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Hcv coinfection, an important risk factor for hepatotoxicity in pregnant women starting antiretroviral therapy

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Summary *Objectives:* This retrospective cohort study evaluated the risk of hepatotoxicity in HIV-1 positive pregnant and non-pregnant women starting combined ART.
Methods: Data were used from the ATHENA observational cohort. The study population consisted of HIV-1 infected, therapy naïve, pregnant and non-pregnant women, followed between January 1997 and February 2008. Demographic, treatment and pregnancy related data were collected. Risk of hepatotoxicity was determined using univariate and multivariate logistic regression. Analyses were adjusted for age, region of origin, baseline HIV-RNA levels and CD4 cell counts, cART regimen and hepatitis B and C coinfection. ALT and AST values of more than 5 times ULN were considered as hepatotoxicity.
Results: Four-hundred and twenty-five pregnant and 1121 non-pregnant women were included. Independent risk factors of hepatotoxicity in all women were the presence of detectable HCV RNA (OR 5.48, 95% CI 2.25—13.38, $p < 0.001$) and NVP use (OR 2.63, 95% CI 1.54—4.55, $p < 0.001$). Stratified for pregnancy, the adjusted risk of hepatotoxicity was significantly associated with HCV coinfection only during pregnancy (OR 23.53, 95% CI 4.69—118.01, $p < 0.001$). NVP use is related to hepatotoxicity in pregnant (OR 5.26, 95% CI 1.61—16.67, $p < 0.005$) as well as in non-pregnant women (OR 2.13, 95% CI 1.11—4.00, $p = 0.02$).

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Conclusion: HCV coinfection and NVP use are associated with a higher risk of cART induced hepatotoxicity in pregnant women.

Introduction

Antiretroviral therapy (ART) is used world-wide to prevent vertical transmission of HIV. In developing countries nevirapine (NVP) is the most frequently used drug to prevent vertical transmission.[1] During the last decade studies from different regions in the world reported conflicting results on the risk on mainly NVP-related liver toxicity in pregnant women.[1–10] One of the possible risk factors of hepatotoxicity is a $CD4^+$ cell count >250 cells/μl. Most studies reported hepatotoxicity predominantly in women with $CD4^+$ cell counts >250/mm^3.[2–3,5,8] A recent retrospective study from the UK found pregnancy to be significantly associated with hepatotoxicity, without an association with NVP use or $CD4^+$ cell count.[9]

The HIV-1-positive ATHENA cohort in the Netherlands comprises a multi-ethnic group of women from different backgrounds with similar access to healthcare facilities. The aim of our study was to examine the effects of pregnancy, ethnicity, $CD4^+$ cell count, hepatitis B (HBV) or C (HCV) coinfection and combined ART (cART) on hepatotoxicity in women.

Patients and methods

Study design and setting

We conducted a retrospective cohort study among women enrolled in the AIDS Therapy and Evaluation in The Netherlands (ATHENA)[11] cohort study between January 1997 and February 2008. Patients have provided written informed consent for their data to be anonymously recorded in a central database that is maintained by the HIV Monitoring Foundation.[11] The study was reviewed and approved by the institutional review boards from all the involved institutions.

Study population

We included all cART naive women from this cohort in their reproductive phase of life (18–45 years), who started cART between January 1997 and February 2008. The women were first classified into two groups: pregnant or non-pregnant. The pregnant group comprised women who started cART for the first time, during pregnancy. We excluded pregnant women who started cART before being pregnant. The non-pregnant group included all women that started cART for the first time, and were never pregnant during the observational follow-up in the ATHENA cohort. cART was defined as a regimen with two nucleoside reverse transcriptase inhibitors (NRTIs) and either a third NRTI, a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). The duratrion of cART use was defined as start date first line of therapy until second line therapy, loss to follow-up date, date of death or date of closure of the dataset (February 2008). Women with high ALT or AST values, three times the upper limit of normal (30 IU) at start cART, were excluded from the study.

