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Paediatric HIV Matters

# Prevalence and associated factors of nonalcoholic fatty liver disease and liver fibrosis among perinatally HIV-infected Asian adolescents

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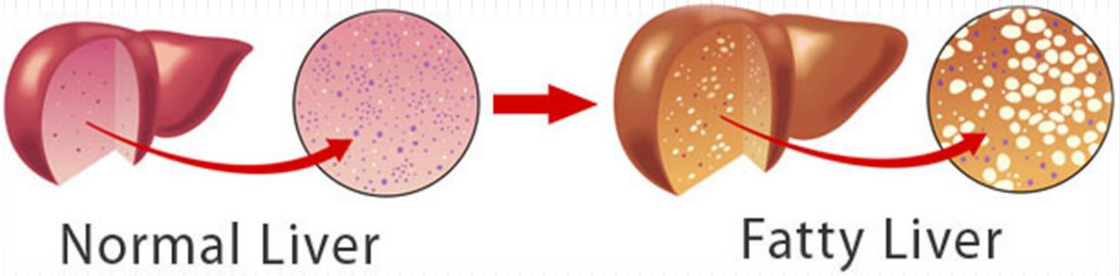
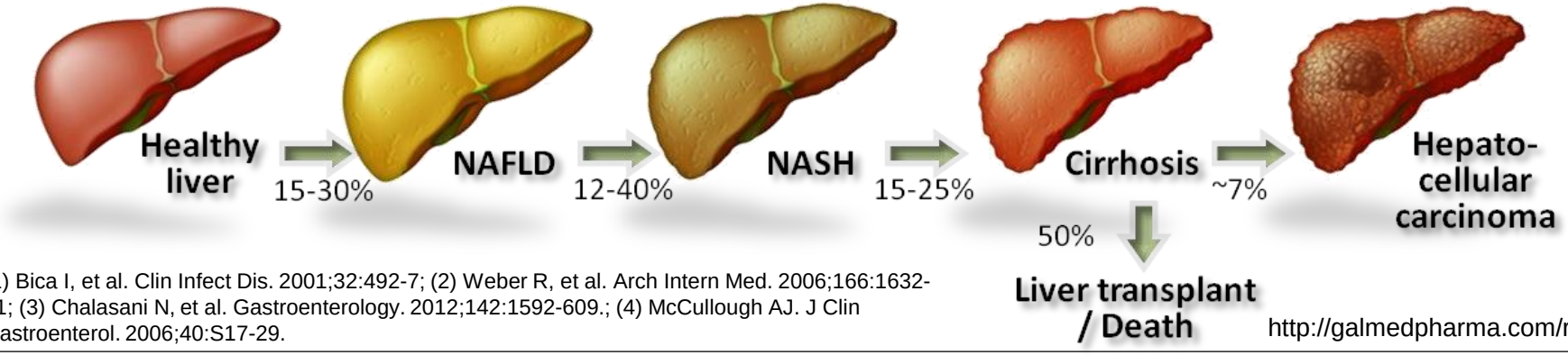
on behalf of HIVNAT 203 study team



# Background

- **Liver disease** is an important non-AIDS related complication in HIV-infected population[1,2]
- **Non-alcoholic fatty liver disease (NAFLD)** is a clinical-pathological syndrome in individuals without excessive alcohol use or chronic active viral hepatitis[3]
- **The disease spectrum** ranges from mild steatosis to nonalcoholic steatohepatitis (NASH), advanced stages of fibrosis, cirrhosis, and hepatocellular carcinoma[3,4]




(1) Bica I, et al. Clin Infect Dis. 2001;32:492-7; (2) Weber R, et al. Arch Intern Med. 2006;166:1632-41; (3) Chalasani N, et al. Gastroenterology. 2012;142:1592-609.; (4) McCullough AJ. J Clin Gastroenterol. 2006;40:S17-29.

# Background

- **NAFLD has been identified in 30-42% of HIV-infected adults** without viral hepatitis coinfection[6,7]
- **The epidemiology of NAFLD among perinatally HIV-infected adolescents** are not well studied in resource-constrained countries
- **The gold standard to diagnose NAFLD** is liver biopsy
  - This method is invasive and might cause complications[5]
- **Non-invasive measurements:** liver ultrasonography (USG), transient elastography (TE) and several liver fibrosis scores have been developed[5]
  - The diagnostic accuracy is unknown

(5) Berzigotti A. Rev Recent Clin Trials. 2014;9:170-7; (6) Crum-Cianflone N, et al. Clin Gastroenterol Hepatol. 2009;8:183-91;
(7) Hadigan C, et al. J Acquir Immune Defic Syndr. 2007;46:312-7.

