The Incidence and Natural History of Osteonecrosis in HIV-Infected Adults

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Background. Osteonecrosis is increasingly recognized as a debilitating complication of human immunodeficiency virus (HIV) infection, but the natural history has not been well described. We previously documented a high prevalence (4.4%) of magnetic resonance imaging (MRI)–documented osteonecrosis of the hip in a cohort of 339 asymptomatic HIV-infected patients. The present study was designed to determine the incidence of newly diagnosed osteonecrosis in this cohort and to describe the natural history of osteonecrosis in HIV-infected patients.

Methods. Asymptomatic HIV-infected patients with a previous hip MRI negative for osteonecrosis underwent follow-up MRI. Patients with asymptomatic or symptomatic osteonecrosis were enrolled in a natural history study, which included serial MRIs and a physiotherapy follow-up.

Results. Two hundred thirty-nine patients underwent a second MRI a median of 23 months after the initial MRI. Osteonecrosis of the femoral head was diagnosed in 3 patients (incidence, 0.65 cases per 100 person-years). During the period of January 1999 through April 2006, symptomatic hip osteonecrosis developed in 13 clinic patients (incidence, 0.26 cases per 100 person-years). Among 22 patients enrolled with symptomatic hip osteonecrosis, 18 had bilateral involvement of the femoral heads, and 7 had osteonecrosis involving other bones. Two (11%) of 18 asymptomatic patients and 13 (59%) of 22 symptomatic patients underwent total hip replacement. The percentage of involvement of the weight-bearing surface of the femoral head and the rate of progression to total hip replacement was significantly greater (P < .001) in symptomatic patients than in asymptomatic patients.

Conclusions. HIV-infected patients are at ∼100-fold greater risk of developing osteonecrosis than the general population. Disease progression is slower in asymptomatic patients than in symptomatic patients. Given the high frequency of total hip replacement in symptomatic patients, studies to assess preventive and treatment strategies are essential.

Since 1996, the broad availability of HAART in the United States has led to a dramatic decrease in the incidence of opportunistic infections and malignancies and prolonged survival for HIV-infected patients [1]. During this period, previously unrecognized complications of long-standing HIV infection and treatment have had an increasing impact on the quality of life for these patients. Osteonecrosis of the hip and of other bones is one such debilitating complication. First described in HIV-infected patients in 1990, numerous case reports and retrospective case studies have subsequently appeared in the medical literature [2]. An increased incidence of previously recognized risk factors for osteonecrosis, such as corticosteroid use, hypercoagulable state, alcohol abuse, and tobacco use, has been associated with osteonecrosis in these patients [3–13]. Additional reported risk factors include the use of antiretroviral drugs (especially protease inhibitors), the presence of lipodystrophy syndrome, and use of megestrol acetate or testosterone [10, 12, 14, 15].

The annual incidence of symptomatic osteonecrosis in the general population has been estimated to be approximately 0.003–0.006 cases per 100 person-years [16, 17]. Recent retrospective case studies of HIV-infected patients have reported incidences ranging from 0.03 to 0.37 cases per 100 person-years [7, 8, 12, 18–
The incidence and natural history of osteonecrosis in HIV-infected adults.

Here, we present a prospective study documenting the incidence of osteonecrosis in asymptomatic HIV-infected patients. In addition, we report longitudinal follow-up data on a cohort of prospectively identified HIV-infected patients with asymptomatic osteonecrosis and a cohort of symptomatic HIV-infected patients who were enrolled after receiving a diagnosis of osteonecrosis.

