**PREVALENCE OF AND RISK FACTORS FOR GOUT IN HIV-POSITIVE ADULTS: A CASE-CONTROL STUDY**

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**BACKGROUND**

Combination anti-retroviral therapy (ART) has transformed the prognosis of HIV infection and normalised life-expectancy. However, the consequence is a growing population of people living with HIV (PLWHIV) with a chronic long-term condition associated with co-morbidities related to the virus and/or its therapy. Amongst the most common comorbidities recognised are dyslipidaemias, hypertension, insulin resistance and diabetes mellitus, all of which are clinical features of the metabolic syndrome.[1] Hyperuricaemia is another recognised manifestation of the metabolic syndrome and is the principal risk factor for gout, the most prevalent inflammatory arthritis worldwide. Gout is a relapsing, remitting painful arthritis which causes substantial morbidity and impaired quality of life.[2,3] Amongst the general population, there is evidence that the prevalence of gout is increasing particularly among older men, aged > 65 years.[4]

There is limited data specifically on gout in PLWHIV. One study which utilised exploratory factor methods to investigate patterns of multimorbidity in PLWHIV included a diagnosis of gout as part of a ‘metabolic’ cluster pattern of disease and reported a point prevalence of 2% (95% CI 1.6-2.9%).[5] In addition, there have been a number of case reports published.[6-11] Observational studies that have estimated the prevalence of gout in their HIV-positive patients have reported rates ranging between 0.4% in Nigeria [12] to 1% among patients attending a tertiary referral centre in India.[13] One UK study investigating the risk of infectious diseases amongst people with gout found that 0.1% of people with gout in the Clinical Practice Research Datalink (a large representative primary care database) had co-existent HIV.[14] Some, but not all studies have implicated different anti-retroviral therapies, and, in two case reports, gout has been described as an ’immune reconstitution’ phenomenon, occurring in ART-naïve patients 4 weeks after onset of an ART regimen.[10,11]

Although there is a paucity of literature on gout and HIV, there is more information about serum urate and HIV, since uric acid excretion is frequently measured in people receiving ART at risk of proximal renal tubule dysfunction. Hyperuricaemia was first described in HIV by Medina-Rodriguez and colleagues in 1993, when they reported a prevalence rate of 41% among 74 HIV-positive cases, as compared with 0% among 72 matched controls.[15] Similar findings were reported by other colleagues.[16-18] Since the development of ART, hyperuricaemia has been reported with the nucleoside reverse transcriptase inhibitor didanosine, stavudine and the protease inhibitor, ritonavir.

Given the important relationship between serum urate and the metabolic syndrome, and population data suggesting that gout is becoming more common, the aim of this study was to explore the prevalence of and risk factors for gout in a large outpatient cohort of PLWHIV using a matched case-control study design.

**Methods**

Ethical permission for this study was granted by the Brighton Local Research Ethics Committee (REC number: 12/LO/1421).

This case-control study was performed 2012-2013. All subjects were registered for outpatient HIV care at one centre in the South of England, UK. All correspondence and test results for this cohort are digitised into a clinical database which is searchable. In total, the records of 2042 PLWHIV were available at the time of this study. We used the keywords: “gout”, “hyperuricaemia” and “uric acid”, to search the database for any subjects who might be eligible as cases for this study. In addition, one rheumatologist provided clinical care for all HIV-positive patients developing rheumatological symptoms at this Centre for the past 8 years. The clinical database of this rheumatologist was also interrogated for cases and used to validate the search technique. The full clinical case notes were extracted for any individual identified by the preliminary search strategy. People were confirmed as cases if there was evidence that they had been diagnosed from a convincing history and a clinical examination by either a primary or secondary care clinician. For each case, two controls were identified, selected from the HIV outpatient database using a random number generator method (once matched for gender and age (+/- 5 years)).

