Correspondence

Teriparatide treatment of osteoporosis in an HIV-infected man: a case report and literature review

Low bone mineral density (BMD) and osteoporosis are prevalent in HIV-infected men. Teriparatide – a human recombinant parathyroid hormone – is used to treat severe osteoporosis; however, its use has not been reported in HIV-infected men.

A 70-year-old HIV-infected man presented with lower back pain after carrying heavy furniture and was found to have L1 and L2 compression fractures. Osteoporosis was confirmed on dual-energy X-ray absorptiometry (DXA) with T-scores of -3.9 (BMD $= 0.606\,g/cm^2$) at the lumbar spine, -2.6 ($0.643\,g/cm^2$) at the total hip, and -2.8 ($0.552\,g/cm^2$) at the femoral neck (Table 1).

The patient had well controlled HIV (CD4$^+$ cell count: 880 cells/ml; undetectable HIV viral load) on tenofovir (TDF)/emtricitabine and atazanavir/ritonavir. He reported a family history of osteoporosis, a 40 pack–years history of tobacco use, and heavy alcohol consumption (>3 drinks daily). Pertinent biochemical studies revealed hypogonadism (morning testosterone level: 116.8 ng/dl), vitamin D deficiency [25-hydroxyvitamin D (25OHD) level: 14.5 ng/ml], and low urinary calcium excretion (<34 mg/day).

Given his severely low BMD, especially at the lumbar spine, therapy with teriparatide was initiated for 24 months with subsequent consolidative therapy with alendronate. At the end of year 2, the BMD had increased significantly, with T-scores -2.8 at the lumbar spine, -2.4 at the total hip, and -2.3 at the femoral neck. Compared to baseline, the relative BMD increases at the lumbar spine, total hip, and femoral neck were 35.4, 3.5, and 12.5%, respectively. By the end of year 3, his BMD increased to a T-score of -2.4 at the lumbar spine, with relatively more robust increases to -1.9 and -2.3 at the total hip and femoral neck, respectively.

Among HIV-infected men, the cause of osteoporosis may be multifactorial. Risk factors for osteoporosis such as hypogonadism, vitamin D deficiency, smoking, and low body weight are more common in HIV-infected men than uninfected men. The direct effects of antiretroviral therapy may also play a role. An association has been reported between TDF, which this patient received, and lower BMD. Through alterations in renal phosphate handling, TDF impairs bone mineralization while increasing bone turnover and osteomalacia. These effects may be more pronounced in vitamin D deficiency [1,2]. Although this patient did not have documented renal phosphate wasting, TDF was switched to abacavir as a precaution.

Screening and treatment guidelines in HIV have typically followed those determined for the general population; however, McComsey *et al.* [3] recommended a screening DXA scan for all HIV-infected men aged at least 50 years. If osteoporosis is identified, men should be screened and treated for secondary causes, as was done in our patient. He was offered testosterone replacement for his hypogonadism and started on calcium and vitamin D supplements due to his low urinary calcium excretion and vitamin D deficiency. HIV-infected men on TDF should also undergo assessment for renal phosphate wasting by calculating the fractional excretion of phosphate using simultaneous measurements of serum and urine phosphate and creatinine [1].

Pharmacologic treatment of osteoporosis should be considered for men aged at least 50 years with hip or vertebral fractures or BMD T-score -2.5 or less at the femoral neck, total hip, or lumbar spine. Considerations should also be made for treatment if the lowest T-score is -1.0 to -2.5 (i.e. 'osteopenia') and the 10-year probability of hip fracture at least 3% or major osteoporosis-related fracture at least 20% based on the US Fracture Risk Assessment Tool (FRAX) [5]. However, FRAX has not been validated in HIV-infected men and may underestimate the risk of fracture in these patients [3].

Teriparatide increases BMD by recruiting osteoblast progenitor cells and directly stimulating mature osteoblasts. US Food and Drug Administration (US FDA) approval is for up to 2 years of use, and antiresorptive therapy, generally with a bisphosphonate, is recommended for consolidation as BMD declines quickly once teriparatide treatment has concluded [6].

