

Musculoskeletal considerations in HIV disease: A critical review

SD Pullen^{1*}

Abstract

Introduction

The vast progress in management of HIV disease with anti-retroviral therapy (ART) in the past three decades has resulted in increased life expectancy for people living with HIV/AIDS. With this new chronicity of the disease has emerged a constellation of musculoskeletal impairments ranging from arthritis to traumatic fractures requiring orthopedic surgery. This manuscript aims to review and critique recent research (2009-2014) investigating musculoskeletal complications of HIV disease, and to propose future directions for management of such diagnoses.

Methods

The literature reviewed was divided into the following categories, in order of publication date: general musculoskeletal complications arising from the HIV virus itself and/or ART, HIV-related bone infections and bone disease, rheumatic disease in HIV infection, vitamin D deficiency in HIV disease, and orthopedic post-surgical complications/risk factors resulting from HIV disease.

Results

A total of 19 articles met the described inclusion criteria and were included in this critical review. From most recent (2014) to oldest (2009), 4 articles were published in 2014, 7 in 2013, 3 in 2012, 1 in 2011, 2 in 2010 and 2 in 2009.

Discussion

While the pathophysiology of HIV-related musculoskeletal complications is well documented in the literature, it is crucial that attention is also focused on treatment. The complex nature of disability in PLWHA necessitates a multidisciplinary approach to treatment to adequately address the diagnostic and treatment needs of this population.

Conclusion

Given the multitude of musculoskeletal complications that arise from the HIV virus and/or ART, research must be continuously conducted to assess risk, prevention and treatment. This research will need to focus on both non-surgical and surgical approaches to management of musculoskeletal complications in the HIV-infected individual.

Introduction

Over the past three decades, the lifespan of people living with HIV/AIDS (PLWHA) has been greatly extended due to the development of anti-retroviral therapy (ART) in the

late 1990s. Most patients who take the recommended ART regimen experience immunological improvement and can experience normal life expectancy.^{1,2} With this increased life expectancy has emerged a symptom burden for PLWHA of impairments such as musculoskeletal and neurological complications and chronic pain.

There is a diversity of literature on varying aspects of HIV, and research has recently focused how the disease – especially given its increased chronicity – affects the musculoskeletal system. This focus is necessary in order to diagnose and properly treat various orthopedic, rheumatologic and pain symptoms and diagnoses amongst PLWHA. This review aims to review and critique recent research (2009-2014) investigating musculoskeletal complications of HIV disease, and to propose future directions for the management of such diagnoses.

Literature suggests that musculoskeletal conditions will affect 72% of HIV-infected individuals during their lifespan.³ Musculoskeletal and orthopedic complications have emerged as potential results of the disease itself and/or the ART treatment regimen. For example, low bone mineral density (BMD) has been associated independently with HIV disease itself and as a direct effect of ART.⁴ The increased life expectancy of people living with HIV increases the possibility that these individuals will develop age-related arthritis, as well as other chronic musculoskeletal impairments as complications of HIV virus and/or because of expected age-related symptoms.⁵ Recent research suggests that the probability of PLWHA developing osteoporosis is three times higher compared to their HIV-negative counterparts^{6,7}. A growing body of literature over recent years has shown that given this loss of BMD, vitamin D deficiency is highly prevalent among people living with HIV.⁸ Low vitamin D (hypovitaminosis D) is widely known to have detrimental effects on bone health, in addition to cardiovascular, metabolic, immune and neurocognitive functions.

Given the increased bone fragility and fracture risk due to low BMD, PLWHA often require orthopedic surgery for fragility fractures and/or other low BMD-related events. Because of their immunocompromise, research has examined the question of increased risk for perioperative or postoperative infection in this population.^{9,10,11,12}

Methods

An electronic search was performed of the Medline database using the PubMed search engine using the search terms, “musculoskeletal OR orthopedic HIV infections complications”. Inclusion criteria were any articles specifically discussing musculoskeletal/orthopedic considerations and/or complications of HIV disease published in English and with adult human subjects. Date

*Corresponding author
Email: sara.pullen@emory.edu

¹ Emory University School of Medicine, Atlanta, Georgia, United States

limits were set to the past five years, as this review seeks to provide a review of current literature and practice.

