AIDS in Italy and proposals for a new therapeutic strategy

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Summary: In Italy, the number of AIDS cases reported up to September 1993 was 18,832. Of these, 3,544 were women (21%), mainly of fertile age. AIDS in pregnancy has aroused great interest in Italy, mainly due to the extent of the phenomenon, which is not equalled in other Western countries. In this contribution to the study of HIV infection in pregnancy, the Authors propose a new procedure for monitoring, asymptomatic HIV-positive pregnant women, using fetal Fibronectin as an indicator of aspecific chorionamnionitis and the threat of premature birth, both considered as a risk factors for transmission of the virus from mother to child.

INTRODUCTION

The first case of AIDS in Italy was reported in 1982. Eleven years later (September 1993) reported patients totalled 18,832, of whom 19,261 had died. However, the total number of AIDS cases at the end of 1993 was estimated to have exceeded 20,000.

Every year 4,000 new cases are recorded, or 6.86 per 100,000 inhabitants/year. This rapid spread has meant that Italy is now the third country in Europe for total number of cases, after France and Spain.

From the very first years of the epidemic, distribution of at-risk classes showed a very distinctive trend which set Italy apart from most of the other European countries: the highest at-risk class is composed of drug addicts (66% of all infected cases), followed by homosexuals (10 %), heterosexuals (8 %), bisexuals (5%) hemophiliacs and those who have undergone repeated blood transfusions (2%).

One definitely underrated finding is that more than half the heterosexuals have partners who are drug addicts. In 25% of these cases, no definite risk factor could be identified.

This particular distribution of at-risk classes in Italy has led to frequent HIV infection among women. The 3,544 cases of AIDS reported by September 1993 represents 21% of the infected population (as opposed to 10% reported in the USA). Of these 3,544 women, 2,398 (57%) were drug addicts, 827 (43%) were heterosexuals; for 219 (36%) the source of infection could not be traced.

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The number of AIDS-affected women is constantly on the increase. In 1986 they represented 17% of the total; they now account for 21%, with further indications of increase. The women involved are mainly fertile (60%), aged between 25 and 35. This has meant that Italy holds the sad record of having the highest number of HIV-positive children in Western countries (377 cases, or 7% of the total, as against the 3% reported in the USA).

HIV AND DRUG ADDICTION

The rapid spread of HIV among Italian drug addicts is closely linked to intravenous drug use, in particular the widespread habit among addicts of exchanging syringes.

Heroin has various negative effects on the body, one of which is depression of the immune system, thus exposing subjects to bacterial, viral and fungoid infections which are more serious than in the healthy population.

As well as poor socio-economic conditions, the abuse of toxic substances such as alcohol, tobacco and cannabinoids means that female drug addicts have a high obstetric risk ([1]).

Pregnant drug addicts suffer from more miscarriages, fetal death, defective fetal growth, premature rupture of membranes, fetal distress during labour, followed after delivery by respiratory distress and acute withdrawal symptoms in the newborn, and breech presentations, with a consequent increases in the number of caesarian sections ([2, 57]).

In 1988, the Italian Multicenter Collaborative Study ([10]) reported an increase in the number of premature babies with low birth weight born to HIV-positive patients, although the fact that 70% of the women in question were drug addicts was not highlighted. In 1989, examining two groups of HIV-positive and HIV-negative pregnant drug addicts, Selwyn *et al.* ([9]) did not report any statistically significant differences between the groups, although they noted the absolute increase in the number of obstetric pathologies. Other Authors have reported similar results. It may therefore be presumed that, at least during the asymptomatic phase of AIDS, HIV is not responsible for the observed pathologies, but that they are due to abuse of stupefying substances, alcohol and tobacco, and to the poor socio-economic conditions in which these pregnancies are conducted.