The HIV database and patient notes were reviewed for every case and control. Data were extracted onto a pre-defined proforma designed to collect information about: demography (age, gender, ethnicity, sexual orientation and occupation); lifestyle (smoking and alcohol); co-morbidities (hypertension, dyslipidaemias, diabetes mellitus, renal disease; medication relevant to gout (NSAIDS, colchicine, allopurinol, other gout treatment, loop diuretic, thiazide diuretic, low-dose salicylate, nicotinic acid, pyrazinamide, cyclosporine, ethambutol, vitamin B12, prednisolone); blood pressure and body mass index (BMI) and episodes of ‘arthritis’, ‘hot, swollen joint’ or confirmed gout episodes.

HIV-specific data was also collected including: duration since diagnosis; mode of transmission; World Health Organisation (WHO) clinical stage of HIV infection ever exposure to ART and type and duration of exposure to different classes of ART, and nadir and most recent CD4 count and viral load. In addition, the results of relevant blood tests were extracted, including: full blood count, urea and electrolytes, liver function tests, lipid profile, urine protein: creatinine ratio, uric acid (most recent values).

Basic summary statistics were used to describe differences in demographic characteristics, HIV factors, comorbidities, and relevant drug therapies between cases and controls. Comparisons were made using Fisher’s exact tests, given the sample size and that the values in some of the cells of the contingency tables were <5. The same approach was used to compare ART use among cases and controls. From the univariate analyses, we derived a multivariate conditional logistic regression model using forward logistic regression, keeping factors which were significantly associated with the risk of being a case (p<0.1), independently of other variables. Analyses were conducted with Stata statistical software (v. 14.0) (StataCorp LP, College Station, Texas, USA).

**Results**

In total, 45 HIV-positive patients were identified with a diagnosis of gout amongst the total cohort of 2042 registered on the database (estimated point prevalence 2.2%, 95% CI 1.6-2.9%). All of the cases identified were male. The mean age of cases was 56 years, 84% were white Caucasian and 9% black African. Their overall median duration of HIV infection was 160 months and all had acquired HIV through sexual contact (mostly men who have sex with men, ‘MSMs’). The majority, 41/45 (91%) were currently taking ART. Serum urate levels had been measured within the past 12 months for 26/45 (58%) cases and the average mean serum urate was 0.40mMol/L (reference range in our laboratory: 0.20-0.42mMol/L).

For each case, two age-matched controls were identified (Table 1). A comparison of the demographic and HIV factors of the selected controls with the main database population showed that they were a representative sample (data not shown). The face validity of our search strategy was explored by comparison of the 45 cases with the 90 controls for the following gout treatments: naproxen, diclofenac, colchicine and allopurinol. As expected, cases were highly significantly more likely to report use of each of these drugs when compared with controls and 18/45 (40%) of cases were currently taking allopurinol, as compared with no controls (p<0.001). Moreover, cases were more likely to have ever been exposed to loop diuretics (p=0.004) and to be currently taking thiazide diuretics (p=0.008) than controls. More of the cases had evidence of exposure to ethambutol and pyrazinamide but the numbers were small and did not attain statistical significance.

There were significantly more non-Caucasians among cases (6.6%) than among the controls (4.4%) (p=0.02). Cases were, on average, 10.5kg heavier than controls (88.0 vs 77.5kg, p<0.001) with more adiposity as defined by body mass index (p=0.006). The cases were more likely to have been diagnosed (p=0.002) and treated (p=0.002) for hypertension and we found that the most recent average systolic and diastolic blood pressure readings were 4 mmHg higher in the cases than controls but these differences were not statistically significant. Cases were also more likely to have ever been treated for hyper-triglyceridaemia (p=0.02) but there were no other differences in prevalence of diagnosis or treatment for dyslipidaemia, diabetes mellitus or renal disease between groups.

A comparison of the HIV status of cases and controls showed no significant differences between cases and controls for duration of HIV infection since diagnosis, latest viral load, detectable vs. not detectable viral activity, proportion of patients exposed or not exposed to ART, latest CD4+ or nadir CD4+.

