# Increased prevalence and severity of radiographic hand osteoarthritis in patients with HIV-1 infection associated with metabolic syndrome: data from the cross-sectional METAFIB-OA study

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**Increased prevalence and severity of radiographic hand osteoarthritis in HIV-1-infected patients associated with metabolic syndrome: data from the cross-sectional METAFIB-OA study**

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**Abstract**

**Objective** To determine radiographic hand OA (HOA) prevalence in HIV-1–infected patients in comparison with the general population and to address whether MetS may increase the risk of HOA during HIV-1 infection.

**Patients.** HIV-1-infected patients with MetS (IDF criteria) aged 45-65 years were matched by age and gender to HIV-1-infected subjects without MetS and underwent hand radiographs. Framingham OA cohort was used as general population cohort.

**Methods.** Radiographic HOA was defined as Kellgren-Lawrence score (KL) ≥ 2 on more than 1 joint. Radiographic severity was assessed by global KL score and number of OA joints. HOA prevalence was compared to that found in the Framingham study, stratified by age and sex. Logistic and linear regression models were used to determine risk factors of HOA in HIV-1-infected patients.

**Results.** 301 patients (88% male, mean age 53.4±5.0 years), were included, 152 with MetS and 149 without it. Overall HOA prevalence was 55.6% and was higher for those with MetS than those without it (64.7% vs 46.3%, p=0.002). When considering men within each age group, HOA frequency was greater in HIV-1-infected patients than the general population (all ages: 55.8% vs 38.7%; p<0.0001), due to the subgroup with MetS (64.9%; p<0.0001), as well as the subgroup without MetS, although not significantly (46.6%; p=0.09).

Risk of HOA was increased with MetS (odds ratio [OR] 2.23, 95% confidence interval [95%CI] 1.26-3.96) and age (OR 1.18, 95%CI 1.12-1.25). HOA severity was greater for patients with MetS than those without. HOA was not associated with previous or current exposure to protease inhibitors or HIV infection-related markers.

**Conclusions** HOA frequency is greater in HIV-1-infected patients, especially those with MetS, than the general population.

**NCT02353767**

Human immunodeficiency virus (HIV)-associated mortality is greatly reduced because of the widespread use of efficient antiretroviral therapy (1). Consequently, in the United States and Europe, HIV-1–infected patients older than 50 years represent more than 50% of the follow-up population (2-4). Likewise, age-related health problems such as cardiovascular diseases have been increasing with increasing age in patients with HIV because of chronic inflammation, immune activation and immunosenescence, and lifelong antiretroviral therapy (5-7). These comorbidities, called non–AIDS-related comorbidities, are more prevalent in HIV-infected patients than people of the same age without HIV, which suggests an extra "hit" of aging related to HIV-1 infection and/or antiretroviral therapy, which can lead to geriatric syndromes with impairment and frailty (8-11).

Osteoarthritis (OA) is the most common rheumatologic disease due to aging, affecting about 6 million people with hip and/or knee OA in France(12) and 27 million in the United States (13). The disease has never been studied in the setting of HIV comorbidities. Among all localizations, hand OA (HOA) is associated with pain, disability and deteriorated quality of life to the same extent as rheumatoid arthritis (14-16). However, to what extent HIV-1–positive patients have OA and HOA is unknown.

OA is a heterogeneous group of diseases that can be differentiated by the risk factors (*i.e.*, aging, obesity, trauma). Each factor has specific pathophysiological pathways, all leading to joint destruction (17, 18). Obesity-associated OA is one of the most-studied phenotypes characterized by the association of obesity or overweight with OA on weight-bearing joints due to mechanical overload (19). However, recently, the demonstration of an association between obesity and HOA has shed light on a potential role of systemic metabolic disturbances in the pathophysiology of OA (20). Indeed, several studies have raised the possibility of an association of metabolic syndrome (MetS) and OA, but which did not persist after adjustment on body mass index or weight in some of them (21-23). In addition to accelerated aging, HIV-infected patients frequently have MetS because HIV infection, *via* chronic inflammation and immune activation, which contributes to dyslipidemia and insulin resistance (24). Moreover, antiretroviral therapy, especially protease inhibitors, can induce a lipodystrophic syndrome characterized by altered body fat composition, dyslipidemia and insulin resistance (25) and subsequent MetS development (26).