METHODS

The methods of the initial prevalence study have been described elsewhere [9]. In brief, 339 HIV-infected adults enrolled in studies of the treatment or natural history of HIV infection at the National Institutes of Health Clinical Center (Bethesda, MD) underwent MRI of both femoral heads. Because the study
Figure 2. Development of osteonecrosis of both femoral heads in a patient with prospectively identified disease. The initial MRI (from 20 July 1999; A) findings were normal. A follow-up screening MRI on 14 June 2001 (not shown) identified bilateral osteonecrosis. Representative high-resolution T-1 scans of each hip obtained shortly thereafter are shown on the left (right hip, 27 June 2001 [B]; left hip, 25 June 2001 [D]) demonstrate the characteristic findings of osteonecrosis (arrows), with linear areas of abnormal signal in the femoral heads bilaterally without gross deformity of the femoral heads. No evidence of sclerosis or marrow edema was noted. The lesions showed mild progression at 1 month, then remained stable until 19 months after the diagnosis (right), when progression can be seen in both hips in the T-1 scans. The T-2 scans (bottom) demonstrate the increase in bone marrow edema and effusion in the left hip on 3 February 2003 (E and G), compared with 25 June 2001 (D and F). The patient underwent total hip replacement on the right hip 23 months after diagnosis and on the left hip 28 months after diagnosis.

initially focused on asymptomatic patients, persons with hip or groin pain were excluded. As part of the initial screening study, all participants completed a standard questionnaire that addressed joint symptoms, medical history, medication use, exercise routine, and substance use.

Participants without evidence of osteonecrosis on the initial screening MRI underwent a second MRI 17–31 months after the first study. The medical records of all patients who participated in the initial trial were reviewed through April 2006; no additional patients with osteonecrosis were identified, other than 1 patient who had already been enrolled in the study.

Patients with MRI-documented osteonecrosis, which was diagnosed either as part of this study or outside the context of this study, were eligible to participate in a natural history study that included additional laboratory evaluation, serial MRIs, and physiotherapy. Participants with osteonecrosis underwent optional additional MRI after approximately 3, 6, and 12 months and annually thereafter. Laboratory and clinical data for all patients were retrieved from a patient database; data through April 2006 are included in this report. This protocol was approved by the National Institute of Allergy and Infectious Diseases institutional review board, and all participants provided written informed consent.

MRI. MRIs were performed using an LX Horizon 1.5-T MRI system (General Electric Medical Systems) in accordance with a previously described method [22]. The percentage of involvement of the weight-bearing surface of the femoral head was determined using previously reported methods and was graded as <25%, 25%–50%, and >50% [23, 24]. All MRI findings were interpreted by one of the investigators (E.C.J.).

Hematologic evaluation. In our previous evaluation for a hypercoagulable state, we found that, among a panel of assays, only anticardiolipin antibody levels were elevated significantly more in patients with osteonecrosis than in HIV-infected patients without osteonecrosis. Therefore, from the prior panel, only anticardiolipin antibody levels were determined in patients with osteonecrosis. Commercially available kits were used (Quantilite; Innova) [9].

Physiatrist evaluation. Participants with MRI evidence of osteonecrosis underwent a detailed clinical evaluation, which included a functional history of vocational and avocational activity and a physical examination of the hips, as previously described [25]. Functional mobility status was determined using the Sickness Impact Profile Ambulation Subscale [26].

Statistical analysis. The incidence of osteonecrosis was calculated by dividing the number of cases of osteonecrosis by the total number of person-years of follow-up for HIV-infected patients regularly observed at our clinic during the period of January 1999 through April 2006, or, for the asymptomatic group, the total number of person-years between the 2 MRIs. For comparison of categorical variables, the $\chi^2$ test or Fisher’s
Table 1. Comparison of select clinical and laboratory characteristics of asymptomatic and symptomatic HIV-infected patients with hip osteonecrosis.

