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High Risk of Liver Enzyme Elevation in Pregnant Women Receiving Protease Inhibitors

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ABSTRACT

•**Background**
Antiretroviral therapy (ART) is recommended for all HIV-infected pregnant women and is highly effective in preventing vertical transmission of HIV. High rates of liver enzyme elevation (LEE) during pregnancy and some cases of severe hepatotoxicity have been reported, but the causes remain unclear. Surveillance including sequential liver function tests is recommended for all HIV+ pregnant women in France. Our objective was to estimate the prevalence, causes and risk factors of LEE in the national prospective French Perinatal Cohort.
•**Methods** We studied the 5748 HIV+ pregnant women treated with ART, enrolled in the French Perinatal Cohort between 2005 and 2014, who had ≥1 normal measure of liver enzymes during pregnancy. Adjusted hazard ratio (aHR) for the association of LEE with ART were estimated using multivariate Cox models with ART as time-dependent variable, separately for women on ART at conception and for those starting ART during pregnancy.
•**Results**
Liver enzyme elevation (grade ≥1) was observed in 17.4% (n=959), grade 3-4 in 2%. Two third occurred in the third trimester. Among women with LEE, 7% had preeclampsia, 11% intrahepatic cholestasis of pregnancy, and less than 1% other identified causes (sickle cell disease, malaria or bile duct obstruction). More than 2/3 of LEE were unexplained. LEE were the reason for many hospitalizations (n=103), cesarean sections or inductions of labor (27), and changes in ART regimens (88). Unexplained LEE was significantly associated with higher risk of preterm births; p=0.002. For the women already on ART at conception, the risk of unexplained LEE was lower with NNRTI-based regimens than with protease inhibitors: aHR=0.5 [0.3-0.7]. The risk was similar with boosted and non-boosted PIs: aHRs = 0.8 [95%CI 0.4-1.7] with no difference among the various PI drugs. Among the women initiating ART during pregnancy, most regimens included PIs (90%). Compared with lopinavir/r (the most prescribed PI), LEE were less frequent for nelfinavir, there was no significant difference for darunavir/r, and atazanavir/r. The few women who initiated NNRTI, NRTI monotherapy or dual therapy as first treatment were excluded from this analysis.
•**Conclusion**
The rate of LEE among HIV-infected women is high and impacts obstetrical care management. In most case, the cause remained undetermined. Our results suggest a possible role of PIs which needs further investigation.

OBJECTIVE

To estimate the prevalence, attributed causes and risk factors for liver enzyme elevation in HIV-infected pregnant women, and especially the role of ART, studying separately women on ART at conception or starting during pregnancy.

PATIENTS AND METHODS

The National French Perinatal Cohort : EPF cohort (ANRS CO1/11)

▪***The French Perinatal Cohort EPF:*** All HIV infected women and their children included since 1986 in 90 French centres. Coverage : about 70% of HIV-infected women in metropolitan France.

▪ **Eligible pregnant women**

→**Descriptive study population N=5748**

▪ All women with at least one liver function test during pregnancy receiving ART between 2005 and 2015 in the CO-01 detailed component of the French Perinatal Cohort

▪Exclusion of active HBV or HCV coinfection

→**Analytical study population : study of association with ART N=5264**

▪Exclusion of patients with preeclampsia or cholestasis of pregnancy

▪Exclusion of patients with abnormal first LFT value

▪ **Variables:** LFTs were collected 3 times during pregnancy: <28WG, > 28WG and at delivery.

▪**Liver enzyme elevation (LEE)** was defined as SGOT or SGPT at least 1.25 x upper limit of normal (ULN, assumed to be 40 IU/L), and then graded from 1 to 4 on a standardized scale.

▪All ART combinations were recorded with dates at initiation and end. Sociodemographic, clinical, and obstetrical and immuno-virological characteristics were collected.

▪ **Statistical analysis:** Cox proportional Hazard models with ART as a time varying variable and occurrence of LEE as outcome were used to test associations.