HIV AND PREGNANCY

The influence of pregnancy on the course of HIV infection has not yet been clearly defined. Preliminary studies on AIDS in pregnancy ([3-8]) hypothesized that the reduction in cell-mediated immunity during the first trimester ([5]) represents a risk factor for progression towards the terminal phase. Later studies ([9, 15, 29]) have not shown any evolution of the disease, either during pregnancy or following it.

Our data [in press: ([6])], based on surveys of lymphocyte subpopulations during the first, second and third trimester of pregnancy in asymptomatic HIV-positive women, checked 6 and 12 months after delivery, show that CD4 lymphocytes gradually fall during the second trimester and then progressively return to pre-pregnancy levels after delivery. However, recent studies by the SIGO (Società Italiana di Ginecologia e Ostetricia) group for HIV ([34]), based on revised national data, show that symptomatic pregnant patients reach the terminal stages of the disease more quickly.

In a prospective study on 103 HIV-positive pregnant women, Gloeb *et al.* ([40]) found a statistically significant difference in the evolution towards manifest stages of the disease between patients at stage II (no symptoms) and stage III (with symptoms). The one-year survival

index for asymptomatic patients was 97.5%, and 84% in cases of generalized lymphoadenopathy. According to the above Authors, in pregnant women with generalized lymphoadenopathy, the risk of developing AIDS is 5-8 times higher than in asymptomatic pregnant women, one year after delivery. Pregnancy therefore appears to be a risk factor, in the sense of acceleration towards the terminal phases of the disease, but only for symptomatic patients (stages III-IV CDC); in asymptomatic patients the normal course of the infection does not seem to be influenced.

HIV AND OBSTETRIC PATHOLOGIES

Several works report increased numbers of obstetric problems in HIV-positive pregnant women: increased frequency of spontaneous abortion, congenital defects, premature birth, opportunistic maternal infections, and aspecific chorioamnionitis.

Spontaneous abortion

One of the most frequently reported pathologies in pregnancy is the increased frequency of spontaneous abortion ([2]), although data are conflicting: it seems that miscarriages are more frequent in Africa than in Western countries. In West Africa, Miotti *et al.* ([43]) report 15% of spontaneous abortions in HIV-positive women, as against 7% in controls. These data have also been confirmed by other Authors, such as Temmerman *et al.* ([51]) in Kenya. However, Selwyn *et al.* ([9]) in the United States and Blanche *et al.* ([38]) in Europe do not report such increased numbers among their cases. Theoretically, if the virus infects trophoblastic tissue in early pregnancy ([47-49]), more spontaneous abortions will be the result, although they may also be caused by the use of stupefying substances and abuse of alcohol and tobacco, also by systemic maternal infections and nutritional deficits.

Congenital defects

In 1988, Marion *et al.* ([11]) reported that babies of HIV-positive mothers sometimes had malformations such as craniofacial dysmorphism characterized by microcephaly, hypertelorism and growth defects, although later studies did not confirm these findings. Qazi *et al.* ([12]) and the European Collaborative Study and others ([21, 38]) have not found increased numbers of congenital defects, and believe that these characteristic signs are due to the use of drugs and alcohol and to the particular population examined (Hispano- and Afro-American). Some studies conducted in Africa by Miotti *et al.* ([43]) and Braddick *et al.* ([45]) do not report increased congenital defects in the populations examined.

Maternal infective complications

Reduced cell-mediated immune activity, observed in the first trimester of pregnancy, makes patients more susceptible to opportunistic infections which often complicate the physiological course of pregnancy. The concomitant immune system deficit found in HIV-positive pregnant women may expose them to several infections, which become more and more evident as the clinical stage of the disease progresses ([13]). In particular, opportunistic infections become more frequent when CD4 lymphocytes fall below the thresold of 300 cells/mm^3.