Data collection

Data were collected on demographics (age, region of origin), clinical and treatment characteristics, side effects, coinfection with HBV and HCV, Alanine-aminotransferase (ALT), Aspartate-aminotransferase (AST), baseline $CD4^+$ T-cell counts and baseline HIV-RNA levels. Baseline was defined as the start of cART. All women had routine check ups with ALT and AST levels being monitored in weeks 2, 4, 12 after start of cART and during a clinical visit every 3 months hereafter and just before the predicted date of birth. cART initiation date, duration and composition of the regimens were retrieved. The occurrence of hepatotoxicity is systemically collected and validated in the ATHENA database.

Outcomes and study definitions

The outcome of interest was the occurrence of hepatotoxicity in pregnant compared to non-pregnant women. The observational period for side effects was 40 weeks after start cART, as this is the mean duration of pregnancy. Hepatotoxicity was defined in accordance with the AIDS Clinical Trial Group criteria[12] as grade 3 when ALT or AST values were 5–10 (150–300 IU) times the upper limit of normal (ULN), and as grade 4 when ALT or AST were >10 times ULN (>300 IU). Patients were considered to have chronic HBV infection when HBsAg could be detected and chronic HCV when HCV antibodies and HCV RNA were present at start cART.

Statistical analyses

Statistical analyses were performed using the SPSS statistical package PASW (version 17.0.2, IL, USA). Three different tests were used to compare Baseline characteristics at the start of cART initiation between non-pregnant and pregnant women. Mann–Whitney test was used to compare medians of age, $CD4^+$cell levels and HIV-RNA levels at start cART. Chi-square test was used to compare regions of origin, coinfections with HBV and HCV. In case of small numbers the Fisher's exact test was used to compare differences in outcome between non-pregnant and pregnant women. Using univariate and multivariate logistic regression analyses we evaluated risk factors for hepatotoxicity. Risk factors accounted for were age, cART regimen, region of origin, baseline HIV-RNA level, baseline $CD4^+$ T-cell levels, coinfection with HBV and with HCV. Further analyses were stratified by regimen and pregnancy status. Variables with a *p*-value <0.20 in the univariate analyses were included in the multivariable logistic regression model.

Results

Between 1997 and 2008, a total of 1924 HIV-1-positive treatment naive women initiated cART. Women were included from the first HIV positive test, and indexed at the time of first cART use. Of these women, 768 became pregnant at least once during follow-up. Only one pregnancy during cART use (the first) was included in the study. Of the women who became pregnant, 125 were already on cART before the start of pregnancy, 23 women started cART after delivery, and 135 women had an induced abortion or miscarriage in the first 16 weeks of the pregnancy. The remaining 485 pregnant women initiated cART during their pregnancy, 462 out of 485 women used cART for more than one week. Thirty-seven women used mono or dual therapy and were excluded. In total, 425 pregnant women, initiating cART with a minimal duration of 7 days, could be included in the study. Of the 1156 women who did not become pregnant during the observational period, 1121 started cART and continued using it for at least one week. Thirty-five women were excluded, due to less then 7 days usage of cART ($n = 34$) or monotherapy ($n = 1$). None of the pregnant women died during follow-up. In the non-pregnant group eight women died, three deaths were AIDS related, three deaths were non-AIDS related and in two cases the cause of death was unknown.