A comparison of the ART use among cases and controls (Table 2) by drug class and individual drug suggested that, if anything, controls tended to be slightly more likely to have ever been exposed to NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) (p=0.056). We found no association with median duration of exposure to any class of ART and gout, nor was there any relationship between duration of exposure to each class and gout (data not shown). Exploring current ART, we demonstrated no associations between any individual drug and gout.

Variables associated with the risk of being a case in the univariate analyses were: ethnicity; body mass index; diagnosis of and treatment for hypertension; treatment for hyper-triglyceridaemia; and ever exposure to NNRTIs. After forward selection, we identified two factors which remained independently significantly associated with being a case: diagnosis of hypertension (OR 4.8, 95% CI 1.8-12.4) and ever exposure to NNRTI (OR 0.3, 95% CI 0.12-0.88).

Ideally, a diagnosis of gout requires observation of the classical needle-shaped crystals from an aspirate of synovial fluid but, as with other database studies, we were unable to verify the diagnostic criteria applied in each case by the primary or secondary care clinician who had recorded their condition. We cannot therefore rule out that some of the ‘controls’ matched for age within this study did in fact have undiagnosed prevalent gout, nor could we verify the diagnosis for the ‘cases’. To examine the size of any ensuing risk of bias, we compared the availability of a serum urate within the past 12 months and explored the face validity of our search strategy by comparing the exposures of cases and controls to drugs used most commonly for the treatment of gout. Only 1/90 controls had a serum urate within the past 12 months and the result was normal whilst 26/45 of the gout cases had a serum urate result available to us and the mean values were at the very upper end of the normal range (0.40 mMol/L), consistent with patients diagnosed and treated for gout. Moreover, a high proportion (40%) of the identified cases were current users of allopurinol (the most common treatment for gout in the UK) as compared with no controls, which again lends face validity to the search strategy.

**Discussion**

In this homogeneous cohort of >2000 PLWHIV (90% male, predominantly Caucasian MSMs), we estimated a point prevalence rate of 2.2% (95% CI 1.6-2.9%) of gout. The cases identified with gout were all male, were more likely to be non-Caucasian, were heavier with greater adiposity, and were more likely to have been diagnosed and treated for hypertension and hyper-triglyceridaemia. Indeed, a diagnosis of hypertension was independently associated with a more than four-fold increased risk of gout. Exposure to NNRTIs resulted in a 70% reduction in the risk of gout so that NNRTIs appeared to be protective in relation to gout.

The results of our study need to be considered alongside a number of limitations. Of the cohort eligible for this study, we found only 45 cases diagnosed with gout***,*** and given the multiple testing this relatively small cohort size does impact on the robustness of our findings***.*** It is possible that some patients diagnosed and treated for gout in primary care may not have been identified by a search of the secondary care database and therefore we may be under-estimating the true point prevalence in this population.

To our knowledge, this is the first case control study to explore the prevalence of and risk factors for gout in an HIV cohort. To maximise our power, we chose two age-matched controls for each case. Our power calculations showed that 45 cases and 90 controls matched 1:2 yielded 80% power to detect an odds ratio of 3.0 for an exposure occurring with 25% prevalence amongst controls. Therefore we acknowledge that we may still have been relatively under-powered to demonstrate significant associations with some of the individual ART drugs and combinations and indeed with some of the more traditional risk factors for gout. Among the general population, gout is associated with: male gender, age, obesity, hypertension, hyperlipidaemia, diabetes mellitus and cardiovascular disease. In this respect, our findings about diagnosis of hypertension and both weight and body mass index are consistent with what is expected and with the findings of Patel and colleagues in another HIV-positive cohort.[19]

Although it is difficult to compare our data with those of other population studies, it would appear that a prevalence rate of 2.2% for gout is in keeping with that found in the general population, especially in the context of a relatively large confidence interval for the current study. For example, a study from the USA on the prevalence of gout among people aged 50-64 years (i.e. older than those in the current study) between 1990-9 reported an age-related prevalence under 2.0%.[2] A study carried out in Germany and the UK reported a prevalence of 1.9%.[3] Where data are available, it appears that the prevalence of gout is increasing, particularly among older men aged > 65 years.[2] Gout is very painful and disabling and has marked negative impact on quality of life and has recently been associated with increased mortality.[20] For all these reasons, it is important to be proactive in its identification and treatment.