The most frequent infections complicating pregnancy are Pneumocystis carinii pneumonia, Candida albicans, active tuberculosis, toxoplasmosis and cytomegalovirus and, of the sexually transmitted diseases, syphilis, Herpes genitalis, Chlamydia and Mycoplasma. In 1992, Schoenbaum *et al.* ([63]) advised careful assessment of the tuberculin reactivity test due to the frequency of reactivation of primary complexes, and recommended primary prophylaxis in all tuberculin-positive patients.

Table 1. — *Frequency of opportunistic infections in pregnancy, in relation to clinical stage of HIV.*

	Stage II	Stages III-IV
P. Carinii pneumonia . .	3.5%	24%
Candida infections (esophagus, bronchi, lungs)	1.5%	17%
Active TBC	1.7%	13%
Toxoplasmosis	0.5%	
CMV	0.4%	
Sexually transmitted diseases		
Syphilis		
Herpes genitalis		
Chlamidia		

Premature birth and caesarian section

The frequency of acute and chronic fetal distress and urgent caesarian sections in HIV-positive pregnancies is still a debated point and the data are still partial and conflicting. In 1989 Minkoff *et al.* [14] reported more premature births, caesarian sections and cases of low weight at birth in HIV-positive pregnant women than in controls, whereas Semprini *et al.* [19], Bird and Snow [30] and Henrion [32] did not find statistically significant differences in their populations with respect to the healthy population.

However, it must be noted that data from Europe and America conflict with those from Africa. In Kenya in 1990, in a study on 177 HIV-positive pregnant women, Braddick *et al.* [44] reported increased premature births and low weight at birth (< 2500 gr), percentages being 17% versus 6% in controls. But such studies, although taking into account the abuse of alcohol as a risk factor, do not highlight other possible risk factors such as systemic maternal infections, malnutrition, loss of weight and serious maternal anemia – all of which may lead to poor fetal growth, premature birth, and fetal or perinatal death. The difference in socio-economic status between African and Western countries may thus, at least partly, explain the discrepancies observed. However, in a recent European study, Berrebi [33] reported a statistically significant rise in obstetric pathologies and urgent caesarian sections due to acute and chronic fetal distress in patients in advanced stages of AIDS.

Chorioamnionitis

In 1989 Ryder *et al.* [45], in a study of 475 HIV-positive African women, reported increased chorioamnionitis, premature birth and perinatal death with respect to a group of 615 HIV-negative women of comparable obstetric anamnesis and age.

Other studies have reported cases of chorioamnionitis. In 1991 Bulfamante *et al.* [35] described the high frequency of aspecific chorioamnionitis, omphalitis, and immaturity of villi and cell infiltrates in the placenta of 91 HIV-positive women. In particular, in 47% of the infected children, the placenta showed signs of aspecific chorioamnionitis, as against 10% in the case of healthy newborns.

In 1992 Nyongo *et al.* [46] reported that in 23% of healthy premature newborns, the placenta showed signs of aspecific chorioamnionitis, compared with 8% in that of at-term newborns. When examination was extended to HIV-positive women, cases of chorioamnionitis rose to 37%.

Premature birth, fetal death, fetal distress and perinatal death have all been ascribed to chorioamnionitis. In HIV-positive pregnant women, one risk factor may be vertical transmission. The mechanism has been hypothesized [35] as due to changes in the trophoblastic barrier, facilitating passage of virus-free or infected lymphocytes to the fetus and thus causing the infection in late pregnancy.

WEIGHT AT BIRTH

Weight at birth is another hotly debated point. Studies in Europe [19, 33] and the United States [9, 14] do not show sta-

tistically significant differences in the birth weights of children born to HIV-positive women, but in Africa several studies ([43, 44]) have reported lower weights.

A recent Italian study ([58]) on revised national data reports a slight reduction in birth weight with respect to expected values, but this does not seem to be linked to HIV, since comparison between the birth weights of infected and non-infected newborns were not statistically significant. However, if the birth weights of newborns from HIV-positive women who are also drug addicts are compared with those of HIV-positive women who are not drug addicts, the difference does turn out to be statistically significant (mean reduction = 116 gr). Lower birth weight therefore appears to be linked more to drug addiction than to the direct action of the virus.

