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Mother-to-Child HIV and HHV-8 Transmission in Neonates at Saint Camille Medical Centre in Burkina Faso

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Abstract: In Sub-Saharan Africa, many HIV infected people are co-infected with Human Herpes Virus 8 (HHV-8). Therefore, the present study aimed to: (1) identify the pregnant women co-infected by HIV and HHV-8 at Saint Camille Medical Centre; (2) use three molecules (Zidovudine, Nevirapine and Lamivudine) to interrupt the vertical transmission of HIV and (3) use the PCR technique to diagnose children, who were infected by these viruses, in order to offer them an early medical assistance. A total of 107 pregnant women, aged from 19 to 42 years were diagnosed to be HIV positive at Saint Camille Centre; among them 13 were co-infected with HHV-8. All included women received the HAART. Two to six months after childbirth their babies underwent PCR diagnosis for HIV and HHV-8. The results revealed that, among these mothers, 68.2% were housewives, 34.6% were illiterates and 60.7% did not have university degree. The prevalence of HHV-8 among these pregnant women was 12.15% and the rate of vertical transmission of both HIV and HHV-8, was 0.0%. The issue of this study revealed that the antiretroviral therapy increased the mother CD4 T-cells, prevented the transcription of the mRNA of HHV-8 and blocked HIV vertical transmission.

Key words: Pregnant women, HIV, HHV-8, HAART, Burkina Faso

INTRODUCTION

Burkina Faso, located in the middle of Western Africa, is delimited in the North and the West by Mali, in the East by Niger, in the South by Ivory Coast, Ghana, Togo and Benin. It is one of the Sub-Saharan African countries that are more touched by the HIV and human herpes virus type 8 infection (HHV-8) (Simpoire *et al.*, 2006a, 2007; Grégoire *et al.*, 2000).

Nowadays, HIV vertical transmission is well established (Ranger-Rogez *et al.*, 2002; Meda *et al.*, 1997). The HIV vertical transmission occurs in the intra-uterine life by mother-foetal micro-transfusion, during the delivery by contact with maternal blood and vaginal secretions or during breast feeding (Meda *et al.*, 1997; Shaheen *et al.*, 1999). In Sub-Saharan Africa, HIV/AIDS, by its morbidity and mortality, constitutes a real public health problem. Therefore, several steps were taken: the awareness against sexual and parenteral transmission of HIV and the prevention of mother-to-child transmission of

HIV using HAART. In 1994 a new herpesvirus, indicated as Human Herpes Virus-8 (HHV-8) has been found in Kaposi Sarcoma (KS) lesions and has been invariably associated to all forms of KS, thus indicating a transmittable etiologic agent for this disease (Chang *et al.*, 1994). However, the mechanism of transmission of HHV-8 is not yet fully elucidated. The HIV affects HHV-8 through different mechanisms. It is debatable whether HIV Tat (Ensolli *et al.*, 1990), inflammatory cytokines released during HIV infection (Mercader *et al.*, 2000), or immunosuppression itself are the main co-factors for the development of KS, but HIV has an unquestionable predisposing effect for the conversion from asymptomatic HHV-8 infection into clinical manifestations. Besides, AIDS-KS is more aggressive and resistant to treatment than other forms of KS (Strathdee *et al.*, 1996). HIV Tat activates lytic cycle replication of HHV-8, via JAK/STAT signalling (Zeng *et al.*, 2007), or by induction of HHV-8 Rta, a product of HHV-8 ORF 50 gene that controls the transition from latency to lytic replication

(Varthakavi *et al.*, 2002). Co-infections also have several effects on the course and progression of HIV. In this regard, the effects of HHV-8 infection over HIV natural history are complex and still not entirely elucidated (Caselli *et al.*, 2005). Certain specific HHV-8 antigens such as LANA (latency-associated nuclear antigen) can activate HIV (Hyun *et al.*, 2001) and ORF 50, a lytic cycle gene, interacts with HIV Tat leading to increased cell susceptibility to HIV infection (Caselli *et al.*, 2003, 2001). The HHV-8 stimulates HIV replication in acutely infected cells as well as reactivation in chronically infected cells (Caselli *et al.*, 2005).