Considering the increased life expectancy, accentuated aging and high prevalence of MetS in HIV-infected patients, we hypothesized that HOA could represent a novel HIV-associated non–AIDS-related comorbidity. Likewise, we aimed to determine whether MetS might be associated with risk of radiographic HOA in HIV-infected patients and whether the prevalence of HOA in HIV-infected patients is greater than in the general population.

## Methods

### Patients

The present study, called METAFIB-OA, is an ancillary study of the Metabolic Syndrome and Fibrosis (METAFIB) study (NCT02353767). METAFIB is a cross-sectional single-center study that recruited 458 HIV-infected patients >18 years old from January 2011 to December 2012 from outpatient clinics. HIV-positive status for at least 5 years was confirmed by western blot analysis or ELISA in patients without chronic viral hepatitis co-infection to investigate the impact of MetS on liver fibrosis. All patients were HIV-1–positive and were separated in 2 subgroups, with (HIV-1+MetS+) and without MetS (HIV-1+MetS-). MetS was defined by the International Diabetes Federation (IDF) criteria (**Supplementary file Table 1**) (27). Patients with MetS+ were matched to those without MetS+ by sex and age (± 5 years), with a ratio of 1:1.

For all patients, metabolic and HIV-1 infection clinical characteristics were recorded at the time of participation to METAFIB-OA cross-sectional study. A fasting blood sample was obtained from all subjects for assessing blood cell count, CD4+ and CD8+ T-cell count, ultra-sensitive HIV-1 viral (usHIV-1) load, lipid levels, glycemia, and insulinemia for homeostasis model assessment insulin resistance (HOMA-IR) calculation by the standard procedure of the hospital. The lowest count (nadir) for the CD4+ and CD8+ T cells was extracted from medical files for patients.

Between September 2011 and April 2012, all patients between 45 and 64 years from the METAFIB were contacted for the ancillary METAFIB-OA study. Exclusion criteria were pregnancy, inflammatory rheumatic disease or Dupuytren's disease. To compare the prevalence of HOA between METAFIB-OA patients and the general population, we used data for the Framingham cohort, a population-based cohort consisting of the Offspring and the Community cohorts, in which HOA prevalence had been previously examined(28, 29).

The study was approved by the Institutional Review Board (Comité de Protection des Personnes, Paris Ile de France V, Paris). All patients gave informed consent.

## Radiographic definition of HOA and severity

For METAFIB-OA study (i.e., between September 2011 and April 2012), all patients underwent bilateral postero-anterior hand radiography at 100% at APHP Saint-Antoine Hospital, and two trained assessors (A-LT and CR-J) scored an equal number of radiographs. The readers were blinded to clinical data and subgroup (MetS+ or MetS-). Hand radiographs were graded by the Kellgren–Lawrence grading scale (KL)(30), which assesses the distal interphalangeal (DIP), proximal interphalangeal (PIP), interphalangeal thumb (IP-1), metacarpal (MCP) and first carpometacarpal (CMC-1) joints with a grading system from 0 to 4 (0, no OA; 1, doubtful OA; 2, definite minimal OA; 3, moderate OA; 4, severe OA). Any patient with at least 1 finger joint scored at KL grade ≥ 2 was considered to have radiographic HOA. Thumb-base OA was also considered separately as unilateral or bilateral with KL score ≥ 2 on 1 or 2 CMC-1 joints (31) because it is more likely related to loading than the other three joints (DIP, PIP, or MCP) (32-35).

Radiographic severity was assessed by 1) the global KL score (sum of the scores for all joints; range 0-128), 2) number of OA joints (KL ≥2; range 1-32), 3) number of patients with erosive HOA according to the Verbruggen-Veys anatomical phase score (VV), consisting of five phases with a numerical value representing the evolution of HOA (N, normal joint; S, stationary OA with osteophytes and joint-space narrowing; J, complete loss of joint space in the whole or part of the joint; E, subchondral erosion; R, remodeling of subchondral plate) (36). The DIP, PIP, IP-1 and MCP joints were assessed. Erosive HOA diagnosis was based by the presence of at least 1 erosive joint on bilateral HOA radiographs (E or R phase).