VERTICAL TRANSMISSION

The first data on fetal transmission of HIV reported percentages around 35% ([2, 6, 10]), but this later turned out to be over-estimated. The data were distorted by the fact that it was impossible to detect the virus in the plasma of newborns, as diagnosis was based on the search for circulating anti-HIV antibodies. The possibility that maternal antibodies could persist as long as 18 months after delivery led to a high frequency of false positives. However, more refined techniques for early diagnosis, and the introduction of increasingly sensitive and specific methods such as the polymerase chain reaction, viral cultures, and immuno-enzymatic methods (Table 2) have allowed earlier and more definite diagnoses and reduced the number of false positives.

When and how the virus is transmitted still remains to be clarified. At the present time, there are three hypotheses, based on differing clinical evidence.

Table 2. — *Sensitivity (%) of diagnosis of HIV in newborns of HIV-positive mothers.*

	0-1 mth	1-3 mths	3-6 mths	>6 mths
Viral culture	40-50	70-90	> 95	> 95
PCR*-VIH	40-50	70-90	> 95	> 95
Ag p24	10-25	20-50	20-50	20-50
IgA anti-HIV	< 10	20-50	50-80	70-90
IVAP**	N.S.	N.S.	> 95	> 95
Elispot	N.S.	N.S.	> 95	> 95

* PCR: polymerase chain reaction.
** IVAP: in vitro antibody production.

1) *Early intrauterine transmission*

Vertical transmission through the placenta has been demonstrated clinically by Sprecher *et al.* ([18]), La Pointe *et al.* ([17]) and Jovaisas *et al.* ([25]), who found the virus in various tissues from fetuses aborted at the 15th, 20th and 28th weeks of pregnancy.

The hypothesis of early transplacental transmission is also based on *in vitro* observations which show that the placental tissue may be infected ([47-49]) by active phagocytosis of HIV-IgG complexes by placental macrophages (Hofbauer cells), with receptors for CD4.

2) *Late intrauterine transmission*

According to some Authors ([50]), the virus may cross the placenta late in pregnancy, thorugh gaps in aging syncytial trophoblasts. Bulfamante *et al.* ([35]) and Ryder *et al.* ([45]) believe that this may favoured by aspecific chorioamnionitis and high concentrations of the free virus in the mother's blood, characterized by the presence of Ag p24. According to Bulfamante *et al.*, an association between chorioamnionitis and omphalitis is observed in 47% of the placentas of newborns later found to be infected.

It should also be emphasized that ascending vaginal infections due to Trichomonas, Gardnerella, Chlamydia and

Mycoplasma may cause alterations either in the amnio-choral membranes, triggering rupture of the membranes and premature labour, on in the placental barrier, thus exposing the fetus to greater risk of intrauterine infections ([49, 53, 59]).

3) *Intrapartum transmission*

Goedert *et al.* ([42]) analysed findings from 22 vaginal deliveries of twins in which one of the twins was infected, and showed that in 18 cases (80%) the infected twin was the first to be born. The hypothesis that the fetus may come into contact with the virus during passage through the birth canal may explain why the second twin is less prone to infection. Goedert *et al.* propose elective caesarian section to avoid perinatal infection. This procedure was suggested in 1986 by Chiodo *et al.* ([16]), although later studies ([10, 17, 21]) did not confirm the usefulness of caesarian section as a means of protection. There are still doubts on the role and utility of caesarian section in HIV-positive pregnancies, although several Authors ([2, 52]) believe that negative opinions should be revised. One comparative study on caesarian section versus vaginal delivery has just been begun by some centres of the SIGO group and its results may shed some light on this point.

Transmission of the virus from mother to child may also occur after delivery, during breast feeding, as HIV has been found in milk ([27]). Cases of horizontal transmission have been reported ([28]).

