

# Correspondence

AIDS 2009, 23:273–278

## Nonsmoking and other cofactors for Kaposi's sarcoma

The recent series of 28 cases of HIV-negative Kaposi's sarcoma in homo/bisexual men reported by Lanternier *et al.* [1], as well as the subsequent editorial comment by Colman and Blackbourn [2], highlights the strong contribution of cofactors to the development of this malignancy. The primary cause of Kaposi's sarcoma is infection with Kaposi's sarcoma associated herpesvirus (KSHV, also known as human herpesvirus 8), but the vast majority of KSHV-infected people do not develop Kaposi's sarcoma. We estimated that the annual incidence of classic Kaposi's sarcoma (cKS) is about 30/100 000 KSHV-seropositive Mediterranean men over 50 years of age, or approximately 0.3% over 10 years [3]. In contrast, the annual incidence of AIDS Kaposi's sarcoma was about 3/100 in untreated HIV-infected KSHV-seropositive homosexual men, or about 30% over 10 years [4]. This illustrates that HIV is a very potent cofactor, increasing the risk of Kaposi's sarcoma by approximately 100-fold.

There must be cofactors for non-AIDS Kaposi's sarcoma. During 2002–2006, my colleagues and I conducted a case–control study of cKS that encompassed the entire island of Sicily. As in our previous case–control study of cKS [5], the risk of cKS was three-fold lower among KSHV-seropositive people who had ever smoked at least one cigarette per week [6]. Moreover, the risk was even lower (five-fold) among current smokers and intermediate (two-fold) among former smokers. A significantly reduced risk of AIDS Kaposi's sarcoma with smoking was noted in two cohorts of HIV-infected homosexual men in the United States [7,8]. Neither Lanternier *et al.* [1] nor Colman and Blackbourn [2] mention nonsmoking.

In a study by Lanternier *et al.* [1], one of the 28 non-AIDS Kaposi's sarcoma (presumptively cKS) patients was noted to have used corticosteroids for asthma. Systematically collected data on medications would be helpful, as the risk of cKS was increased more than two-fold with asthma in our earlier study [5] and with corticosteroid use in both studies [5,6].

Diabetes mellitus may also prove to be a cofactor. Four (14%) of the 28 non-AIDS Kaposi's sarcoma patients were noted to have diabetes, although the expected prevalence in this population is unknown [1]. The risk of cKS was increased four-fold with diabetes in our recent study [6], but this was not seen in the previous study [5].

Finally, inherited susceptibility surely contributes to the development of Kaposi's sarcoma among people who

have been infected with KSHV. In addition to HLA, as mentioned by Colman and Blackbourn [2], other genes that regulate innate immunity and cytokine balance could be equally important [9,10].

Identification of cofactors can lead to useful interventions to complement drugs directed against KSHV lytic replication [11]. The ultimate goal is not cKS, because the absolute risk is very low [3], but rather to reduce the very serious morbidity and mortality from Kaposi's sarcoma in Africa [12,13]. Neither I nor anyone would recommend smoking to reduce the risk of Kaposi's sarcoma. Instead, understanding the mechanism that underlies this epidemiologic association could lead to an effective prophylactic or treatment. Nicotine probably will not fulfill this function [14]. Something else will.

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*Received: 2 October 2008; revised: 22 October 2008; accepted: 22 October 2008.*

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DOI:10.1097/QAD.0b013e32831f4674

### Efavirenz-induced osteomalacia

We report the case of a 45-year-old white woman who presented with a 3-month history of generalized bone pain and proximal myopathy. She was unable to climb stairs or to get up from a chair without using her hands. Her BMI was 19 kg/m<sup>2</sup>.

She received efavirenz, lamivudine and abacavir for HIV infection. Her CD4 lymphocyte count was 150 cells/ $\mu$ l, her HIV plasma viral load was undetectable. She was treated with levetiracetam for epilepsy. Her last seizure occurred 1 year previously and resulted in several rib fractures. She had a history of chronic hepatitis C infection. The hepatitis C virus (HCV) load was 560 000 copies/ml, aspartate transaminase 72 U/l (reference <35), alanine transaminase 48 U/l (reference <34), gamma glutamyl transferase 136 U/l (reference 1–38). She was an intravenous drug user but currently stable on levomethadone substitution therapy (15 ml twice daily).