| Characteristic | Asymptomatic cohort (n = 18) | Symptomatic cohort (n = 22) | P
|---------------|-----------------------------|-----------------------------|---
| Age, median years (range) | 45 (33–59) | 46 (21–61) | NS
| Male sex | 17 (94.4) | 20 (90.9) | NS
| CD4 cell count, median ×10⁹ cells/L (range) | 590 (284–1117) | 332 (12–965) | .011
| HIV load, median copies/mL (range) | 1073 (<50 to 123,973) | <50 (<50 to 242,844) | NS
| Duration of HIV infection, median years (range) | 11.1 (3.4–17) | 12.0 (1.6–19.5) | NS
| History of opportunistic infection | 6 (33.3) | 15 (68.2) | .055
| Protease inhibitor use | 17 (94.4) | 20 (90.9) | NS
| Duration of protease inhibitor use, median years (range) | 3.2 (0.1–5.4) | 3.3 (0.5–8.8) | NS
| Prior treatment | | | |
| Corticosteroids | 13 (72.2) | 17 (77.3) | NS
| Megestrol acetate | 1 (5.6) | 7 (31.8) | .053
| Testosterone | 12 (66.6) | 8 (36.4) | NS
| Lipid lowering agents | 10 (55.6) | 7 (31.8) | NS
| Medical history | | | |
| Hyperlipidemia | 10 (55.6) | 11 (50.0) | NS
| Lipodystrophy | 13 (72.2) | 16 (72.7) | NS
| Alcohol abuse | 2 (11.1) | 7 (31.8) | NS
| Positive ACA IgG | 14 (77.7) | 6 (30) | .004
| ACA >23 U | 7 (38.9) | 2 (10) | .058
| Bilateral hip osteonecrosis | 9 (50) | 18 (81.8) | .046
| Total hip replacement | 2 (11.1) | 13 (59.1) | .003

NOTE. Data are no. (%) of patients, unless otherwise indicated. ACA, anti-cardiolipin antibodies; NS, not significant.

* Characteristics are at the time of diagnosis, except for bilateral hip osteonecrosis and frequency of progression to total hip replacement. Baseline characteristics for 15 of the asymptomatic patients have been previously reported [9] and are included to allow comparison of the entire cohort of asymptomatic patients with symptomatic patients.

P values were determined using either the χ² test, Fischer’s exact test, or the nonparametric Mann-Whitney U test.

Diagnosed by patient report and confirmed by physical examination by a physician.

ACA values were available for 18 asymptomatic and 20 symptomatic patients.

RESULTS

Incidence. Of 339 asymptomatic participants who underwent an initial screening MRI, 15 were found to have osteonecrosis, as previously reported [9]. Of the 324 participants without evidence of osteonecrosis, 81 patients either declined to undergo a second MRI or did not return to the clinic during the follow-up period, and 4 died before undergoing an additional MRI (figure 1).

Two hundred thirty-nine participants (median age, 43 years; range, 23–70 years) underwent a second screening MRI during the period from February 2001 through January 2002, a median of 23 months (range, 17–31 months) after the initial MRI. Clinical and laboratory characteristics of the 239 patients are similar to those previously reported for the entire cohort and to those of patients who did not undergo a second MRI [9]. On the basis of the follow-up MRI, 3 patients (1.3%) received a diagnosis of osteonecrosis of the femoral head (bilateral for all patients), for an incidence of 0.65 cases per 100 person-years (95% CI, 0.13–1.89 cases per 100 person-years). An additional patient, whose screening and follow-up MRIs yielded normal findings, received a diagnosis of symptomatic left hip osteonecrosis 3 years after his second MRI. The patients with newly diagnosed osteonecrosis did not differ significantly from the patients without osteonecrosis with regard to sex, age, exposure group, duration of HIV infection, or antiretroviral treatment history (data not shown).

All MRI-identified lesions had features characteristic of osteonecrosis (i.e., diminished signal on T1-weighted images with a corresponding bright signal on fat-suppressed, T2-weighted images) (figure 2). The initial negative MRI results were reviewed after the diagnosis of osteonecrosis, and again, no abnormalities were noted. Thus, 4 (1.7%; 95% CI, 0.5%–4.2%) of the 239 asymptomatic patients with previously negative MRI results developed MRI-documented osteonecrosis within 5 years.
Table 2. Clinical and radiographic outcomes for asymptomatic and symptomatic HIV-infected patients with hip osteonecrosis.

