Incidence and Risk Factors for Microscopic Hematuria in a US Military HIV Cohort

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Background

- Microscopic hematuria (MH) is a common finding on screening urinalyses in persons living with HIV (PLWH).
- A study in the pre-HAART era revealed that a complete urologic evaluation was generally non-diagnostic in young males with a benign history and normal renal function.
- Studies have shown a decreased incidence of hematuria in PLWH in the HAART era.
- We performed a nested case-control study in the prospectively enrolled US Military HIV Natural History Study (NHS) to evaluate characteristics of PLWH with and without MH.

Methods

- Study Data Source: The US Military HIV NHS
  - Prospective, observational, multicenter cohort study enrolling US military active-duty service members and Military Health System beneficiaries living with HIV.
  - Participants are followed every 6 months for clinical and laboratory evaluation.
- We evaluated male participants diagnosed with HIV and enrolled in the NHS between 1 Jan 2007 and 31 Dec 2019 and assessed for incident hematuria.
  - Cases: those with incident hematuria, which was having a first episode of urinalysis within the study period with ≥ 5 RBCs/hpf on microscopy.
  - Controls: those with an analyzable urinalysis without microscopy evidence of hematuria. An analyzable urinalysis was defined as a urinalysis with hematuria data (RBC microscopy) available.
  - Data were censored using the last study visit as the end date for each individual.
  - Data were analyzed using continuous-time history analysis.
  - Data were captured from the day of HIV diagnosis through the date of incident hematuria for cases and at any time from HIV diagnosis through the end of study follow-up for controls, unless otherwise specified.
- We used descriptive statistics to compare cases and controls with respect to demographics, comorbidities, and laboratory findings to determine risk factors for microscopic hematuria.
- Cox regression models evaluated for independent associations with the development of incident microscopic hematuria since HIV diagnosis.
- Negative binomial regression models evaluated predictors of multiple episodes of hematuria since HIV diagnosis.

Results

Table 1: Characteristics of Microscopic Hematuria Cases vs Controls*

Characteristic	Cases (n = 142)	Controls (n = 687)	P value
Duration of study follow-up, days	1081 ± 1072	1598 ± 1075	<0.01
Number of urinalyses per participant with available RBC microscopy	9 ± 6.5	5.4 ± 3.6	<0.01
Age at HIV diagnosis, years	29 ± 8.7	28 ± 7.2	0.14
Race/Ethnicity			0.97
African American	66 (46.5)	318 (46.3)	
White	48 (33.8)	228 (33.2)	
Hispanic	16 (11.3)	87 (12.7)	
Other	12 (8.5)	54 (7.9)	
Active-duty military at HIV diagnosis	135 (95.1)	665 (96.8)	0.31
History of smoking	26 (18.3)	161 (23.4)	0.18
Body mass index, kg/m^2	26.3 ± 4.0	26.2 ± 3.8	0.74
CD4 nadir, cells/mm^3	381 ± 185	404 ± 194	0.20
Duration from HIV diagnosis to ART initiation, days	295 ± 417	227 ± 381	0.11
TDF included in first HAART regimen**	88 (79.3)	428 (75.4)	0.37
Hypertension	33 (23.2)	82 (11.9)	<0.01
History of urinary tract infection	13 (9.2)	17 (2.5)	<0.01

*Data expressed as mean ± standard deviation or number (%), as appropriate.
**n = 111 for cases vs 568 for controls
ART = antiretroviral therapy; RBC = red blood cell; TDF = tenofovir disoproxil fumarate

Figure 1. Frequency of episodes of hematuria in PLWH, 2007-2019 (n=829)

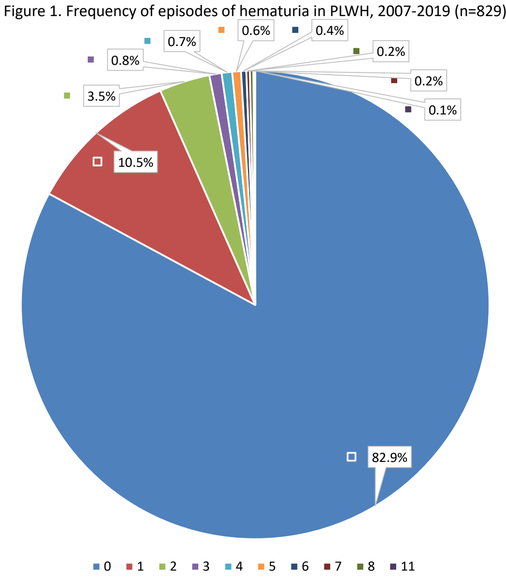

Table 2. Cox Regression Models to Predict the Hazard of the First Hematuria Diagnosis Since HIV Diagnosis