Teriparatide preferentially increases BMD at the lumbar spine, a site rich in trabecular bone, over the total hip and femoral neck, where it has more modest effects. Thus, one of the recommended uses for teriparatide is for severely reduced BMD, especially at the lumbar spine. This applied to our patient. Trials have demonstrated a reduction in vertebral fractures that is most pronounced in men with pre-existing fractures [4]. Teriparatide does not carry a risk of esophagitis, atypical femoral fractures, or osteonecrosis of the jaw, which can be seen rarely with bisphosphonates. However, patients on teriparatide

Table 1. Yearly change in bone mineral density with treatment.

	Baseline	Year 1 12 months of treatment with teriparatide	Year 2 24 months of treatment with teriparatide	Year 3 12 months of consolidation with alendronate
Lumbar spine – total				
BMD (g/cm²)[a]	0.606	0.772	0.821	0.858
SD for young adult peak BMD (T-score)[a]	−3.9	−3.2	−2.8	−2.4
% Change from baseline[b]		+11.4%	+35.4%	+41.6%
Total hip				
BMD (g/cm²)[a]	0.643	0.660	0.665	0.747
SD for young adult peak BMD (T-score)[a]	−2.6	−2.5	−2.4	−1.9
% Change from baseline[b]		+2.7%	+3.5%	+16.2%
Femoral neck				
BMD (g/cm²)[a]	0.552	0.604	0.621	0.620
SD for young adult peak BMD (T-score)[a]	−2.8	−2.4	−2.3	−2.3
% Change from baseline[b]		+9.4%	+12.5%	+12.3%

[a]Calculated on a Hologic QDR 4500 Dexa scanner with Discovery A software.
[b]The 2% margin of error.

should be monitored for hypercalcemia and hypercalciuria, which are the most common side effects.

To our knowledge, this is the first case report highlighting teriparatide's efficacy in treating osteoporosis in the setting of HIV infection. Investigation is warranted to determine whether teriparatide reduces fracture incidence in HIV-infected individuals.

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Hepatitis B reverse seroconversion in a patient with well controlled HIV infection: a case report and a review of the literature

Hepatitis B virus (HBV) reverse seroconversion is the reactivation of HBV infection despite serologic evidence of recovery from a previous HBV exposure. It is rare in patients with HIV. We describe a case of HBV reverse seroconversion in a patient with well controlled HIV and longstanding serologic evidence of recovery from a previous HBV exposure and review 11 additional cases reported in HIV-infected patients.

The current patient is a 66-year-old man who was diagnosed with HIV in 2004 (CD4$^+$ T-lymphocyte cell count $= 104$ cells/μl, 6%, HIV-RNA $= 464\,641$ copies/ml). At that time, he was also diagnosed with end-stage renal disease due to focal segmental glomerulonephritis and required ongoing management with hemodialysis. He initiated antiretroviral therapy (ART) in 2004 with lamivudine, zidovudine, and lopinavir/ritonavir, and achieved virologic suppression. He eventually failed this regimen in 2007, with evidence of lamivudine resistance. He subsequently received several additional ART regimens due to the emergence of other HIV-resistance mutations. He had inconsistent recovery of his CD4$^+$ cell count (range between 52 and 305 cells/μl) from 2004 through 2010 (Table 1). He is currently receiving darunavir, ritonavir, raltegravir, and etravirine; he has achieved consistent virologic suppression and immunologic recovery with this regimen for nearly 4 years (CD4$^+$ T-lymphocyte cell range $= 243-535$ cells/μl).

Since the time of HIV diagnosis, the patient's hepatitis B status has been evaluated periodically (Table 1). Both qualitative and quantitative assessments of hepatitis B surface antibody (anti-HBs) have been performed. The patient had no history of intravenous drug use and has not reported sexual activity since 2009. In 2004, at the time of HIV diagnosis, the hepatitis B surface antigen (HBsAg) and anti-HBs were negative, and hepatitis B core antibody (anti-HBc) was positive. In 2006, the anti-HBs became positive, indicating immunologic recovery to HBV. This antibody remained positive for many years, but quantitatively began to decline in 2009. In 2013, the anti-HBs became undetectable and the HBsAg became positive, indicating active HBV infection due to reverse seroconversion. The HBV e antigen also became positive at that time, indicating active viral replication. The alanine aminotransferase level became elevated, and the HBV plasma viral load measurement was greater than 170 million copies/ml. Tenofovir was added in an attempt to control the newly active HBV infection. A repeat HBV viral load performed 3 months after tenofovir initiation was 5150 copies/ml.

