certain indigenous New World Amerindian groups, including the Navajo and Pueblo in New Mexico [2], the Seminole in Florida, the Guaymi in Panama [8], and the Cayapo and Kraho in Brazil [9]. In the United States, the seroprevalence rates for HTLV-I and II are low, but the viruses have been found in IVDUs, female prostitutes, patients attending sexually transmitted disease clinics, recipients of multiple blood transfusions, and volunteer blood donors [1, 10]. Furthermore, more than half of the HTLV-infected persons among the volunteer blood donors in the United States are infected with HTLV-II; of these, the majority are women of child-bearing age [10].

The predominant modes of transmission of HTLV-I are from mother to child (mainly through breast milk) [11-13], sexual contact [14], intravenous drug use [7], and blood transfusion [15, 16]. Epidemiologic studies of HTLV-II infection have suggested similar routes of transmission, including sharing contaminated needles, sexual contact, and blood transfusion [1, 17-19]. However, very little is known about the vertical transmission of HTLV-II, in part because until recently a well-defined endemic population was not known for this virus [8, 9]. In addition, because of the passive transfer of maternal antibodies, babies born to HTLV-infected mothers have to be serologically monitored for >1 year to detect true HTLV seropositivity. Indeed, mother-to-child transmission studies in HTLV-II-infected women demonstrated the presence of maternally transferred antibodies in infants for as long as 24 months [20]. In the present investigation, we took a retrospective approach in which all the children of HTLV-II-positive mothers for whom breast-feeding history was available were screened for the presence of HTLV infection, and molecular analysis was done to link the virus strain infecting mother and child.

### Materials and Methods

**Study population.** Serosurveys for detection of antibodies to HTLV-I/II in Yucatan, Mexico, from January to December 1990 identified a low prevalence of HTLV-I/II (5/282, 1.8%) in a group of female prostitutes [21]. Further analysis with type-specific oligopeptides and oligoprimers has shown that these prostitutes are infected with HTLV-II [22]. To better understand the natural history of familial occurrence of HTLV-II and mother-to-child transmission, we undertook serologic and molecular analyses of specimens from 2 of these HTLV-II-positive prostitutes and their children. The first subject, a 33-year-old woman (Y-06), started prostitution at the age of 15 years; she

Received 2 March 1993; revised 4 May 1993.

Informed consent was obtained from all study subjects and parents of minors according to Mexican Health Ministry guidelines.

Reprints or correspondence: Dr. Renu B. Lal, Retrovirus Diseases Branch, Division of Viral and Rickettsial Diseases, MS G-19, CDC, 1600 Clifton Rd., Atlanta, GA 30333.

**The Journal of Infectious Diseases** 1993;168:586-91  
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0022-1899/93/6803-0007\$01.00

has no history of blood transfusion or intravenous drug use. She has 4 sons, aged 17 years (Y-18), not breast-fed; 13 (Y-19), not breast-fed; 8 (Y-17), breast-fed for 4 years; and 3 (Y-20), breast-fed for 2 months. The second prostitute is a 47-year-old woman (Y-01) with 2 sons (ages 33 and 21), each of whom was breast-fed for only 2 months. One other prostitute (Y-03), who does not have any children, was included as a control for the molecular characterization of the virus.

**HTLV antibody tests.** Serum specimens from the women and the sons were tested by Western blot (WB) assay incorporating purified recombinant transmembrane protein and external glycoproteins specific for HTLV-I (rgp46<sup>I</sup>) or HTLV-II (rgp46<sup>II</sup>) protein with a whole virus lysate (Diagnostic Biotechnology, Singapore). A serum specimen was HTLV-positive if antibody reactivity was detected to at least two different HTLV structural gene products (*gag* p24 and *env* gp46 and/or r21e) and was typed on the basis of serologic reactivity to the type-specific recombinant proteins [23].