Baseline characteristics

Baseline demographic, laboratory and treatment characteristics are shown in Table 1. Pregnant women were younger (28 versus 33 years, p-value < 0.001), originated more often from Sub-Sahara Africa (SSA) (59% versus 50%, p-value $= 0.006$), had higher median $CD4^+$ cell counts (0.37 versus 0.18, p-value < 0.001) and lower HIV-RNA levels (p-value < 0.0001). Asian women were equally balanced among pregnant ($n = 25$; 5.2%) and non-pregnant ($n = 77$; 6.7%) women. Pregnant women were more often treated with a protease inhibitor (PI) based regimen (74.8%) compared to non-pregnant women (42.0%). In pregnant women 305/425 (71.8%) started cART with a $CD4^+$ cell count $> 250 \, \mu l$, as opposed to 303/1121 (27.0%) in the non-pregnant women. The median duration of cART use in pregnancy was 15.9 weeks (IQR: 9.9–20.8). The median duration of the firstline cART regimen in non-pregnant women was 31.4 weeks (IQR: 9.6–85.4). The majority of women ($> 90\%$) were infected heterosexually.

Hepatotoxicity in women overall

In all women a total of 77 cases (5.0%) of grade 3 or 4 hepatotoxicity were reported (Table 1). Independent risk factors of hepatotoxicity in all women were the presence of detectable HCV RNA (OR 5.48, 95% CI 2.25–13.38, $p < 0.001$) and NVP use (OR 2.63, 95% CI 1.54–4.55, $p < 0.001$) (Table 2). The rate of hepatotoxicity was lower in pregnant ($n = 16$, 3.8%) compared to non-pregnant ($n = 61$, 5.4%) women. After adjustment for region of origin, hepatitis B and C coinfection, cART regimen, age at

start cART, HIV-RNA level and $CD4^+$ cell count at base line, the risk of hepatotoxicity did not differ between pregnant and non-pregnant women (OR 0.70, 95% CI 0.38–1.28, $p = 0.25$).

When analyses among all women were stratified by cART regimen, HCV coinfection remained an independent significant risk factor for hepatotoxicity in efavirenz and PI-using women only (OR 5.23, 95% CI 1.88–14.57, $p = 0.002$) (data not shown).

Hepatotoxicity in pregnant and non-pregnant women

When the analysis was stratified by pregnancy, similar risk factors were identified (Table 3). In pregnant women detectable HCV-RNA and a NVP based regimen were both independently associated with a significantly higher risk of hepatotoxicity (OR 23.53, 95% CI 4.69–118.01, $p < 0.001$ and OR 5.26, 95% CI 1.61–16.67, $p = 0.005$), while in non-pregnant women HCV coinfection was not found to be a significant risk factor. Separate analysis of cART in non-pregnant women demonstrated a moderate increased risk of hepatotoxicity for NVP compared to PI use (OR 2.13, 95% CI 1.11-4.00, $p = 0.02$). The median time from cART initiation to grade 3 or 4 increase in ALT/AST levels was 7.56 (0.57–39.29) weeks in non-pregnant and 4.57 (0.14–17.00) weeks in pregnant woman, not a significant difference ($p = 0.17$).

We did a sensitivity analyses by excluding HCV coinfected women. In this analysis NNRTI use remained a significant risk factor for the occurrence of hepatotoxicity after treatment initiation.

Finally, NVP induced hepatotoxicity resulted in discontinuation of NVP in 89% (n=14) and 43% (n=26) in pregnant and non-pregnant women respectively.

Discussion

In this study we analysed the occurrence of hepatotoxicity after the start of cART in a group of HIV-1 infected pregnant and non-pregnant women. Overall we observed 5.0% hepatotoxicity within 40 weeks after the start of cART in all women. This rate did not differ between pregnant and non-pregnant women. The risk of hepatotoxicity in pregnant women was strongly associated with the presence of HCV-RNA. NVP was associated with an increased risk of hepatotoxicity in pregnant and non-pregnant women.

Hepatotoxicity

The occurrence of 5% hepatotoxicity is in agreement with proportions reported in several other studies ranging from 1.2 to 9%.[1–4,6,8,9] Only one study, performed in Asian patients, reported a substantially higher rate of hepatotoxicity (15.6%) in pregnant women using NVP.[7] This study however had only a small proportion of patients tested for HBV or HCV, and the presence of a coinfection in this study may have added to the high percentage of hepatotoxicity, as HIV-positive Asian communities were found to have a high prevalence of HCV.[13]

Table 1 Demographic and clinical characteristics of pregnant and non-pregnant women initiating cART.