We found no convincing associations between gout and HIV-associated factors in the current study. A number of early HIV studies reported hyperuricaemia in association with advanced disease, AIDS and malignancies.[15,17] It has also been suggested that untreated HIV infection *per se* is a cause of hyperuricaemia but the data are conflicting and there are potentially a number of aetiological mechanisms including: increased cell turnover; mitochondrial toxicity; treatment of tuberculosis with pyrazinamide and/or ethambutol; and the increased risk of lymphoproliferative conditions. More data are needed but it is possible that the modern trend for earlier diagnosis and treatment of HIV may reduce the risk of gout in HIV-positive patients.

ART has been implicated as a risk factor for hyperuricaemia over many years. The first drug implicated was the purine analogue didanosine,[21] and this led to the suggestion that serum urate could be used as a marker of compliance with the drug.[22] In 2006, Walker and colleagues replicated the association with didanosine but also reported hyperuricaemia associated with stavudine and found that use of both drugs in combination resulted in significantly higher levels of urate when compared to either drug alone.[18] The same study also found an increased risk from zalcitabine and protease inhibitors but suggested a beneficial effect of tenofovir disoproxil fumarate on urate and no effect of abacavir. In this study, male gender and stavudine use were the strongest predictors of urate variability. Boosted protease inhibitor use has also been associated with gout in some studies.[9,16] However, these studies were somewhat confounded by having patients with other risk factors for gout, including patients taking pyrazinamide for TB and patients with lymphoproliferative disorders. It is difficult to directly compare the results of the current study with those reported above since: nobody in this cohort was taking didanosine or stavudine; most patients had well-controlled, uncomplicated disease and, although we considered exposure to pyrazinamide and ethambutol, too few patients were exposed to distinguish significant effects. It is possible that we found no effect of protease inhibitors because the study was under-powered or it may be that, if the cardio-metabolic side effects of these drugs are well-managed according to current guidance, the resultant benefits include a decrease in the risk of gout.

Our finding suggesting a protective effect of NNRTIs probably reflects that the patients at highest risk of cardiovascular disease as defined by blood pressure, lipid profiles and obesity are being preferentially treated with NNRTIs to decrease their cardiovascular risk and, as expected, since serum urate is a marker of the metabolic syndrome, the effect is to reduce urate and accordingly decrease the risk of gout. Interestingly Bagnis and colleagues also reported this effect.[16]

We note with interest that gout has been described as an immune reconstitution inflammatory syndrome (IRIS) in two case reports, occurring within one month of the commencement of an ART regimen in two patients, one starting: tenofovir disoproxil fumarate (TDF), emtricitabine and efavirenz [10] and the other starting lamivudine, TDF, atazanavir and ritonavir respectively.[11] Our study cannot provide any evidence about IRIS but, as far as is currently understood, gout is not an autoimmune disease in the same way as rheumatoid arthritis or multiple sclerosis. Furthermore, rapid cell turnover is a well-recognised risk factor for gout and hyperuricaemia, so much so that prophylactic treatment is administered to patients starting chemotherapy for a haematological malignancy or lymphoproliferative condition.

In conclusion, this case-control study explored the prevalence of and risk factors for gout in PLWHIV. We found a 2.2% prevalence of gout. As expected, co-existent hypertension is a major risk factor associated with a four-fold increased risk of gout but we found that NNRTIs were associated with a 70% reduction in the risk of gout. The cross-sectional nature of this case-control study precludes the suggestion of a cause-effect relationship, but our observations may highlight an area of interest for future research.