Results

A total of 19 articles met the described inclusion criteria and were included in this critical review. From most recent (2014) to oldest (2009), 4 articles were published in 2014, 7 in 2013, 3 in 2012, 1 in 2011, 2 in 2010 and 2 in 2009. The following categories were identified in the review of the relevant literature: general musculoskeletal complications arising from the HIV virus itself and/or the ART medication regimen (n=4); HIV-related bone infections and bone disease (n=5); Rheumatic disease in HIV infection (n=4); Vitamin D deficiency in HIV disease (n=2) and orthopedic post-surgical complications/risk factors resulting from HIV disease (n=4). Table 1 describes the summarized findings in each category in order of publication date.

Discussion

This article reviewed literature published in the last 5 years regarding musculoskeletal complications of HIV disease. Both HIV infection itself and the pharmacological treatment of the disease can cause a wide range of musculoskeletal impairments such as increased risk of fractures, osteonecrosis and spondyloarthropathy.¹³ Both HIV and ART have been established as independent risk factors for osteoporosis.⁶ The high prevalence of hypovitaminosis D amongst PLWHA puts this population at risk for fractures and osteoporosis/osteopenia, and people with HIV should be screened carefully for low BMD – especially those with a history of bone disease and “traditional” risk factors such as low dietary intake, female sex, dark skin pigmentation and low sun exposure.⁸ The establishment of optimal Vitamin D dosing regimens in this population is needed, as well as the impact of such supplementation in preventing comorbidities.⁸ Bone and joint infections account for approximately 67% of musculoskeletal infections in HIV-infected patients.¹⁴ Rheumatic manifestations can include arthritis, spondyloarthritis, diffuse infiltrative lymphocytosis syndrome (DILS), vasculitides, connective tissue disease, myopathies and musculoskeletal diseases. Most anti-rheumatic therapies appear to be safe and effective in HIV-positive patients when used according to protocol.¹⁵ Give the increased chronicity of the disease; a certain percentage of people with HIV will inevitably require orthopedic surgery.¹² A literature review of orthopedic post-operative infections of HIV-positive patients shows only four in the past five years in the United States. There is a need for robust studies examining the effect of reduced CD4 counts and viral load suppression, and prolonged antibiotic use to determine actual risk of infection in PLWHA compared to their HIV-negative counterparts.¹⁶ Certain orthopedic surgeries can greatly improve quality of life and functional outcomes for HIV-positive individuals. Further research is warranted to evaluate pre- and peri-

operative measures that may prevent or decrease infection in this population.¹² Jacofsky (2013) proposes a paradigm shift in the thought that these surgeries should not be performed on patients who are HIV-positive, for fear of postoperative infection risk: the realm of orthopedic medicine has historically perhaps overestimated the risk for post-operative complications based on HIV-positive status alone.¹⁷ That said, it should be noted that despite recent findings of statistically insignificant differences in orthopedic postoperative complications of HIV-positive versus negative individuals, caution should be practiced given the smaller nature of these studies. Orthopedic postoperative complications are relatively rare, and therefore larger, more robust studies need to be conducted to show statistical significance with bigger cohorts until we can draw conclusions for certain about the role of HIV in postoperative complications.¹⁷

Conclusion

While the pathophysiology of HIV-related musculoskeletal complications is well documented in the literature, it is crucial that attention is also focused on treatment. With increased life expectancy for PLWHA will inevitably come normal age-related issues in this population, which may or may not present differently than those experienced by their HIV-negative counterparts. These impairments may range from mildly bothersome to true disability, and healthcare workers across the spectrum will need to be prepared for the increased demands of caring for aging PLWHA. The complex nature of disability in PLWHA necessitates a multidisciplinary approach to treatment to adequately address the needs of this population, drawing on the expertise of physicians, nurses, physical and occupational therapists, mental health experts and nutritionists.