# Objectives

- **To determine the prevalence and associated factors** of NAFLD
- **To evaluate the diagnostic accuracy** of non-invasive liver fibrosis scores
- **To assess the correlation** between liver fibrosis scores and TE

# Methods: Study design and settings

- **Study design:** A multicenter, matched case-control study
- **Study settings:** 4 pediatric HIV centers in
  - **Thailand:** Bangkok, Chiang Mai, Khon Kaen
  - **Indonesia:** Jakarta

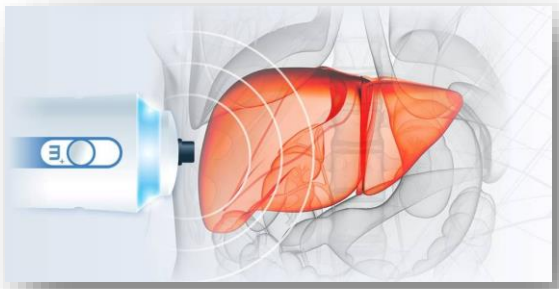
# Methods: Study population

- **Inclusion criteria:** HIV-infected adolescents aged 10-25 years with virologic suppression
  - **Case:** history of transaminitis (ALT >30 or AST >50 U/L) within past 12 months
  - **Control:** normal liver enzymes (ALT $\leq$30 U/L and AST $\leq$50 U/L) matched with cases on age and sex
- **Exclusion criteria:** hepatitis B/C co-infection, significant alcohol consumption, or history of secondary hepatic fat accumulation

# Methods: Outcome assessment

## Definition of NAFLD

**Any grade of fatty liver by USG** and/or **Significant liver fibrosis**



- **Liver ultrasonography (USG)** to evaluate fatty liver
  - Performed by pediatric radiologists
  - **Severity:** score 1 (mild); score 2 (moderate); and score 3 (severe)
- **Transient elastography (TE)** to evaluate liver stiffness
  - Performed by experienced technicians
  - **TE ≥7.4 kPa:** significant liver fibrosis

# Methods: Laboratory evaluations

- **Laboratory evaluations:** complete blood count, platelet count, liver function test, lipid profile and diabetic profile
- **Non-invasive liver fibrosis scores** were calculated

| Liver fibrosis scores | APRI | FIB-4 |
|---|---|---|
| Calculation | [(AST / ULN AST) x 100] / Platelets ($10^9$/L) | Age × AST / platelet count × (square root) ALT |
| Mild/moderate fibrosis | >0.5 to 1.5 | >1.5 to 3.25 |
| Advanced fibrosis | >1.5 | >3.25 |

Abbreviation: APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 score.

# Methods: Statistical analysis

- **The prevalence of NAFLD** and its 95% confidence interval were calculated
- **Demographic characteristics and laboratory results** were compared using chi-square test and Wilcoxon rank sum test for categorical and continuous data, respectively
- **Logistic regression analysis** was performed to determine associated factors for NAFLD
- **The diagnostic accuracy,** including sensitivity and specificity, of non-invasive liver fibrosis scores were evaluated
- **The correlation** of liver fibrosis scores and TE were assessed