	Total 1546	Non-pregnant women n = 1121 (%)	Pregnant women, n = 425	P-value
Age at start cART				
Median (IQR)	32 (26.7–36.7)	33 (28.3–38.1)	28 (23.6-32.0)	<0.0001
Origin				
NL, W Europe	300 (19.4)	232 (20.7)	68 (16)	0.006
SSA	805 (52.1)	556 (49.6)	249 (58.6)	
Other	441 (28.5)	333 (29.7)	108 (25.4)	
CD4 at start				<0.0001
Median (IQR)	220 (119–360)	180 (70–275)	370 (232–530)	
Missing	176	165	11	
RNA level at start				
Median	3.7 × 10 log 4	7.8 × 10 log 4	6.4 × 10 log 3	<0.0001
(Range)	(17–2.1 × 10 log 8)	(17–2.1 × 10 log 8)	(25–7.5 × 10 log 5)	
Missing	240	233	7	
HBV coinfection				
Yes	76 (4.9)	55 (4.9)	21 (4.9)	0.25
No	1355 (87.6)	975 (87.0)	380 (89.4)	
Missing	115 (7.4)	91 (8.1)	24 (5.6)	
HCV coinfection				
AB+	1154 (74.6)	814 (72.6)	340 (80.0)	<0.001
AB+ and RNA+	34 (2.2)	23 (2.1)	11 (2.6)	
AB+ and RNA-	3 (0.2)	1 (0.1)	2 (0.5)	
Missing AB or RNA	355 (23.0)	283 (25.2)	72 (16.9)	
cART regime				
NNRTI-based	685 (44.3)	582 (51.9)	103 (24.2)	<0.0001
Nevirapine	359	257	102	
Efavirenz	326	325	1	
PI-based	789 (51.0)	471 (42.0)	318 (74.8)	
Nelfinavir	403	136	267	
Lopinavir	224	199	25	
Saquinavir/R	58	39	19	
Indinavir	34	29	5	
Others	70	68	2	
Both	27 (1.7)	23 (2.1)	4 (0.9)	
Triple NRTI only	45 (2.9)	45 (4.0)		
Hepatotoxicity				
N (%)	77 (5.0)	61 (5.4)	16 (3.8)	0.18

Coinfection with HBV or HCV has been reported to be an independent risk factor for antiretroviral-associated hepatotoxicity, including NVP-related hepatotoxicity.[14] First, there could be enhanced toxicity of pre-existing HCV- or HBV-coinfection. Secondly, cART may be associated with recovery of cell-mediated immunity, leading to immune-mediated HBV- and HCV-specific liver cell damage and transaminase elevation.[15] This is supported by a review of cohort studies, investigating the incidence of hepatotoxicity among patients receiving cART, that failed to identify a consistent association between a particular drug or drug class and the development of subsequent hepatotoxicity.[14] Most studies among asymptomatic pregnant and non-pregnant women lack data on hepatitis coinfection. In The Netherlands, HBV and HCV serology is routinely assessed in HIV-positive patients, irrespective of liver enzymes or pregnancy. In our large cohort only 19.4% and 23.0% of women had missing data on coinfection, which enabled us to demonstrate the impact of a coinfection on cART or pregnancy-induced hepatotoxicity.

