

# Research Letter

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## Testosterone replacement therapy and polycythemia in HIV-infected patients

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**We conducted a case-control study to assess testosterone use as a primary risk factor for polycythemia in 21 HIV-infected men. Any testosterone use within two months of first elevated hemoglobin was associated with polycythemia (matched odds ratio 6.55; 95% CI 1.83–23.4; P = 0.004) and intramuscular administration demonstrated a stronger association than topical use. No adverse cardiovascular or thrombotic events were observed. HIV-infected patients taking testosterone should undergo routine hematologic monitoring with adjustment of therapy when appropriate.**

HIV can be complicated by hematologic abnormalities, most commonly anemia, thrombocytopenia and granulocytopenia [1,2]. Reporting of HIV-associated polycythemia is rare [3,4]. Case reports [1,2,5–7] and one series [3] raise the possibility of an association between HIV infection and myeloproliferative disorders. Notably, some patients described in the literature meet criteria for polycythemia vera [2,4,5]. Certain case reports demonstrate resolution of polycythemia with zidovudine [1,6,7] and one paradoxically reports zidovudine-induced polycythemia [8].

The association between testosterone-replacement therapy and polycythemia has been well described [9–11]. Intramuscular testosterone is associated with a higher risk for polycythemia than topical administration [9]. Smoking has also been associated with polycythemia and may contribute to the effects of other risk factors [3,9,12]. However, little is known about the mechanisms of polycythemia in HIV [3]. We conducted a case-control study to test the hypothesis that testosterone use is the primary risk factor for polycythemia in HIV-infected patients.

The Center for Special Studies at New York-Presbyterian Hospital-Weill Cornell Medical Center is a multidisciplinary clinic established in 1988 for the care of people living with HIV/AIDS. We retrospectively reviewed the clinic's electronic medical record (EMR) for patients with polycythemia from 1988–2008. Polycythemia was defined as a sustained ( $\geq 8$  weeks) hemoglobin value of  $\geq 18.5$  g/dl for men and  $\geq 16.5$  g/dl for women. [13]. Two controls per case were randomly

selected from the group of clinic patients matched on sex, age  $\pm 5$  years, date of initial clinic visit  $\pm 6$  months and duration of clinic follow-up equal to or greater than the case's follow-up at time of polycythemia diagnosis. Clinical and laboratory data were extracted onto standardized case report forms. The EMR was further reviewed for information on Hepatitis C co-infection, smoking history, zidovudine use, and testosterone-replacement therapy within 2 months of polycythemia diagnosis. Chart review was performed to identify adverse consequences of polycythemia, including cardiovascular or thrombotic events, and additional clinical conditions that may have contributed to elevated hemoglobin. Data were de-identified and entered into a customized Microsoft<sup>®</sup> Access 2007 Database and analyzed using Stata<sup>®</sup> version 11.0 (Stata Corporation, College Station, Texas, USA). We performed univariate and multivariate conditional logistic regression to identify risk factors for polycythemia. This study was approved by the Institutional Review Board of Weill Cornell Medical College.

Twenty-five patients met criteria for polycythemia (21 male; 4 female). Using the number of unique patients with  $\geq 5$  clinic visits during the time frame of the study as the denominator ( $n = 6007$ ), the estimated prevalence of polycythemia was 0.42% (95% CI 0.27–0.61). Mean hemoglobin at diagnosis of polycythemia was  $18.9 \pm 0.42$  g/dl in men and  $17.0 \pm 0.83$  g/dl in women. Among the four female cases, one was diagnosed with chronic obstructive pulmonary disease (COPD) and severe pulmonary hypertension while the other three did not have a documented explanation for elevated hemoglobin. Because of the relatively small number of female cases and primary hypothesis related to testosterone use, our case-control study focused on the 21 male patients.

