

Antiretroviral drugs usage in HIV-positive pregnant women

Maciej Osiński¹, Czesław Żaba²

¹Department of Dermatology, Poznan University of Medical Sciences, Poland

Head: Prof. Wojciech Silny MD, PhD

²Department of Forensic Medicine, Poznan University of Medical Sciences, Poland

Head: Czesław Żaba MD, PhD

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Abstract

In the last decade an enormous success in the prevention of mother-to-child transmission of HIV infection occurred globally, but there are still problems with availability of antiretroviral therapies (ART) in low-middle income countries. According to WHO guidelines, it is critical whether the pregnant woman is eligible for ART or not. Unfortunately, in most cases of HIV-positive pregnant women ART is started later than it is suggested in WHO guidelines. A risk of the mother-to-child infection with no ART amounts to around 19-36%. In the untreated group of infants, in 20% of cases, progression to AIDS occurs in the first year of life. Infection with HIV in infants is more difficult to diagnose and treat in comparison to adult HIV infection. Currently, use of the appropriate therapy allows to prevent mother-to-child infection in almost 100% of cases of HIV-positive pregnant women.

Key words: prophylaxis against vertical infection with HIV, HIV infection, antiretroviral drugs in pregnancy.

Use of antiretroviral drugs by women in pregnancy

Cohort studies indicate that cases of documented mother-to-child transmission of HIV infection decrease in number [1]. In the recent decade, an enormous success has been noted in prophylaxis against vertical transmission of infections [2].

The care of the HIV-infected mother and her child requires optimization and must be adjusted to individual needs. In its recent recommendations (2010), the World Health Organization (WHO) distinguishes between two groups of HIV(+) pregnant women, including:

- 1) Women receiving prophylactic antiretroviral (ARV) therapy, or pregnant women who should receive antiretroviral therapies (ART) exclusively due to prophylaxis against vertical transmission of HIV infection to the child and in whom ART is not necessary to improve their health (*pregnant women who are not eligible for ART*).
- 2) Women undergoing ARV therapy, or pregnant women who should receive ART in order to, firstly, prevent vertical transmission of HIV and secondly, protect their health and prevent progression of HIV infection to AIDS (*pregnant women eligible for ART*) [3].

No proof is available which would suggest an increase in the number of unfavourable effects of antiviral drug

administration in pregnant women although no unequivocal studies are available either which would examine response to ART in this group of patients [4].

An important problem is posed by increasing resistance to non-nucleoside inhibitors of reverse transcriptase. Efavirenz and nevirapine have a prolonged half-life (efavirenz – 3 weeks). In samples obtained from mothers given a single dose of nevirapine, a detectable concentration of the drug in the body persists for 2-3 weeks [5-7].

The fact is of significant clinical importance since many patients receive a prophylactic ART, which they terminate following delivery or after weaning [3]. In an American study, administration of a single dose of nevirapine was found to be followed by development of viral resistance to the drug in 35.7% of women [8].

Therefore, in a pregnant woman requiring ART not only for prophylaxis against vertical transmission of HIV infection but also due to her deteriorating clinical condition and in whom ARV prophylaxis was used in previous pregnancies, an appropriate therapeutic option should be chosen basing on the ART previously applied in the patient, as specified by the patient upon anamnesis. It is important to obtain replies to the following questions: was the previous therapy(ies) introduced at the moment when it was indispensable and was the application of nevirapine sin-

Address for correspondence: Maciej Osiński, Department of Dermatology, Poznan University of Medical Sciences, 49 Przybyszewskiego, 60-355 Poznan, Poland, e-mail: maciejosiński88@gmail.com

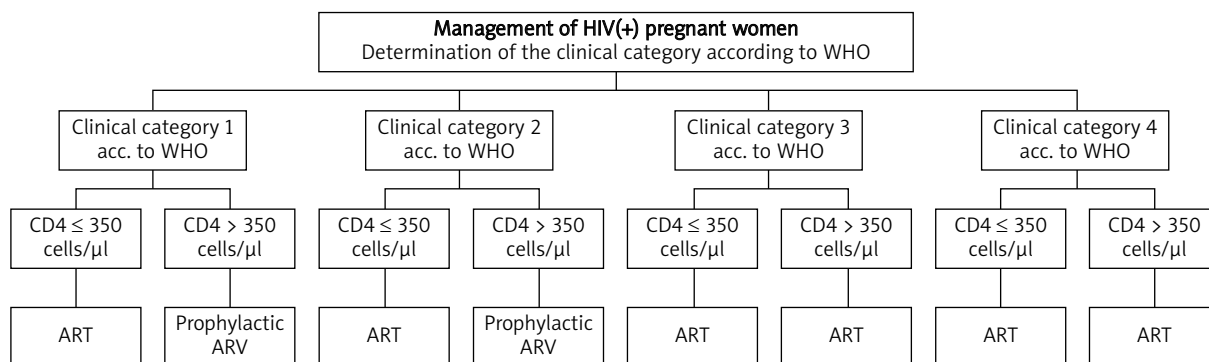


Fig. 1. Algorithm of management of HIV(+) pregnant women on the basis of WHO data

