Risk of Acute Liver Injury with Modern Antiretroviral Therapy By Viral Hepatitis Status

C. Gowda[1], C.W. Newcomb[2], Q. Liu[2], D.M. Carbonari[2,3], J.D. Lewis[2,3,4], K.A. Forde[2,3,4], D.S. Goldberg[2,3,4], K.R. Reddy[3,4], J. A. Roy[2,3], A.R. Marks[5], J.L. Schneider[5], J.R. Kostman[6], J.P. Tate[7,8], J.K. Lim[7,8], A.C. Justice[7,8], M.B. Goetz[9], D.A. Corley[5], V. Lo Re III[2,3,10]

[1]Division of Infectious Diseases, Nationwide Children's Hospital, Columbus, OH; [2]Center for Clinical Epidemiology & Biostatistics; [3]Center for Pharmacoepidemiology Research and Training; and [4]Division of Gastroenterology, Univ of Pennsylvania, Philadelphia, PA; [5]Division of Research, Kaiser Permanente Northern California, Oakland, CA; [6]Jonathan Lax Treatment Center, Philadelphia, PA; [7]VA Connecticut Healthcare System, West Haven, CT; [8]Yale Univ School of Medicine, New Haven, CT; [9]VA Greater Los Angeles Healthcare System and David Geffen School of Medicine at UCLA, Los Angeles, CA; [10]Division of Infectious Diseases, University of Pennsylvania, Philadelphia, PA

ABSTRACT

Background: The risk of hepatotoxicity with modern antiretroviral therapy (ART) remains unknown. We determined the comparative risk of acute liver injury (ALI) for antiretroviral drugs, classes, and regimens, by viral hepatitis status.

Methods: We followed a cohort of 10,083 HIV-infected persons in Kaiser Permanente Northern California (n=2,099) from 2004-2010 and the Veterans Aging Cohort Study (n=7,984) from 2004-2012. Within the first year of ART, we determined occurrence of: 1) liver aminotransferases >200 U/L, and 2) severe ALI (coagulopathy with hyperbilirubinemia). We used Cox regression to determine hazard ratios (HRs) with 95% confidence intervals of endpoints among initiators of: 1) nucleos(t)ide analogue combinations, 2) antiretroviral classes, and 3) ART regimens, all stratified by viral hepatitis status.

Results: Liver aminotransferases >200 U/L developed in 206 (2%) persons and occurred more frequently among HIV/viral hepatitis-coinfected than HIV-monoinfected persons (116.1 versus 20.7 events/1,000 person-years; p<0.001). No evidence of differential risk was found between initiators of abacavir/lamivudine versus tenofovir/emtricitabine among coinfected (HR, 0.68 [0.29-1.57]) or HIV-monoinfected (HR, 1.19 [0.47-2.97]) groups. Coinfected patients had a higher risk of aminotransferases >200 U/L after initiation with a protease inhibitor than non-nucleoside reverse transcriptase inhibitor (HR, 2.01 [1.36-2.96]). Severe ALI (30 events; 0.3%) occurred more frequently in coinfected persons (15.9 versus 3.1 events/1,000 person-years; p<0.001), but was too uncommon to evaluate in adjusted analyses.

Conclusions: Within the year after modern ART initiation, aminotransferase elevations were infrequently observed and rarely led to severe ALI. Protease inhibitor use was associated with a higher risk of aminotransferase elevations among viral hepatitis-coinfected patients.

BACKGROUND & SPECIFIC AIMS

- Prior studies of ART-associated acute liver injury (ALI) have focused on antiretrovirals used in the early ART era and did not stratify by viral hepatitis status.
- Evaluation of potential hepatotoxicity due to modern ART in clinical practice is important to ensure the safety of these medications in HIV-infected patients.
- **SPECIFIC AIMS:**

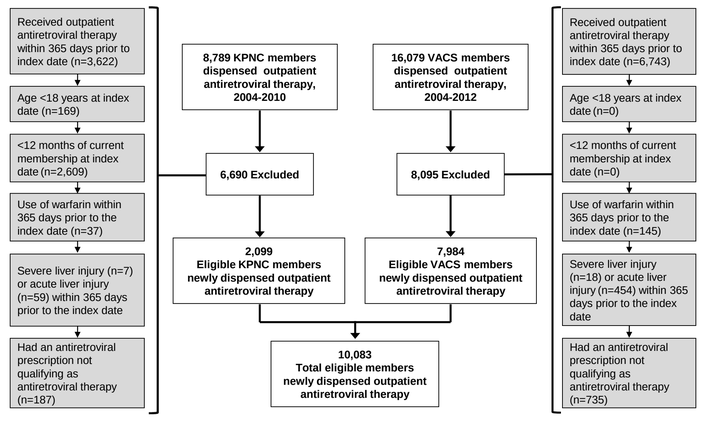
  (1) To determine the absolute and comparative risks of ALI associated with nucleos(t)ide analogue (NRTI) combinations, antiretroviral classes and commonly used ART regimens, separately among those with and without viral hepatitis coinfection.

  (2) Determine factors associated with ALI.