<table>
<thead>
<tr>
<th>Symptom or change</th>
<th>Asymptomatic cohort</th>
<th>Symptomatic cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Mild (not requiring pain medications)</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Moderate-severe (requiring pain medications)</td>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>Radiographic changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resolution</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Improvement</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Stable</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Progression</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>New lesion</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>

NOTE. Data are no. of hips. Clinical symptoms at the last clinical follow-up visit for patients with longitudinal clinical data and radiographic changes over time for patients with serial radiographic studies are shown. Hips that required total hip replacement were excluded from both clinical and radiographic analysis.

Table 3. Comparison of the extent of involvement of the weight-bearing portion of the femoral head at the time of diagnosis of hip osteonecrosis in asymptomatic and symptomatic HIV-infected patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Asymptomatic cohort</th>
<th>Symptomatic cohort</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of hips</td>
<td>27</td>
<td>30</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Percentage of femoral head involved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>13 (48)</td>
<td>1 (3.3)</td>
<td></td>
</tr>
<tr>
<td>25–50</td>
<td>9 (33.3)</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>5 (18.5)</td>
<td>26 (86.7)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of hips.

* Determined using the \( \chi^2 \) test.
Figure 3. Serial MRIs of an asymptomatic patient with bilateral hip osteonecrosis, demonstrating improvement over time. The initial screening MRI (from 18 July 1999; top) revealed bilateral osteonecrosis of the femoral heads (arrows). As illustrated by a follow-up MRI (from 25 June 2004; bottom), the lesion in the left hip resolved over time, and the lesion in the right hip decreased in size (arrow).

Clinical signs in the asymptomatic osteonecrosis cohort that differed significantly from the clinical signs in HIV-infected patients without MRI evidence of osteonecrosis [25]. Serial examination findings are available for 15 of the 18 patients for up to 6 years after the initial diagnosis (table 4). The majority of patients had some range of motion abnormality at each time; other abnormalities were seen less frequently.

Symptomatic cohort. Of the 22 patients with symptomatic hip osteonecrosis (figure 1), 18 had bilateral involvement of the femoral heads, and 7 had symptomatic osteonecrosis involving other bones, including the shoulders (5 patients), knees (3 patients), and ankles (1 patient) (figure 4). Potential risk factors for osteonecrosis were also common in this cohort (table 1).

After a median duration of follow-up of 26 months, 13 patients (59%) underwent THR at a median of 10 months (range, 1–45 months) after diagnosis; 8 of these required THR within 1 year after diagnosis. Three of these patients underwent bilateral THR, one of whom had previously undergone bilateral core decompression and bilateral shoulder surgery to help relieve symptoms; a fourth had a bone graft in the second hip; a fifth underwent a shoulder replacement before the THR. The majority of patients that did not require THR had persistent pain requiring use of nonsteroidal or narcotic pain medications (table 2). Four patients were lost to long-term follow-up, and 2 died (one died of lymphoma, and the other died of an unknown cause).

Findings of radiographic studies (16 MRIs, 1 CT, and 1 plain film examination) were available for 18 patients (30 hips) at approximately the time of diagnosis. Eighty-seven percent of the hips (26 hips in 18 patients) had >50% involvement of the femoral head. Serial imaging data were available for 10 patients (table 2). Two patients developed new lesions in the contralateral hip. No patient showed improvement or resolution.

Eight (89%) of 9 subjects who underwent physiatric evaluation had range of motion loss noted by passive range-of-motion testing, pain at end range, and with provocative tests, morning stiffness, gelling, and hip pain. Seven subjects (78%) described a limitation related to functional mobility.

In a comparison of the baseline characteristics of the symptomatic and asymptomatic patients with osteonecrosis (tables 1 and 3), the most striking difference was the percentage of involvement of the femoral head, which was significantly greater in symptomatic patients, \( P < .0001 \). The natural history was also markedly different: THR was significantly more common in symptomatic patients \( (P = .003) \). Kaplan-Meier survival analysis (figure 5, top) demonstrated a significantly more rapid progression to THR in symptomatic patients, compared with asymptomatic patients \( (P < .001, \) by log rank test). A similar analysis, which combined data for all patients, highlighted the relationship between the percentage of involvement of the femoral head and clinical outcome: only patients with

<table>
<thead>
<tr>
<th>No. of years after diagnosis of osteonecrosis to evaluation</th>
<th>Passive range of motion abnormality</th>
<th>PROM</th>
<th>Pain</th>
<th>Functional mobility limitations</th>
<th>Morning stiffness upon awakening</th>
<th>Gelling</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year ((n = 10))</td>
<td>8</td>
<td>4</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>2 Years ((n = 8))</td>
<td>7</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3 Years ((n = 7))</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>6 Years ((n = 3))</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

* Gelling, stiffness, or limited mobility after sitting for any period of time.