NVP is significantly associated with an increased risk of hepatotoxicity (OR 5.26, 95% CI 1.61–16.67, $p = 0.005$) in pregnant women and less evident in non-pregnant women (OR 2.13. 95% CI 1.11–4.00, $p = 0.02$). This has been reported before[3,8] and may be due to pregnancy related physiological effects: changing pharmacokinetics by altered activity of CYP2D6 and CYP3A4.[16]

Coinfection with HCV increases the risk of hepatotoxicity in pregnant women (23.53 (4.69–118.01; $p < 0.001$). Pregnancy has been shown to be an independent risk

Table 2 Risk factors for hepatotoxicity, analysis for all women.

	n	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
All women					
Non pregnant	1121	1		1	
Pregnant	425	0.68 (0.39–1.19)	0.18	0.70 (0.38–1.28)	0.25
Age quartiles					
<27	406	1			
27–32	399	0.91 (0.46–1.77)	0.77		
32–37	371	1.35 (0.72–2.51)	0.35		
>37	370	1.04 (0.54–2.02)	0.90		
Origin					
NL, W Europe	300	1			
SSA	805	1.10 (0.59–2.04)	0.77		
Other	441	1.07 (0.54–2.13)	0.84		
CD4					
<200	592	1			
200–350	414	0.78 (0.42–1.42)	0.41		
350–500	184	1.04 (0.50–2.16)	0.92		
>500	180	0.95 (0.45–2.04)	0.90		
Missing	176	1.09 (0.52–2.27)	0.82		
HIV-RNA					
Undetectable	118	1			
Detectable	1188	1.14 (0.45–2.90)	0.79		
Missing	240	1.51 (0.53–4.25)	0.44		
HBV					
Negative	1355	1			
Positive	76	1.31 (0.51–3.36)	0.57		
Missing data	115	0.50 (0.16–1.61)	0.25		
HCV					
AB−	1154	1		1	
AB+, RNA+	34	4.81 (2.01–11.50)	<0.001	5.48 (2.25–13.38)	<0.001
AB+, RNA-	3	NA	—	NA	—
Missing	355	0.59 (0.31–1.14)	0.12	0.59 (0.311.14)	0.12
Medication					
NVP	359	1		1	
EFV	326	0.64 (0.35–1.17)	0.14	0.57 (0.31–1.07)	0.08
PI	789	0.37 (0.22–0.64)	0.001	0.38 (0.22–0.65)	<0.001
Both NNRTI/PI	27	0.88 (0.20–3.89)	0.99	0.86 (0.19–3.83)	0.84
NO NNRTI/PI	45	0.25 (0.03–1.87)	0.24	0.22 (0.03–1.66)	0.14

factor for developing hepatotoxicity in other diseases. Pregnancy is also associated with immune suppression, and therefore may be responsible for susceptibility and poor outcome of infectious diseases. Pregnant women with hepatitis E developed fulminant hepatic failure more frequently with mortality rates over 20%.[17] This may add to the argument of testing for HCV in HIV pregnant women, especially when a NVP-based regimen is considered.

The strength of our study lies in the elaborate and detailed baseline demographic and clinical data recorded from a well-characterized population in the ATHENA cohort. Women from all social, ethnic and economic backgrounds have the same access to health care in the Netherlands. Therefore, selection bias was not likely to occur.

Nonetheless our data have several limitations. Our study is limited by its observational design. The data were recorded by individual hospital data collectors and were restricted to protocol. Furthermore, additional details on the clinical severity of hepatotoxicity were not obtainable. Occasionally data on $CD4^+$ cell counts and liver enzymes were lacking. Data on alcohol consumption were not available.

Table 3 Risk factors for hepatotoxicity, analysis for pregnant and non-pregnant women.