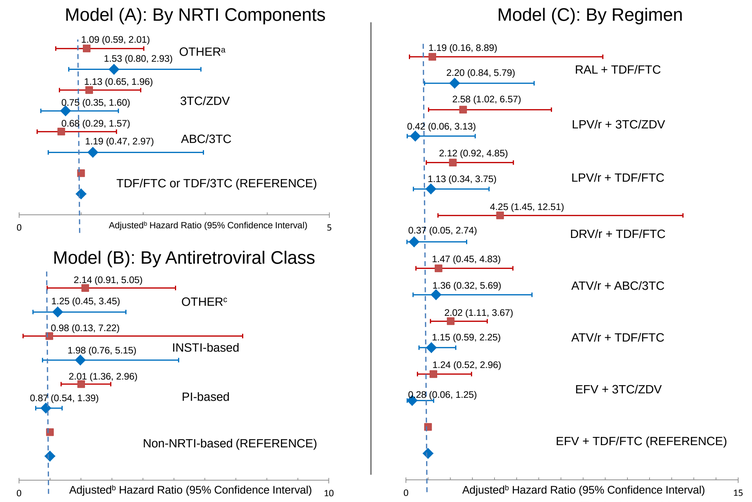
METHODS

- **Study Design:** Retrospective cohort study
- **Data Sources (two databases merged)**:
  - Kaiser Permanente Northern California (KPNC), 2004-2010
  - Veterans Aging Cohort Study (VACS), 2004-2012
- **Patients**: 1) HIV+, 2) ≥18 years, 3) dispensed ART in outpatient setting
  - Index date = initial ART dispensation date
  - Follow-up continued until: 1) 12 months after index date, 2) endpoint, 3) death, 4) change/discontinuation of ART, or 4) last KPNC or VACS contact
- **Study Outcomes**:
  - (1) Liver aminotransferases (AST or ALT) >200 U/L
  - (2) Severe ALI = INR ≥1.5 + total bilirubin >2 times ULN (within 30 days)
  - (3) Acute liver failure (ascertained among hepatitis-uninfected patients) = Hospitalization with INR ≥1.5 + hepatic encephalopathy or liver transplant
- **Data Collection**: Clinical and lab variables collected at baseline (12 months prior to index date) and through follow-up
- **Statistical Analyses**:
  - One-year cumulative risk and incidence rates
  - Hazard ratios (HRs) of endpoints in initiators of NRTI combinations, ART classes, and ART regimens, all stratified by hepatitis status
  - Risk factors for aminotransferases (AST or ALT) >200 U/L using Cox regression

PATIENT SELECTION



COMPARATIVE RISKS OF AMINOTRANSFERASES >200 U/L



Abbreviations: ABC=abacavir; ATV/r=boosted atazanvir; DRV/r=boosted darunavir; EFV=efavirenz; FTC=emtricitabine; INSTI=integrase inhibitor; LPV/r=boosted lopinavir; NRTI=nucleos(t)ide reverse transcriptase inhibitor; PI=protease inhibitor; TDF=tenofovir; ZDV=zidovudine; 3TC=lamivudine

[a] "Other" includes regimens with <2 NRTIs or alternative NRTI combinations than those listed.

[b] Each model adjusted for baseline alanine aminotransferase >40 U/L, calendar year of ART initiation, and data source.

[c] "Other" refers to regimens with none or >1 of the listed antiretroviral class.

RISK FACTORS ASSOCIATED WITH ALI

Potential risk factor	Adjusted[a] HR of ALT or AST >200 U/L (95% CI)	Unadjusted[b] HR of Severe ALI (95% CI)
Age ≥50 years	0.89 (0.66 – 1.19)	**2.66 (1.25 – 5.69)**
Viral hepatitis coinfection	**4.21 (3.10 – 5.72)**	**4.65 (2.26 – 9.51)**
Heart failure	0.76 (0.24 – 2.42)	**6.26 (1.90 – 20.66)**
HIV RNA (per $\log_{10}$ copies/mL)	0.90 (0.75 – 1.08)	**1.82 (1.10 – 3.01)**
Baseline ALT ≥ 40 IU/mL	**2.49 (1.85 – 3.34)**	1.92 (0.93 – 3.96)

[a] Model adjusted for all covariates shown here as well as sex, race, body mass index, history of alcohol dependence/abuse, diabetes, pre-ART CD4 count, calendar year of ART initiation and data source.

[b] Due to low number of severe ALI events, adjusted analyses could not be performed

CONCLUSIONS

- 206 (2%) HIV-infected patients developed aminotransferases >200 U/L within first year of ART, but **severe ALI was observed in <1%.**
- **No acute liver failure events** observed in viral hepatitis-uninfected patients.
- Among HIV-monoinfected persons, no differences in risk of AST or ALT>200 U/L by NRTI combination, antiretroviral class, or commonly used ART regimens.
- Among hepatitis-coinfected patients, initiation of **PI-based ART**, including darunavir and atazanavir, was **associated with higher risk of AST or ALT>200 U/L** compared with use of NNRTI-based ART, **but severe ALI events very rare**.
- These results **support the hepatic safety of modern ART regimens.**