Before this scoring, both readers (A-LT and CR-J) underwent a training session to assess the inter- and intra-observer reproducibility with 20 hand radiographs from routine practice. Reproducibility between the readers was estimated first by the Cohen kappa coefficient for inter-reader concordance and then by the intraclass correlation coefficient (ICC) for intra-reader concordance. For the total KL scale, the scores were 0.64 (95%

confidence interval [95% CI] 0.61-0.67) and 0.95 (95% CI 0.80-0.98), respectively. For the VV score, the ICCs were 0.9 (95% CI 0.91-0.99) and 0.98 (95% CI 0.91-0.99), respectively.

**HOA symptoms**

Patients from METAFIB who participated to the ancillary METAFIB-OA study completed a brief standardized questionnaire at the time of radiography about their dominant hand, menopausal status for women, and history of psoriasis. For joint pain assessment, the following binary question was asked: "On most days, do you have any pain, aching or stiffness in any of your joints?"

**Biomarker assessment**

A blood sample was performed at the time of the inclusion in the main METAFIB study, so some months before METAFIB-OA. High-sensitivity C-reactive protein (hsCRP) was measured by nephelometry on an IMMAGE analyzer (Beckman-Coulter, Villepinte, France). We measured plasma levels of high-sensitive interleukin 6 (IL-6) level, reflecting global inflammation and aging, soluble CD14 (sCD14) and soluble CD163 (sCD163) (Quantikine ELISA Kit, R&D Systems, Oxford, UK), 2 markers of monocyte/macrophage activation involved in HIV-related chronic immune activation(37), and leptin (Quantikine; R&D Systems, Oxford, UK) and total adiponectin (ALPCO, EUROBIO, Les Ulis, France), 2 adipokines involved in MetS (38, 39) and OA (40).

**Statistical analysis**

Descriptive data are presented as mean ± SD, median (interquartile range [IQR]) or number (%). HIV+MetS+ and HIV+MetS- patients and subjects with and without HOA were compared by chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables.

We compared HOA prevalence from the METAFIB-OA with the community-based cohort from the Framingham study that estimated HOA prevalence by a slightly modified version of the KL scale (*i.e.*, HOA diagnosis with ≥ 1 joint radiographic OA by a modified KL scale) by chi-square test by gender and age group.

To determine the factors associated with HOA or thumb-base OA, we calculated crude odds ratios (ORs) with 95% confidence intervals (CIs) by univariate modeling in the entire population. We explored variables related to demographic characteristics, HIV-1 infection features and metabolic disturbances. Variables associated with HOA diagnosis on univariate analysis with $p < 0.2$ were entered in a backward stepwise multivariate conditional logistic regression model. Multivariate linear regression was used to determine factors associated with structural radiographic severity, as defined above (3 definitions). MetS was entered in the logistic model along with other variables and kept in the final model, whatever the level of significance. Results are presented as β regression coefficients. All measurements were log-transformed to remove positive skewness and were compared between patients with and without HOA by the Wilcoxon rank-sum test. Univariate and multivariate analyses with a logistic model were adjusted for MetS. All analyses involved use of STATA v12.1 (StataCorp, College Station, TX, USA) and $p <0.05$ was considered statistically significant.

## Results

### Population characteristics

The main METAFIB study included 222 HIV1+MetS+ and 222 HIV1+MetS- subjects; 173 patients with MetS+ and 166 without MetS- 45 to 64 years old were screened for the METAFIB-OA study (**Figure 1**). Characteristics of the study population are in **Table 1**, with stratification by MetS status. The 2 groups did not differ except for all MetS characteristics (p<0.0001), as expected. HOA symptoms were reported by 27% of the population.

### HOA prevalence and structural severity in the METAFIB-OA group

Radiographic HOA prevalence and severity are stratified by gender in **Table 2.** Overall radiographic HOA was significantly more frequent in patients with MetS than those without it (64.5% vs 46.3%; p=0.002). Stratification by gender yielded similar results (64.9% in male with MetS vs 46.5% in male without MetS, p=0.002 and 61.1% in female with MetS vs 44.4% in without MetS, p=0.002). The same difference was observed for thumb-base OA.