The median year of diagnosis of polycythemia was 2005 (interquartile range 2002–2007). The mean age was  $45.7 \pm 8.0$  years in cases and  $46.0 \pm 8.2$  in controls. CD4 cell count and HIV RNA levels were similar among cases and controls (Table 1). Any testosterone use within two months of first elevated hemoglobin value was associated with polycythemia (matched odds ratio 6.55; 95% CI 1.83–23.4; P = 0.004). Testosterone was administered most commonly via the intramuscular route in cases and tended to be associated more strongly with polycythemia than was use of topical testosterone. There was a trend for an inverse association between current or recent zidovudine use and polycythemia. In multivariate analysis, any testosterone use (OR 7.65; 95% CI 1.99–

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**Table 1. Univariate Analysis of Factors Associated with Polycythemia in HIV-Infected Patients.**

	Cases (N = 21)	Controls (N = 42)	Matched Odds Ratio	95% CI	P-value
CD4 cell count (mean [SD]; mm <sup>3</sup> ) <sup>a</sup>	473 (248)	450 (237)	1.02	0.92–1.14	0.71
HIV RNA below level of quantification (%)	11 (52%)	25 (60%)	0.68	0.20–2.31	0.54
Log HIV RNA (mean [SD]; copies/ml) <sup>b</sup>	3.56 (0.90)	3.89 (1.06)	0.47	0.12–1.75	0.26
Hepatitis C co-infection (%)	6 (29%)	11 (26%)	1.13	0.34–3.70	0.84
Cigarette smoking <sup>c</sup>	10 (48%)	16 (38%)	1.48	0.51–4.30	0.47
Zidovudine use <sup>c</sup>	8 (38%)	8 (19%)	2.73	0.79–9.50	0.11
Any testosterone use <sup>c</sup>	14 (67%)	9 (21%)	6.55	1.83–23.4	0.004
Topical testosterone <sup>c</sup>	5 (24%)	3 (7%)	3.33	0.80–13.9	0.099
Intramuscular testosterone <sup>c</sup>	10 (48%)	6 (14%)	4.33	1.34–14.0	0.015

<sup>a</sup>Odds ratio is per 50 cells/mm<sup>3</sup>.

<sup>b</sup>Log HIV RNA was calculated only for subjects with measurable viremia (n = 10 cases and n = 17 controls).

<sup>c</sup>Within two months of first elevated hemoglobin in cases or equivalent time point in controls.

29.4; P = 0.003) and zidovudine (OR 3.57; 95% CI 0.86–14.8; P = 0.078) were independently associated with polycythemia, though only testosterone use demonstrated statistical significance.

Five of 21 (24%) cases did not use testosterone, but had other explanations for their polycythemia: pulmonary hypertension (1), COPD (2), and plasma volume contraction (2). In 2/21 cases (10%) there was no documented reason for elevated hemoglobin. No cases met criteria for polycythemia vera and no adverse cardiovascular or thrombotic events were noted among cases or controls.

To our knowledge, this study is the first systematic investigation of polycythemia in HIV-infected patients. In our analysis, testosterone use and smoking were associated with polycythemia. While other etiologies of polycythemia were identified, testosterone use was the leading explanation of elevated hemoglobin in our patients. Notably, 10% of cases did not have a documented explanation for polycythemia. We cannot comment on the role of HIV infection itself in these polycythemia cases given our study design. Furthermore, the lack of systematic data on testosterone levels in our study subjects precluded analysis of a potential relationship between hemoglobin and testosterone levels [9]. Although we did not observe any adverse clinical consequences attributable to polycythemia in our study, we cannot exclude the possibility that polycythemia is clinically important given our small sample size, limited duration of follow-up, and the predisposition of HIV-infected patients to atherosclerotic and thrombotic disease. Nonetheless, HIV-infected patients taking testosterone should undergo routine hematologic monitoring [9] and adjustment of testosterone dose or cessation of testosterone therapy as appropriate based on hemoglobin values. Patients with polycythemia should be queried about prescription or non-prescription use of testosterone.

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