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Nikavir in Chemoprevention Regimens of Vertical HIV Transmission

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1. Introduction

The first cases of HIV infection in the Russian Federation were identified in 1987. Between 1987 and 1996 over 90% of individuals acquired infection via homosexual contacts (Segeda, 2006; Berrous, 2000).

Since 1996 there has been a dramatic growth of incidence rate due to the parenteral use of psychoactive drugs (Montgomery, 2000; UNAIDS, 2001; Des Jarlais, 2001). Since then, in the Russian Federation a narcodependent type of epidemic process has formed. It is characterized by high intensity and a rapid growth of the incidence rate (Adabekov & Mamaev, 2005; Rakhmanova, 2004).

Due to a large share of women of the active reproductive age among the HIV-infected individuals and the tendency for its further growth as well as the increasing percentage of HIV distribution through sexual transmission (Terentyeva, 2006), there is a current annual growth of pregnancy and delivery rates among women infected with HIV (Terentyeva, 2006). Compared with 2000, in 2010 the absolute number of deliveries has increased 15 times. By 2010 deliveries by HIV-infected women accounted to 0.4% of the total number of deliveries in the Russian Federation.

The actual increase in the share of women among the newly identified cases of HIV infection may be regarded as an indirect evidence of activation of heterosexual transmission of HIV. 62% of HIV-positive pregnant women identified in 2010 were infected through sexual contacts. Along with the growth of heterosexual route of infection an associated risk of mother-to-child transmission of HIV has increased as well.

The mortality rate among children born from HIV-positive mothers is high. 25% of HIV-positive and 12% of HIV-negative children die before the age of five (Rogers, 1984; Rakhmanova, 2006).

By the end 2010, 12000 individuals with HIV infection were registered in Permsky Krai, over one third of them (35%) being females. Between 1999 and 2010 1634 children were born from HIV-infected mothers. 40 of them died and 73 have got HIV infection. Every 192nd delivery is in a woman infected with HIV (in the Russian Federation the ratio is 1 per 250).

Thus, a current high intensity of epidemic process of HIV infection has emphasized the necessity for HIV prevention among the newborns. Considering an unprecedented growth of the incidence rate and low birth rate in the Russian Federation this issue is a priority.
Mother-to-child transmission of HIV occurs during pregnancy, delivery and during the postpartum period while breast-feeding. In 1994 the US Center for Disease Control (CDC) recommended a three-stage chemoprevention with zidovudine (Retrovir) for mothers during pregnancy, delivery and postnatally for children (Barlett & Gallant, 1964; Friis, 2001). Along with the rejection of breast-feeding those measures decreased the risk of infection by 2% (Connor, 1994; European Collaborative Study, 2005; Jasseron, 2008; Townsend, 2008). The earliest recommendations on the vertical chemoprophylaxis of HIV were provided by Rakhmanova in 1997 and later by V. Pokrovsky and O. Yurin (2000-2001). Currently, there are American (CDC, 2008) and European (FACS, 2008) Guidelines. Nevertheless the number of antiretroviral agents available for prevention of vertical HIV transmission is rather small. Moreover, their recognized toxicological manifestations considerably restrict the possibility of HIV chemoprevention. Therefore the search, development and clinical implementation of the new low-toxic anti HIV agents with prolonged action are all of immense importance.

2. History of creation of Nikavir

In the middle of the 1980s academician A. Krayevsky initiated investigations of the anti-HIV activity of a group of nucleoside containing compounds, newly synthesized at the laboratory of the Engelhardt Institute of Molecular Biology of the Russian Academy of Sciences, which including a modified phosphate group in 5'-position. 5'-H-phosphonat 3'-azido-3'-desoxythymidine in the form of sodium salt appeared to be a highly active substance with the best cytotoxic properties. It was named phosphazide; its brand name is Nikavir (Fig. 1).

![Fig. 1. Formula of Nikavir (phosphazide).](https://www.intechopen.com)
the number of virus antigen expressing cells was 69%. With addition of Nikavir the number of live cells increased to 72% and the number of virus antigen expressing cells dropped to 20%. Similar results were obtained with the addition of zidovudine but compared to Nikavir it proved its considerably higher level of toxicity. The selectivity index of Nikavir was twice the number than that of zidovudine (Tarussova, 1990).

Later, a group of researchers from Canada proved a considerably lower toxicity of Nikavir with lymphoblastoid cell lines compared to zidovudine. Nikavir and zidovudine showed a marked efficiency with experimental HIV-1 infection in cord blood mononuclear cells. However, cytotoxic effect of zidovudine appeared by 33 times higher than that of Nikavir. Selectivity index of Nikavir was by 13.6 times higher than that of zidovudine (Machado, 1999).

It is known that in response to each antiretroviral agent drug resistant HIV-1 mutants are developed. It is the result of structural changes of HIV-1 genome due to substitution of one or several nucleic bases. It was found that HIV-1 resistance to Nikavir formed significantly slower than to zidovudine (Selimova, 1999). Resistance to Nikavir develops within a 72 days passivation of the virus (10 infectious cycles) whereas resistance to zidovudine occurs within 26 days (6 infectious cycles). The fact that extensive selection with Nikavir yielded only a single D67N substitution, also associated with resistance to zidovudine, rather than other zidovudine-resistance associated mutations as well, may also be a positive indication in regard to the potential of Nikavir to combat HIV disease (Machado, 1999).

Preclinical toxicological and pharmacokinetic studies of Nikavir were performed at the Institute of Experimental Cardiology of Russian Cardiological Scientific Production Complex. It was established that Nikavir belongs to the category of low-toxic drugs. LD$_{50}$ (average lethal dose) for mice of BABL/c line given in a single intragastric introduction was equal to 8200-8830 mg/kg, that for intra-abdominal introduction ~ 2260-2390 mg/kg. Zidovudine proved to be far more toxic: in intragastric intake its LD$_{50}$ was 2380-2730 mg/kg and 1320-1660 mg/kg in intra-abdominal introduction. During rat testing Nikavir LD$_{50}$ in intragastric and intra-abdominal introduction were 12200-12950 mg/kg and 2490-2510 mg/kg respectively. No damaging effect was established in the investigation of chronic toxicity in daily (90 days) intragastric introduction of Nikavir to rats (Khandazhinskaya, 2010).