**Declaration of Conflicting Interests**

Professor Karen Walker-Bone has received honoraria for providing independent educational lectures and developing educational resources for HIV health professionals from Gilead Sciences and Janssen. Dr Duncan Churchillhas received honoraria, educational grants, travel scholarships and research grants from Gilead Sciences, Merck Sharp & Dohme, ViiV Healthcare, and Janssen.

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**Table 1: Comparison of demographic characteristics, HIV factors, comorbidities and relevant drug therapies among 45 HIV-positive cases with a diagnosis of gout as compared with 90 age-matched controls**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | **Cases** | **Controls** | **p-value** |
| **(n=45)** | **(n=90)** |
| Mean age (SD)(years) |  | 56.1 (8.7) | 55.9 (8.3) | 0.87 |
| Ethnicity, No (%) | Caucasian | 38 (84.4) | 86 (95.6) | 0.02 |
|  | Black African | 4 (8.9) | 4 (4.4) |
|  | Other | 3 (6.7) | 0 |
| Mean height (SD) (cm) |  | 173.2 (7.9) | 175.7 (6.3) | 0.121 |
| Mean weight (SD) (kg) |  | 88.0 (20.8) | 77.5 (13.6) | <0.001 |
| Mean BMI (SD) (kg/m2) |  | 28.5 (4.0) | 25.3 (4.4) | 0.003 |
| Mean systolic BP (mmHg) |  | 131.6 (19.1) | 127.3 (16.4) | 0.18 |
| Mean diastolic BP (mmHg) |  | 83.3 (12.9) | 79.8 (10.1) | 0.09 |
|  |  |  |  |  |
| Smoking status | Never smoked | 17 (38.6) | 31 (34.8) | 0.84 |
| In the past and stopped | 12 (27.3) | 23 (25.8) |
| Current | 15 (34.1) | 35 (39.3) |
| Alcohol intake | Never | 6 (15.4) | 16 (19.8) | 0.78 |
| <15 units/week | 18 (46.2) | 33 (40.7) |
| >15 but < 25 units/week | 7 (18.0) | 11 (13.6) |
| >25 units/week | 8 (20.5) | 21 (25.9) |
| Past history of alcohol intake >15 units/week |  | 8 (18.2) | 15 (16.7) | 0.83 |
| **HIV Factors** | | | | |
| Median duration HIV infection (IQR) (months) |  | 160 (108-230) | 155.5 (126-233) | 0.79 |
| Mode of acquisition HIV infection | MSM | 39 (87.7) | 79 (87.8) | 0.85 |
| Heterosexual | 6 (13.3) | 10 (11.1) |
| Unknown | 0 | 1 (1.1) |
| Stage of HIV Infection | Stage 1 | 8 (17.8) | 29 (32.2) | 0.11 |
| Stage II | 17 (37.8) | 27 (30.0) |
| Stage III | 17 (37.8) | 33 (36.7) |
| Stage IV | 2 (4.4) | 0 |
| Stage V | 1 (2.2) | 1 (1.1) |
| Most recent viral load detectable | No (%) | 8 (17.8) | 9 (10.0) | 0.20 |
| Naïve to anti-retroviral therapy |  | 6 (13.3) | 13 (14.4) | 0.86 |
| **Comorbidities** | | | | |
| Diagnosed with hypertension | Ever | 24 (53.3) | 24 (26.7) | 0.002 |
| Prescribed therapy for hypertension | Ever | 23 (51.1) | 22 (24.4) | 0.002 |
| Elevated triglycerides | Ever | 39 (86.7) | 70 (78.7) | 0.26 |
| Prescribed therapy for hypertriglyceridemia | Ever | 6 (13.3) | 2 (2.3) | 0.02 |
| Prescribed lipid lowering therapy | Ever | 18 (40.0) | 32 (36.4) | 0.68 |
| Proteinuria (protein:creatinine ratio of >30 mg/mmol) | Ever | 12 (28.6) | 26 (28.9) | 0.97 |
| Constant proteinuria (protein:creatinine ratio of >30 mg/mmol) |  | 4 (9.3) | 4 (4.4) | 0.27 |
| Constantly elevated creatinine (>106 micromol/L) |  | 2 (4.8) | 6 (6.7) | 0.99 |
| Constantly impaired eGFR (<60mL/min) |  | 5 (11.9) | 6 (6.7) | 0.31 |
| Diagnosis of impaired glucose tolerance or type I or type II diabetes | Ever | 9 (20.0) | 11 (12.2) | 0.23 |
| Co-infected with hepatitis B or C | Ever | 3 (6.7) | 9 (10.0) | 0.75 |