A few recent studies have examined the physical and functional benefits physical therapy interventions and their potential impact within this population.^{18,19,20} A 2014 study reported that upon surveying HIV physicians, 70% of the sample reported referring patients to PT and 51.5% of those referrals were for musculoskeletal conditions.¹⁸ Due to the well-documented issues of musculoskeletal issues within the HIV-positive population, access to and effectiveness of rehabilitation should be highlighted as a priority area of research in the HIV and rehabilitation domain.²¹ Given the multitude of musculoskeletal complications that arise from the HIV virus and/or ART, research must be continuously conducted to assess risk, prevention and treatment. This research will need to focus on both non-surgical and surgical approaches to management of musculoskeletal complications in the HIV-infected individual.

References

1. Burgess MJ & Kasten MJ. Human Immunodeficiency Virus: what primary care physicians need to know. *Mayo Clinic Proc.* 2013 Dec (88)12: 1468-74.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Table 1: Study characteristics for studies included in the critical review, by category (n=20).

Category	Study and year published	Summarized main conclusions
General musculoskeletal complications arising from HIV disease itself and/or ART (n=4)	Warriner AH, Mugavero M, Overton ET (2014) ²²	It is well documented in the literature that HIV-positive individuals are at greater risk of developing low bone mineral density (BMD) than their HIV-negative counterparts, leading to greater risk of osteoporosis and fractures. It is unknown if the etiology of this risk is due to the disease itself, the medications used to manage the virus, or a combination of both. HIV-positive individuals should be screened carefully, and treated if indicated, for osteoporosis - especially if those individuals have additional/traditional risk factors for low BMD.
	Burgess MJ & Kasten MJ (2013) ¹	Primary care clinicians can provide essential care of both chronic and acute HIV-related issues. These clinicians can provide support including preventive care, counseling, cardiovascular health, osteoporosis and diabetes care - all of which have become increasingly prevalent in HIV-positive individuals as they age.
	Peters B, et al. (2013) ²³	Deaths attributed to noninfectious, chronic comorbid diseases among HIV-infected individuals have increased in recent years. There is a need for a strategic approach to screening for these comorbidities, which include bone disease. The authors present a screening approach that encompasses risk factors for "lifestyle-related chronic disease" in PLWHA, which identifies high-risk patients and provides a tool for sequential targeted management. This tool could improve patient-provider communication, facilitate patient-centric self-screening measures and utilize health-based social networking to disseminate educational messages and provide support.
	Takhar SS & Hendey GW (2010) ¹³	Given the advancements in HIV treatment, there are now fewer opportunistic infections but an increase in osteopenia and osteonecrosis. Musculoskeletal conditions affecting HIV-infected patients can be divided into 4 categories: disseminated diseases (neoplastic, infectious), bone disorders (osteopenia, osteoporosis, osteonecrosis, osteomyelitis), joint disease (septic arthritis, spondyloarthritis, HIV-associated arthritis), and myopathies (pyomyositis, polymyositis). Physicians must be aware of these manifestations of orthopedic disease to promote early diagnosis, treatment and appropriate referrals.
Bone infections/disease (n=5)	Cotter AG & Mallon PW (2014) ⁴	There is an onset of BMD reduction upon initiation of ART, in conjunction with reduction in HIV viremia. Given that T cells and B cells partially regulate bone metabolism, the authors propose that earlier initiation of ART while CD4-T cells are still in a higher range may reduce the effect of BMD loss by cancelling immune responses in bone metabolism that accompany ART initiation. The authors emphasize the need for future research examining the interaction between immunity, virus, ART and bone metabolism.
	Castronuovo D, et al. (2013) ²⁴	In addition to general risk factors for low BMD, the HIV virus itself, ART and chronic inflammation have been shown to contribute to bone loss in the context of HIV infection. Risk factors for low BMD amongst PLWHA include the duration of HIV infection and exposure to ART. Current recommendations for fracture screening and treatment in this population include careful screening for both HIV-related and traditional risk factors and measurement of BMD. Treatment recommendations include, when indicated, bone protective therapy such as bisphosphonates and Vitamin D supplementation.
	Pattamapasong N, Louthrenoo W (2011) ¹⁴	Immunocompromised patients are more susceptible to a variety of infections including bone infection. These infections can result in infectious arthritis, osteomyelitis, pyomyositis and soft tissue or skin infection. The primary roles of radiology are to provide diagnostic information, determine extent of the disease and assist with treatment planning. Treatment of musculoskeletal infection for HIV-infected individuals is typically the same as treatment of their HIV-negative counterparts: antimicrobial therapy and surgical drainage if indicated.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Table 1: (continued).