Kaposi Sarcoma (KS) is a mesenchymal tumour, originally described in Eastern Europe, relatively rare in the general population (Kaposi, 1982). The KS incidence showed a steep increase in the early 1980's in concomitance with the pandemy of Human Immunodeficiency Virus (HIV) type I infection (Cook-Mozaffari *et al.*, 1998). However, the introduction of Highly Active Anti Retroviral Therapy (HAART) has strongly decreased KS incidence in AIDS patients, mostly due to an enhancement of immune response in HIV infected subjects (Eltom *et al.*, 2002). However, among HIV positive subjects, HHV-8 prevalence rate is much higher: in US, different surveys have reported a HHV-8 prevalence in HIV positive subjects ranging around 35-49% (O'Brien *et al.*, 1999). In Africa, HIV prevalence and AIDS-KS incidence reach the highest levels, although not uniformly distributed throughout the continent (Dukers and Rezza, 2003). Several authors assume that HHV-8 seroconversion can occurs early in life but they do not describe mother-to-child transmission of HHV-8 nevertheless a horizontal transmission: (Lyll *et al.*, 1999; Minhas *et al.*, 2008; Fiore *et al.*, 2004). It is now established that infectious HHV-8 is released in saliva in healthy seropositive individuals, although it is unknown the mechanism through which the virus, shed in the saliva, might reach target cells (Simpore *et al.*, 2006a). A theory for an alternative pathway of transmission from mother to child of viral infections through saliva has been proposed (Coluzzi *et al.*, 2003). In this hypothesis, the infection frequently takes place during childhood and is favoured by the bite of hematophagous arthropods as a promoting factor and the application of saliva containing infectious virus by the parents, to heal the itching and scratching at the site of the bite, as a risk behavior. If this transmission route actually plays a role in HHV-8 infection, then the local density of biting arthropods would be an important factor.

This research has the following goals: (1) to identify the pregnant women co-infected by HIV and HHV-8 in the Medical Centre of Saint Camille, (2) to use HAART in

order to reduce the rates of vertical transmission of HIV, (3) to employ real time PCR technique to diagnose the children infected by these viruses and (4) to draw the attention of authorities on the need for protecting from now on, the most vulnerable and exposed groups (children and newly-born babies) and thus contribute to a better orientation of the fight against mother-to-child co-transmission of HIV and HHV-8.

MATERIALS AND METHODS

Patients: From January 21, 2007 to March 16, 2009, 107 pregnant women HIV seropositive with less than 32 weeks of amenorrhoea and aged from 18 to 42 years old (average age of 26.64 ± 4.75), have freely agreed after counselling, to make the test of HHV-8 and to follow the protocol of the PTME.

Blood taking: After informed consent, 10 mL of blood samples was collected from pregnant women in 2 tubes containing EDTA. The first tube was used for CD4+ count while the second tube was centrifuged at 3000 rpm for 10 min to remove plasma for HHV-8 and HIV PCR test. After the consent of the HIV positive parents, 5 mL of blood was taken from their children at the age of 2-6 months. Their plasma was kept at -80°C until the HIV and HHV-8 PCR tests were performed.

Biological tests: The CD4+ T-cell count was enumerated by FACS Calibur (Becton Dickinson, San Jose, CA, USA) and the viral loads test for HIV and HHV-8 were carried out by real time PCR with Applied BioSystem instrument (ABI PRISM 7500), using respectively the kit Direct HIV-1 RNA of Diatech (Italy) and TM quantification kit for HHV-8 (Hoffmann La Roche A, Germany).

For the qualitative RT-PCR test, total RNA was obtained by using the Dia Tech RNA extraction kit and Qiagen columns (Qiagen GmbH, Hilden, Germany). Samples were amplified by 1 cycle under the following conditions: 42°C 60 min, 94°C 5 min and the 50 other cycles were run under the following conditions: 93°C for 30 sec, 60°C for 30 sec, 72°C for 30 sec, 72°C for 15 min for extension final. Electrophoresis was performed on a 3% agarose gel in 1X TBE BUFFER (40 mM Tris-Borate, 1 mM EDTA, pH 8.0) for 1 hour at a constant voltage of 120 V. The fragments were visualised after staining with Ethidium bromide and photographed under UV light.

The second maternal to child transmission (MTCT-HIV) program (2006-2010) was adopted in 2006, but its execution was not immediate in all the country. It proposes the use of three molecules (Zidovudine,

Nevirapine and Lamivudine) for infected mother and two molecules (Zidovudine and Névirapine) for the new-born babies.