Radiographic structural severity based on KL total score and number of OA joints was significantly more pronounced in MetS+ patients than those without it (p=0.002). Few cases of erosive HOA were observed in MetS+ subgroup (n=5, 3.3%) as well as in MetS- subgroup (n=2, 1.3%), with no significant difference between them.

### Comparison of METAFIB-OA group with aged-matched general population from the Framingham cohort

For patients 45 to 64 years old, mean HOA prevalence was greater in the METAFIB group than the Framingham population (55.5% vs 39.3%, p<0.0001) (**Table 3**). This difference was mainly due to MetS+ patients in the METAFIB-OA cohort (64.5% in HIV+MetS+ vs 39.3% in Framingham, p<0.0001, for all ages), but there was also a numeric difference of HOA prevalence between Framingham cohort and HIV+MetS- patients (for all ages: 46.3% in HIV+MetS- vs 39.3% in Framingham p=0.09).

Considering the differences in sex ratios between the 2 cohorts and the impact of aging on OA development, we compared HOA prevalence stratified on sex and age. The prevalence of HOA was significantly higher for men in the METAFIB cohort than men in the Framingham study within each age group. Furthermore, a comparison of age-matched men from the Framingham and the METAFIB cohort by presence and absence of MetS showed that this difference was due to a higher prevalence of HOA in the METAFIB cases (for all ages: 64.9%) than in Framingham subjects (38.7%; p<0.0001). However, we also found greater prevalence of HOA in METAFIB male controls than men from the Framingham study, although not significantly (for all ages, 46.6%, vs 38.7%; p=0.09).

The METAFIB cohort contained few females (n=36, but prevalence of HOA was greater for the METAFIB women than Framingham women, although not significantly (**Table 3**). Conversely, unilateral or bilateral thumb-base OA frequency did not differ between the METAFIB group and Framingham cohort (data not shown).

**Determinants of HOA**

In univariate analysis, age, CD4 T-cell count, detectable hsHIV-1 viral load, HOMA-IR, triglycerides level and presence of MetS were associated with HOA (**Table 4**).

In multivariate analysis, only presence of MetS (adjusted OR=2.23, 95% CI 1.26-3.96; p=0.002) and age (adjusted OR per year=1.18, 95% CI 1.12-1.25; p=0.00001) remained independently associated with HOA (**see Figure 1 in the supplement).** These 2 factors were associated with HOA severity **(See Table 2 in the supplement**).

Considering each metabolic component separately, only insulin resistance assessed by HOMA-IR and triglycerides level were associated but not significantly with HOA on univariate analysis (p=0.06 and p=0.07, respectively) but not after adjustment (**Table 4**).

For thumb-base OA, only age remained significantly associated with HOA (OR=1.10, 95% CI (1.04-1.17); p=0.001), with a nonsignificant association with MetS (OR=1.86, 95% CI 0.98-3.45; p=0.06) (**See Table 3 in the supplement**).

Of note, HOA diagnosis and severity were not associated with HIV-1 infection characteristics or HIV infection-related markers (Table 4, Supplementary tables 2 and 3).

**Association between biological markers and HOA**

To further elucidate the mechanism, MetS or HIV-related characteristics, that may favor HOA, we tested a set of metabolic or HIV-related biomarkers. Plasma sCD14 level was significantly higher in patients with than without HOA (2203.8 vs 2010.8 pg/mL; p=0.02) (**See Table 4 in the supplement**). This finding was corroborated by univariate analysis finding log(sCD14) level associated with HOA in the whole study population (OR=4.9, 95% CI 1.1-21.6; p=0.03). However, after adjustment for MetS, this association became nonsignificant (OR=3.9, 95% CI 0.9-17.2; p=0.07). Plasma levels of adipokines, hsCRP and sCD163 did not differ by HOA diagnosis.

## Discussion

In this study, radiographic HOA prevalence was determined for the first time in HIV-infected patients and found to be higher than in the general population from the Framingham cohort. This frequency was further increased in HIV-infected patients with MetS. Age and MetS were associated with HOA during HIV-1 infection. Furthermore, these 2 factors were also associated with HOA radiographic severity.