gle dose followed by the so-called tail regimen or administration of other retroviral drugs (involving nucleoside reverse transcriptase inhibitors, NRTI) in order to prevent development of viral resistance to the drug [3] (Figure 1).

Prophylactic antiretroviral therapy (pregnant women who are not eligible for antiretroviral therapies)

HIV infection tests should be suggested to every pregnant woman during the first control visit after conceiving [3]. In HIV(+) women, who are not pregnant and in whom during routine examination, CD4+ cell number is higher than 350 cells/μl and clinical condition is satisfactory, no ARV therapy is applied but when such a woman becomes pregnant, an appropriate prophylaxis should be introduced against the risk of vertical transmission of the virus, involving administration of blood load reducing anti-retroviral drugs. As compared to previous recommendations of WHO, earlier introduction of ARV therapy during pregnancy is recommended in order to further reduce the risk of vertical HIV transmission *in utero*. Currently, the institution suggests that ARV therapy should be introduced already in the 14th week of pregnancy or as early as possible [3].

In such a pregnant woman, two therapeutic options are available. The first one (option A) requires that the pregnant woman is given zidovudine twice a day in the course of pregnancy, a single dose of nevirapine at the beginning of delivery and a combination of zidovudine and lamivudine twice a day during delivery and 1 week thereafter. If the child is fed with milk substitute, he/she should be given nevirapine daily or a single dose of the drug during delivery and, then, zidovudine twice a day until the child is 4-6 weeks old. Breastfed children should be given nevirapine daily and the administration can be discontinued not earlier than a week after weaning or following 4 to 6 weeks if breastfeeding was discontinued before the infant reached the 6th week of life (not earlier, however, than one week after weaning).

If the mother demonstrates documented administration of zidovudine during pregnancy for at least 4 weeks,

omitting the perinatal and postnatal administration of a single dose of nevirapine and a combination of zidovudine plus lamivudine (typically administered for 7 days after delivery) can be contemplated [3].

Studies indicate that an earlier start of *in utero* prophylaxis is advantageous. Such an action reduces the risk of vertical transmission of HIV while waiting for results of cytometric determination of lymphocytes T CD4+ number. It may happen that the pregnant woman manifests no subjective symptoms or objective signs but, nevertheless, her results will provide indications to introduce combination ART (cART). Unfortunately, results of epidemiological studies indicate that most of women do not start cART at the recommended time [3].

In pregnant women who require ARV therapy exclusively for prophylaxis against vertical transmission of HIV from mother-to-child, in most cases such a therapy effectively prevents the transmission of HIV *in utero*. A single dose of nevirapine helps block perinatal transmission of the virus. Administration of the combination of two nucleoside reverse transcriptase inhibitors (e.g. zidovudine, lamivudine) reduces the chance for development of nevirapine-resistant strains of the virus [3, 9-11]. Children fed with milk substitutes should be given nevirapine once a day for 4 to 6 weeks (interchangeably with a single dose of nevirapine administered after delivery) and zidovudine twice a day for the same period of time. No evidence is available for efficacy of nevirapine administration every 24 h but studies on newborns given a single dose of nevirapine and fed later with milk substitutes proved efficacy of the drug in prophylaxis for vertical transmission of HIV [3].

Another option (option B) involves administration, to pregnant women, of a combination including three antiretroviral drugs until delivery or, in cases of breastfeeding, up to the 7th day after weaning. The recommended drug combinations include tenofovir + lamivudine (or emtricitabine) + efavirenz or zidovudine + lamivudine + efavirenz or zidovudine + lamivudine + abacavir or a preparation consisting of two protease inhibitors: lopinavir + ritonavir + zidovudine + lamivudine. Irrespec-

tively of the manner in which the infant is fed, he/she should receive nevirapine once a day and zidovudine twice a day until his/her 4th to 6th week of life. [3]

According to current data, it is not possible to estimate which method of prophylaxis is more effective. The choice between the options should be made after considering local conditioning, diagnostic possibilities, cooperation with the patient and, finally, costs and availability of drugs. Randomised studies in which ARV therapy was started in the 28th-36th week of pregnancy failed to demonstrate significant differences in efficacy of the two therapeutic options [12].