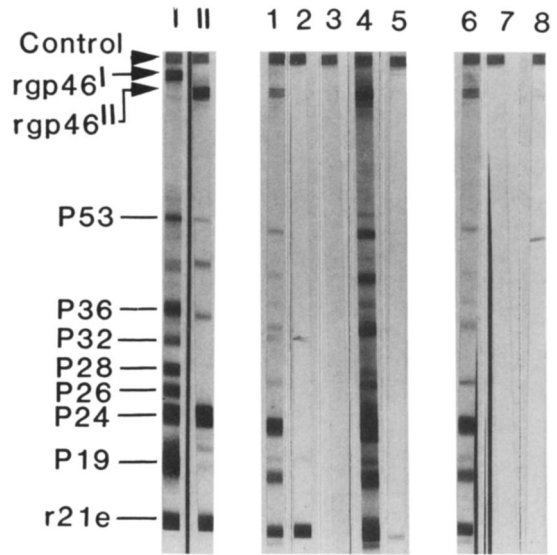
**Polymerase chain reaction (PCR) assay.** PCR amplification was done to detect HTLV sequences in DNA specimens from several study subjects. Three gene regions (long terminal repeat [LTR], *pol*, and *env*) of DNA from each individual were amplified by PCR using conditions as described previously [22]. T cell lines infected with HTLV-I (MT-2) or -II (Mo-T) were used as positive control, and an uninfected cell line (HuT-78) was used as a negative control. Primers from the transmembrane glycoprotein of HTLV-II (GP21F1 and GP21R1) were derived from previously published sequences used to demonstrate genetic heterogeneity among HTLV-II isolates [24].

**Molecular cloning and sequencing of PCR products.** The amplified PCR products were cloned into the pCR II vector (In Vitrogen, San Diego) according to the manufacturer's instructions, and competent INVaF' cells were used for transformation. Cloned DNA was isolated and checked for correct size by restriction enzyme digestion with *EcoRI* and run on 1.5% agarose gel. The clones that gave inserts of the expected size were then expanded by using standard DNA miniprep procedures [25] and sequenced (Sequenase version 2.0; United States Biochemicals, Cleveland).

**Results**

**Serologic analysis and risk factors.** WB analysis of specimens from the children of 2 prostitutes demonstrated that the 8-year-old son (Y-17) of Y-06 had antibodies to both *gag* (p24) and *env* (rgp46<sup>II</sup>, r21e) gene products, indicating HTLV-II positivity (figure 1, lane 4). Sera from 2 of his brothers (Y-18 and Y-20) had an indeterminate pattern and reacted with r21e only (figure 1, lanes 2 and 5). No HTLV-specific sequences could be amplified by PCR in DNA from Y-18. None of the other children reacted with any HTLV-specific proteins in WB assay (figure 1).

Further analysis by PCR using type-specific oligoprimers confirmed that Y-17 was infected with HTLV-II (table 1). Analysis of HTLV-II subtypes by restriction enzyme digestion of PCR amplicon from the transmembrane region demonstrated that both the mother (Y-06) and the child (Y-17)



**Figure 1.** Recombinant Western blot containing immunodominant transmembrane epitope (r21e) and type-specific epitopes of HTLV-I (rgp46<sup>I</sup>) and -II (rgp46<sup>II</sup>). Control HTLV-positive sera reacted with *gag* (p24) and *env* (r21e, rgp46<sup>I</sup>, or rgp46<sup>II</sup>) proteins. Lanes 1-5: sera from prostitute Y-06 and her children Y-18, Y-19, Y-17, and Y-20, respectively. Lanes 6-8: sera from prostitute Y-01 and her children Y-37 and Y-38, respectively.

were subtype HTLV-IIa, whereas the 2 other women from the same geographic region were infected with HTLV-IIb (data not shown).

Evaluation of the various risk factors for HTLV-II infection in subject Y-17 revealed no history of intravenous drug use, blood transfusion, or use of nondisposable needles for childhood vaccinations. The child has a stable home, attends an elementary school, and is not sexually abused. He was breast-fed for the first 4 years of his life, in contrast to his seronegative 3-year-old brother, who was breast-fed for only 2 months (table 1). This suggests that breast-feeding for an extended period was the possible route of transmission. Since earlier specimens were not available, transplacental transmission cannot be ruled out.

**Nucleotide sequence analysis.** To confirm the mother-to-child transmission, limited genomic sequence analysis was done to determine the exact pattern of the isolate(s) infecting the child, and results were compared with those of the similar molecular regions in DNA specimens from the mother and the 2 other prostitutes from the same area. The analysis of the LTR<sup>65-297</sup> region (236 bases) of the isolate from Y-17 demonstrated 100% concordance with the sequence of the isolate from his mother (Y-06; figure 2). Comparison of Y-06 and Y-17 isolates with a North American prototypic isolate (Mo-T) demonstrated point mutations at six positions, with several deletions and insertions, giving an overall similarity of 96.6% (figure 2). In contrast, LTRs of isolates from the other 2 women (Y-01 and Y-03) were at least 7%-8% divergent from Mo-T and were more closely related to another

