Mechanism of Bone Disease in HIV and HCV: Impact of Tenofovir Exposure and Severity of Liver Disease

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Poster 783

Introduction

- HIV infection and highly active antiretroviral therapy (HAART) are associated with higher rates of osteoporosis and fragility fractures.[1]
- HCV co-infection independently predicts fracture risk in several HIV-infected cohorts.[2,3]
- Our previous analyses of the Veterans' Affairs Clinical Care Registry identified cumulative tenofovir (TDF) exposure and HCV co-infection as independently predictive of osteoporotic fracture in the HAART era, with greater risk in patients with more severe liver disease (cirrhosis or higher AST-to-Platelet Ratio Index [APRI]).[4,5]

Objective

- To evaluate effects of HIV and HCV on bone health and determine the mechanisms and relative contributions of TDF exposure and liver disease severity on bone health in HIV and HCV-infected patients.

Methods

- Prospective, cross-sectional study of 298 male veterans with HIV, HCV, or HIV/HCV co-infection and uninfected controls.
- Inclusion criteria: Age≥ 40; eGFR ≥ 60 ml/min/1.73 m^2 ; no known osteoporosis.
- All HIV patients were virologically suppressed on HAART.
- All HCV patients were HCV treatment-naïve.
- Study Measurements:
  - Bone mineral density (BMD) by DXA scan
  - Bone turnover markers (BTM): serum C-telopeptide (CTX), bone-specific alkaline phosphatase (BSAP) and osteocalcin (OC).
  - Regulatory/Inflammatory cytokines: receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG) and tumor necrosis factor (TNF-α).
  - Severity of liver disease: APRI score
- Statistical Analysis:
  - Groups means compared by ANOVA and by ANCOVA adjusting for age, race and BMI in all models.
  - Additional multivariate models controlling for APRI score, BTM, TDF exposure (categorized as current, past or never) or TDF duration, respectively.
  - Correlation by Spearman's correlation coefficient.

Results

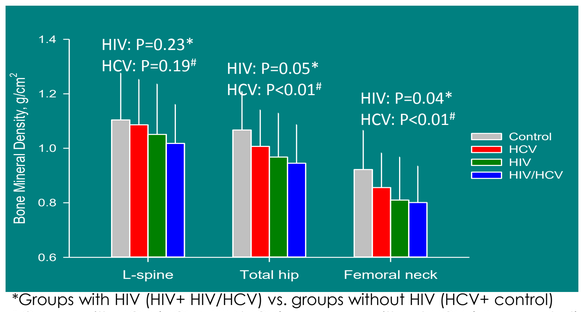
Table 1. Baseline characteristics

Variable	Controls (N=107)	HCV (N=79)	HIV (N=81)	HIV/HCV (N=31)	P-Value (Unadj.)
Age (yrs)*	52.9 (6.8)	55.4 (4.7)	55.9 (8.3)	55.1 (6.2)	0.01
Race/Ethnicity (%AA/C/H)	79/19/2	77/19/4	43/47/10	74/23/3	< 0.01
BMI (kg/m^2)*	29.9 (6.1)	28.7 (4.9)	27.7 (4.8)	27.6 (5.7)	0.04
% Smokers	68	63	33	45	< 0.01
% Glucocorticoid Use	12	7	15	7	0.51
% Alcohol Use	3	4	8	3	0.66
% Osteopenia / Osteoporosis#	45/0	55/6	53/11	65/10	< 0.01
APRI score*	0.28 (0.11)	0.70 (0.60)	0.38 (0.25)	0.93 (0.91)	< 0.01
CD4 count*			559 (273)	555 (329)	0.95
% with TDF Use Current/past/never users			83/9/8	81/13/6	0.83
TDF Duration (yrs)*			5.1 (2.9)	4.3 (2.7)	0.20

* Data reported as mean (standard deviation) # Based on femoral neck T-score

A. HIV and HCV Independently Lower BMD

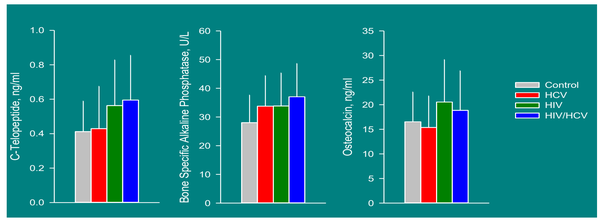
Controlling for age, race and BMI (**model 1**)



