Drugs Side Effects in Pregnant Women Infected with HIV Referred to Imam Khomeini Hospital, Voluntary Counseling and Testing Center Tehran, Iran 2009 – 2013

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Abstract: *Objective*: To have enough information about the prevalence of the ARV side effects in pregnant women infected with HIV and their infants and also evaluate drug efficacy in decreasing HIV infection in their children.

Method: This descriptive study was based on information of 40 pregnant women infected with HIV files at voluntary and counseling center, Imam Khomeini Hospital, Tehran, Iran during 2009 -2013. In this study, we evaluated epidemiologic, demographic, clinical, laboratory data and drugs side effects,.

Results: The most commonly used drug group was AZT/3TC/EFV; about 75.5% of patients received mother to child prevention and 27.5% received ARV Antiretroviral therapy treatment. 5% anemia, 2.5% rash and 2.5% pre rupture of membranes were reported and no preeclampsia or gestational diabetes were reported in patients files. Only one abortion (2.5%) was occurred in late first trimester. Except rash, other adverse effects were solely reported in ARV treatment group. All neonates had normal Apgar score. Fetal defects were not reported at birth.

Conclusion: In this evaluation, safety of ARV in pregnancy period and at birth was observed especially in the group received prevention of mother to child transmission (PMTCT). So we advise ARV treatment or PMTCT in pregnancy period.

Keywords: HIV, pregnant women, Antiretroviral (ARV), adverse effects.

INTRODUCTION

After high active antiretroviral therapy (HAART), transmission rate of HIV dramatically decreased from 20-25% to 2% in recent years [1]. According to global summary of the AIDS Epidemic reported by WHO, number of people living with HIV has been estimated more than 35 million [2].

Prevalence of HIV among the general population in Iran remains low, but it stands at 15.07 percent among IV drug users. Measures taken over the past ten years have resealed slower progression of the epidemic among IV drug users. Nevertheless this group remains the most important factor, fueling HIV epidemic in Iran [3].

The number of women living with HIV has increased recently. Base on that there is increased number of children being born with HIV in recent years. Although the absolute number of these children remains low, failure to scale up effective prevention of mother to child transmission (PMTCT) programs could prove problematic in the future [3].

UNAIDS has articulated 10 specific targets to guide collective action until 2015, as an example, to eliminate new infections among children and substantially reduce the number of mothers dying from AIDS-related causes [4].

Two main risk factors for transmission have consistently been maternal plasma and breast milk viral load followed by maternal immunologic status and clinical stage. Some associated maternal risk factors include low CD4 cell counts, anemia, advanced clinical disease stage, mastitis and actual maternal seroconversion during pregnancy or breastfeeding [6, 7].

Among infected ARV users infants, about 25 to 40 percent of infant infections were estimated to occur in uterus, 50% around the time of labor/delivery or through very early breastfeeding and the remainder during the breastfeeding period. A majority of transmission from the uterus is thought to occur during the third trimester [8]. ARV intervention is the cornerstone of strategies to prevent mother to child HIV transmission [9].

In 2013, WHO recommended the initiation of a combination ARV regimen for all HIV – infected pregnant or breastfeeding women, regardless of their

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CD4 cell count. In addition, all infants born to HIV-infected mothers should receive post exposure ARV prophylaxis [10]. Abundant efforts access ARV for prenatal prevention have also brought about a marked decrease in prenatal HIV transmission [11].

With appropriate ARV prophylaxis, the risk of HIV infection for an infant via prenatal transmission is now estimated to be less than 2 percent in the United States and Europe [12-14].

Since enough data about ARV adverse effects or its efficacy in pregnant women and their infants do not exist; this study was carried out in order to help choosing proper decisions to decrease HIV infection in children.

METHOD

In this descriptive study, we evaluated the files of pregnant women infected with HIV referred to Imam Khomeini Hospital, Voluntary Counseling and Testing Center and their information were documented until delivery / labor.

All patients' information remained confidential. Analysis was conducted by using SPSS17 statistical software. There were some defects related to registration of laboratory test and patients clinical information which were due to patients lacking in cooperation to visit their physician regularly.

RESULTS

In this study we evaluated 40 files of pregnant women infected with HIV. Demographic information can be seen in Table **1**. Of 5% drug abusers, one of them was ice user and another was unknown. Of those participants which contracted HIV through sexual transmission, all had spouses with HIV positive results. In the study site one of criteria for AZT cessation was Hb ≤ 7.5 (regarding CDC criteria).

There was no thrombocytopenia and leucopenia observed in one of the cases which was laid under ARV treatment pre-pregnancy and leucopenia was removed in second trimester. Significant laboratory data are shown in Tables **2** and **3** and in Table **4** co-infections are shown.