These women freely agreed to answer a questionnaire referring to their school level and their function in the civil service. Following the instructions lavished, mothers are committed to not suck the wounds of their children through the mouth or chewing food by mouth for their infants in order to prevent horizontal transmission of HHV-8.

Ethical committee: The Committee of Ethics of the Saint Camille Medical Centre made sure that each person provided an informed consent before blood was taken for this study.

Statistical analysis: Demographic and clinical profiles were recorded on computer files and analyzed by standard software SPSS-10 and EpiInfo-6. Statistical significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

In this research, we asked to 107 women HIV seropositive enrolled in the PMTCT programme to respond to the questionnaire that we have submitted them and to accept the test of HHV-8 not only for themselves in may also their future children. Table 1 shows the information on the level of school training,

occupation and maternity of HIV seropositive women distributed according to the age. We note that 34.6% of them were illiterate and only 4.7% went to university. The majority because of their low school level were integrated very little in the public service (4.7%). They carry out especially a life of housewives (68.2%) and the commercial ones (27.1%).

Table 2 shows a prevalence of 12.15% (95% CI: 6.88-20.23) for HHV-8 among HIV seropositive pregnant women, the CD4 cells rate, the viral load of HIV-RNA and HHV-8-DNA in the HIV seropositive women and a prevalence of the vertical transmission for these viruses according to the serologic status of the mothers. Concerning the serology of the HHV8, there was no statistically significant difference as for the ages of the mothers ($p = 0.34$) or for the ages of the children ($p = 0.54$). However, there was a statistically significant difference between HHV-8 seropositive ($492.4 \pm 43.7 \text{ CD4}^+ \mu\text{L}^{-1}$) and HHV-8 seronegative ($462.7 \pm 20.9 \text{ CD4}^+ \mu\text{L}^{-1}$) for the rate of CD4 ($p < 0.001$).

The effectiveness of the HAART (Zidovudine, Nevirapine and Lamivudine) in the prevention of vertical transmission of HIV was confirmed by Simporé *et al.* (2007) and Medrano and Soriano (2009). The results obtained in this study showed that the MTCT-HIV is feasible in Saint Camille Medical Centre in Ouagadougou (CMSC) and in all the territory of Burkina Faso. In fact in the present research, the rate of vertical transmission of HIV is 0/107 (0.0%) (Table 2),

Table 1: Data on school training and occupation of HIV seropositive women

Age group (years)	School training of the HIV seropositive women						Occupation of the HIV sepositve positive women.				
	Age	Numbers	Illiterates	PSC	PSFC	BAC	University	Housewives	Commercial	Civils servant	
X<28 years	24.7 (19-28)	32	10/32 31.2%	12/32 37.5%	5/32 15.6%	3/32 9.4%	2/32 6.3%	23/32 73.5%	7/32 23.7%	2/32 5.8%	
29-35	30.9 (29-35)	59	21/59 35.6%	25/59 42.4%	6/59 10.1%	4/59 6.8%	3/59 5.1%	38/59 64.4%	18/59 30.5%	3/59 5.1%	
X>35	37.9 (36-42)	16	6/16 37.5%	7/16 43.7%	2/16 12.5%	1/16 6.3%	0/16 0.0%	12/16 75.0%	4/16 25.0%	0/16 0.0%	
Total	30.4 (19-42)	107	37/107 34.6%	44/107 41.1%	13/107 12.1%	8/107 7.5%	5/107 4.7%	73/107 68.2%	29/107 27.1%	5/107 4.7%	

PSC: Primary school certificate, BAC: Bachelor, PSFC: Patent studies of the first cycle

Table 2: The count μL^{-1} of CD4+, the viral load of HIV mL^{-1} and the HHV-8 mL^{-1} of the women and the prevalence of the vertical transmission according to the serologic statues of the mothers

	Mothers HIV+					Children		
	No.	Age (years)	CD4 ⁺ (μL^{-1})	HIV (mL^{-1})	HHV-8 (mL^{-1})	PCR HIV	Age (months)	HHV8+
HHV-8+*	13/107			12363.0	85.4			0/13
	12.1%	31.6±7.7	492.4±43.7	0.0-31278.0	75-129	0/13	4.5±0.9	0.0%
HHV8- ^o	94/107			7829.5				0/94
	87.9%	30.2±4.4	462.7±20.9	0.0-68838.0		0/94	4.8±1.7	0.0%
Total	107	30.4±4.9	466.3±19.1	8053.0	85.4			0/107
				0.0-68838.0	75-129	0/107	4.8±1.7	0.0%
χ^2 -value		$p = 0.336$	$p < 0.001$				$p = 0.535$	

which is very different from those of Simpure *et al.* (2006b) and of Deschamps *et al.* (2009) which respectively presented percentages of 10.4 and 9.2% of mother-to-child transmission of HIV.