Chronic toxicity was studied in dogs following 2-month oral dosing (tablets 0.2 g), 400 mg/kg during the first month and 200 mg/kg body weight during the second. It was found that tablets (400 mg/kg, 20-fold human dose) taken by dogs for a month caused some reduction of appetite and motor activity. Reduction of the doses to 200 mg/kg did not result in toxic effects in chronic experiments. Toxicity was also not observed in pathological experiments after the completion of the chronic testing. It showed that Nikavir was well assumed and did not affect hematological (granulocytopenia and anemia) or biochemical parameters of liver, kidney and pancreas functioning and metabolic reactions (Khandazhinskaya, 2010).

Basic methods (predominant lethality identification and the Ames test) did not show any mutagenic action as well as the DNA-damaging and allergic effects. Experimental studies on pregnant rats demonstrated a sufficiently lower embriotoxic and teratogenic action of Nikavir compared with zidovudine (Khandazhinskaya, 2010).

Nikavir is a prodrug: after its per oral introduction to dogs only zidovudine can be identified in their blood. However 40-50 minutes after intragastric introduction to mice of tritium-labeled Nikavir both Nikavir and zidovudine were found in blood plasma. The peak radioactivity level of zidovudine was considerably higher than of Nikavir (Skoblov, 2004).
The pharmacokinetic studies established that Nikavir is characterized by a smoother pharmacokinetic curve compared to zidovudine (Galegov, 2004; Khandazhinskaya, 2010). The half-life time of Nikavir from blood plasma surpasses zidovudine by 4 times and this allows to recommend fewer daily intakes.

Thus, due to its high anti-HIV efficiency \textit{in vitro}, low cytotoxicity, favorable pharmacokinetic indices and low toxicity in laboratory animals Nikavir was recommended for clinical evaluation studies.

The first phase of clinical investigation (safety and tolerance) was conducted in 1997. It showed that Nikavir was well-tolerated by all patients. There were no main side-effects observed in zidovudine administration (anemia, neutropenia) as well as less frequent untoward gastrointestinal manifestations, headache and insomnia (Yurin, 1998). It should be noted that not a single case of anemia known to the major side-effect of zidovudine was observed.

Further clinical trial (therapeutic efficiency) was conducted as a multicenter clinical trial under coordination of the Russian Federal AIDS Center, Moscow. The local participating centers were Republican Clinical Infection Hospital in Izhora settlement (St. Petersburg), Regional AIDS Centers in Tver, Nizhny Novgorod and Tyumen (Yurin, 2001).

At the first stage Nikavir was used as a monotherapy. The trial included 103 patients (75 males and 28 females, average age 26 years). According to HIV-infection classification (USA, CDC, 1987) 69.9% were diagnosed A2 stage, 23.3% had A1 stage and 6.8% had B1 and B2 stages. The therapy course lasted 12 weeks. Patients received daily doses ranging from 400 mg to 1200 mg Nikavir. Its therapeu tic efficiency was assessed by such clinical criteria as disease progression or its absence; immunological criteria included changes CD4+ T-lymphocytes count per 1 mm$^3$ of blood; virological criteria included changes of HIV RNA levels per 1 ml of plasma. CD4 lymphocytes were counted with flow cytometry method using Fac Scan apparatus (Becton Dickenson, USA) and monoclonal antibodies (Becton Dickenson, USA). HIV RNA levels were measured with PCR method (Amplicor Roche HIV-1 Monitor, Hoffmann-La Roch, Switzerland).

During treatment no cases of HIV progress were noted. The pretreatment baseline mean CD4 lymphocytes count was 350 cells/mm$^3$. After 4 weeks of treatment the mean CD4 lymphocyte index increased by 20 cells and by 80 cells following 12 weeks (p<0.05). A reliable decrease of HIV RNA levels was observed starting with the second week of therapy (-0.53 lg copies/ml, p<0.05), which remained unchanged after 4 and 12 weeks of therapy (-0.53 and -0.44 lg copies/ml respectively).

The most frequent negative Nikavir-related effects were mild nausea and malaise registered in 30% of patients receiving maximal daily dosage of 1200 mg. No essential changes in hematological indices were revealed. For 1% of patients therapy was temporary stopped due to a moderate granulocytopenia. In 5.8% of cases Nikavir therapy was initiated in spite of grade 1-2 toxicity thrombocytopenia. In all cases the on-going therapy was associated with notable increase of thrombocyte count and disappearing signs of toxicity. During the trial no worth considering changes in biochemical blood values were registered.

The conducted trial demonstrated good efficiency and tolerability of Nikavir monotherapy and allowed to recommend a regimen of 400 mg twice daily (Yurin, 2001).

The next stage was aimed at investigation of possible outcomes following change of zidovudine to Nikavir regimens due to the development of untoward events of grade 2-4 toxicity. In 47 patients zidovudine was substituted by Nikavir because of nausea and vomiting (40.4% of cases), anemia (46.8%) and granulocytopenia (12.8% of cases) whereas
44.7% of patients received Nikavir as monotherapy and 55.3% as a component of highly active antiretroviral therapy (HAART). No cases of Nikavir-associated untoward events were observed and there were no cases of discontinued therapy. Mild nausea was noted in 6.4% of cases and 2.1% had grade 1 toxic anemia. Besides, 36-48 weeks following substitution of zidovudine by Nikavir a considerable growth of CD4 lymphocytes by 70-100 cells/mm³ was found (Yurin, 2000).

Since 1999 Nikavir was approved for clinical application in the chemotherapy of HIV-infected patients. Currently it is manufactured in the tablet form of 200 mg N 20 and is used for treatment of HIV and AIDS in Russian Federation.

3. Comparative studies of embryotoxic and teratogenic properties of zidovudine and Nikavir

In terms of anemia, significantly fewer Nikavir-associated hemopoetic impairments make it a more perspective drug for therapeutic application for HIV-infected pregnant women than zidovudine. Because of this, evidence-based findings obtained in the comparative studies of embryotoxic and teratogenic properties of zidovudine and Nikavir performed in 2005 at the laboratory of drug toxicology of Institute of Experimental Cardiology under the guidance of professor E. Arzamastsev are of a considerably interest.