**Table 2: Comparison of ever and current exposure to cART by class and drug among 45 cases diagnosed with gout and 90 age-matched controls**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Cases** | **Controls** | **p-value** |
| **(n=45)** | **(n=90)** |
|  |  |  |  |
| Ever exposed to a PI | 31 (68.9) | 58 (64.4) | 0.61 |
| Ever exposed to an NRTI | 42 (93.3) | 88 (97.8) | 0.20 |
| Ever exposed to an NNRTI | 33 (73.3) | 78 (86.7) | 0.056 |
|  |  |  |  |
| Median total duration PI exposure (years) (IQR) | 3370 (916-5967) | 3469 (1980-6403) | 0.43 |
| Median total duration NRTI exposure (years) (IQR) | 4105 (1249-6967) | 3959 (2124-6954) | 0.57 |
| Median total duration NNRTI exposure (years)(IQR) | 1815 (962-3108) | 2132 (646-3830) | 0.98 |
|  |  |  |  |
| Longest duration of exposure to PIs (>12.7 years) versus never exposed to PIs | 10 (32.3) | 20 (34.5) | 0.75 |
| Longest duration of exposure to NRTI (> 15.4 years) versus never exposed to NRTIs | 14 (33.3) | 29 (33.0 | 0.87 |
| Longest duration of exposure to NNRTIs (> 8.3 years) versus never exposed to NNRTIs | 9 (27.3) | 28 (35.9) | 0.40 |
|  |  |  |  |
| Current cART regimen includes: |  |  |  |
| Abacavir | 4 (8.9) | 4 (4.5) | 0.44 |
| Atazanavir | 2 (4.4) | 2 (2.3) | 0.60 |
| Darunavir | 20 (44.4) | 38 (42.7) | 0.85 |
| Efavirenz | 7 (15.6) | 25 (28.1) | 0.11 |
| Emtricitabine | 23 (51.1) | 57 (64.0) | 0.15 |
| Etravirine | 5 (11.1) | 9 (10.1) | 0.86 |
| Lamivudine | 6 (13.3) | 6 (6.7) | 0.21 |
| Lopinavir | 1 (2.2) | 1 (1.1) | 0.99 |
| Maraviroc | 0 | 2 (2.3) | 0.55 |
| Nevirapine | 5 (11.1) | 10 (11.2) | 0.98 |
| Raltegravir | 6 (13.3) | 5 (5.6) | 0.12 |
| Ritonavir | 24 (53.3) | 42 (47.2) | 0.50 |
| Tenofovir | 24 (53.3) | 59 (66.3) | 0.15 |
| Zidovudine | 2 (4.4) | 3 (3.4) | 0.99 |
| Stribild | 2 (4.4) | 0 | 0.11 |
| PI | 25 (55.6) | 42 (46.7) | 0.33 |
| NRTI | 31 (68.9) | 68 (75.6) | 0.41 |
| NNRTI | 17 (37.8) | 44 (48.9) | 0.22 |