**Table 1.** Western blot (WB) and polymerase chain reaction (PCR) data of HTLV-II-positive prostitutes and their sons.

Donor no. (age, years/ sex)	WB results	PCR	Risk factors
Y-06 (33/F)	p24; rgp46 <sup>u</sup> /r21e	HTLV-II	Prostitution for 17 years
Y-18 (17/M)	r21e	Negative	Two sex partners
Y-19 (13/M)	—	ND	None
Y-17 (8/M)	p24; rgp46 <sup>u</sup> /r21e	HTLV-II	Breast-fed for 4 years
Y-20 (3/M)	r21e	ND	Breast-fed for 2 months
Y-01 (47/F)	p24; rgp46 <sup>u</sup> /r21e	HTLV-II	Prostitution for 32 years
Y-37 (33/M)	—	ND	Breast-fed for 2 months
Y-38 (21/M)	—	ND	Breast-fed for 2 months
Y-03 (22/F)	p24; rgp46 <sup>u</sup> /r21e	HTLV-II	Prostitution for 3 years

NOTE. Subjects Y-17 through Y-20 are sons of Y-06; subjects Y-37 and Y-38 are sons of Y-01. F, female; M, male; ND, not done.

HTLV-II isolate (G12.1), derived from a Guaymi Indian from Panama (unpublished data). Comparison of functionally active sites within the LTR demonstrated remarkable conservation of a 21-bp repeat motif and of polyadenylation and promoter sites.

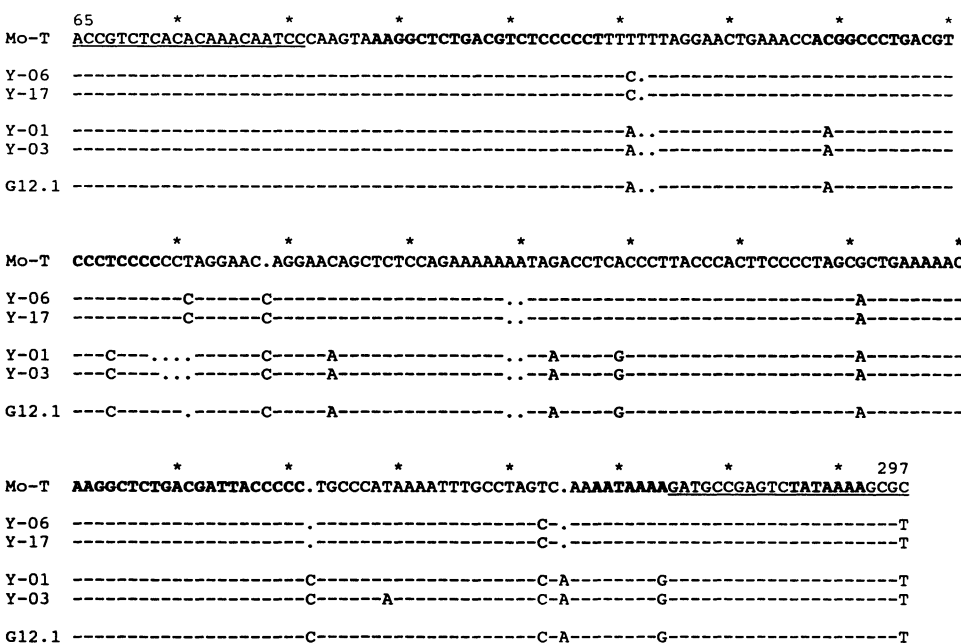
Similarly, *pol*<sup>4762-4919</sup> (157 bp) and *env*<sup>5523-6003</sup> (480 bp) sequences from Y-06 and Y-17 isolates were nearly identical to those of the prototypic Mo-T sequence (100% and 99.4%, respectively); the nucleotide positions where point mutations were found in any of the isolates are shown in figure 3. The *pol* sequences of Y-01 and Y-03 isolates demonstrated 9 base changes from Mo-T, of which 2 resulted in amino acid changes. A similar analysis of the *env* region demonstrated 17 base changes in sequences of Y-01 and Y-03 isolates, of

which 6 resulted in amino acid changes. In addition, the Y-01 isolate had an additional base change (C<sup>5977</sup>→A) that resulted in an amino acid change (P<sup>265</sup>→H). Both *pol* and *env* sequences of Y-01 and Y-03 isolates were 4%–6% divergent from the prototypic Mo-T sequence and from the sequences of Y-06 and Y-17 isolates and were more closely related to the Panamanian G12.1 sequence (figure 3).