INFECTION IN NEWBORNS

The percentage of vertical transmission of HIV varies considerably (15-60%), according to the cases and populations examined ([52, 53]). In Italy, the latest data report transmission values between 18% and 20%.

AIDS shows a bimodal trend in infected children. In 80-85% of cases the infection overlaps that of adults; in the remaining 15-20% its course is very rapid, with severe damage to the immune system, hepatosplenomegaly, encephalopathy, lymphoadenopathy, and serious infective complications. In particular, the presence of Ag p24 at birth is a poor prognostic index, due to the onset of encephalopathy in 60% of cases, most of these children die between three and four years of age.

In 80-85% of cases the infection is slower and may persist for more than 10 years, although serious infections and death may occur. Overall, 20-25% of infected children die within three years.

In 1990 Blanche *et al.* ([54]) hypothesized that the rapid course of AIDS found in 20-25% of children born to HIV-positive mothers is due to transplacental passage of the virus in early pregnancy, when it attacks immature immunocompetent organs, with consequent serious involvement of the immune system. These Authors believe that, in 80% of cases in which the infection follows a trend similar to that in adults, vertical transmission of the virus occurs in late pregnancy or during delivery, i.e., when the immune system is already sufficiently well developed.

FACTORS INFLUENCING VERTICAL TRANSMISSION

The percentage of vertical transmission is influenced by several factors, some of which are still poorly understood D'Arminio *et al.* ([41]) have recently reported a higher percentage of transmission in advanced pregnancy in HIV-positive women (stages III-IV CDC) Newell ([36]) reports 30% transmission in symptomatic HIV-positive women, as opposed to 14% in asymptomatic ones. Another poor prognostic index appears to be positivity to Ag p24, indicating maternal viremia: 30% of the children of Ag p24-positive mothers are infected, versus 10% of Ag p24-negative mothers ([52]).

In 1989 Ryder *et al.* ([45]) reported a higher percentage of transmission in women with CD4 lymphocytes under 400 cells/mm^3. Goedert *et al.* ([59]) point to premature birth as one of the risk factors for transmission in children born before the 38th week of pregnancy the percentage of transmission was 60%, but for those born at term it was only 22%. Bulfamante *et al.* ([35]) and Ryder *et al.* ([45]) report risk due to aspecific chorioamnionitis and sexually transmitted diseases.

In 1989 Goedert *et al.* ([59]) and Rossi *et al.* ([60]) noted high concentrations of antibodies with affinity for gp 120 epitope (envelope protein). This antibody, of maternal origin, appears to protect the fetus if present in abundance.

Table 3. — *Vertical transmission risk factors.*

1. Maternal factors
   - Clinically advanced stage of disease
   - CD4 < 400 cells/mm^3
   - Antigen p24
   - High serum levels of B2 microglobulin
2. Antibodies protecting against gp 120
3. Age of mother
4. Presence of other sexually transmitted diseases
5. Viral factors
   - more virulent viruses
6. Obstetric factors
   - premature delivery
   - vaginal birth
   - forceps and/or vacuum extractor
   - other invasive procedures during birth

Treatment and outcome of pregnancy

In the light of recently acquired knowledge, proper monitoring of HIV infection in pregnancy faces two problems. One regards the mother, particularly if symptomatic, when pregnancy may worsen the immunological situation, with possible attack by opportunistic infections. The second is the need to set up protective measures to avoid vertical transmission of the virus to the fetus.

The first approach with HIV-positive pregnant patients involves a series of tests, apart from routine obstetric care, for accurate assessment of the patient's clinical state ([2]).