A search of the published medical literature identified 11 case reports of HBV reverse seroconversion in HIV-infected patients [1–7]. Six of these cases were reported prior to the advent of highly active antiretroviral therapy (HAART). All six patients [1–3] (age range 26–80 years old) had documented immunity against HBV before acquiring HIV, and only one patient [3] was reported to have initiated ART (zidovudine). Recovery from HBV reverse seroconversion was documented in only two patients and one death occurred due to acute hepatitis [2]. A common limitation of these pre-HAART cases is the lack of reported information regarding HIV infection, including use of ART, CD4$^+$ T-lymphocyte cell counts, and HIV plasma viral loads.

The remaining five cases of reverse seroconversion were all reported in patients with a history of poorly controlled HIV [4–7]. Two of these cases also occurred closely following the discontinuation of lamivudine, suggesting a temporal relationship with reverse seroconversion and the removal of HBV active ART [4–5]. In all five cases, patients were able to re-establish serologic evidence of HBV recovery with antiviral therapy.

Poorly controlled HIV is the common characteristic among previously reported cases of HBV reverse seroconversion in HIV-infected patients. The resulting immune suppression with CD4$^+$ T-lymphocyte decline felt to be a reason for HBV reactivation. In contrast, the current case presents a patient that experienced HBV reverse seroconversion despite nearly 4 years of consistently controlled HIV infection with high CD4$^+$ T-lymphocyte levels on ART.

Atypical HBV testing results may also occur in patients with HIV co-infection [8]. The case patient initially presented with a positive anti-HBc alone. An isolated anti-HBc can occur during advanced HIV and usually indicates resolved HBV with an undetectable anti-HBs, but may also indicate occult infection requiring confirmatory HBV-DNA testing [9,10]. While the current patient did not receive DNA testing, a positive

Table 1. History of HIV and hepatitis B laboratory data.

Laboratory value	2004	2006	2007	2008	2009	2010	2011	2012	2013
CD4$^+$ T-lymphocyte cell count (cells/μl)	104	112	134, 198	115, 65	52, 138, 305, 278,	115, 89	243	408, 535	430
Anti-HBs	−	+	+	+	+	+	+	+	−
Quantitative anti-HBs (IU/ml)		62, 71	83	72	49, 52	41, 28	25,17,19	12	<1, <1
HBsAg	−	−		−	−			−	+
Anti-HBc	+	+		+	+			+	+
HBeAb				−	−			−	−
HBeAg				−	−			−	+
HBV DNA									>170 million
ALT (IU/l)	14	8	10	20	7	8	7	16	88
AST (IU/l)	16	15	17	10	18	14	11	21	18

ALT, alanine aminotransferase; anti-HBc, hepatitis B core antibody; anti-HBs, hepatitis B surface antibody; AST, aspartate aminotransferase; HBeAb, hepatitis B e antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

anti–HBs was repeatedly identified on subsequent tests providing evidence of long-term HBV recovery and eliminating the possibility of occult infection.

A temporal relationship between reverse seroconversion and removal of HBV-active ART agents has also been suggested in previous studies. In the current case, reverse seroconversion occurred several years after ART changes, suggesting that a change in ART was not the cause of this patient's reverse seroconversion.

Overall, it is difficult to determine the direct causes for our patient's HBV reverse seroconversion. Previous cases support ongoing monitoring of HBV status in patients with poorly controlled HIV or upon removal of HBV-active ART. The current case is unique by further suggesting a need for periodic quantitative HBV sero-status monitoring even in those with properly controlled HIV.

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Experiences and expectations of participants completing an HIV cure focused clinical trial

The expectations of the eventual outcomes of HIV cure research potentially differ between investigators and people living with HIV (PLHIV) [1]. Understanding expectations and experiences of PLHIV participating in 'cure-focused' clinical trials, particularly the risks of participation, will improve the design of future studies and the process of informed consent. This is particularly important as intervention studies do not deliver immediate clinical benefit, so participant involvement is often altruistic [2], and current studies are also not intended to cure or eradicate HIV; so they are subject to the 'curative misconception' [3]. It is therefore critical that investigators leading cure–related trials become aware of the information that participants may need and what participants perceive as acceptable risks [4]. In this study, we surveyed participants to understand their experiences of a cure-focused clinical trial and their general expectations of this field of research.