Tests were performed among 80 pregnant rats of Wistar line divided into 4 equal groups. Group 1 included animals for control, group 2 received zidovudine (dose of 100mg/kg of body weight once a day), group 3 received Nikavir (dose of 100mg/kg of body weight once a day). As the period of zidovudine half-excretion is less than that of Nikavir group 4 received zidovudine in the total daily dosage of 100 mg/kg in 2 doses (50 mg/kg at 9 a.m. and 5 p.m.).

The tested doses corresponded to a 12.5 multiple of the maximum daily doses of 600 mg/individual or 8 mg/kg approved for pregnant women with HIV.

Intragastric introduction of zidovudine and Nikavir to pregnant rats in the tested doses of 100 mg/kg provided the significant (p<0.05) evidence of the body mass retardation in pregnant rats compared with the controls on the 3rd week, while the less marked body mass retardation was observed in Nikavir administration and a two-dose introduction of zidovudine (Table 1).

No statistically significant difference was established in such parameters evaluated for embryotoxicity of zidovudine and Nikavir as the duration of pregnancy, numbers of alive fetuses, implantation places, yellow bodies, fetal body mass, cranioclaudal size in the pregnant rats receiving preparations in the dose of 100 mg/kg and the controls. Likewise data of preimplantation and postimplantation death in experimental groups did not significantly differ from those in the controls as well (Table 2).

<table>
<thead>
<tr>
<th>Observation periods</th>
<th>Animal groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td>1st week</td>
<td>110±1.6</td>
</tr>
<tr>
<td>2nd week</td>
<td>121±1.7</td>
</tr>
<tr>
<td>3rd week</td>
<td>135±3.0</td>
</tr>
</tbody>
</table>

Table 1. Body mass dynamics in pregnant rats (% ratio of baseline parameters) in intragastric introduction of zidovudine and Nikavir.
Table 2. Embriotoxicity indices of zidovudine and Nikavir administered in the intragastric dose of 100 mg/kg introduced to rats within 1-19 days of gestation.

Microscopy and microanatomical examination (standard Wilson-Dyiban dissection) of fetuses perinatally exposed to zidovudine and Nikavir in tested doses did not reveal any malformations or defects of the visceral development. The incidence rate of malformations in the experimental groups did not significantly differ from the controls.

Development of the skeletal system in rat fetuses treated perinatally with zidovudine and Nikavir in the tested dose of 100 mg/kg was studied. The analysis of the alizarin stained total samples from the experimental groups showed the reduction in the number of ossification centers in the 2\textsuperscript{nd} and 4\textsuperscript{th} metacarpal bones, the 3\textsuperscript{rd} and the 4\textsuperscript{th} metatarsal bones, sublingual and pubic bones. These changes were more evident in the zidovudine group on a daily dose of 100 mg/kg. (Table 3).

Table 3. Fetal skeletal development on the 20\textsuperscript{th} day of prenatal development.
It was established that an intragastric once-daily dose of 100 mg/kg and a 50+50 mg/kg dose of zidovudine as well as Nikavir daily dose of 100 mg/kg given within 1-19 days of gestation did not cause any change in the number of the offspring born. Body mass dynamics and offspring postnatal mortality indices in the experimental zidovudine and Nikavir groups treated perinatally did not significantly differ compared with the controls (Table 4).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Animal groups</th>
<th>Controls</th>
<th>Zidovudine 100 mg/kg</th>
<th>Zidovudine 50+50 mg/kg</th>
<th>Nikavir 100 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of born offspring</td>
<td></td>
<td>8.8±1.4</td>
<td>8.1±0.9</td>
<td>8.5±1.2</td>
<td>8.3±1.5</td>
</tr>
<tr>
<td>Postnatal mortality, %</td>
<td></td>
<td>3.6</td>
<td>4.2</td>
<td>3.9</td>
<td>3.8</td>
</tr>
<tr>
<td>Body mass, g</td>
<td>At birth</td>
<td>7.6±0.2</td>
<td>7.3±0.6</td>
<td>7.4±0.5</td>
<td>7.3±0.7</td>
</tr>
<tr>
<td></td>
<td>7th day of life</td>
<td>20.3±1.3</td>
<td>18.3±1.8</td>
<td>20.1±1.1</td>
<td>19.1±1.6</td>
</tr>
<tr>
<td></td>
<td>14th day of life</td>
<td>37.3±3.5</td>
<td>35.5±1.6</td>
<td>36.4±1.5</td>
<td>35.6±1.7</td>
</tr>
<tr>
<td></td>
<td>28th day of life</td>
<td>43.8±3.1</td>
<td>47.7±2.0</td>
<td>45.9±1.8</td>
<td>46.0±1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>56.3±2.5</td>
<td>58.1±2.6</td>
<td>56.7±2.5</td>
<td>57.5±2.1</td>
</tr>
</tbody>
</table>

Table 4. Postnatal development in the group receiving 100 mg/kg of zidovudine and Nikavir doses in the prenatal period (1-19 days of gestation).

Other parameters of the offspring development observed (hair covering, incisor eruption, opening of eyes, helix detachment, vagina opening, testicle descending, time of reflex maturation, etc.) were within the normal term limits for this animal species. In conclusion it should be noted that daily intragastric administration of zidovudine and Nikavir in a once-daily dose of 100 mg/kg (a 12.5 multiple of the maximum daily doses for pregnant women) to pregnant rats from within 1-19 days of gestation was found to retard their body mass gain in the third trimester. A twice-daily dose of zidovudine (50+50 mg/kg) at 9 a.m. and 5 p.m. partly moderates its negative effect on the body mass gain. A once-daily dose intragastric introduction of zidovudine and Nikavir as well as a twice-daily dose zidovudine (50+50 mg/kg) do not influence such embryotoxicity criteria as the duration of pregnancy, number of yellow bodies, number of alive fetuses, number of implantation places, embryo body mass, cranioclaudal size, as well as preimplantation and postimplantation death rate.