Antiretroviral therapy (pregnant women eligible for antiretroviral therapies)

Criteria for introduction of ART in a pregnant woman are identical to those applicable to a not pregnant woman. Antiretroviral therapies should be started in a pregnant woman with a confirmed HIV infection, in whom:

- 1) number of CD4⁺ cells is lower or equal to 350/mm³, independently of WHO clinical category of the woman,
- 2) the woman was assigned to the WHO clinical category 3 or 4, independently of the number of lymphocytes CD4⁺ [3, 13].

In cases when a HIV(+) pregnant woman was assigned to the WHO clinical category 1 or 2, cytometric estimation of lymphocyte T helper CD4⁺ number is required to make a decision as to further management of the patient [4].

Such an HIV(+) pregnant woman should start ART as early as possible and the treatment should be continued in the mother prenatally, perinatally, during breastfeeding and, subsequently, till the end of her life.

In such pregnant women, the first line ART involves a combination of zidovudine with lamivudine, regarded to provide the backbone of the therapy, which should be accompanied by administration of a drug from the NRTI group, nevirapine or efavirenz. Alternatives include combinations of tenofovir (nucleotide analogue) + lamivudine (or emtricitabine) + efavirenz and tenofovir + lamivudine (or emtricitabine) + nevirapine, although in the first trimester of pregnancy, administration of efavirenz should be avoided and substituted by nevirapine [4].

Efavirenz, included in category D of drugs administered in pregnancy in the FDA classification carries a documented teratogenic activity. The drug has a prolonged half-life and women who take the drug should use effective contraception for 12 weeks after discontinuation of the therapy [14]. Efavirenz was shown to induce developmental defects of neural tube [15].

In a child of the above described pregnant woman, independently of the manner of feeding, prophylaxis should be applied in the form of daily administration of nevirapine or administration of zidovudine twice a day beginning at birth or as soon as possible thereafter till 4th-6th week after birth [16].

Particular attention should be paid to providing the patients with access to an appropriate ART since both in pregnant women and women who are not pregnant it significantly reduces the risk of progression of HIV infection to AIDS as well as decreases morbidity and mortality. Thus, in such cases application of ART favourably affects health of the mother and health of her child, and represents the most effective prophylaxis for vertical transmission, particularly in cases of severe infection with the virus and in situations of an increased risk of mother-to-child transmission of HIV infection and, due to improved health of the mother, it augments probability of carrying the foetus till term [16].

Management following delivery

At first, it was assumed that newborns following birth should not be fed with milk of infected mothers and in developed countries with an appropriate access to milk substitutive products such mothers are still discouraged from breastfeeding their children. However, the problem is more complex in countries of Sub-Saharan Africa [17]. World Health Organization informs that breastfeeding accompanied by ARV treatment of both the child and the mother represents the best solution in poorer countries, which seems to be the principal alteration of recommendations related to HIV prevention of mother-to-child transmission following delivery as compared to earlier recommendations [16]. Long-term breastfeeding without ARV increases the risk of MTCT (mother-to-child transmission) by around 10-20 % [18]. Daily application of zidovudine for 6 weeks in newborns and infants linked to prophylactic application of zidovudine by the mother during pregnancy for at least 4 weeks represents a significant prophylaxis against mother-to-child infection in the perinatal period [19]. Moreover, it has been shown that administration of zidovudine for 6 weeks to the child provides a significant protection, even if the mother received ART during her pregnancy for less than 4 weeks. In children of mothers who received ART during pregnancy for at least 4 weeks, a shorter administration of ART was also found to be effective [16].

Management of infections and psychological status

HIV infection is frequently associated with numerous STI (sexually transmitted infections). Those infection are caused by numerous pathogens: viral: HSV-1 and HSV-2, *Varicella zoster virus* [20, 21], HPV (human papilloma virus) [22] bacterial: *Treponema pallidum subspecies pallidum* (syphilism) [23] and miscellaneous such as: *Gardnerella vaginalis*, peptostreptococi, *Mobiluncus* sp., *Mycoplasma hominis*, *Mycoplasma genitalum*, *Ureaplasma urealyticum*, *Atopobium vaginae*, *Chlamydia trachomatis* [24-27] and fungal infections: *Candida albicans* and *Can-*

didia non albicans infections (i.e. *C. glabrata*, *C. krusei*, *C. parapsilosis*) [28] Therapeutic procedure is depended strictly on causative agent.

HIV infection, pregnancy and other health and socio-economic problems related to HIV MTCT are significant stress factors for pregnant woman and her environment, therefore professional psychological help may be required in such situation [29].

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