Her laboratory findings included a low phosphate at 0.4 mmol/l (reference range 0.8–1.45), mild hypocalcaemia at 2.0 mmol/l (reference 2.2–2.7) and a raised alkaline phosphatase at 393 U/l (reference <104). Serum albumin was slightly low at 31 g/l (reference 35–53), but total protein was within normal range. Parathyroid hormone was significantly elevated at 233.4 ng/l (reference 15–65), 25-hydroxycholecalciferol [25(OH) vitamin D<sub>3</sub>] was less than 7 ng/ml (reference 10–60), and 1,25-dihydroxycholecalciferol [1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> or calcitriol] was low at 10.7 ng/l (reference 17–53). The isoenzyme profile of the alkaline phosphatase showed a raised bone fraction at 264 U/l (reference <60). Beta crosslaps were elevated at 0.844 ng/ml (reference <0.6), indicating increased bone resorption. Calcitonin, renal function parameters and urinary calcium excretion were within normal range but urinary phosphate excretion was low at 6.9 mmol/day (reference 25–64).

Bone scintigraphy revealed activity in the right iliac crest and hip, several ribs, and bilaterally in some metatarsal

bones (Fig. 1). The findings on computed tomography were in keeping with old rib fractures but did not show a radiologic equivalent for the scintigraphic activity.

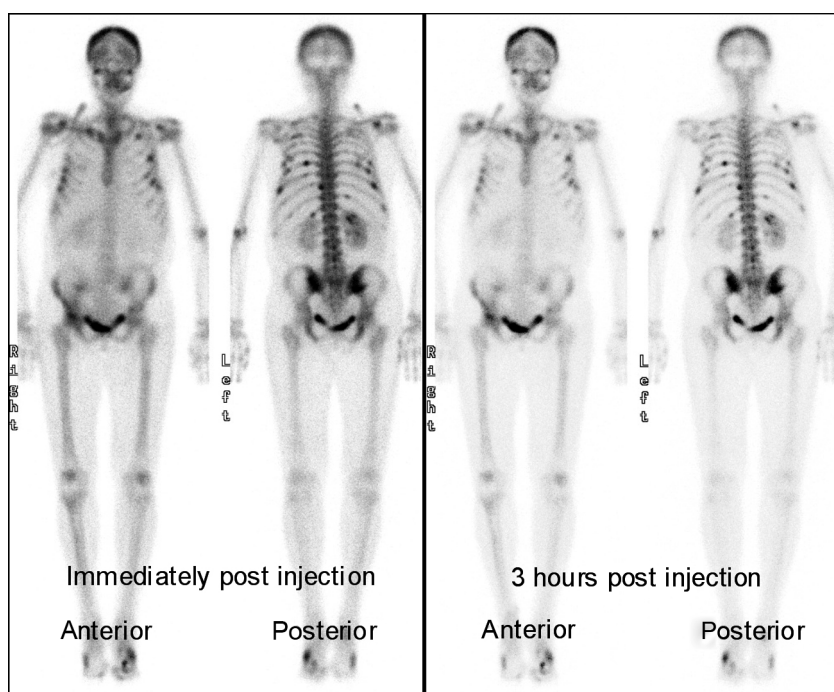
The combination of low-normal calcium, low phosphate, raised alkaline phosphatase with raised bone isoenzyme, raised parathyroid hormone and nondetectable 25(OH) vitamin D<sub>3</sub> is pathognomonic for osteomalacia. The clinical presentation included severe proximal myopathy and a waddling gait.

There was no evidence of coeliac disease or any other malabsorption syndrome. Anticonvulsant medication and other cytochrome P450 inducers, including rifabutin and rifampicin, are associated with osteomalacia due to induction of hepatic metabolism [1–3]. However, this patient received levetiracetam, which is not metabolized via the cytochrome P450 pathway [4].

We propose that the vitamin D deficiency was caused by increased hepatic turnover due to CYP450 enzyme induction by efavirenz. The patient experienced symptoms of withdrawal from levomethadone when efavirenz was commenced suggesting increased enzyme activity [5].

Substitution of vitamin D<sub>3</sub> and calcium did not result in normal serological bone metabolism markers. After changing the antiretroviral regimen from efavirenz-boosted to ritonavir-boosted saquinavir, the laboratory parameters began to normalize. Three months later, the patient was pain free and no longer showed any proximal weakness. Calcium, phosphate, alkaline phosphatase, parathyroid hormone and vitamin D<sub>3</sub> levels were within normal range.

Vitamin D<sub>3</sub> (cholecalciferol) is metabolized by the cytochrome P450 system. It is hydroxylated to 25(OH) vitamin D<sub>3</sub> by hepatic microsomal CYP2R1 [6]. 25(OH) vitamin D<sub>3</sub> is further hydroxylated in the kidneys by



**Fig. 1. Bone scintigraphy.** Several skeletal lesions show radioactive activity immediately and 3 h after injection.

1 $\alpha$ -hydroxylase, into two dihydroxylated metabolites, the main biologically active hormone 1,25(OH)<sub>2</sub> vitamin D<sub>3</sub> and 24R,25(OH)<sub>2</sub> vitamin D<sub>3</sub>.