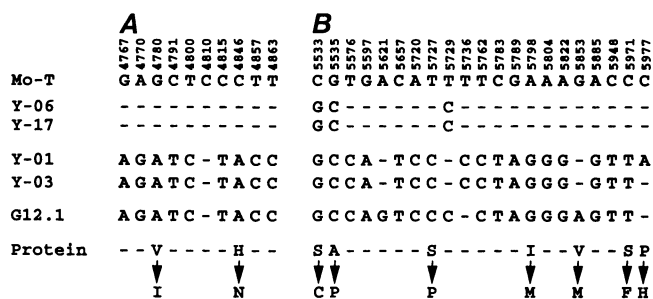
Comparison of the protein sequence in the *pol* region demonstrated substitutions at amino acids V<sup>849</sup>→I and H<sup>871</sup>→N in sequences from Y-01, Y-03, and G12.1. A similar analysis of the *env* region demonstrated substitutions at amino acids S<sup>117</sup>→C, A<sup>118</sup>→P, and S<sup>183</sup>→P in all the Mexican isolates and the G12.1 cell line. In addition, sequences from Y-01, Y-03, and G12.1 had substitutions at I<sup>206</sup>→M and S<sup>263</sup>→F when compared with those of Mo-T, Y-06, or Y-17. The amino acid substitution at positions 183 and 206 were contained within the immunodominant epitope of the HTLV-II external glycoprotein [26]. Finally, a substitution at amino acid V<sup>224</sup>→M was observed only in the G12.1 isolate, and a substitution at P<sup>265</sup>→H was seen only in the Y-01 isolate. More importantly, while sequences from both Y-06 and Y-17 demonstrated 100% similarity in all three gene regions examined (both at the nucleotide and protein level), the Y-01 and Y-03 sequences demonstrated several base-pair differences between them, and most were conservative mutations. This analysis further supports the hypothesis that the virus isolate infecting the child (Y-17) is identical to that in the mother (Y-06).

**Discussion**

Previous seroepidemiologic surveys have demonstrated that the natural transmission routes of HTLV-I are through



**Figure 2.** Nucleotide sequence of long terminal repeat region (LTR<sup>65-297</sup>) of HTLV-II isolates from mother (Y-06) and child (Y-17) and 2 other prostitutes from same area (Y-01 and Y-03) and Panamanian Guaymi Indian isolate (G12.1). Polymerase chain reaction amplification (primers underlined) was done with DNA from peripheral blood mononuclear cells, and amplified products were cloned, sequenced, and compared with prototypic Mo-T sequence. Bold regions represent three 21-bp repeats, polyadenylation site, and TATA box; dash represents identical base in other isolates; dot represents deletion of base. Y-06 and Y-17 sequences were identical and were closely related to prototypic Mo-T sequence; Y-01 and Y-03 isolates were closely related to G12.1.



**Figure 3.** Nucleotide sequence of *pol*<sup>4760-4917</sup> (A) and *env*<sup>5523-6005</sup> (B) regions of HTLV-II in Mexican specimens. Primers for *pol* were SK110/111 and for *env* were BSEFO<sup>5523-5542</sup> (CATGGACATGCC-CATACAGG) and E2.2<sup>6005-5984</sup> (GAGGTTGGTAGCAATGGG-TCCA). Only nucleotide changes and, where appropriate, amino acid changes are shown with respect to corresponding regions in prototypic Mo-T sequence. Dash indicates no nucleotide or amino acid change. Y-06 and Y-17 sequences were almost identical to Mo-T, whereas Y-01 and Y-03 sequences were closely related to Panamanian isolate.

sexual contact and from mother to child [11–14]. However, unlike well-characterized routes of transmission for HTLV-I, little is known about the transmission routes for HTLV-II. Recent studies have provided indirect evidence for both blood transfusion-related and sexual transmission of HTLV-II [17–19], but no molecular evidence has been presented to link the donor with the recipient. In this report, we provide the first case of a mother-to-child HTLV-II infection, presumably transmitted through breast-feeding, in an 8-year-old boy.

The serologic and PCR analyses demonstrated that both the mother and the child were infected with HTLV-II. Limited sequencing data provided strong evidence that the isolates infecting the mother and the child were 100% identical in the LTR, *pol*, and *env* regions. Sequence analysis of the LTR region showed that the sequences of the mother and child were only 3% divergent from the prototypic Mo-T sequence, whereas the sequences of 2 other prostitutes from the same area were 7%–8% divergent from the Mo-T sequence and were more closely related to the sequence of an isolate derived from an HTLV-II-infected asymptomatic Guaymi Indian from Panama. Furthermore, several contiguous deletions were observed near the second 21-bp motif in isolates from both Y-01 and Y-03. While the functional relevance of these mutations is not clear from these studies, minor variations in the HTLV-I LTRs have been shown to affect the activity level of the promoter in some cellular environments [27].