Several diseases such as atherosclerosis complications and cancer have emerged as key points in the global therapeutic management of HIV-infected patients. Surprisingly, although OA represents the most common age-related joint disease and with the growing interest in the role of systemic cardiometabolic disturbances in OA pathophysiology, only one preliminary study showed that in 35 HIV-infected men, total body and android fat mass were inversely related to knee cartilage volume measured by MRI (41). Here, taking advantage of the unique METAFIB study including HIV-1–infected patients with or without MetS, we observed a higher prevalence of radiographic HOA in HIV-infected patients as compared with the Framingham cohort, representing the general population. Differences between the 2 cohorts were obvious in men, but the small sample of women limits the power of the statistical analysis. In men, although the prevalence of HOA increased with age in both cohorts, HOA occurred more frequently in HIV-1-infected patients, especially those with MetS. Interestingly, men from the METAFIB cohort without MetS showed a higher prevalence of HOA, although not significantly, than men from the Framingham cohort in each age group. Such a result emphasizes the effect of aging during HIV infection beyond that of MetS.

Several studies have suggested an association between obesity and HOA (20). With obesity, the conditions hypertension, dyslipidemia, and glucose intolerance alone or together could increase the risk of OA. In the Rotterdam cohort (42), prevalence of HOA was higher in overweight patients with hypertension and diabetes than patients with only overweight. Here, the model of HIV-1 infection further supports the "metabolic" OA phenotype because the prevalence of HOA was greater in patients with than without MetS (17-19). Of note, obesity was not associated with HOA diagnosis in the METAFIB-OA study: such a result agrees with those from the population-based Netherlands Epidemiology of Obesity cohort, finding HOA linked more to metabolic systemic factors than weight itself (22). Radiographic severity was more severe in patients with MetS, so MetS is a risk factor and also an aggravating factor of radiographic HOA during HIV infection. Radiographic HOA could progress quickly in these patients because radiographic severity is associated with radiographic progression (43).

The association between HIV and HOA complicated by MetS and aging emphasizes the involvement of systemic metabolic inflammatory mediators. Interestingly, plasma sCD14 level was associated with HOA but less so after adjustment for MetS, which suggests that sCD14 and thus macrophage activation induced by MetS could be a link between MetS and HOA and its severity. Of note, plasma sCD14 level is associated with symptoms and radiographic progression in knee OA, and synovial fluid sCD14 level is associated with activated macrophages infiltrating knee synovium (44). HOA in patients with MetS may have increased synovial inflammation, as is found in patients with knee OA and type 2 diabetes (45).

Separate analyses of thumb-base OA showed that this localization was not more prevalent in HIV patients than the general population. Such a result was expected because mechanical factors and the morphology of the trapezo-metacarpal joint are crucial for this localization. However, thumb-base OA was more prevalent in HIV patients with than without MetS. So, metabolic disturbances may represent an additional risk factor, focal mechanical injury being a precipitating event (46, 47).

This study has several limitations. First, hand radiography was performed 1 year after assessment of MetS and serum samples taken for examining exploratory markers. However, OA progression is a very slow process, so this bias may have minimal effect on our findings. Second, the Framingham study used the modified version of the KL scoring system, with HOA definition based on the presence of osteophytes and/or definite joint-space narrowing(29), whereas the original KL scale, used in METAFIB-OA, defined HOA exclusively by presence of osteophytes. Furthermore, in the Framingham study, the evaluation of OA in the thumb base included assessment of both the CMC-1 and triscaphoid joints, whereas only the CMC-1 joints were assessed in METAFIB-OA. Hence, the scoring system of the Framingham study would classify more joints with definite OA. Consequently, the differences between the 2 cohorts may have been underestimated. Finally, only 25% of patients reported hand pain. However, this frequency agrees with data from other cohorts and OA pain may fluctuate through time (14, 29). Third, to compare HOA between the French METAFIB-OA group and the general population, we have used the Framingham cohort although characteristics of general population in United States and France are certainly different. However, no HOA assessment in a population-based cohort is available in France until now.

In conclusion, HIV-1 infection represents a special setting in which the risk of radiographic HOA and its severity is increased, due to accelerated aging and MetS. Beyond classical OA phenotypes, the “HIV-related OA” subtype could be thus individualized.