Fig 1 – Selection of study population

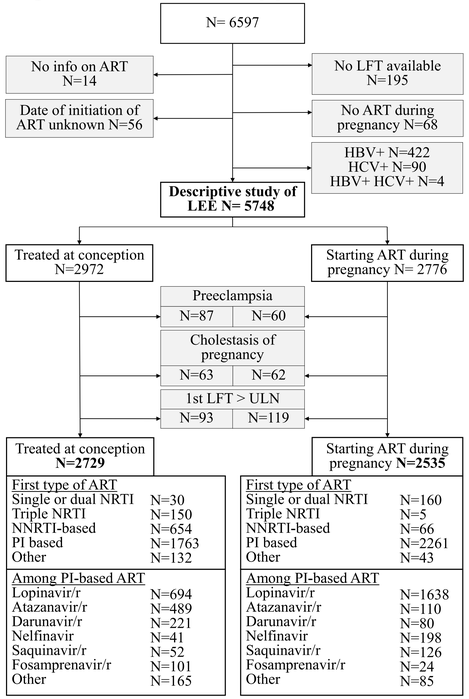

Table 1 – Association between ART and LEE
Patients treated at conception

ART type	HR	[95%CI]	p	AHR*	[95% CI]	p
PI-based	1	ref	0.004	1	ref	0.02
3 NRTI	0.2	[0.03-1.5]		0.4	[0.05-3.2]	
NNRTI-based	0.5	[0.3-0.7]		0.5	[0.3-0.8]	
Raltegravir-based	0.4	[0.05-2.6]		0.3	[0.04-1.9]	

*Adjusted for NRTIs, first CD4 and VL, BMI, year of delivery, twin pregnancy, and geographical origin

Table 2 – Association between ART and LEE
Patients initiating ART during pregnancy

ART	HR	[95%CI]	p	AHR*	[95% CI]	p
Darunavir/r	1.5	[0.9-2.7]	0.01	1.3	[0.7-2.5]	0.03
Fosamprenavir/r	2.1	[0.9-5.1]		2.0	[0.7-5.5]	
Atazanavir/r	0.9	[0.5-1.7]		0.8	[0.4-1.5]	
Indinavir/r	0.9	[0.4-2.2]		0.7	[0.2-2.4]	
Saquinavir/r	1.3	[0.8-2.1]		1.6	[0.9-2.6]	
Lopinavir/r	1	ref		1	ref	
Nelfinavir	0.3	[0.1-0.6]		0.3	[0.1-0.7]	
Zidovudine	0.7	[0.5-0.9]	0.01	0.8	[0.5-1.5]	NS
Lamivudine or Emtricitabine	0.9	[0.6-1.3]	NS	1.0	[0.6-1.8]	NS
Tenofovir	1.0	[0.7-1.5]	NS	0.8	[0.4-1.5]	NS
Abacavir	2.2	[1.5-3.2]	<0.01	1.9	[0.98-3.6]	0.06
Didanosine	0.7	[0.2-2.1]	NS	0.3	[0.03-1.7]	NS

*Adjusted for first CD4 and VL, BMI, year of delivery, twin pregnancy, geographical origin, gestational age at ART initiation, number of ART sequence, and parity

RESULTS

Descriptive study and consequences of LEE

- **The rates of LEE were**
  - **17% (n=959) for any LEE (grades 1-4)**
  - **2% (n=112) for severe LEE (grades 3-4)**
- **Among women with LEE, 7% had preeclampsia, 11% intrahepatic cholestasis of pregnancy, and less than 1% other identified causes (sickle cell disease, malaria or bile duct obstruction). More than 2/3 were unexplained.**
- **LEE was the main reason reported for**
  - **27 cesarean sections or inductions of delivery (3% of LEE)**
  - **103 hospitalizations (11%) and 88 changes in treatment (9%)**
- **Preterm delivery was significantly associated with LEE even after exclusion of preeclampsia and cholestasis of pregnancy : 16% of preterm births among patients with LEE vs 11.5% among women without LEE, p=0.002.**

Analytical study of ART

- ***Among women treated at conception***
  - **Compared with PI-based ART, less LEE occurred in women on NNRTI-based ART (Table1). The difference did not reach significance for other types of ART**
  - **Among PIs, the occurrence of LEE was similar in this group. There was no difference in the risk of LEE among NRTIs.**
- ***Among women starting ART during pregnancy***
- **Most women received PI-based ART (90%)**
  - **Among these, compared with lopinavir, nelfinavir was associated with a lower risk of LEE. Other PIs studied were not significantly associated with LEE (Table 2).**
  - **Among NRTIs, abacavir (vs no abacavir) tended to be associated with a higher risk of LEE.**

CONCLUSION

- **Rates of LEE are high during pregnancy among HIV-infected women, and this affects obstetrical care management.**
- **Among women on ART at conception, compared with NNRTI, PI-based treatments were associated with occurrence of LEE.**

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