There was no TB or syphilis co-infection; however 4 patients had received INH prophylaxis due to PPD positive result. One patient had diabetes mellitus and two had HTN, prior to the current pregnancy. PROM and abortion were separately observed in 2.5% (1 case for each) in first trimester.

Table 1: Demographic Characteristics of Participants

Variable	Frequency	Percent
Age group		
<=25	6	15.00
26-30	17	42.50
31-35	12	30.00
>35	5	12.50
Education		
Less than/ high school	17	42.50
Diploma	19	47.50
Academic	4	10.00
Job		
Unemployed	32	80.00
Employed	8	20.00
Location		
Town	39	97.50
Village	1	2.50
Drug abuse		
Yes	2	5.00
No	38	95.00
Pregnancy status		
Wanted	25	62.50
Un-wanted	15	37.50
Transmission way		
Sexual	27	67.50
Blood	2	5.00
Other	11	27.50
Spouse status		
Infected	34	87.18
Un infected	5	12.82

Table 2: Mean of Hemoglobin and CD4 among Participants

	Mean	Std. Err.	[95% Conf. interval]
Hemoglobin 1	12.19	0.37	11.40, 12.99
Hemoglobin 2	11.31	0.39	10.47, 12.14
Hemoglobin 3	12.07	0.29	11.44, 12.70
CD4 interim	439.25	23.60	391.51, 486.99

1: First trimester; 2: Second trimester; 3: Third trimester.

Table 3: Laboratory Characteristics among Participants

Variable	Frequency	Percent
HB in Trimester 1		
>7.5	21	52.50
≤7.5	0	-
Unknown	19	47.50
HB in Trimester 2		
>7.5	26	65.00
≤7.5	0	
Unknown	14	35.00
HB in Trimester 3		
>7.5	31	77.50
≤7.5	2	5.00
Unknown	7	17.00
CD4		
<200	4	10.00
200-499	22	55.00
≥500	14	35.00

Table 4: Prevalence of Co-infection with HCV and HBV among Participants

Variable	Frequency	Percent	95% Confidence interval
HCV	4	10	3.4, 24
HBV	2	5	0.4, 17.4

All studied women delivered by caesarian section (c/s). All neonates had normal routine exam and normal Apgar score and fetal defects were not reported at birth. HIV prophylaxis was prescribed to all, although HIV test results were negative in all of them at birth.

Drug information and drug groups are showed in Tables **5** and **6**.

About 75% of patient received PMTCT and 27.5% were lied under ARV treatment. In later group, some patients received ARV treatment prior to being referred to the study site while other patients were in PMTCT group who were then based on clinical and laboratory changes, lied in ARV treatment group.

The common combined ARV regimen used in this study was AZT/3TC/EFV (80%) followed by AZT/3TC/ Kaletra (10%). Other regimens included AZT/3TC/NVP (7.5%) and TDF/3TC/EFV (2.5%). AZT/3TC/NVP group was stopped and substituted with TDF/3TC/EFV owing to drug resistance in one case. Also drug resistance was observed in 2 pregnant women in AZT/3TC/EFV group, so EFV was substituted with NVP. Rash and drug resistance were induced by EFV and NVP respectively, so they were stopped and substituted with Kaletra.

Table 5: Distribution of Type Drugs Consumption among Participants

Variable	Frequency	Percent
ARV		
Treatment	11	27.50
Prophylaxis	29	72.50
Drugs		
AZT	39	97.5
3TC	40	100
EFV	33	82.50
KALETRA	4	10.00
TDF	1	2.50
NVP	3	7.50
Drug groups		
AZT, 3TC, EFV	32	80.00
AZT, 3TC, KALETRA	4	10.00
AZT, 3TC, NVP	3	7.5
TDF, 3TC, EFV	1	2.5

Table 6: Prevalence of Side Effect and Drug Resistance among Participants

Variable	Frequency	Percent	95% Confidence interval
Side effect	3	7.50	1.57, 20.39
Drug resistance	4	10	3.4, 23.6
Type of Drug resistance			
AZT/3TC/NVP	1	2.5	0.00, 14
AZT/EFV	1	2.5	0.00, 14
CALETRA	1	2.5	0.00, 14
NVP	1	2.5	0.00, 14

On the whole, 10% drug replacement was observed due to drug resistance. One of the patients under AZT/3TC/Kaletra treatment had Hb= 7.1, but the rest in that group continued the regimen without any problem until labor. In this study, 5% anemia and 2.5% rash were occurred.