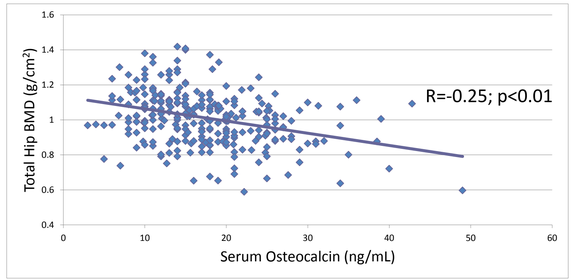
*Groups with HIV (HIV+ HIV/HCV) vs. groups without HIV (HCV+ control)
Groups with HCV (HCV+ HIV/HCV) vs. groups without HCV (HIV + control)

- HIV and HCV associated with decreased BMD at total hip and femoral neck, but not at lumbar spine.
- HCV: APRI score did not predict decreased BMD (p=0.89).
- HCV and HIV's associations with decreased BMD persists after controlling for APRI score (p=0.02 and p=0.04) (**model 2**).
- TDF use associated with ↓ BMD in HIV patients (current use: p<0.01; past use: p=0.03; duration: p=0.02). (**model 4 and 5**)
- Controlling for TDF use, HIV no longer predictive of decreased BMD (p=0.07).

B. HIV Significantly Increases Bone Turnover, HCV Does Not.



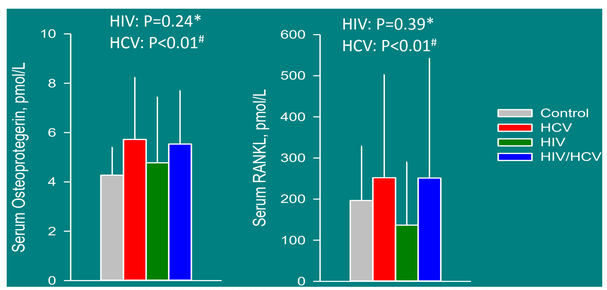
- HIV associated with ↑ in CTX, BSAP, and OC (p<0.01 for all); HCV associated with no change in CTX (p=0.49), increase in BSAP (p<0.01)and a trend toward lower OC (p=0.11).
- HIV no longer associated with decreased BMD when controlling for BTMs (p=0.11 with OC)(**model 3**).



Correlations of OC levels and Total Hip BMD

- Mean BTMs correlated with BMD (OC: r=-0.25; CTX: r=-0.19; BSAP: p=-0.24; p<0.01 for all)

C. HCV is Associated with Elevated Regulatory Cytokines: RANKL and OPG; HIV is Not.



*Groups with HIV (HIV+ HIV/HCV) vs. groups without HIV (HCV+ control)
Groups with HCV (HCV+ HIV/HCV) vs. groups without HCV (HIV + control)

- HIV not associated with higher levels of TNF-α (p=0.29)
- Trend toward increased TNF-α with HCV (p=0.12)
- TNF-α levels correlated with BSAP (p=0.02) but not with CTX(p=0.56) or OC (p=0.24).
- TNF-α not correlated with BMD (p=0.67 for total hip BMD)

Table 2. Multivariable Models Predicting Femoral Neck BMD

	Model 1 (HIV, HCV, BMI, Race, Age)	Model 2 (Model 1 + APRI Score)	Model 3 (Model 1 + serum OC)	Model 4 (Model 1 + TDF use category)	Model 5 (Model 1 + TDF use duration)
HIV	-0.035 (p=0.04)	-0.035 (p=0.04)	-0.027 (p=0.11)	0.080 (p=0.07)	0.024 (p=0.74)
HCV	-0.039 (p=0.01)	-0.043 (p=0.02)	-0.043 (p<0.01)	-0.040 (p=0.01)	-0.044 (p<0.01)
APRI Score	N/A	0.003 (p=0.89)	N/A	N/A	N/A
Osteocalcin	N/A	N/A	-0.003 (p=0.02)	N/A	N/A
TDF Current Use	N/A	N/A	N/A	-0.12 (p<0.010)	N/A
TDF Past Use	N/A	N/A	N/A	-0.12 (p=0.03)	N/A
TDF Use Duration	N/A	N/A	N/A	N/A	-0.009 (p=0.02)

Conclusions

- HIV and HCV independently reduce BMD but through different pathophysiologic mechanisms.
- In HIV, lower BMD is largely explained by 1) high bone turnover state (significantly ↑BTMs) and 2) TDF exposure.
- In HCV, lower BMD is due to a low bone turnover state (no significant effect on BTMs) and is not correlated with liver severity as measured by APRI score.
- Bone turnover markers were correlated with BMD.
- Changes in inflammatory marker (TNF-α) did not correlate with changes in BTMs or BMD in our cohort.

References

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