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**Conflicts of interest**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: all authors had financial support from BMS for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.



All co-authors had full access to all of the data (including statistical reports and tables) in the study and take the responsibility for the integrity of the data and the accuracy of the data analysis.

## Authorship

All authors fulfill the 4 following criteria:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Table 1. Baseline characteristics of the METAFIB-OA cohort**

| | **Total (n=301)** | HIV-1+ MetS+ (n=152) | HIV-1+ MetS- (n=149) | P value |
|---|---|---|---|---|
| **Demographic features** | | | | |
| Male gender, n (%) | 265 (88.0) | 134 (88.2) | 131 (87.9) | 0.9 |
| Age (years), mean (SD) | 53.4 (5.0) | 53.5 (4.9) | 53.4 (5.1) | 0.7 |
| Post-menopausal status (n=37) n (%) | 26 (70.3) | 14 (77.8) | 12 (63.2) | 0.5 |
| Predominant side, n (%) | | | | |
| Right-handed | 250 (83.1) | 133 (87.5) | 117 (78.5) | |
| Left-handed | 32 (10.6) | 13 (8.6) | 19 (12.8) | |
| Mixed | 19 (6.3) | 6 (3.9) | 13 (8.7) | 0.1 |
| **Hand OA features** | | | | |
| Hand trauma history, n (%) | 62 (20.6) | 26 (%) | 36 (%) | 0.2 |
| Psoriasis, n (%) | 13 (4.3) | 4 (2.6) | 9 (6.0) | 0.2 |
| Pain, n (%) | 80 (26.6) | 42 (27.6) | 38 (25.5) | 0.7 |
| **HIV features** | | | | |
| Duration of HIV infection (years), mean (SD) | 17.7 (7.3) | 17.0 (7.1) | 18.3 (7.5) | 0.2 |
| CDC-C stage, n (%) | 81 (26.9) | 43 (28.3) | 38 (25.5) | 0.8 |
| CD4 level (/mm$^3$), mean (SD) | 623 (265) | 625 (257) | 621 (274) | 0.9 |
| CD4/CD8 ratio, mean (SD) | 0.87 (0.37) | 0.86 (0.4) | 0.87 (0.3) | 0.4 |
| Undetectable usHIV viral load, n (%) | 240 (79.7) | 82 (53.9) | 90 (60.8) | 0.2 |
| Duration of exposure to protease inhibitors (months), mean (SD) | 47.7 (29.2) | 26.9 (31.1) | 27.4 (33.6) | 0.8 |
| **Metabolic syndrome components** | | | | |
| Waist circumference (cm), mean (SD) | 92.2 (10.8) | 98.2 (10.1) | 86.3 (8.1) | <0.0001 |
| BMI (kg/m2), mean (SD) | 24.9 (5.8) | 26.4 (4.8) | 23.3 (6.3) | <0.0001 |
| Obesity (BMI≥30), n (%) | 32 (10.6) | 26 (17.1) | 6 (4.0) | <0.0001 |
| Hypertension, n (%) | 56 (18.6) | 40 (26.3) | 16 (10.7) | <0.0001 |
| Triglycerides (mmol/l), mean (SD) | 1.95 (1.9) | 2.47 (1.7) | 1.42 (2.0) | <0.0001 |
| HDL-cho (mmol/l), mean (SD) | 1.21 (0.4) | 1.05 (0.3) | 1.36 (0.4) | <0.0001 |
| LDL-cho (mmol/l), mean (SD) | 2.9 (0.9) | 3.1 (0.8) | 2.8 (0.9) | 0.0003 |
| Glycemia (mmol/L), mean (SD) | 5.45 (1.08) | 5.85 (1.3) | 5.05 (0.64) | <0.0001 |
| HOMA-IR score, mean (SD) | 2.42 (2.79) | 3.51 (3.50) | 1.31 (0.92) | <0.0001 |
| Type 2 diabetes, n (%) | 65 (21.6) | 57 (37.5) | 8 (5.4) | <0.0001 |

Data are number (%) or mean (SD) for the total population, and number (%) and median (interquartile range [IQR]) for cases and controls.
Hypertension was defined as systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg. Diabetes was defined as glycemia >6 mmol/L. OA: osteoarthritis, MetS: metabolic syndrome, usHIV: ultra-sensitive HIV, CDC: Centers for Disease Control and Prevention, BMI: body mass index; HDL: high-density lipoprotein; LDL: low-density lipoprotein, cho: cholesterol, HOMA-IR score: Homeostasis Model Assessment of Insulin Resistance, MetS+: presence of metabolic syndrome, MetS-: absence of metabolic syndrome.