Table 4. — *Testing in HIV-positive pregnant women.*

- Clinical examination
- Lymphocyte subpopulations
- Ag p24
- B2 microglobulin
- Immunoglobulins IgG, IgM
- Antibody titer search for:
  Hepatitis B, hepatitis C
  Cytomegalovirus
  Toxoplasmosis
  Mantoux test
- Screening for sexually transmitted diseases
- Pap-test

The need to monitor pregnant asymptomatic HIV-positive women with particular care has been emphasized by several Authors, and some ([32]) also note the need for primary or secondary prophylaxis for the most common infections. If CD4 lymphocytes fall below 200 cells/mm^3, Bird ([55]) recommends primary prophylaxis with cotrymaxyazole for pneumonia due to Pneumocystis carinii, and secondary prophylaxis against toxoplasmosis, Candida and Herpes with spiramycin, fluconazole and acyclovir during the asymptomatic phase. Schoenbaum *et al.* ([63]) advise careful assessment of TBC reactivity, due to the possibility of reactivating primary complexes, and prophylaxis for all tuberculin-positive patients.

The possibility that HIV infection in the symptomatic phase may accelerate during or following pregnancy has led some Authors ([56]) to use zidovudine in pre-

gnancy. Preliminary (unpublished) data indicate that AZT not only slows lymphocyte depletion in the mother, but also partly protects the fetus by reducing the percentage of viral transmission without major side-effects on either mother or fetus (8.3% vs 25.5%).

However, it should be emphasized that the long-term effects of AZT on the fetus are not accurately known. American studies only report reversible anemia in some newborns. In one of our cases (unpublished data), AZT started at the 16th week and continued for two weeks causing severe maternal anemia, with arrest of fetal growth, oligohydramnios and fetal distress. When AZT was suspended, all parameters returned to normal within three weeks. However, the long-term effects of this therapy cannot yet be evaluated, since the pregnancy is still under way.

Some Authors ([53]) suggest the use of hyperimune Ig in late pregnancy, although the possible selection of resistant and particularly active viral strains has also been hypothesized.

As regards the fetus, clearly it must be protected from uterine infection if at all possible. During pregnancy, iatrogenic uterine infections must be avoided: villocentesis, amniocentesis and corbocentesis can all pass the virus to the fetus.

All the latest data agree in identifying the late phase of pregnancy and birth as the moment when the infection passes to the fetus ([35, 42, 45]); according to Blanche *et al.*, this stage accounts for 80% of infected newborns. Some delivery room procedures, usually used for monitoring labour ([26]) but which could expose the fetus to infection and must therefore be avoided, are:

- electrode on fetal scalp;
- fetal scalp blood sampling;
- amniorrhexis;
- use of forceps or vacuum extractor;
- episiotomy (whenever possible).

Some Authors recommend abundant vaginal douching with an ordinary disinfectant during the phases of late labour and expulsion.

As already mentioned, caesarian section deserves separate discussion, since several Authors ([2, 52]) believe that the negative opinions on the possibility of reducing the percentage of transmission during birth are unduly pessimistic and should be revised.

PROPOSAL FOR A NEW STRATEGY FOR PREVENTION OF UTERINE INFECTION

In order to avoid vertical transmission of HIV, some American Authors suggest giving all pregnant patients AZT from the 16th week onwards. Preliminary data have not shown important side-effects on either mother or fetus, although zidovudine does appear to reduce the percentage of vertical transmission.

In our admittedly limited experience, zidovudine presents some risks, apart from the fact that its long-term effects in HIV-positive pregnancies are still not known. The fact that it can reduce the percentage of vertical transmission should mean that it can be used in a population of patients at high risk, selected according to the above-mentioned risk factors (CD4 <300 cells/mm^3, Ag p24, stage III-IV). In 1993 Newell ([36]) reported a link between the mother's clinical stage of the disease and infection of newborns (30% of infected babies born from symptomatic mothers vs. 14% from asymptomatic ones).

These data, also confirmed by other Authors ([38, 41]), indicate that AZT in symptomatic HIV-positive pregnant women should be limited, at least until its exact effects on both fetus and newborn are known.