# Results

- **From August 2014 to May 2015,** 60 pairs of case and control were enrolled

# Table 1. Demographic characteristics of 120 perinatally HIV-infected Asian adolescents

| Characteristics* | Total (n = 120) | Case (n = 60) | Control (n = 60) | *P* |
|---|---|---|---|---|
| Age, years | 17 (14.6-19.2) | 17 (14.6-19.0) | 17 (14.8-19.3) | 0.94 |
| Female | 62 (52) | 31 (52) | 31 (52) | 0.99 |
| Body mass index | | | | 0.07 |
| • Normal | 87 (73) | 46 (76) | 41 (68) | |
| • Underweight (<5$^{th}$ Percentile)† | 23 (19) | 7 (12) | 16 (27) | |
| • Obese (>85$^{th}$ Percentile)† | 10 (8) | 7 (12) | 3 (5) | |
| WHO clinical stage 3-4 prior to ART | 57 (56) | 32 (62) | 25 (51) | 0.29 |
| CD4 percentage prior ART | 10 (3-20) | 7 (2-20) | 14 (5-20) | 0.25 |
| Current ART regimen | | | | 0.59 |
| • NNRTI-based | 81 (68) | 40 (67) | 41 (68) | |
| • Boosted PI-based | 35 (29) | 17 (28) | 18 (30) | |
| • Others | 4 (3) | 3 (5) | 1 (2) | |
| Duration of ART, years | 10 (7-12) | 11 (7-12) | 9 (7-12) | 0.63 |
| Current CD4 cells, cell/mm$^3$ | 725 (588-946) | 694 (546-979) | 762 (612-928) | 0.33 |

Abbreviation: ART, antiretroviral therapy; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; WHO, World Health Organization.
*Data presented as n (%) for categorical data and median (IQR) for continuous data.
†For individuals aged >18 years, underweight and overweight are defined as body mass index <18 kg/m$^2$ and >25 kg/m$^2$, respectively.

# Table 2. Laboratory results of 120 perinatally HIV-infected Asian adolescents

| Laboratory tests* | Total (n = 120) | Case (n = 60) | Control (n = 60) | *P* |
|---|---|---|---|---|
| **Liver function** | | | | |
| • **AST, U/L** | **22 (19-27)** | **24 (21-33)** | **21 (18-24)** | **<0.001** |
| • **ALT, U/L** | **21 (16-30)** | **29 (21-39)** | **16 (12-22)** | **<0.001** |
| • **Gamma GT, U/L** | **36 (24-73)** | **47 (25-95)** | **32 (22-50)** | **0.02** |
| **Hematology** | | | | |
| • Hemoglobin, g/dL | 13 (12-14) | 14 (12-15) | 13 (12-14) | 0.09 |
| • Platelet, x$10^3$cells/$mm^3$ | 284 (250-337) | 274 (248-327) | 297 (254-354) | 0.09 |
| **Lipid profile** | | | | |
| • Cholesterol ≥200 mg/dL | 26 (21.7) | 14 (23.3) | 12 (20) | 0.66 |
| • HDL ≤40 mg/dL | 28 (23.5) | 18 (30.5) | 10 (16.7) | 0.08 |
| • LDL ≥130 mg/dL | 21 (17.5) | 14 (23.3) | 7 (11.7) | 0.09 |
| • Triglyceride ≥150 mg/dL | 15 (12.5) | 8 (13.3) | 7 (11.7) | 0.78 |
| **Diabetic profile** | | | | |
| • FPG, mg/dL | 82 (77-87) | 83 (79-87) | 81 (76.5-87.5) | 0.43 |
| • HOMA-IR | 1.5 (0.9-2.7) | 1.5 (0.9-2.1) | 1.5 (1.0-2.8) | 0.33 |
| • HOMA-IR >3.16 | 19 (16) | 8 (14) | 11 (19) | 0.48 |

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; FPG, fasting plasma glucose; Gamma GT, gamma-glutamyl transferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.
*Data presented as n (%) for categorical data and median (IQR) for continuous data.

# Results: Prevalence of NAFLD

**The overall prevalence of NAFLD was 23% (95%CI:15-31%)**

No significant difference between cases vs. controls (20% vs. 25%, *P* = 0.51)

**Table 3. Non-invasive measurements for diagnosis of NAFLD among 120 perinatally HIV-infected Asian adolescents**

| Measurements* | Total (n = 120) | Case (n = 60) | Control (n = 60) | *P* |
|---|---|---|---|---|
| **Abnormal liver ultrasonography** | 19 (16%) | 8 (13%) | 11 (18%) | 0.15 |
| • Fatty liver, score 1 | 16 (13%) | 5 (8%) | 11 (18%) | |
| • **Fatty liver, score 2** | **1 (0.8)** | **1 (1.7)** | **0 (0)** | |
| • **Fatty liver, score 3** | **2 (1.7)** | **2 (3.3)** | **0 (0)** | |
| **Transient elastography**, kPa | 4.9 (3.8-5.9) | 5.2 (4.2-6.1) | 4.4 (3.6-5.8) | 0.10 |
| • TE ≥7.4 kPa | 11 (9%) | 5 (8%) | 6 (10%) | 0.75 |
| **APRI** | **0.2 (0.2-0.3)** | **0.3 (0.2-0.3)** | **0.2 (0.1-0.2)** | **<0.001** |
| • **APRI >0.5** | **4 (3%)** | **4 (3%)** | **0 (0)** | **0.06** |
| **FIB-4 score** | 0.3 (0.2-0.4) | 0.3 (0.2-0.4) | 0.3 (0.2-0.4) | 0.96 |
| • FIB-4 >1.5 | 0 (0) | 0 (0) | 0 (0) | NA |

Abbreviation: APRI, Aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4 score.
*Data presented as n (%) for categorical data and median (IQR) for continuous data.