Table 4. Longitudinal physiatric evaluation findings for 18 asymptomatic subjects with osteonecrosis.
Figure 4. MRIs for a patient with multiple lesions due to osteonecrosis (arrows). T1-weighted images show bilateral osteonecrosis of the shoulders (top), bilateral osteonecrosis of the hips (middle), bilateral osteonecrosis of the distal femurs (bottom left), and osteonecrosis of the left proximal tibia (bottom right).

>50% involvement later required THR ($P<.001$, by log rank test) (figure 5, bottom).

**DISCUSSION**

The results of this prospectively studied cohort provide strong evidence that HIV-infected patients are at substantially increased risk for the development of symptomatic or asymptomatic osteonecrosis. Moreover, there is a high rate of progressive disease and a need for THR—especially in patients in whom osteonecrosis affected >50% of the weight-bearing portion of the femoral head, which included the majority of symptomatic patients.

Our finding of incidence rates of 0.65 cases per 100 patient-years for asymptomatic patients and 0.26 cases per 100 patient-years for symptomatic patients is ~100-fold higher than the estimated incidence in the general population [16, 17]. The prevalence of osteonecrosis in the initial cohort of 339 asymptomatic patients who were evaluated by MRI is also extraordinarily high at 5.6% and is similar to prevalences reported among patients at high risk for osteonecrosis in the context of a variety of underlying diseases (table 5) [27]. The 5.6% prevalence represents a minimum estimate, because additional cases involving asymptomatic disease may have developed in this population since the last series of MRIs.
A high rate of asymptomatic osteonecrosis is not unique to HIV-infected patients: asymptomatic disease has been identified with a high frequency in MRI surveys of patients with alcoholism or systemic lupus erythematosus and in renal transplant recipients, many of whom were receiving corticosteroids, as well as a cohort of patients with primary antiphospholipid syndrome, none of whom had received corticosteroid treatment (table 5) [22, 27–31]. Given that the primary difference between asymptomatic and symptomatic patients is the extent of involvement of the femoral head, it appears likely that the 2 groups represent a continuum of the same process, with the size of the lesion being the primary determinant of symptoms.

The incidence of osteonecrosis among HIV-infected patients increased after the introduction of HAART that included protease inhibitors ~10 years ago [20, 32], raising the possibility that this class of drugs or these combination regimens played an etiologic role. However, on the basis of current data, it is difficult to conclude that protease inhibitors or antiretroviral combinations are independently associated with the development of osteonecrosis [5, 6, 9, 12, 19, 33]. It is important to note, however, that a number of risk factors for the development of osteonecrosis are associated with HIV infection, management of HIV-related complications, or antiretroviral therapy, including pancreatitis, hyperlipidemia, osteopenia/osteoporosis, and use of corticosteroids. Chronic inflammation in the context of long-standing HIV infection may also contribute to the development of osteonecrosis, as has been postulated for systemic lupus erythematosus [34].

Corticosteroid use is noteworthy, because it has been consistently identified as one of the most important risk factors for osteonecrosis among HIV-infected persons, as well as among other patient populations [6, 12]. Protease inhibitors may exacerbate the effects of corticosteroids by altering their cytochrome p450-mediated metabolism. In a study that was prompted in part by our observations in the initial screening MRI study, we have demonstrated that low doses of the protease inhibitor ritonavir significantly increase systemic exposure to prednisolone in healthy volunteers [35]. Corticosteroids are used in the management of a number of HIV-related opportunistic infections, such as Pneumocystis pneumonia, as well as for non–HIV-related medical conditions, such as asthma and allergic reactions; they have also been used to explore the role of immune activation in the pathogenesis of HIV-related immunodeficiency. In one such study, osteonecrosis was identified by MRI in 2 (18%) of 11 asymptomatic patients, highlighting the potential risks in this population and further emphasizing how corticosteroids must be used cautiously in HIV-infected patients [36].