	Ofotokun I, McIntosh E & Weitzman MN (2012) ⁶	The recent emergence of the field of "osteimmunology" has provided a conceptual framework to explain how the immune and skeletal systems interact. Given that HIV infection and ART are defined independent risk factors for osteoporosis, this framework is imperative in understanding the mechanisms and treatment options for HIV-related skeletal decline. Inflammation and immune dysregulation play a large role in bone turnover and bone loss, which result in osteoporosis and other bone disorders.
	McComsey GA, et al (2010) ²⁵	Initiation of ART is associated with a decrease in BMD over the first 2 years at a similar magnitude to the BMD loss sustained during the first 2 years of menopause. The causes of low BMD among HIV-infected individuals appear to be multifactorial and representative of a complex interaction between the virus, traditional osteoporosis risk factors and ART-related side effects. The authors propose that HIV infection should be considered an independent risk factor for bone disease. They recommend screening patients with fragility fractures, HIV-infected post-menopausal women, and all HIV-positive men >50 years of age.
Rheumatic disease in HIV (n=4)	Lawson E, Walker-Bone K (2013) ²⁶	The immune restoration inflammatory syndrome upon initiation of ART causes de novo autoimmune, rheumatic disorders among HIV-positive patients. It is controversial whether this is caused by the HIV virus itself, or if the HIV creates "an environmental milieu" that supports these conditions. The authors call for high-quality controlled epidemiological studies using standardized criteria to further investigate the causation of autoimmune disease in HIV disease.
	Gedmintas L, Solomon DH (2012) ⁷	The increased chronicity of HIV disease has precipitated the increase of chronic health problems seen in this already vulnerable patient population. Recent research suggests that the probability of PLWHA developing osteoporosis is three times higher compared to their HIV-negative counterparts. Rheumatologists must be prepared to treat not only HIV-related bone complications such as avascular necrosis (AVN) and osteoporosis, but also take measures to prevent bone loss in HIV-infected patients.
	Patel N, Patel N & Espinoza LR (2009) ²⁷	The combination of HIV disease and rheumatic manifestations is the result of a complex web of immunologic, genetic, and environmental factors. Geriatric care for people living with HIV will become increasingly prevalent due to the increased life expectancy of this population. Additionally, younger patients with HIV will likely require years of therapy to address chronic issues such as bone disease.
	Nguyen BY, Reveille JD (2009) ¹⁵	Rheumatic manifestations in the HIV-positive population can include arthritis, spondyloarthritis, diffuse infiltrative lymphocytosis syndrome (DILS), vasculitides, connective tissue disease, myopathies and musculoskeletal diseases. Anti-tumor necrotic factor (anti-TNF) agents do not appear to adversely affect CD4 count or viral load if the HIV infection is otherwise controlled with ART. Most anti-rheumatic therapies appear to be safe and effective in HIV-positive patients when used according to protocol.
Vitamin D deficiency in HIV disease (n=2)	Eckard AR, McComsey GA (2014) ²⁸	Long-term survivors of HIV disease have an increased risk of developing co-morbidities such as osteoporosis, cardiovascular disease and overall immune dysfunction – all of which are affected by vitamin D levels. Vitamin D supplementation has widely been recommended for PLWHA, however there is a need for future study examining the effect of vitamin D supplementation and CD4 count, insulin resistance/diabetes, and cardiovascular disease.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Table 1 (continued).

