

# Risk Factors Associated With Osteonecrosis of the Hip in an HIV-Infected Population in the New Antiretroviral Therapy Era

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## ABSTRACT

**Background:** Avascular necrosis (AVN) has been shown to have a higher prevalence in the HIV population. This is partly due to high prevalence of already established risk factors such as hyperlipidemia, alcohol abuse, steroid use as well as the use of protease inhibitors. There have not been any studies looking at risk factors for avascular necrosis in the more recent antiretroviral therapy era.

**Methods:** We conducted a case control study among HIV infected individuals who receive care at the Partnership Comprehensive Care Practice at Drexel University, Philadelphia, PA. Cases were retrospectively identified with AVN defined by surgical pathology or imaging. For each case, one control was randomly selected who showed no evidence of AVN and matched for gender and age. Chi-square, Fisher exact and unpaired t-tests were used to compare AVN and control groups on dichotomous or numeric variables. A logistic regression model was used to evaluate the effect of hypothesized risk factors.

**Results:** We included 33 cases in our study from 2003 through 2015, 76% were male, 62.5% African American with a median age of 46+/-7. Using logistic regression analysis of the possible risk factors, we found that cases were 4.65 times more likely to have a detectable viral load (p=.003). We did not find an association between steroid use or protease inhibitor and AVN.

**Conclusions:** A detectable HIV viral load seems to be an independent risk factor for AVN. In contrast to prior case control studies, our study did not find an association between protease inhibitor use and avascular necrosis. It is possible that newer protease inhibitors are not associated with avascular necrosis.

## BACKGROUND

Osteonecrosis or avascular necrosis (AVN), refers to loss of blood supply to bone forming cells, leading to bone death. The prevalence of asymptomatic osteonecrosis in HIV infected individuals, diagnosed through MRI screening has been estimated to be 4.4% [3] and reported incidence of 0.3-0.45% [4-7]. In comparison, the incidence of symptomatic osteonecrosis in the general population has been estimated to be between 0.01% and 0.135% [2,8,9]. The higher incidence of AVN among HIV infected individuals suggests that it may be a complication of either HIV infection itself or its treatment consisting of antiretroviral therapy (ART).

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## BACKGROUND

Several risk factors such as steroid use, alcohol abuse, hyperlipidemia, pancreatitis and hypercoagulable states have been associated with AVN [2,10]. In the earlier ART era, prior to 2000, the use of protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) were found to be associated with a higher incidence in AVN, likely due to metabolic complications related to lipodystrophy (2,10). Osteonecrosis had been described in HIV patients before the ART era but there was a sharp increase in AVN after the introduction of PIs and with ART as the standard of care (10). As HIV infected individuals are living longer, adverse consequences of long-term exposure to ART have been emerging. Therefore there is great debate on whether the increased osteonecrosis incidence is due to the metabolic effects of PIs or rather due to the improved survival of patients on ART (11). A French study found that the incidence of AVN directly increased with the duration of HIV infection and ART use (12), which may support the latter hypothesis. In the new ART era, with the availability of newer PIs and integrase inhibitors with improved side effect profiles, there have been few studies evaluating changes in risk factors for osteonecrosis.

## OBJECTIVE

❖ This study aims to evaluate risk factors for osteonecrosis in the new ART era.

## METHODS

- ❖ We conducted a retrospective case control study among HIV infected individuals who receive care at the Partnership Comprehensive Care Practice (PCCP) at Drexel University College of Medicine between 1/1/2003 and 5/31/2015.
- ❖ Case subjects were identified with a history of pathologically proven AVN who had hip replacement surgery at Hahnemann University Hospital and receive care at PCCP.
- ❖ Case subjects were also identified by reviewing the electronic medical record database Allscripts® for subjects who had a diagnosis of AVN and had available MRI imaging of the hip suggestive of AVN.
- ❖ Control subjects were identified by reviewing Allscripts® for subjects with no history of AVN or hip pain and matched to cases on age +/- 3 years and gender.
- ❖ Demographics, clinical data, laboratory data, HIV data, and histories of alcohol and steroid used were collected.
- ❖ Chi-square, Fisher exact and unpaired t-tests were used to compare AVN and control groups on dichotomous or numeric variables. A logistic regression model was used to evaluate the effect of hypothesized risk factors.

## RESULTS

**Table 1. Univariate Analysis of Associations Between Avascular Necrosis and Subject Characteristics**

Characteristic	% of subject		OR (95% CI)	p
	Cases (n=33)	Controls (n=33)		
Male sex (%)	75.8%	75.8%	1.0	1.0
African American ethnicity	62.5%	75.8%	1.88(.64-5.47)	.25
BMI≥30kg/m <sup>2</sup>	36.4%	53.1%	1.46(.84-2.55)	.17
History of smoking	69.7%	60.6%	1.50(.54-4.14)	.44
History of alcohol use	0%	15.2%	0	.05
History of steroid use	12.1%	3%	4.41(.47-41.80)	.36
History of hepatitis C	15.2%	15.2%	1.0	1.0
Duration of HIV infection in yrs (mean±SD)	13.42±5.77	14.91±5.83		.24
HIV viral load<20 copies/mL	33.3%	69.7%	4.60(1.63-12.97)	<.01*
CD4 cell count ≤200 cells/mL	15.2%	15.2%	1.0	1.0
CD4 nadir cells/mL (mean±SD)	126±137	322±255		<.01*
Triglyceride level ≥300 mg/dL	6.9%	0%		.24
Current PI use	75.0%	69.7%	.77(.26-2.3)	.63
Current tenofovir use	84.8%	78.8%	1.51(.43-5.35)	.52

**Table 2. Multivariate Analysis of Associations Between AVN and Subject Characteristics**

Characteristic	Adjusted OR	p
Male Sex	.78	.70
Smoking history	1.35	.60
Steroids use	3.81	.28
PI use	.63	.47
Detectable HIV VL	4.65	<.01*

## RESULTS

- ❖ We included 33 cases in our study from 2003 through 2015, 76% were male, 62.5% African American with a median age of 46+/-7.
- ❖ Individuals with AVN had a significantly lower CD4 nadir and a detectable HIV viral load in comparison to the control group.
- ❖ Using logistic regression analysis of the possible risk factors, we found an odds ratio of 4.65 for detectable viral load and AVN (p<.01).

## DISCUSSION

- ❖ We did not find an association between traditional AVN risk factors including steroid use or alcohol use.
- ❖ The use of current PIs or tenofovir were not associated with AVN, thus it is possible that the newer antiretroviral agents are not associated with AVN.
- ❖ It appears that HIV infection itself maybe the strongest risk factor for AVN in our study population

## CONCLUSION

A detectable HIV viral load seems to be an independent risk factor for AVN. In contrast to prior case control studies our study did not find an association between protease inhibitor use and avascular necrosis. It is possible that newer protease inhibitors are not associated with avascular necrosis.

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