**Table 2. Radiographic hand OA and severity in the whole METAFIB-OA cohort and in cases and controls**

| | **Total (n=301)** | **HIV-1+ MetS+ (n=152)** | **HIV-1+ MetS- (n=149)** | **p** value |
|---|---|---|---|---|
| **OA** | | | | |
| **HAND OA ≥1 joint KL ≥2** | | | | |
| Men | 148 (49.2) | 87 (57.2) | 61 (40.9) | |
| Women | 19 (6.3) | 11 (7.2) | 8 (5.3) | |
| Total cohort | 167 (55.5) | 98 () | 69 (46.3) | **0.002** |
| **Thumb-base OA** | | | | |
| KL ≥2 on 1 or 2 sides | | | | |
| Men | 55 (18.3) | 37 (24.3) | 18 (12.1) | |
| Women | 6 (2.0) | 3 (2.0) | 3 (2.0) | |
| Total cohort | 61 (20.3) | 40 (26.1) | 21 (14.1) | **0.01** |
| **Erosive OA** | | | | |
| Men | 7 (2.3) | 5 (3.3) | 2 (1.3) | |
| Women | 0 | 0 | 0 | |
| Total cohort | 7 (2.3) | 5 (3.3) | 2(1.3) | 0.5 |
| **SEVERITY CRITERIA** | | | | |
| Sum of KL scores | 5.2 ± 8.8 | 6.7 ± 0.9 | 3.7 ± 0.5 | **0.002** |
| No. of joints with KL ≥2 | 2.5 ±4.1 | 3.2 ± 0.4 | 1.8 ± 0.2 | **0.002** |

Data are number (%) or mean ± SD
HOA: hand OA, KL: Kellgren-Lawrence score, MetS+: presence of metabolic syndrome, MetS-: absence of metabolic syndrome

**Table 3. Prevalence of radiographic hand OA in the general population (Framingham cohort study) and in the METAFIB-OA study by age.**

| Age groups (years) | Framingham total population (n=1508) | METAFIB cohort (n=301) | METAFIB HIV-1+ MetS+ (n=152) | METAFIB HIV-1+ MetS- (n=149) | *METAFIB vs Framingham* | *METAFIB Cases vs Framingham* | *METAFIB Controls vs Framingham* |
|---|---|---|---|---|---|---|---|
| **Men + women (45-64)** | **39.3** | **55.5** | **64.5** | **46.3** | *<0.0001* | *<0.0001* | *0.09* |
| **MEN** | n=641 | n=265 | n=134 | n=131 | | | |
| 45-49 | 10.3 | 28.6 | 32.1 | 25.7 | *0.004* | *0.006* | *0.03* |
| 50-54 | 31.9 | 50.0 | 57.1 | 41.5 | *0.003* | *0.001* | *0.23* |
| 55-59 | 43.9 | 68.6 | 80.6 | 55.9 | *0.0004* | *<0.0001* | *0.20* |
| 60-64 | 56.4 | 88.1 | 100 | 76.2 | *0.0002* | *0.0001* | *0.08* |
| **All ages (45-64)** | **38.7** | **55.8** | **64.9** | **46.6** | *<0.0001* | *<0.0001* | *0.09* |
| **WOMEN** | n=867 | n=36 | n=18 | n=18 | | | |
| 45-49 | 13.5 | 38.5 | 50.0 | 20.0 | *0.02* | *0.006* | *0.68* |
| 50-54 | 26.0 | 46.7 | 57.1 | 37.5 | *0.08* | *0.07* | *0.47* |
| 55-59 | 45.8 | 100 | 100 | 100 | *0.005* | *0.06* | *0.03* |
| 60-64 | 63.2 | 0 | 0 | 0 | *0.19* | *NA* | *0.19* |
| **All ages (45-64)** | **39.7** | **52.8** | **61.1** | **44.4** | *0.12* | *0.07* | *0.68* |