To assess the tendency to premature delivery and the diagnosis of aspecific chorioamnionitis, which may favour viral transmission, our Centre assays fetal fibro-

nectin levels in vaginal secretions, sampled every two weeks from the 28th week onwards. The vaginal tampon used for sampling also searches for aspecific vaginitis, Chlamydia, Trachomatis, Candida, Neisseria gonorrhoeae, Gardnerella, hemolytic Streptococcus B and Mycoplasma.

Ascending vaginal infections, hypoxemia and primary infections of the chorion may lead to alterations in the amnio-choral membranes, premature rupture of membranes and premature labour. The mechanism is due to the activity of bacterial endotoxins and inflammatory cytokines favouring the release of powerful collagenases which degrade the extracellular matrix of the chorion and the decidua. Mechanical or proteolytic destruction of the extracellular matrix of the chorion-decidua interface then leads to the release of proteins from the extracellular chorionic matrix in cervical mucus and vaginal secretions. Fetal fibronectin, which is one of these proteins, proves to be a good index of initial alteration of the amniochoral membranes and consequently of the risk of premature delivery ([62, 63]). Vaginal tampons – cheap, easy to insert, and comfortable for the patient – have the advantage of indicating a tendency towards premature delivery and the existence of placental infections such as aspecific chorioamnionitis and other vertical transmission risk factors.

Fetal fibronectin is measured by a Fetal Fibronectin Immunoassay kit with FDC-6 monoclonal antibodies which can discriminate the fetal from the adult form. The assay is positive for values of >50 ng/ml in vaginal secretions and >60 ng/ml in cervical mucus. In asymptomatic patients before the 35th week of pregnancy, negative for Ag p24 and with CD4 lymphocytes of >300 cells/mm^3, if fetal fibronectin is positive, we recommend tocolytic therapy associated with antibiotics with cotrymoxyazole (active against aspecific chorioamnionitis). After the 35th week, when the fetal lung is fully developed, we suggest antibiotic therapy and, if deemed necessary to avoid infection during birth, delivery by caesarian section.

CONCLUSIONS

In 1993 Pantaleo *et al.* ([64]) and Embretson *et al.* ([65]) demonstrated that, during the asymptomatic phase, HIV replication occurs mainly in lymphatic tissue (lymph nodes, Peyer plaques, tonsils and spleen). In particular, using the polymerase chain reaction method, the former Authors reported how, during the asymptomatic phase, viral replication in lymph nodes is 5-10 times greater than that found peripherally, where detection is difficult and sometimes impossible. The mechanism hypothesized is that the virus is "kidnapped" or trapped by the villous processes of follicular dendritic cells in the germinative centre of the lymph node. The nodes, which become hyperplastic, trap the infected lymphocytes or the virus in the form of immunocomplexes.

As the infection develops, the lymph node ultrastructure is gradually destroyed, allowing the virus to escape from the lymphatic system. Pantaleo *et al.* ([64]) report that, in the symptomatic phase of the disease ,the degree of viral replication is the same in both lymph nodes peripheral blood. The different degree of activity and site of the virus in the various phases may explain observed discrepancies in the percentages of transmission between symptomatic and asymptomatic patients (30% vs. 14%). It may therefore be presumed that the rate of HIV transmission in asymptomatic patients with reduced viral replication in peripheral blood is in itself low, and that vertical transmission is favoured by situations allowing the virus an easier transplacental passage, such as chorioamnionitis, premature rupture of membranes, and premature delivery.

Thus, although the use of zidovudine may be justified in symptomatic patients

at high risk of vertical transmission, this is not the case in asymptomatic patients at lower risk, as the real long-term effects on the fetus are not known.

In our view, close monitoring of pregnancy in asymptomatic HIV-positive women, with early medical or surgical therapy to avoid the risk of vertical transmission caused by chorioamnionitis, premature rupture of membranes or pre-term delivery, is sufficient to minimize the rate of neonatal infection, without exposing the fetus to the further risk due to the administration of zidovudine.

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