Participants were adults receiving antiretroviral therapy (ART) who had completed a clinical trial examining the effects of 14 days of the histone deacetylase inhibitor (HDACi), vorinostat, on HIV latency [5]. This was an intensive study requiring frequent blood sampling and rectal biopsies. At the time of initial recruitment to this study in January 2010, this was the first trial to examine repeated doses of an HDACi in PLHIV, and it was unknown whether there could be short-term adverse effects from the medication, activation of replication of HIV or other viruses, or the potential for HIV virological failure. The long-term effects of HDACi still remain largely unknown.

To examine the expectations of participants before entering the study and the experiences after study completion, a survey was administered. Survey items focused on the experiences and satisfaction with trial participation and the desirability of two potential HIV cure scenarios. The first scenario considered was the desirability of a 'sterilizing cure' which was described as being completely cured with the ability to stop ART and no need for further visits to the doctor for HIV care. The second scenario enquired about the desirability of a 'functional cure' or remission, where HIV was still present, doctor visits to monitor HIV were still required, but ART could be ceased. We also asked participants to rank the importance of five potential benefits of HIV cure: stopping ART, stopping doctor visits, not being able to transmit HIV, unable to be re-infected with HIV, and being considered as someone not infected with HIV. Importantly, survey items did not focus on how this clinical trial might cure HIV as this was not the objective of the trial. Scenarios were compared by Wilcoxon signed-rank (sterilizing versus functional cure) and Kruskal−Wallis (five potential benefits) tests.

All 20 participants completing the clinical trial also completed the survey. Participants expressed high levels of satisfaction with the study and would consider future studies. When using a scale of 0−100, median satisfaction with the overall study experience was 90 (interquartile range 85−95), 85% of patients would consider enrolling in a similar study focused on HIV cure if approached, whereas 30% acknowledged concerns about vorinostat impacting their health at study entry. When considering possible cure scenarios, 90% rated a 'sterilizing cure' very desirable compared to 55% for a 'functional cure' ($P = 0.02$). When ranking five potential benefits of cure, greatest importance was placed on stopping HIV transmission (47% 'most important') and least importance on stopping doctor visits to monitor HIV (0% 'most important') ($P < 0.01$ when comparing all five scenarios) (Table 1).

High levels of participant satisfaction were achieved during an intensive clinical trial focusing on HIV cure. A sterilizing HIV cure was viewed as more desirable than a functional cure, and the potential benefit of not transmitting HIV was considered most important. Currently, there is a scarcity of data on community expectations of HIV cure research, which is surprising, considering the large number of clinical trials currently underway or scheduled to commence in this field [6]. The high priority on blocking HIV transmission was interesting as this is rarely considered in the rationale for the cure agenda [7] or cure-related studies − given the efficacy of current ART in blocking transmission [8]. These results will allow researchers to more accurately

Table 1. Participant expectations on completing an intensive HIV cure focused clinical trial.

Potential cure scenarios ranked most important					P value
Not passing HIV on to others	Not getting HIV for a second time	Being considered a person not infected with HIV	Stopping HIV medications	No longer need to see a doctor for HIV	
47%	32%	32%	25%	0%	<0.01

Desirability of sterilizing versus functional cure outcomes					
	Very desirable	Somewhat desirable	Somewhat undesirable	Very undesirable	
Sterilizing cure 'You are completely cured. So you no longer need to take HIV medications or see doctors about HIV'	90%	10%	0%	0%	
Functional cure 'The virus is still in your blood, but your body is able to keep the virus in check on its own. You no longer need to take HIV medications but you still need to visit your doctor for testing to monitor HIV'	55%	35%	0%	10%	0.02

inform participants about the long-term rationale for current studies and more clearly discuss potential cure scenarios, including whether alternate terms such as 'remission' may be more appropriate than 'cure' in the context of currently available data [4,9]. A broad approach engaging both the general media to enable clear interpretation of results of similar studies [10] and active community engagement is essential to understand and manage expectations of PLHIV in this growing and important field of HIV research.

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