DISCUSSION

ARV treatment in pregnant women infected with HIV involves two separate but related goals: reduction of mother to child transmission (MTCT) and treatment of maternal HIV diseases. The most important factor to decrease MTCT risk can be considered as mother and child prophylaxis treatment.

Early diagnosis and ARV treatment in pregnant women infected with HIV and their infants are two important factors in reducing HIV transmission among them. An important point being discussed in various studies is early and late ARV drugs side effects in pregnant women and their infants. This issue is significant to avoid drug toxicity in the mother and fetus. In our study it was considered to mention affair and also reported drug resistance.

In 2013, WHO guidelines recommended the initiation of a combination of TNF +3TC (or emtricitabine) + EFV in all HIV-infected pregnant or breast feeding women. For women who cannot tolerate first line regimen, it was recommended to use alternative agents AZT to replace TNF and nevirapine to replace EFV in the three –drug regimen [10] for the subset of HIV-infected women in resource limited settings on first line therapy who develop virology, clinical failure, omit develop or significant toxicities, and also who cannot tolerate the first line regimen, a switch should be made to a second –line regimen containing a protease inhibitor, such as kaletra [10].

In our study, combination regimen was used in all patients. AZT /3TC/EFV combination was used in 80% of patients based on state guideline (with attention to drug availability, cost, resistance, side effects and efficacy).

While 3.8 – 38% of pregnant women in general population will develop anemia during pregnancy, depending on nutritional status and trimester [15], prevalence of anemia was 5% in HIV-infected studied women.

Consistent to our study, in a cohort study in Thailand in 2001-2006, among 246 pregnant HIV-infected women, prevalence of anemia was reported 5.3% [16].

In one case with anemia (Hb= 7.1), AZT was stopped and substituted with TNF (due to drug resistance), however in other cases decrease of Hb was only observed for a short period of time, and AZT was continued without any problem.

In this study 2.5% of patients were developed rash but significant nausea or vomiting were not reported while in the mentioned study in Thailand nausea (vomiting) and rash developed 1.2% and 0.4%, respectively [16].

HBV co-infection is common in many developing countries and increases the risk of hepatotoxicity from ARV by three to five folds [17]. In a study in Nigeria of 1564 patients, the risk for serious hepatotoxicity, 24 weeks after initiation of ARV was 3.1 percent in patients co -infected with HBV compared to 0.5% in patients with HIV alone; the hepatotoxicity was not associated with either baseline HBV DNA concentration or HBe Ag status [18].

In our study 4 HCV and 2 HBV co-infections were observed while one of them had HBV and HCV co-infection simultaneously, so on the whole, HBV and HCV co-infection rate was 12.5%. Despite the fact that these patients had received ARV, there was no report of hepatotoxicity. Therefore, it is assumed that high prevalence of HCV co-infection may be associated with infected partner or use of contaminated syringe.

In this center, in order to decrease HIV transmission, recommended delivery method is caesarean section [15]. Almost all patients underwent C/S and the only exception was the abortion case (2.5%) which happened in late first trimester. This case was a 41 year old pregnant woman that afflicted with diabetes mellitus and HIV prior to this pregnancy. Based on many studies up to now, no evidence is gained to relate HIV to abortion. 2.5% (1case) showed PROM symptoms. However, there was no post-delivery infection observed, compared to 8.7% PROM and 17.4% post-delivery infection in another study in this center (2004-2008) [19]. In the pointed study in Thailand PROM was 1.6% [16].

The overall rate of preeclampsia in the general population is 2-8% [20]. Some studies have reported higher rates of preeclampsia in the recipient ARV women [16]. In our study, gestational HTN was reported but no preeclampsia was seen. Approximate rate of gestational diabetes in general population is 2-5%. According to some studies, gestational diabetes in ARV recipient women is similar to general population but other studies have reported higher rates in HIV-infected women than general population.

In consistent with other study showing 5.9-9.2% of LBW, no LBW was observed in this study [22].

Inadequate antenatal care for pregnant women might be the cause of LBW in other studies. In our study all of neonates had normal Apgar score. Fetal defects were not reported at birth. The use of ARV during pregnancy has generally been found safe in trials to date and the benefits for PMTC have been judged to outweigh the potential adverse reactions that may occur [9]. Our study has also approved the mentioned theory. In this study, two important issues were assessed: first, to study ARV prophylaxis efficacy in prevention of fetus affliction and second, to research on fetus defects rate in pregnant HIV infected women who had received ARV. ARV safety was observed during pregnancy until delivery. Although infants should be followed up several months after birth to reach the final goal, our efforts can be steps to achieve UNAIDS goals to eliminate new infections among children up to 2015.

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