A single-dose intragastric 100 mg/kg zidovudine and Nikavir given within 1-19 days of gestation did not cause any malformations and developmental defects in the offspring. However, in the introduction of theses preparations in a daily intragastric dose of 100 mg/kg within 1-19 days of gestation both the decrease in the number of ossification centers and retardation of embryonic skeletal ossification were observed. It was due to the effect of zidovudine and Nikavir that there were no ossification centers in the 2nd and 4th metacarpal bones, the 3rd and the 4th metatarsal bones, sublingual and pubic bones of the embryos. The noted changes were more marked in the embryos of the experimental group which received a once-daily dose of 100 mg/kg zidovudine in the perinatal period. Adverse effects reduced in a twice-daily dose introduction of zidovudine (50+50 mg/kg) and a once-daily intragastric 100 mg/kg dose of Nikavir. During the observation period no further adverse influence of the tested agents on the following offspring development was noted. It was not accompanied by any term deviations.
and was within the normal time limits natural for the normal physiological development of this animal species.

Thus, studies on animal models have provided reliable evidence that compared to zidovudine, Nikavir possesses a less damaging impact on fetal development and thus may be a more preferable choice for ART in HIV-infected pregnant women.

4. Experience of Nikavir use in various regiments of vertical HIV transmission chemoprophylaxis

The first experience of Nikavir use in different regiments of vertical HIV chemoprophylaxis was obtained by the staff workers of the Russian Federal AIDS Center (Detkova, 2003). Three groups of 96 HIV-infected pregnant women were observed. Groups 1 and 2 received Nikavir in the dose of 200 mg/kg 3 times a day after 14 gestation weeks (within 16 to 36 weeks of gestation, the average time 25-27 weeks of gestation). Group 1 of 27 women were administered intravenous zidovudine in labour. Newborns were given oral zidovudine syrup (Retrovir) in the dose of 2 mg/kg body mass every 6 hours for 6 weeks. Group 2 (17 women) were given a single dose of 200 mg Viramun at the onset of labour. Newborns were given Viramun suspension in the dose of 2 mg/kg body mass once daily for 3 days. Group 3 included 52 women who did not receive chemoprevention. The only preventive measure was exclusion of breastfeeding.

A total of the women under observation delivered alive babies (27 newborns in group 1, 17 newborns in group 2 and 52 newborns in group 3). Body weight parameters of newborns given chemoprevention slightly surpassed those in group 3 though the difference was not significant (3022±223 and 2731±558 g respectively, p=0.196). The children were followed-up during 72 weeks. By 72 weeks 34.6% of group 3 were diagnosed HIV-infection (stable positive serological evidence HIV DNA in PCR). Children in group 1 were born healthy. Only one newborn in group 2 was diagnosed HIV which was possibly due to the continuous drug addiction of his mother and her inappropriate following the Nikavir regimen during pregnancy (adherence to preventive therapy was <60%).

Application of Nikavir in pregnancy showed its good tolerability. The major therapy-associated side-effect was a mild gastric syndrome found in 25% of women. Application of Nikavir aimed at prevention during pregnancy was not found to affect either the pregnancy course in HIV-infected pregnant women or maturation and vital capacity of newborns. No significant association between application of Nikavir as intrapartum prevention and both the pregnancy course in HIV-infected pregnant women and maturation and vital capacity of newborns was established.

A further clinical trial of efficiency and safety of chemoprevention with Nikavir in pregnant HIV-infected women was carried out at the Republican Clinical Infection Hospital (Izhora settlement, St. Petersburg) (unpublished data) as well as at Regional AIDS Centers in St. Petersburg (Zakharova, 2008) and Perm (Ivanova, 2010). The clinical trial conducted at the Republican Clinical Infection Hospital in 2005-2006 involved 20 pregnant women aged 20-31 at 26-28 weeks of gestation with normal laboratory values. Group 1 (10 women) was given 200 mg Nikavir 3 times daily. Their viral load <3000 copies/ml. Group 2 (10 women) was given 200 mg Nikavir 3 times daily + Epivir in conventional dosage. Their baseline viral load was 3000-30000 copies/ml.

Assessment of therapy was based on registration of clinical and laboratory indicators of HIV progress. Nikavir therapy demonstrated good tolerance (100% of patients have finished research). No severe adverse events were observed. There were only 2 associated with therapy registered...
cases of moderate abdominal pain which did not require its cessation. No deviations in laboratory findings were noted.

The end of Nikavir therapy was followed by elevation of the mean CD4 lymphocyte counts. Of note, before delivery 50% of women were referred to a higher immunological category. Such elevation tendency persisted until the end of the investigation.

There was a marked reduction of viral load noted in the process of therapy. In 4 weeks of treatment the level of viral load reduced below the level of detection in 60% of women in both groups and in 90% before the delivery but it was less than 1000 copies/ml.

No cases of perinatal HIV transmission were registered.

Thus Nikavir appears to be a highly efficient agent for treatment of HIV-infected pregnant women as its effect has been confirmed by the obtained clinical and immunological evidence.

A clinical Nikavir trial at St. Petersburg Regional AIDS Center involved 30 pregnant women aged 20-35 years (mean age 26 years) at 14-34 weeks of gestation and infection term from 1 to 6 years. 36.6% of examined women presented with a history of drug addiction and 50% chronic hepatitis C. A total of patients did not receive anti-retroviral preparations.

In accordance with the baseline viral load 23 patients were administered Nikavir as a monotherapy and 7 patients received dual therapy.

In a monotherapy schedule Nikavir was given in a dosage of 200 mg in 3 doses. In combined dual therapy Nikavir was supplemented with Epivir in a daily dosage of 150 mg in 2 doses. In accordance with the Russian Federation standards at the onset of labour the women were given intravenous zidovudine. Newborns received an extended therapy with zidovudine in syrup (Retrovir) for 6 weeks following the delivery.

The pretreatment viral load in the majority of women (67%) did not exceed 10000 copies/ml. By the 4th week the total of the group demonstrated a significant reduction of viral load indices (p<0.05). At 28 weeks of gestation the total number of patients with undetectable optimal level of viral load was 33%. At 36 weeks the reduction tendency was stable. In the following postpartum period HIV RNA levels did not exceed the baseline indices (Table 5).