Radiographic hand OA definition was presence of ≥ 1 affected joint with KL score ≥2.
MetS+: presence of metabolic syndrome, MetS-: absence of metabolic syndrome, KL: Kellgren-Lawrence score

**Table 4. Univariate and multivariate analysis of associations between sociodemographic factors, HIV infection characteristics and metabolic variables and radiographic hand OA in the METAFIB-OA study population**

| Variable | HAND OA Diagnosis | | | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|---|---|---|
| | HAND OA+ (n=167) | HAND OA– (n=134) | P value | OR | 95% CI | P value | OR | 95% CI | P value |
| **Socio-demographic variables** | | | | | | | | | |
| Age (years), mean (SD) | 55.1(5.0) | 51.4 (4.3) | **$10^{-5}$** | 1.18 | 1.12–1.25 | **$10^{-5}$** | 1.18 | 1.11–1.25 | **$10^{-5}$** |
| Male gender, n (%) | 148 | 117 | 0.5 | 0.88 | 0.44–1.78 | 0.5 | - | | |
| Previous hand trauma, n (%) | | | | | | | | | |
| **HIV characteristics** | | | | | | | | | |
| Duration of HIV infection (years), mean (SD) | 18.0 (7.4) | 17.3 (7.1) | 0.5 | 1.01 | 0.98–1.04 | 0.5 | - | | |
| CD4 level (/mm3), mean (SD) | 600 (251) | 652 (281) | 0.1 | 0.99 | 0.99–1.00 | 0.1 | 0.99 | 0.99–1.00 | 0.2 |
| Undectable hsHIV viral load, n (%) (n=290) | 87/161 (29.0) | 85/129 (28.2) | **0.03** | 1.64 | 1.02–2.65 | 0.05 | 1.37 | 0.80–2.34 | 0.3 |
| Duration of exposure to protease inhibitors (months), mean (SD) | 27.5 (32.6) | 26.6 (31.8) | 0.7 | 1.00 | 0.99–1.01 | 0.8 | - | | |
| **Metabolic variables** | | | | | | | | | |
| Waist circumference (cm), mean (SD) | 92.8 (10.5) | 92.0 (11.2) | 0.4 | 1.01 | 0.99 –1.03 | 0.6 | - | | |
| Obesity (BMI≥30), n (%) | 14 (4.7) | 18 (6.0) | 0.1 | 0.98 | 0.94–1.02 | 0.3 | - | | |
| Hypertension, n (%) | 35 | 21 | 0.2 | 1.43 | 0.79–2.59 | 0.3 | - | | |
| Triglycerides (mmol/l), mean (SD) | 2.14 (2.36) | 1.72 (1.1) | 0.07 | 1.19 | 0.99–1.43 | 0.07 | 1.06 | 0.9–1.25 | 0.5 |
| HDL-chol (mmol/l), mean (SD) | 1.2 (0.4) | 1.2 (0.4) | 0.7 | 0.93 | 0.51–1.70 | 0.8 | - | | |
| HOMA-IR score, mean (SD) (n=297) | 2.48 (2.78) | 2.36 (2.81) | 0.06 | 1.02 | 0.93–1.10 | 0.7 | - | | |
| Diabetes, n (%) | 36 (%) | 29 (%) | 0.6 | 0.99 | 0.57–1.73 | 0.9 | - | | |
| MetS, n (%) | 98 (32.6) | 54 (%) | **$10^{-3}$** | 2.10 | 1.32–3.34 | **0.002** | 2.18 | 1.26–3.96 | **0.005** |

Radiographic hand OA definition was presence of ≥ 1 affected joint with a KL score ≥2. Hypertension was defined as systolic pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg. Diabetes was defined as glycemia >7 mmol/L. HOA+: hand OA presence, HOA-: hand OA absence. OR, odds ratio; 95% CI, 95% confidence interval. MetS: metabolic syndrome, BMI: body mass index; HDL: high density lipoprotein; HOMA-IR score (Homeostasis Model Assessment of Insulin Resistance)

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