We have documented a rapid progression of disease in symptomatic patients, such that 59% of patients had progression sufficient to require THR. Although the inclusion of patients from outside of our clinic may have resulted in a selection bias, the referred patients had conditions that progressed to the point that required surgery at a rate similar to those identified prospectively within our clinic population and at rates similar to another report, in which nearly 50% of symptomatic HIV-infected patients with osteonecrosis of the hip required THR [37]. In our cohort, this appears primarily to be related to the extent of disease involvement at the time of diagnosis, which was significantly greater in symptomatic patients. Moreover, THR was performed only for patients who presented with >50% involvement of the femoral head, regardless of the presence of symptoms at diagnosis. The natural history of osteonecrosis in other populations has not been clearly defined but depends on the stage and size of the lesion; one review of published studies found that 80% of hips that had been treated...
Table 5. Incidence and prevalence of osteonecrosis in select at-risk patient populations.

<table>
<thead>
<tr>
<th>Population, reference</th>
<th>Incidence, no. of cases per 100 person-years</th>
<th>Prevalence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-infected patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic osteonecrosis(^a)</td>
<td>0.65</td>
<td>5.6</td>
</tr>
<tr>
<td>Symptomatic osteonecrosis(^a)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>General population [16]</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Patients with systemic lupus erythematosus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not receiving therapy [31]</td>
<td>...</td>
<td>0</td>
</tr>
<tr>
<td>Receiving therapy, asymptomatic osteonecrosis [28]</td>
<td>...</td>
<td>33</td>
</tr>
<tr>
<td>Receiving therapy, symptomatic osteonecrosis [28]</td>
<td>...</td>
<td>11</td>
</tr>
<tr>
<td>Patients with various autoimmune disorders, receiving high-dose corticosteroid treatment, asymptomatic osteonecrosis [28]</td>
<td>...</td>
<td>35</td>
</tr>
<tr>
<td>Patients with acute lymphoblastic leukemia receiving therapy, asymptomatic osteonecrosis [43]</td>
<td>...</td>
<td>6</td>
</tr>
<tr>
<td>Bone marrow transplant recipients receiving therapy, symptomatic osteonecrosis [44]</td>
<td>...</td>
<td>11</td>
</tr>
</tbody>
</table>

\(^a\) From the present report.

conservatively ultimately required THR [38]. Although some studies suggest that core decompression can mitigate the natural history [38], the utility of this procedure remains controversial and may be applicable to only a limited number of patients.

Asymptomatic disease is not benign, because the conditions of 2 patients progressed to the point that THR was required during a median follow-up period of 5.8 years, and the duration of follow-up may not be adequate to determine whether the remaining patients’ conditions will remain stable. In a prospective study of small, asymptomatic lesions in 40 patients with symptomatic osteonecrosis in the contralateral hip, collapse of the asymptomatic hip occurred in 29 patients a mean of ∼7.5 years after diagnosis (range, 6–11.5 years), and all 29 patients required surgical intervention (20 required THR) [39].

Given the high frequency of disease progression that requires THR in HIV-infected patients with symptomatic osteonecrosis (59%), interventions to prevent progression must be critically evaluated. Conservative management does not appear to affect the natural history, and the role of core decompression remains controversial. However, recently published studies, including one randomized trial, have suggested that bisphosphonates can modulate the natural history of osteonecrosis of the femoral head [21, 40, 41]. In light of these data, additional investigations of bisphosphonates for the treatment of HIV-associated osteonecrosis are warranted; reports of bisphosphonate-associated osteonecrosis of the jaw should, however, temper routine use of these drugs for these causes until safety has been established [42].

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