<table>
<thead>
<tr>
<th>Observation time</th>
<th>&lt;400 copies/ml</th>
<th>400-1000 copies/ml</th>
<th>1000-10000 copies/ml</th>
<th>10000-50000 copies/ml</th>
<th>&gt;50000 copies/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment, patients</td>
<td>3 (10%)</td>
<td>1 (3%)</td>
<td>19 (67%)</td>
<td>3 (10%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>After 4 weeks of therapy, patients</td>
<td>9 (37%)</td>
<td>3 (13%)</td>
<td>9 (37%)</td>
<td>2 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>28 weeks of gestation, patients</td>
<td>8 (35%)</td>
<td>2 (9%)</td>
<td>11 (47%)</td>
<td>2 (9%)</td>
<td>0</td>
</tr>
<tr>
<td>36 weeks of gestation, patients</td>
<td>7 (37%)</td>
<td>4 (21%)</td>
<td>8 (42%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1 month postpartum, patients</td>
<td>2 (11%)</td>
<td>0</td>
<td>13 (68%)</td>
<td>4 (21%)</td>
<td>0</td>
</tr>
<tr>
<td>3 months postpartum, patients</td>
<td>2 (10%)</td>
<td>4 (20%)</td>
<td>13 (65%)</td>
<td>0</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>6 months postpartum, patients</td>
<td>3 (16%)</td>
<td>2 (11%)</td>
<td>10 (52%)</td>
<td>4 (21%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 5. The intra-treatment dynamics of viral load in pregnant women.
Patients with viral load over 10000 copies/ml received the dual therapy (Nikavir+Epivir). Already by the 4th week of therapy the viral load in half of the patients reduced to the undetectable level and remained at that level till 36 weeks of gestation. The same was true about the patient who was transferred from the monotherapy group due to the increase of her viral load above 10000 copies/ml.

Starting with the 4th week of treatment an overall significant increase of the mean values of the percentile CD4 lymphocytes indices irrespective of the drug intake regimen was noted. After discontinuation of treatment CD4 lymphocytes indices returned to the baseline.

The mean Hb values did not exceed the norms before initiation of therapy (117 g/l). It was noted that mean Hb values decreased during chemoprophylaxis. Hb decrease lower 100 g/l was improved with administration of iron-containing preparations. By 36 weeks of gestation mean Hb values were not different from baseline (Table 6).

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Observation time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
</tr>
<tr>
<td>Mean value, g/liter</td>
<td>116.5±9.2</td>
</tr>
<tr>
<td>Minimal value, g/liter</td>
<td>89</td>
</tr>
<tr>
<td>Maximal value, g/liter</td>
<td>150</td>
</tr>
<tr>
<td>&lt;100 g/liter, patients</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>&gt;100 g/liter, patients</td>
<td>27 (90%)</td>
</tr>
</tbody>
</table>

Table 6. Hb level in Nikavir treatment of pregnant women.

The controllable biochemical blood serum values did not correlate with the therapeutic regimen and did not deviate from the normal during the whole observation time.

Proper adherence to therapy was associated with good tolerance of the applied regimens.

In the majority of patients the labour course and the delivery methods did not differ from those in the average population.

Viral load monitoring findings in children provided by the attending pediatricians confirmed the absence of HIV-1 virus in 100% of newborns at three examinations during a 6 months period.

Thus, the obtained findings allow considering Nikavir one of the most perspective agents for the practice of perinatal prophylaxis of vertical transmission of HIV-1 virus. However, a continuous monitoring of Hb levels and viral load for the prompt correction of the switch regimen from monotherapy to combination (dual) therapy as well as an additional administration of iron-containing preparations is necessary.

The clinical trial conducted at Perm Regional AIDS Center involved 38 HIV infected and their 38 newborns. Group 1 (20 women, aged 18-30) was given Nikavir+Epivir therapy. Group 2 (18 women aged 19-32) was given one the HAART regimens (Nikavir+Epivir+Viramun or Kaletra). The total of patients on chemoprevention schedule did not take the agents previously. The therapy was started at 23-32 weeks of gestation depending on the time of their first visit.

During the first hour of labor a dose of 2 mg/kg/h of zidovudine was given intravenously followed by 1 mg/kg/h until the end of the labor. Starting with the 8th hour of life the newborns were given of zidovudine in syrup (Retrovir) in an oral dose of 2 mg/kg every 6 hours during 6 weeks.
45% women in group 1 and 44% women in group 2 had transvaginal delivery. Pre-term delivery was registered in 2 women – 1 from each group at 32 and 34 weeks of gestation respectively. There were no cases of intrapartum complications and breast-feeding. Prior to chemoprophylaxis a total of group 1 women were clinically diagnosed the stage A1 HIV infection. Half of group 2 women were diagnosed the stage B1 HIV infection associated with oral candidiasis and grade 1 anemia. On clinical examination of both groups performed 1.5 months after delivery no progression of HIV was revealed. The structure of associated diseases included viral hepatitis C in 45% and 60% of women from group 1 and group 2 respectively. Chlamydial infection was identified in 5% of women in group 1. Prior chemoprophylaxis the baseline viral load in group 1 women ranged from 500 to 382000 copies/ml (mean 8280); 4 weeks after the start of chemoprevention it dropped by 6 times to 886; it was undetectable at 36 weeks of gestation (<500 copies/ml). The pretreatment baseline mean CD4 lymphocytes count was 478 cells/mm$^3$ and 545 cells/mm$^3$ before delivery (Fig. 2).

The baseline viral load in group 2 women was >200 000 copies/ml, 4 weeks after the start of chemoprevention it dropped by about 300 times. Prepartum viral load was undetectable (<500 copies/ml) and 1.5 months after delivery with discontinuation of treatment it increased to over 20000 copies/ml. The pretreatment baseline mean CD4 lymphocytes count was twice lower compared with group 1; after 4 weeks of HAART and before delivery it increased and insignificantly lowered 1.5 month postpartum when treatment was discontinued. Therefore, following the discontinuation of HAART in group 2 viral load parameters increased while CD4 lymphocytes count decreased.

Fig. 2. Parameters of viral load and CD4 lymphocytes at various terms of examination of women administered Nikavir+Epivir.
The total of children born to HIV-infected mothers was referred to the category of risk with diagnosed perinatal HIV infection contact and was examined for the presence of HIV-1 DNA. The obtained results were negative.