	Pinzone MR, et al. (2013) ⁸	In addition to “classic” risk factors such as low dietary intake, female sex, dark skin pigmentation and low sun exposure, vitamin D status has been shown to also be associated with HIV-related factors of immune activation and side effects of ART. The authors corroborate the latest EACS guidelines to screen for hypovitaminosis D in HIV-positive individuals who also have history of bone disease, kidney disease or other known risk factors. Vitamin D supplementation/repletion is recommended when 25-hydroxyvitamin D levels fall below 10 ng/ml. The authors call for the establishment of optimal Vitamin D dosing regimens in this population as well as the impact of such supplementation in preventing comorbidities.
Orthopedic post-surgical complications/risk factors resulting from HIV disease (n=4)	Issa K, et al. (2103) ⁹	The authors examine outcomes of cementless, primary total hip arthroplasty (THA) due to osteonecrosis in HIV-positive patients (n=34) compared with their HIV-negative counterparts (n=70). Results revealed no significant difference in aseptic implant survivorship (at both five and ten-year follow-ups) between the two cohorts. Postoperative Harris hip scores, activity scores, and SF-36 physical and mental component scores were statistically similar between both cohorts. There were two late infections in HIV cohorts and none in the comparison cohort, pointing to this as a potential complication to monitor.
	Lin CA, Kuo AC, Takemoto S. (2013) ¹⁰	This review examined comorbidities and perioperative complications in HIV-positive patients after primary total hip and knee arthroplasty from 2000-2008, compared with their HIV-negative patients who underwent the same surgeries. The Nationwide Inpatient Sample database estimated that 5,681,024 patients were admitted to hospitals for total hip or knee arthroplasties during this period, 8229 of whom were HIV-positive. There was no statistical difference in total complications for hip or knee replacement surgeries and HIV was not shown to be an independent risk factor for total postoperative infection rate.
	Snir N, et al (2014) ¹¹	Thirty-one HIV-positive, non-hemophiliac patients who underwent total hip arthroplasties (THA) at one hospital during a 12-year period were screened for the postoperative complications of deep infection and revision. Results showed that low rates of complications and need for revisions can be achieved in this population and the authors suggest that THA may improve quality of life in some HIV-positive patients who are appropriate surgical candidates.
	Guild GN, Moore TJ, Barnes W, Hermann C (2012) ¹²	The authors examined whether there is a higher postoperative infection rate after orthopedic trauma for people who are HIV positive and aimed to identify potential preoperative variables that could predict postoperative infection in people living with HIV. Sixty-four HIV positive patients were assessed who underwent orthopedic surgery requiring instrumentation or implant over a 6-year period in one hospital. Results showed an infection rate of 23% among the HIV positive patients compared with a 3.9% rate for the historical control, HIV negative group. The authors concluded that HIV positive patients with CD4 counts <300 undergoing emergent orthopedic trauma surgery are at greater risk for infection. Other factors associated with postoperative infection were hospital stay, polytrauma and low serum albumin.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