	Pregnant women					Non-pregnant women				
	n	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value	n	Univariate OR (95% CI)	P-value	Multivariate OR (95% CI)	P-value
Age quartiles										
<27	189	1		1		217	1		1	
27—32	129	2.65 (0.76—9.26)	0.13	2.47 (0.65—9.38)	0.18	270	0.52 (0.23—1.18)	0.12	0.51 (0.22—1.17)	0.11
32—37	79	1.83 (0.40—8.35)	0.44	1.43 (0.26—7.78)	0.68	292	0.99 (0.50—1.98)	0.98	1.03 (0.51—2.08)	0.94
>37	28	3.56 (0.62—20.40)	0.15	4.72 (0.59—37.82)	0.14	342	0.66 (0.32—1.37)	0.26	0.63 (0.30—1.32)	0.22
Origin										
NL, W Europe	68	1				232	1			
SSA	249	0.91 (0.24—3.39)	0.88			556	1.19 (0.59—2.40)	0.64		
Other	108	0.62 (0.12—3.16)	0.56			333	1.22 (0.57—2.61)	0.62		
CD4										
<200	73	1				519	1			
200—350	113	0.42 (0.07—2.58)	0.35			301	0.92 (0.48—1.75)	0.80		
350—500	102	1.46 (0.35—6.03)	0.60			82	0.90 (0.31—2.63)	0.85		
>500	126	0.96 (0.22—4.16)	0.96			54	1.40 (0.47—4.16)	0.54		
Missing	11	NA	—			165	1.13 (0.54—2.38)	0.75		
HIV-RNA										
Detectable	74	1		1		44	1			
Undetectable	344	1.41 (0.31—6.40)	0.65	1.66 (0.33—8.35)	0.54	844	0.75 (0.22—2.52)	0.64		
Missing	7	6.00 (0.47—76.14)	0.17	5.98 (0.34—103.94)	0.22	233	0.87 (0.24—3.18)	0.84		
HBV										
AB+	380	1		1		975	1		1	
AB−	21	2.97 (0.63—14.12)	0.17	3.73 (0.63—21.94)	0.15	55	0.95 (0.29—3.13)	0.93	1.09 (0.33—3.66)	0.89
Missing data	24	1.23 (0.15—9.80)	0.81	1.24 (0.12—12.35)	0.86	91	0.37 (0.09—1.54)	0.17	0.79 (017—3.63)	0.76
HCV										
AB−	340	1		1		814	1		1	
AB+, RNA+	11	27.18 (6.45—114.57)	<0.001	23.53 (4.69—118.01)	<0.001	23	2.20 (0.63—7.64)	0.22	2.56 (0.72—9.17)	0.15
AB+, RNA−	2	NA	—	—	—	1	NA	—	NA	
AB missing	72	3.55 (1.09—11.52)	0.035	3.09 (0.82—11.72)	0.10	283	0.32 (0.14—0.75)	0.009	0.34 (0.14—.86)	0.02
Medication										
NVP	102	1		1		257	1		1	
EFV	1	NA		NA		325	0.47 (0.25—0.90)	0.02	0.47 (0.25—0.90)	0.02
PI	318	0.23 (0.08—0.64)	0.005	0.19 (0.06—0.62)	0.005	471	1.07 (0.24—4.88)	0.93	1.09 (0.23—5.06)	0.91
Both NNRTI/PI	4	NA		NA		23	0.26 (0.03—1.95)	0.19	0.27 (0.04—2.09)	0.21
NO NNRTI/PI						45	0.66 (0.34—1.27)	0.21	0.63 (0.33—1.22)	0.17

NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; EFV, efavirenz /R = boosted ritonavir; NL, The Netherlands; W Europe, western Europe; SSA, sub-Saharan Africa Detectable: >500 HIV copies; Undetectable: <500 HIV copies; CD4, CD4+ T-cells; HCV, hepatitis C virus; AB, antibody; RNA, HCV-RNA; HBV, hepatitis B; OR, odds ratio; NA, not applicable.

Conclusion

HCV coinfection is strongly associated with hepatotoxicity in pregnant HIV-infected women starting cART. NVP use increased the risk of hepatotoxicity in pregnant as well as in non-pregnant women. Hepatotoxicity was independent of $CD4^+$ cell count, region of origin, detectable HIV-RNA levels and age.

Contributors

Ingrid J.M. Snijdewind: substantial contribution to conception and design of the study, analysis and interpretation of data, drafting the paper, final approval of the version to be published.

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Conflict of interest

The authors have no conflicting interests.

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