The agents proved an appropriate tolerance in both therapeutic regimens. No significant side effects and adverse events associated with the tested agents were noted. The parameters of vital capacity were in compliance with the normal natural course of pregnancy. The haemogram analysis was performed to predict the possible side effects of chemoprevention. In this connection it was found that at the time of conception both red blood cell counts and white blood cell counts were normal. In both groups the Hb level was insignificantly decreased: 101 g/l in group 1 and 106 g/l in 17% of group 2 respectively. 4 weeks after the start of therapy and at 36 weeks of gestation no changes in the parameters of peripheral blood were noted \((p>0.05)\). The total of women received the preventive therapy of anemia including the diet and iron-containing preparations in conventional doses. By 36 weeks of gestation a tendency of thrombocyte count elevation was observed – 297.9 and 271.8 g/l respectively. At different terms the findings of the functional liver tests (ALT, AST, bilirubin) were within the normal limits in both groups.

Thus, absence of HIV-1 infection in children born to HIV-infected pregnant women testifies high efficiency of both chemoprevention regimens with Nikavir both in combination with Epivir and in HAART. An evident positive outcome of this therapy is confirmed by the significant decrease of viral load to undetectable level of viral RNA during therapy starting with the 4th week of gestation up to delivery. Simultaneous elevation of CD4 lymphocytes is undoubtedly an evidence of beneficial effect of both regimens of chemoprevention on the immune status of HIV-infected pregnant women. Excellent adherence to chemoprevention therapy (100%) was associated with good tolerance of the employed agents. The safety of Nikavir application both in combination with Epivir and in HAART schedule was proved by the absence of toxic effect on biochemical blood values at various gestation terms. An insignificant elevation of thrombocyte count by 36 weeks of gestation in both groups may be regarded as a physiological factor preparing the organism of a woman to delivery.

The obtained results allow to regard Nikavir to be one of the most potent perspective agents used in the schedules of chemoprevention of vertical transmission of HIV-1 infection.

5. Comparative characteristics of methods of perinatal chemoprophylaxis with Nikavir

5.1 Actuality

Currently, the choice of available antiretroviral agents for chemoprevention of perinatal infection is not extensive. The standard schedules of HAART are widely used. A number of various prevention patterns based on the expert opinion, theoretical research and evidence of preclinical animal studies has been suggested. However, substantiation of choice of methods of chemoprevention of perinatal HIV infection, efficiency and safety of different preparations and their side-effect estimation have not been sufficiently investigated.

Thus, method of chemoprophylaxis of vertical transmission of HIV-1 with Nikavir+Epivir in HAART schedule which is known to produce less side-effects compared to the analogue schedules with Combivir is becoming actual.

The present investigation was performed in June 2007 – October 2008 in the setting of Perm Regional AIDS Center and is based on the analysis of epidemiology data as well as the evidence from clinical and laboratory studies.
5.2 Adherence to HAART for perinatal prevention in HIV infected pregnant women

An important factor of the prevention of the perinatal transmission of HIV virus is the formation of an adherence to persistent intake of antiretroviral preparations. With the aim of the analysis of the adherence to chemoprevention two groups of patients with the past history of intravenous psycho-active agents were suggested a self-completed questionnaire. The group 1 included 31 women who had not been administered chemoprevention therapy due to the early gestation term. The group 2 contained 23 women undergoing HAART. The age in both groups was 18-25 years.

The answers to the question on the time of registration their pregnancy at the women consultation center were as follows: 45.2% in the group 1 and 30.4% in the group 2 were registered at the term before 12 weeks of gestation. Thus, the majority of the respondents delayed their visit to their gynecologist for registration of their pregnancy for later than 12 weeks of gestation (54.8% and 69.4% respectively). Their attendance of gynecological check-ups was self-assessed as neither regular nor frequent by 22.6% of respondents in group 1 and 17.4% in group 2. 77.4% attended gynecologist at the women consultation center but only 64.5% attended the HIV/AIDS Prevention Center.

It is worth noting the fact that before starting chemoprophylaxis almost 30% of woman did not visit gynecologist regularly and 9% missed such visits during the antiviral therapy. A considerable part of pregnant women (80.6% and 73.9% respectively) strictly followed the administrations of their doctors while the others neglected the professional advice. Thus, 3% of women in group 1 and 6% in group 2 have taken responsibility to decide themselves which of the doctor’s recommendations they are to follow. And 16.2% noted that prior chemoprophylaxis they underwent only those examinations which considered being necessary. However, with the beginning of antiretroviral therapy women become more responsible and underwent all the administered examinations.

The majority of women in both groups consider the ultimate goal of chemotherapy to be the birth of a healthy child (83.6% and 95.6% respectively). 45.3% of women did not express apprehension of chemoprevention and revealed an adequately positive attitude to it. The investigation analyzed persistent detrimental habits in pregnant HIV infected women which they could not abandon even being pregnant. About half of them smoked (45.1% and 43.5% respectively) and 3.2% women of group 1 took alcohol. 2 patients of group 1 (6.4%) gave a negative answer to the question about the influence of irregular and incorrect intake of antiretroviral preparations on the therapeutic effect. A considerable number of pregnant women strictly followed recommendations of their doctors (80.6% and 73.9% respectively) while others neglect certain administrations on diet (34.7% and 54.6% respectively).

In summary, investigation of adherence to perinatal chemoprevention in HIV infected pregnant women demonstrated high level of motivation aimed at birth of a healthy child. However, along with following the therapeutic regimen their specialist check-up visiting was neither regular nor timely. The majority of women kept to their harmful habits (smoking) and did not follow recommendations on their diet which was possibly due to their low social status. Consequently, every third pregnant woman before administration of chemoprevention and every second woman during chemoprevention did not attend their obstetricians and gynecologists regularly. In this connection one should note the necessity of organization of School of Adherence to Chemoprevention which can provide social-
psychological counseling aimed at formation of positive motivation to doctor's recommendations, following the daily regimen and regular intake of antiretroviral preparations as well as refuse of detrimental habits which is of a particular importance for pregnant drug-addicts.

5.3 Purpose
- to study efficiency of Nikavir in combination with Epivir and Kaletra in chemoprophylaxis of perinatal transmission of HIV-1 infection on the basis of the RNA HIV-1 plasma parameters and the estimated number of children with negative quality PCR reaction for DNA HIV-1 at the age of 1.5 months and 3 months;
- to provide a comparative evaluation of safety and tolerability of Nikavir and Combivir in the HAART chemoprevention schedule in HIV infected pregnant women.