2. May MT, et al. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS*. 2014 May;28(8):1193-202.
3. Atalay A, Özdemir O, Guven GS, Başgöze O. HIV infection and shoulder pain: a challenging case. *Rheumatology International*. 2006;26(7):680-682.
4. Cotter AG, Mallon PW. The effects of untreated and treated HIV infection on bone disease. *Curr Opin HIV AIDS*. 2014 Jan;9(1):17-26.
5. Swensen S, Schwarzkopf R. Total joint arthroplasty in human immunodeficiency virus positive patients. *Orthop Surg*. 2012 Nov;4(4):211-5.
6. Ofotokun I1, McIntosh E, Weitzmann MN. HIV: inflammation and bone. *Curr HIV/AIDS Rep*. 2012 Mar;9(1):16-25.
7. Gedmintas L, Solomon DH. HIV and its effects on bone: a primer for rheumatologists. *Curr Opin Rheumatol*. 2012 Sep;24(5):567-75.
8. Pinzone MR1, Di Rosa M, Malaguarnera M, Madeddu G, Focà E, Ceccarelli G, d'Ettorre G, Vullo V, Fisichella R, Cacopardo B, Nunnari G. Vitamin D deficiency in HIV infection: an underestimated and undertreated epidemic. *Eur Rev Med Pharmacol Sci*. 2013 May;17(9):1218-32.
9. Issa K1, Naziri Q, Rasquinha V, Maheshwari AV, Delanois RE, Mont MA. Outcomes of cementless primary THA for osteonecrosis in HIV-infected patients. *J Bone Joint Surg Am*. 2013 Oct 16;95(20):1845-50.
10. Lin CA, Kuo AC, Takemoto S. Comorbidities and perioperative complications in HIV-positive patients undergoing primary total hip and knee arthroplasty. *J Bone Joint Surg Am*. 2013 Jun 5;95(11):1028-36.
11. Snir N, Wolfson TS, Schwarzkopf R, Swensen S, Alvarado CM, Hamula M, Dayan AJ. Outcomes of total hip arthroplasty in human immunodeficiency virus-positive patients. *J Arthroplasty*. 2014 Jan;29(1):157-61.
12. Guild GN, Moore TJ, Barnes W, Hermann C. CD4 count is associated with postoperative infection in patients with orthopaedic trauma who are HIV positive. *Clin Orthop Relat Res*. 2012 May;470(5):1507-12.
13. Takhar SS, Gregory W, Hendey GW. Orthopedic Illnesses in Patients with HIV. *Emerg Med Clin North Am*. 2010;28(2):335-342.
14. Pattamapaspong N1, Louthrenoo W. Musculoskeletal infection in acquired immunodeficiency syndrome. *Semin Musculoskelet Radiol*. 2011 Nov;15(5):541-53.
15. Nguyen BY, Reveille JD. Rheumatic manifestations associated with HIV in the highly active antiretroviral therapy era. *Curr Opin Rheumatol*. 2009 Jul;21(4):404-10.
16. Kigera JW1, Straetemans M, Vuhaka SK, Nagel IM, Naddumba EK, Boer K. Is there an increased risk of post-operative surgical site infection after orthopaedic surgery in HIV patients? A systematic review and meta-analysis. *PLoS One*. 2012;7(8):e42254.
17. Jacofsky D. The incidence and consequences of early wound infection after internal fixation for trauma in HIV-positive patients. *Orthopedics*. 2013 May;36(5):378-9.
18. Pullen S, et al. Physical Therapy as an Adjunct Treatment for People Living with HIV/AIDS: An Allied Health Perspective. *J Allied Health*. 2014;43(2):e11-7.
19. Pullen S, et al. Physical Therapy for People Living with HIV/AIDS: A Provider Needs Assessment - Phase II. *J Allied Health*. 2014;43(3).
20. Shephard RJ. Physical impairment in HIV infections and AIDS: responses to resistance and aerobic training. *J Sports Med Phys Fitness*. 2014.
21. O'Brien KK, Nixon SA. Evidence-based management of an individual living with HIV. *Physiotherapy Canada*. 2010 Summer. 62(3):202-205.
22. Warriner AH, Mugavero M, Overton ET. Bone alterations associated with HIV. *Curr HIV/AIDS Rep*. 2014 Sep;11(3):233-40.
23. Peters B, et al. Screening for chronic comorbid diseases in people with HIV: the need for a strategic approach. *HIV Med* 2013 Jan Suppl 1:1-11.
24. Castronuovo D, Cacopardo B, Pinzone MR, Di Rosa M, Martellotta F, Schioppa O, Moreno S, Nunnari G. Bone disease in the setting of HIV infection: update and review of the literature. *Eur Rev Med Pharmacol Sci*. 2013 Sep;17(18):2413-9
25. McComsey GA, Tebas P, Shane E, Yin MT, Overton ET, Huang JS, Aldrovandi GM, Cardoso SW, Santana JL, Brown TT. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. *Clin Infect Dis*. 2010 Oct 15;51(8):937-46.
26. Lawson E, Walker-bone K. The changing spectrum of rheumatic disease in HIV infection. *Br Med Bull*. 2012;103(1):203-21.
27. Patel N, Patel N, Espinoza LR. HIV infection and rheumatic diseases: the changing spectrum of clinical enigma. *Rheum Dis Clin North Am*. 2009 Feb;35(1):139-61.
28. Eckard AR, McComsey GA. Vitamin D deficiency and altered bone mineral metabolism in HIV-infected individuals. *Curr HIV/AIDS Rep*. 2014 Sep;11(3):263-70.

Competing interests: None declared. Conflict of interests: None declared. All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.