With regard to the serologic status of HHV-8 for mothers, on 107 HIV positive women, 13 (that is to say 12.1%) were positive in HHV-8 DNA PCR test. This rate of prevalence that we found is definitely higher than those obtained respectively by Fujii *et al.* (1999) in Japan (0.2%) and Zavos *et al.* (2005) in Greece (9.6%). However, similar rates were obtained by Simpure *et al.* (2006a) in Ouagadougou (11.4%) as for our previous findings (Ilboudo *et al.*, 2007) in Ouagadougou (15.8%). Present results are on the other hand lower than those of Viviano *et al.* (2009) in Eastern Europe (19.6%), Ceffa *et al.* (2007) in Mozambique (51.1%), Chironna *et al.* (2006) in Albanians (28.8%) and Tsai *et al.* (2005) in Taiwan (24.5%). These differences in rate of prevalence show that the infection of human herpes virus type 8 constitutes a real problem of world public health in the world because it can induce KS. Consequently, an adequate instrument of prevention and care should be implemented in order to eradicate this plague which affects these people without discrimination. In addition, HHV-8 infection is highly prevalent among HIV-infected individuals. Significant associations with sexually transmitted infections such as hepatitis B and syphilis add evidence to the theory of a common transmission route.

Possible reasons where our results differ from previous study: in present research, we did not find women with Kaposi's sarcoma. That is why, we advance two hypotheses: (1) women have higher rates of CD4 sufficiently high that HHV8 cannot speak, (2) HHV-8 strain circulating in Burkina Faso is less pathogenic and did not induce usually KS. According to Mancuso *et al.* (2008) the pathogenicity varies depending on the strain of HHV-8. The type A KSHV strain is almost exclusively present in fast progressors, while C type is mainly present in slow progressing and the HHV-8. A subtype is associated with rapidly evolving classic Kaposi's sarcoma. We must then determine what type of HHV-8 strain is circulating in Burkina Faso.

The HHV-8 infection is common in childhood and the rate of seroprevalence increases with age, suggesting that intrafamilial, horizontal transmission is the main modality of the spread of HHV-8 (Calabrò *et al.*, 2001; Mayama *et al.*, 1998; Planoulaine *et al.*, 2000). In present study with PCR test, the rate of HHV-8 mother-to-child transmission is 0.0% (0/13). According to any researchers, initial studies on vertical transmission showed that HHV-8

seroreactivity in newborns is mainly due to transplacental passage of maternal antibodies (Calabrò *et al.*, 2000; Gessain *et al.*, 1999). However, rare cases of KS in newborns were described in the scientific literature and HHV-8 DNA was also detected at birth in the Peripheral Blood Mononuclear Cells (PBMCs) of a very low percentage of infants from Zambia (Brayfield *et al.*, 2003; Mantina *et al.*, 2001; Boivin *et al.*, 2000). These findings indicate that in utero or intrapartum HHV-8 infection might, albeit rarely, occur in countries where HHV-8 is endemic. The rates of HHV-8 detection in cervicovaginal secretions (CVSs) was also higher among African women than among women from areas of nonendemicity or subendemicity (Boivin *et al.*, 2000; Lampinen *et al.*, 2000; Whitby *et al.*, 1999), highlighting that the HHV-8 load in the female genital tract might influence vertical transmission.

In conclusion, although this study was limited to a relatively low number of HIV seropositive pregnant women co-infected with HHV-8, it demonstrates that, eradication of mother-to-child co-transmission of these viruses is possible in Burkina Faso. The increased viral load may in turn account for a higher risk for perinatal HHV-8 transmission in this HIV-1-infected population. That is why HIV seropositive pregnant women co-infected with HHV-8 may have HAART in order to get a good rate of CD4 T-cells. In addition, for the prevention of mother-to-child transmission of HHV-8, mothers should avoid sucking the injuries of their children through the mouth or chew food before giving them as recommended by several African cultures. Furthermore, the present study has been performed on PMTCT of HIV and HHV-8. It should turn out interesting to genotype the HHV-8 strain circulating in Burkina Faso.

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