5.4 Materials
The start of antiretroviral prevention was determined by the time of the first appointment with a gynecologist for pregnancy diagnosis. Chemoprevention of vertical HIV mother-to-child virus transmission with various agents was performed in 36 women with A1 (62%) and B2 (38%) HIV stage (USA, CDC, 1987) at 23-32 gestation weeks as well as their 36 newborns. B2 stage manifested with moderate symptoms of oral mucosa candidiasis. 65% of observation group were diagnosed anemia mild to moderate degrees. No intrapartum complications occurred. There were no cases of breast-feeding.

The group 1 included 18 pregnant HIV infected women aged 19-32 (mean age 24 years) receiving Nikavir+Epivir+Kaletra chemoprevention. The group 2 included 18 women aged 19-28 (mean age 23.5 years) receiving Combivir+Kaletra chemoprevention. From the 28th week of gestation until the delivery they received Nikavir administered in the dosage of 600 vg for 3 intakes daily. Combivir and Kaletra were given in standard schedule.

During the first hour of labor 2 mg/kg/h of zidovudine were given intravenously followed by 1 mg/kg/h until the end of the labor.

Starting with the 8th hour of life the newborn babies were given a 6 weeks course of zidovudine in syrup (Retrovir) in the dosage of 2 mg/kg every 6 hours.

Epidemiological analysis of the routes of infection revealed the leading share of sexual HIV-1 transmission: 83% of pregnant women in Nikavir chemoprevention schedule group 1 and 89% in group 2. Parenteral route was revealed in 17% and 11% of cases respectively. Thus, there was a mixed type of epidemic process, the sexual transmission rate 5-8 times surpassing the parenteral one (cases of intravenous drugs).

5.5 Methods
The evaluation of the results of the investigation was based on analysis of the clinical, epidemiological and laboratory monitoring of HIV infection course in pregnant women and their newborns.

Manifestations of HIV epidemic process were studied according to the following criteria:
- identification of the routes of HIV infection of pregnant women;
- estimation of the HIV infection risk factors for newborn children (analysis of delivery methods, chemoprevention schedules, cases of breast feeding).

Clinical assessment included evaluation of HIV manifestations in pregnant women before chemoprevention, 4 weeks after its start, before delivery at 36 weeks of gestation and 1.5
month after delivery. At the same terms the patients were examined by different specialists to register HIV associated diseases and adverse effects of therapy. Women were examined by infectionists, gynecologists, obstetricians, immunologists, etc. and the newborns by neonatologists, infectionists, pediatricians and other specialists according to indications.

The HIV diagnosis in women was based on enzyme immunoassay (EIA) detecting HIV antibodies ("Jenscreen Ulra HIV Ag/At") and immunoblot analysis (IMB) ("Blot-HIV") for HIV-1 virus specific proteins antibodies. HIV diagnosis in newborns was excluded on the basis of EIA and IMB monitoring during the period of observation starting at birth and thereafter at the age of 1.5 and 3 months.

Laboratory examination included leucocyte and thrombocyte counts performed with MEK-7222 hemoanalyzer and standard urinalyses. Biochemical blood values were identified with Conelab, 20 automated analyzer supplied with ion selection section for evaluation of the functional state of the liver and kidneys. The studied parameters were compared with the standards established for Perm.

The associated diseases of HIV infected pregnant women were revealed with serological IMB tests for HBsAg, hepatitis C virus, herpes simplex, cytomegalovirus, toxoplasmosis, chlamydia and Wassermann test.

Instrumental methods included ECG, ultrasonic examination abdominal and pelvic organs if indicated.

Cellular immunity in pregnant HIV infected women was assessed by the absolute and percentage levels of CD4 lymphocyte subpopulation with monoclonal antibodies ("Beston Diskinzon" USA) at "FACS Caliber" cytofluorimeter by flow cytometer method. The obtained findings were compared with the norms established by the Russian Federal AIDS Center (Pokrovsky, 2001).

Molecule-biological diagnosis in pregnant HIV infected women receiving chemoprevention was based on the detection of HIV-1 RNA plasma levels with polymerase chain reaction (PCR) and "Amplisensy HIV-monitor FRT" test-systems ("Interlabservice") before antiretroviral therapy, 4 weeks after it was started, 4 weeks before the supposed delivery term and 1.5 month after delivery.

For the early diagnosis of HIV in newborns detection of HIV-1 DNA plasma levels with PCR and "Amplisense DNA HIV-96" test-systems ("Interlabservice") was carried out. They were performed two tests at the age of 1.5 and 3 months.

Adherence to antiretroviral perinatal prevention regimen in pregnant HIV infected women was studied with the questionnaire method assessing their social profile, clinical and laboratory examinations, intake of preparations and attitude to chemoprevention.

For 28 week of gestation until the delivery they received Nikavir administered in the dosage of 600 mg for 3 intakes daily. Combivir and Kaletra were given in conventional doses. During the first hour of labor 2 mg/kg/h of zidovudine were given intravenously followed by 1 mg/kg/h within the labor.

For the early diagnosis of HIV in newborns detection of HIV-1 DNA plasma levels with PCR and "Amplisense DNA HIV-96" test-systems ("Interlabservice") was carried out. They were performed two tests at the age of 1.5 and 3 months.

Starting with their eighth hour of life the newborn babies were given a 6 weeks course of zidovudine in syrup (Retrovir) orally in the dose of 2 mg/kg every 6 hours.

5.6 Statistical analysis

The overall data of pregnant HIV infected women receiving the targeted agents in therapeutic doses have been statistically assessed. Descriptive and frequency ratio analyses of the total adverse events revealed within the investigation period have been performed.
In considering antiretroviral efficiency the data of the number (index) of women with RNA HIV-1 levels lower than 500 cells/ml blood serum (test-system sensitivity rate) were analyzed. The number of DNA HIV-1 negative children aged 1.5 and 3 months has been assumed to be the paramount index of antiretroviral efficiency. Safety was assessed using the mean indices of clinical and laboratory control.

5.7 Results
5.7.1 Clinical examination; evaluation of side effects
Tolerance of therapeutic schedules proved to be satisfactory. No marked therapy-related side effects and adverse events were revealed. Vital indices corresponded to physiological course of pregnancy.
No signs of HIV progress were noted on the clinical evaluation of women in both groups performed 1.5 month after delivery.
Parameters of side effects of chemoprevention were analyzed within the on-going clinical observation considering hemoglobin levels, erythrocyte, thrombocyte and leucocyte count values at the established terms.
Pregnancy in group 1 women was associated with the concurrent anemia grade 1-2 (mean Hb 101 g/l) while women in group 2 had normal red blood values (mean Hb 114 g/l). Following a 4 week intake of preparations hemoglobin level decreased to 109 g/l (Fig. 3).