Enzymatic induction results in accelerated turnover of vitamin D<sub>3</sub> and 25-OH-D<sub>3</sub> to more inactive compounds and decreases the availability of 25(OH) vitamin D<sub>3</sub>, which may lead to a lowered production of 1,25-(OH)<sub>2</sub>D<sub>3</sub> by the kidney. Additionally, drugs as rifampicin and phenobarbital lead to the upregulation of 25-hydroxyvitamin D<sub>3</sub>-24-hydroxylase (CYP24) gene expression, a mitochondrial enzyme responsible for inactivating vitamin D metabolites [7].

To our knowledge, there is only one case report of asymptomatic efavirenz-associated vitamin D deficiency in an African patient that moved to Scandinavia [8]. Another dark-skinned HIV-infected individual was reported to develop symptomatic osteomalacia on therapy with rifabutin [3]. To our knowledge, this is the first report of a white patient presenting with symptomatic osteomalacia due to efavirenz-induced vitamin D deficiency.

It is well known that efavirenz and other non-nucleoside reverse transcriptase inhibitors can induce enzymes of the cytochrome P450 system. However, vitamin D deficiency is rarely recognized in patients receiving the drug, possibly due to the unspecific symptoms of early osteomalacia. We recommend a high level of suspicion in patients complaining of pain or weakness. Regular measurements of calcium, phosphate and alkaline phosphatase may help diagnose the condition early.

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Received: 3 October 2008; accepted: 22 October 2008.

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DOI:10.1097/QAD.0b013e32831f4685

## Which helminth coinfections really affect HIV disease progression?

The study by Walson *et al.* [1] published in the recent issue of *AIDS* describes the results of the first randomized, placebo-controlled trial to evaluate the impact of soil-transmitted helminth infection on CD4<sup>+</sup> cell count and viral load among HIV-1, geohelminth coinfecting adults. Walson *et al.* [1] found that the elimination of *Ascaris* infection is associated with a mean 109 cell/ $\mu$ l rise in CD4<sup>+</sup> cell count ( $P=0.003$ ) and a 0.54 log<sub>10</sub> reduction in viral load ( $P=0.09$ ). Although these results lend support to the hypothesis that helminthes may have a direct impact on markers of HIV disease progression, the study is worth evaluating further methodologically as the interpretation of its results may have far-reaching implications for public health policy and practice.

The study by Walson *et al.* [1] contains multiple ambiguities, beginning with its analytic plan. It is unclear whether the authors compared the time-dependent trends in CD4<sup>+</sup> cell counts and viral load between the two study arms or whether they evaluated cross-sectional differences in serial fashion. The difference between these two methods is significant as a 0.54 log<sub>10</sub> viral load decline in the experimental arm is much less impressive if there were a concurrent drop in viral load of similar magnitude in the control arm. It would be helpful to have presented the mean CD4<sup>+</sup> cell count and viral load for each helminth species, before and after treatment, in both arms. It is also unclear whether the authors accounted for the inherent variability of HIV-1 RNA measures. This is important when dealing with small viral load changes ( $<1.0$  log<sub>10</sub>), as viral setpoint differences in the order of 0.3 log<sub>10</sub> occur via natural variation [2–4]. These inherent fluctuations can affect statistical power calculations and potentially cause a regression-to-the-mean effect if not controlled for in the study's design or analysis.

It is not only the variability of viral load measures that could have affected the results, but also the absolute values. At a level of 4.75 log<sub>10</sub>, the mean baseline viral load of this study population is higher than other studies [5–8]. A subgroup analysis from our own cohort demonstrated that helminth elimination was associated with a greater viral load decline among individuals with a baseline viral load higher than 5.0 log<sub>10</sub> [6]. Walson *et al.* [1] report that mean baseline viral load of the *Ascaris*-infected participants was 0.21 log<sub>10</sub> higher among experimental participants compared with the controls. For all other helminth species, viral loads were higher in controls compared with the experimental arm. Thus, it may be that the viral load decline was actually attributable to higher baseline HIV RNA levels and not to the particular helminth species.

In support of their findings, Walson *et al.* [1] cite previous studies that purportedly reported species-specific effects of helminth infection on HIV viral load and CD4<sup>+</sup> cell

count. However, in our study among Zambian adults [6], we reported that individuals with moderate to high intensity infections experienced a nonsignificant trend of 0.12 log<sub>10</sub> viral load reduction after intestinal helminth clearance. These moderate-to-high intensity infections just happened to occur among individuals infected with *Ascaris* and hookworm. When we assessed the impact of each species on viral load (controlling for infection intensity), we found no species-specific differences.