# Table 4. Associated factors for NAFLD among 120 perinatally HIV-infected adolescents

| Parameters | Univariate analysis | | |
|---|---|---|---|
| | OR | 95%CI | *P* |
| Age >18 years | 1.5 | 0.6-3.7 | 0.36 |
| Female sex | 1.5 | 0.6-3.5 | 0.37 |
| Obesity | 2.5 | 0.7-9.7 | 0.18 |
| CD4 prior ART <15% | 1.7 | 0.6-5.0 | 0.31 |
| WHO stage 3-4 prior ART (vs. Stage 1-2) | 1.1 | 0.7-1.9 | 0.72 |
| Current PI used (vs. NNRTI used) | 1.2 | 0.6-2.6 | 0.59 |
| AST>50 | 3.5 | 0.2-57.9 | 0.38 |
| ALT>30 | 1.3 | 0.5-3.4 | 0.65 |
| Glucose >100 | 3.5 | 0.2-57.9 | 0.38 |
| HOMA-IR >3.16 | 1.7 | 0.6-5.1 | 0.32 |
| Cholesterol >200 | 2.2 | 0.9-5.8 | 0.1 |
| HDL $\leq$40 | 1.5 | 0.6-4.0 | 0.39 |
| LDL $\geq$130 | 2.0 | 0.7-5.5 | 0.19 |
| Triglyceride $\geq$150 | 1.9 | 0.6-6.1 | 0.29 |

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HOMA-IR, homeostasis model assessment-insulin resistance; HDL, high density lipoprotient; LDL, low density lipoprotein; WHO, World Health Organization.

**No significant factor associated with NAFLD**

# Results: Liver fibrosis scores

- **Abnormal APRI has low sensitivity** 18% (95%CI: 2-52%), **but high specificity** 98% (95%CI: 94-99%) for diagnosis of significant liver fibrosis

- **Poorly correlated of liver fibrosis scores with TE**
  - **APRI:** correlation coefficient: 0.27, *P* <0.01
  - **FIB-4:** correlation coefficient: 0.25, *P* <0.01

# Discussion

- **The prevalence of NAFLD among perinatally HIV-infected adolescents is high (23%)**
  - The prevalence among healthy children was 2.6-9.8%[8,9]
  - The prevalence among HIV mono-infected adults was 30-42%[6,7]
- **The most common associated factors with NALFD** include obesity, insulin resistance, diabetes mellitus, dyslipidemia, ARTs
  - This study did not demonstrated any significant associated factor of NAFLD
- **Non-invasive liver fibrosis score (APRI) had low sensitivity** (18%) to detect significant liver fibrosis
  - The sensitivity of abnormal APRI was 46% for identifying liver fibrosis on biopsy in children with chronic viral hepatitis[10]

(8) Tominaga K, et al. Dig Dis Sci. 1995;40:2002-9; (9) Schwimmer JB, et al. Pediatrics. 2006;118:1388-93;
(10) McGoogan KE, et al. J Pediatr Gastroenterol Nutr. 2010;50:344–6.

# Limitations

- **No liver biopsy** (gold standard) was performed
- **Variation of radiologic evaluations** across participating sites
- **Self-reporting of alcohol consumption** may have been inaccurate
- **Limited number of participants**

# Conclusions

- **About one-fifth of perinatally HIV-infected adolescents** met criteria of NAFLD
- **The prevalence of NAFLD was not different** between adolescents with history of transaminitis and controls
- **No significant factor was found** to be associated with NAFLD in this study
- **APRI is poorly correlated** with TE, and **has low sensitivity** to detect hepatic fibrosis
- **Longitudinal follow-up** to monitor the progression and provide appropriate interventions in a timely manner is definitely required

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