Fig. 3. Dynamics of Hb levels in pregnant HIV-infected women.

Erythrocyte count level parameters prior chemoprevention was 3.5x10¹²/l and 3.9x10¹²/l in group 1 and 2 respectively. After 4 weeks of therapy and at 36 weeks of gestation a certain decrease of this parameter in group 2 women was noted (Fig. 4).
In both groups no thrombopenia was noted before initiation, during and after chemoprevention (Fig. 5).

During pregnancy the leucocyte formula values were within the normal limits in women of both groups (Fig. 6).

Thus, 4 weeks after the start of therapy and at 36 weeks of gestation there was no significant decrease in the peripheral blood parameters. The total of women underwent anemia preventive treatment with diet and preparations of iron in the standard daily dosing schedule.

In both groups no statistically significant difference in functional liver test values (ALT, AST, bilirubin) at different terms of pregnancy was found.

5.7.2 Immunological and virological evaluation of chemoprevention schedules efficiency

Assessment of chemoprevention efficiency was based on HIV-1 RNA viral load level and the CD4 lymphocyte count before antiretroviral therapy, 4 weeks after its start, at 36 weeks of gestation and 1.5 month after delivery.

At the beginning of treatment CD4 lymphocytes values were 1.5 times lower in group 1 patients (259 and 376 cells/mm$^3$ consequently). With the concurrent chemoprevention there was an almost double increase in group 1 prepartum CD4 lymphocytes levels (by 1.93 times) and that by 1.3 times in group 2 compared to the baseline values. After interruption of therapy in group 1 (1.5 month after delivery) CD4 lymphocytes count decreased to 321 cells/mm$^3$ (Fig. 7).

![Fig. 4. Erythrocyte values in pregnant HIV-infected women.](www.intechopen.com)
Fig. 5. Thrombocyte count values in pregnant women.

Fig. 6. Leucocyte values in pregnant HIV-infected women.
Fig. 7. CD4 lymphocytes profile in pregnant women.

Fig. 8. Viral load profile in pregnant women.
The baseline HIV-1 RNA viral load in group 1 was 253,226 copies/ml of blood; 4 weeks after the start of chemoprevention it dropped by 293 times (3 \( \log_{10} \)); it was undetectable before delivery while 1.5 month after interruption it increased to 27,472 copies. At the beginning of chemoprevention HIV-1 RNA viral load in group 2 ranged between 80,10 and 1,930,000 copies/ml (mean 93,153), it dropped to undetectable level before delivery (<500 copies/ml) and remained unchanged till delivery (Fig. 8).

5.7.3 Assessment of HIVchemoprophylaxis efficiency in newborns

Efficiency assessment of chemoprevention of mother-to-child transmission of HIV infection in both groups was based on exclusion of HIV in newborns with perinatal HIV contact aged 1.5 and 3 months. All children of HIV-infected mothers were assigned to the risk category with the diagnosis of perinatal HIV contact and were examined for the presence of HIV-1 DNA using PCR at the above mentioned terms. There were no positive results. According to the current regulations children of HIV-infected mothers are to be followed-up till the age of 18 months. At present they are under the on-going observation.

5.8 Summary

Negative HIV-1 test in 100% of 3 months children born from HIV mothers is a reliable proof of a high efficiency of applied HAART schedules aimed at perinatal chemoprevention. Efficiency of HAART schedules in vertical HIV transmission both with Nikavir+Epivir+Kaletra and combivir+Kaletra was confirmed by a significant stable decrease of viral load from the 4th week of gestation until delivery. Increase of CD4 lymphocyte parameters in the time of chemoprevention is the evidence of the positive effect of such therapy schedules on the immune status of pregnant HIV-infected women.

A considerably high degree of adherence to chemoprevention was associated with good tolerability of the applied schedules. Safety of HAART schedules was proved by the absence of toxic outcomes in biochemical indices in pregnant HIV-infected women at different terms of pregnancy. However, application of Combivir+Kaletra schedule revealed the tendency to the decrease of red blood parameters (hemoglobin and erythrocytes) and thrombocytes at the 4th week of therapy and before delivery. In HAART schedule with Nikavir+Epivir+Kaletra no decrease of hemoglobin, erythrocytes and thrombocytes counts at the fourth week of therapy and before delivery was revealed.

6. Conclusion

Despite the rapid development of chemoprophylaxis of HIV infection for as many as almost 30 years the range of ART preparations used currently is limited. The most widely applied agent is zidovudine though its major recognized side effect is still hemotoxicity (in the first place anemia). As in this respect Nikavir appears to be a considerably more advantageous component of chemoprophylaxis of HIV vertical transmission comparing to zidovudine its application seems to be extremely beneficial. The above mentioned positive data on successful replacement of zidovudine in cases of its intolerance (namely, anemia cases) with Nikavir makes it the preparation of choice. Besides, there is a reported evidence from the previous comparative Nikavir - zidovudine studies of a better tolerance of Nikavir in prevention of parenteral transmission of HIV (Ivanova, 2007).
Low toxicity and good tolerance of Nikavir open up new perspectives for its therapeutic application in HIV patients suffering from chronic liver diseases (Kvartchenko, 2006). Finally, some recent studies have reported on the successful application of Nikavir in the treatment of coinfections: HIV+ hepatitis C (Gankina, 2010), HIV + tuberculosis (Panteleyev, 2010). Treatment of such categories of patients is an extremely challenging task of paramount importance. At present several on-going intensive studies continue to investigate potentials of Nikavir in the treatment of coinfections.

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8. References


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Like any other book on the subject of HIV/AIDS, this book is not a substitute or exhausting the subject in question. It aims at complementing what is already in circulation and adds value to clarification of certain concepts to create more room for reasoning and being part of the solution to this global pandemic. It is further expected to complement a wide range of studies done on this subject, and provide a platform for the more updated information on this subject. It is the hope of the authors that the book will provide the readers with more knowledge and skills to do more to reduce HIV transmission and improve the quality of life of those that are infected or affected by HIV/AIDS.

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