	Model 1				Model 2				Model 3				Model 4				Model 5				Model 6			
	Hazard Ratio		95%CI		Hazard Ratio		95%CI		Hazard Ratio		95%CI		Hazard Ratio		95%CI		Hazard Ratio		95%CI		Hazard Ratio		95%CI	
African American	0.757		0.500	1.146	0.723		0.473	1.105	0.756		0.453	1.262	0.730		0.482	1.105	0.747		0.494	1.131	0.795		0.500	1.265
Latino	0.887		0.490	1.608	0.854		0.464	1.573	0.897		0.441	1.826	0.833		0.459	1.512	0.882		0.486	1.600	0.994		0.518	1.907
Other Race	0.993		0.524	1.883	0.954		0.503	1.809	1.236		0.595	2.568	0.977		0.515	1.850	0.978		0.516	1.852	1.176		0.592	2.337
Active Duty	1.001		0.443	2.258	0.831		0.364	1.895	0.837		0.337	2.078	0.965		0.424	2.196	0.986		0.436	2.229	1.169		0.402	3.397
Officer	0.979		0.544	1.761	1.007		0.563	1.804	0.819		0.370	1.816	1.018		0.562	1.842	0.999		0.556	1.795	1.219		0.629	2.363
Age at HIV Positive	0.990		0.964	1.017	0.981		0.956	1.008	0.981		0.949	1.013	0.984		0.958	1.010	0.987		0.962	1.014	0.973		0.942	1.004
Smoke	0.877		0.567	1.359	0.821		0.525	1.285	0.903		0.534	1.527	0.904		0.583	1.401	0.882		0.570	1.366	0.703		0.419	1.181
BMI	0.991		0.945	1.039	1.002		0.956	1.050	1.019		0.962	1.079	1.002		0.956	1.050	0.990		0.944	1.039	1.019		0.967	1.074
Number of Urine Tests	1.084	***	1.053	1.117	1.104	***	1.072	1.138	1.098	***	1.060	1.137	1.080	***	1.049	1.112	1.077	***	1.045	1.110	1.098	***	1.060	1.137
CD4 Nadir	1.001		1.000	1.002																				
Protein					0.420	***	0.307	0.576																
WBC									1.026		0.855	1.232												
Urinary Tract Infection													2.071	*	1.126	3.807								
Hypertension																	1.200		0.782	1.841				
First ART Regimen: TDF																					0.555	*	0.338	0.913
LR Chi-square	26.62	**			54.94	***			24.66	***			28.62	**			24.7	**			28.6	**		
n	818				814				667				818				818				670			

*p<.05. **p<.01. ***p<.001.

Results (cont.)

- Our cohort was young (mean age of 29 years), with a plurality of African-Americans (46%), predominately active-duty (96%), with mean CD4 well over 200 cells/mm^3.
- Of 829 included participants, 142 (17.1%) had MH, of whom 87 (61.3%) had only one MH event.
- Cases had a shorter mean duration of study follow-up but more analyzable urinalyses per participant.
- There were no significant differences between cases and controls in demographics, CD4 count nadir, time from HIV diagnosis to HAART initiation, or inclusion of tenofovir disoproxil fumarate (TDF) in the initial regimen.
- On univariate analysis, more cases had a history of urinary tract infection (UTI) or a hypertension diagnosis through the time of incident MH compared to controls, but were less likely to have proteinuria or pyuria at the time of MH.
- Cox regression models revealed that a history of UTI was associated with increased hazard for MH (HR 2.07, $p < 0.05$).
- The presence of proteinuria (HR 0.42, $p< 0.01$) and TDF use (HR 0.56, $p< 0.05$) were associated with decreased hazard for MH compared to controls.
- Negative binomial regressions produced similar results.

Conclusions

- A history of UTI, though not concurrent pyuria, was associated with an increased hazard for MH.
- The use of TDF in the initial regimen and the presence of proteinuria were associated with a decreased risk for MH.
- Future studies are needed to clarify these findings; however, they provide reassurance that in a young, otherwise healthy cohort, MH is typically self-limited and unrelated to intrinsic renal pathology, comorbidity, or HIV-related factors.

Disclaimer / Funding Statement

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