The analysis of the *pol* and *env* regions demonstrated that isolates from Y-06 and Y-17 were closely related to the prototypic Mo-T isolate, whereas the isolates from Y-01 and Y-03 were more closely related to the G12.1 isolate. More importantly, the sequence within these regions in the isolate from Y-17 was 100% identical to that of the isolate from his mother (Y-06). The remarkable conservation of the se-

quence, especially in the *env* gene, supports a previous report of extremely low genetic drift of HTLV-II in vivo [28]. Indeed, site-specific mutagenesis studies have shown that the HTLV-I envelope protein is under high functional constraints to conserve its structure [29]. Further subtyping of the virus on the basis of restriction sites indicated that both the mother and child were infected with HTLV-IIa, whereas other prostitutes from the same region had HTLV-IIb. The presence of both of these subtypes in Mexican prostitutes suggests that the genetic heterogeneity observed for HTLV-II isolates from IVUDs is not restricted to the United States [24]. Taken together, these findings strongly support the notion that the virus strains infecting the mother and child are identical. However, because of limited HTLV-II sequence data from different isolates, we cannot exclude the possibility that the molecular matching pattern used in the present investigation contains motifs that are identical in other isolates.

Analysis of various risk factors that could be associated with the possible transmission of HTLV-II in the child led us to believe that long-term breast-feeding (up to 4 years) might be the possible route of infection. Previous studies have indicated that breast-fed babies from HTLV-I-infected mothers are far more likely to become infected (20%–25%) than are bottle-fed babies (3%), suggesting that in utero and peripartum transmission also occurs but at a lower efficiency than breast milk transmission [30]. In fact, a prospective follow-up study of HTLV-II-infected women in New York City demonstrated the absence of HTLV-II infection in 20 non-breast-fed babies born to 19 HTLV-II-infected mothers, suggesting that the transplacental transmission of HTLV-II is not the common route of transmission [20]. More recently, breast milk from HTLV-II-infected mothers has been shown to contain HTLV-II genomic sequences [31], raising the possibility of transmission of this virus by breast-feeding. While the exact mechanism of transmission is not known, it is possible that some of the virus-infected cells penetrate the mucosal barriers during their passage from the oral cavity to the gastrointestinal tract. The possibility that the initial step in transmission could be lymphocyte-facilitated infection of the gut epithelium has recently been proposed [32]. Furthermore, oral administration of HTLV-I-infected human breast milk lymphocytes to marmosets and rabbits has demonstrated successful transmission of HTLV-I [33, 34].

The absence of HTLV-II infection in the 3-year-old sibling of Y-17 who was breast-fed for only 2 months is of interest. While it is possible that this child may represent an early seroconverter or harbors a latent HTLV-II infection, a prospective follow-up study of babies born to HTLV-I-infected mothers from Jamaica has demonstrated no evidence of latent HTLV infection [35]. The possibility remains that passively acquired maternal antibodies can provide effective protection against HTLV infection in babies breast-fed for <6 months, especially since maternal antibodies have been

shown to provide an efficient barrier to impede viral spread in the blood circulation [33, 36]. Alternatively, the markers of higher virus load, such as higher antibody titer and antigen expression, that are associated with more frequent mother-to-child transmission [35] may not have been sufficient to cause the effective transmission in this child.

The data presented here suggest that breast-feeding for an extended period was the only recognizable route of transmission of HTLV-II from the infected mother to the child. In accordance with the US Public Health Service guidelines, HTLV-II-infected mothers should refrain from breast-feeding when suitable alternatives are available. Studies in HTLV-I-endemic areas have demonstrated that mother-to-child transmission can be prevented by using powdered milk or freeze-thawed mother's milk [37]. Alternatively, mother's milk can be heat-inactivated at 56°C for 30 min before feeding, as this is known to inactivate HTLV-I and virus-carrying cells [38]. While the search for a direct link of mother-to-child transmission of HTLV-II continues, it is also important to develop intervention strategies to effectively block the transmission of HTLV.

#### Acknowledgments

We thank J. Kaplan and W. Heneine for critically reviewing the manuscript and John O'Connor for editorial corrections.

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