Walson *et al.* [1] also claim that past studies were inherently limited because they were not randomized. The assertion is oversimplistic, as the validity of their results is diminished by the post-hoc nature of their stratified analysis. Findings that do not reflect an *a priori* hypothesis are prone to spuriousness. Multiple comparisons that are not planned from study outset inevitably yield a significant association, merely by chance alone. Such post-hoc analyses, therefore, can only generate and not test hypotheses [9]. Walson *et al.*'s [1] *a posteriori* analysis, therefore, raises questions as to why HIV was impacted by infection with *Ascaris*, but not by hookworm or *Trichuris*.

The authors postulate that *Ascaris* may have a greater impact on HIV pathogenesis because it is the largest geohelminth and, therefore, may stimulate host immunity more than other species. There are problems with this argument. First, there is no evidence that *Ascaris* activates host immunity more than other intestinal helminthes. Second, it is not the larger size of the organism but the greater intensity, invasiveness, and immunogenicity of the infection that likely would cause a more robust activation of host immunity [10]. It is possible that *Ascaris* could influence HIV immunology more than other helminthes not because of its size or infectious load, but because it may more intimately interact with gut-associated lymphoid tissue implicated as integral to mechanisms of HIV immunopathogenesis [11]. However, this might apply to other geohelminthes as well.

Ultimately, the results of the current study suggest that the story of HIV–helminth interactions is far from over. Additional, well designed studies must be conducted to more definitively address the issues raised, focusing not just on helminth infections as a whole, but species-specific effects as well.

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Received: 8 September 2008; accepted: 24 October 2008.

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DOI:10.1097/QAD.0b013e32831fc692

## Which helminth coinfections really affect HIV disease progression?

We appreciate the thoughtful comments by Modjarrad [1] on our recent study, ‘Albendazole treatment of HIV-1 and helminth co-infection: a randomized, double-blind, placebo-controlled trial’ [2]. Modjarrad [1] highlights several important issues that merit clarification, specifically concerning the analytical plan, merits of randomization, and species-specific outcome evaluations.

As outlined in our paper, we conducted a traditional randomized clinical trial. Individuals were enrolled at baseline, randomized to the intervention or placebo, and followed up at a prespecified standardized single time-point. CD4 cell counts and HIV-1 RNA levels at follow-up were compared between the two trial arms (albendazole and placebo) after controlling for baseline values. The mean initial CD4 cell counts and viral load by species are provided in the table of the manuscript by Walson *et al.* [2]. This was not a cross-sectional observational study, and the trial was designed with a single follow-up time, so the methods of analysis mentioned by Modjarrad [1] would not be applicable.

Modjarrad [1] erroneously suggests that the analyses were conducted *a posteriori*. As noted in the methods section of our paper, the statistical analysis plan was determined *a priori*. The decision to include a modified intent-to-treat analysis of follow-up CD4 cell counts and HIV-1 RNA levels as well as the decision to stratify results by helminth species were *a priori* decisions. In fact, a post-hoc analysis of changes in CD4 cell count and HIV-1 RNA between the randomization arms suggests a significant benefit of

deworming on CD4 cell counts in all helminth-infected individuals (decrease in CD4 cell count of 72 cells/ $\mu$ l in the placebo arm compared with a decrease of 26 cells/ $\mu$ l in the treatment arm;  $P=0.043$ ) as well as in the *Ascaris lumbricoides* infected cohort (decrease in CD4 cell count of 99 cells/ $\mu$ l in the placebo arm compared with an increase of 9 cells/ $\mu$ l in the treatment arm;  $P=0.005$ ). Because we had not elected *a priori* to include ‘change in CD4’ or ‘change in RNA’ as an outcome, we did not include these findings in our paper and presented only data derived from the *a priori* statistical analysis plan.

Modjarrad [1] seems to confuse issues of randomized trial design with analyses of multiple outcomes. It is important to recognize the inherent superiority of the randomized controlled trial over observational studies. Prior observational studies of helminth infection in HIV-1 infected individuals have been limited by potential confounding. These studies have compared helminth-infected and helminth-uninfected individuals or have included historical controls. Significant differences exist at baseline in rates of disease progression, immune activation, and natural variation in the rate of CD4 cell count decline and plasma HIV-1 RNA levels between these comparison groups. The strength of the randomized controlled trial study design is precisely that differences due to natural variation are randomly distributed between the comparison groups. If our analysis resulted in a type II error (not finding an effect when one truly exists), this would most likely be due to limitations in sample size (statistical power) and not due to inherent differences between the groups.

Finally, as we noted in our conclusions, we concur with Modjarrad [1] that this study raises additional questions concerning the species-specific nature of the effects observed and that additional well designed randomized trials should be conducted to answer these questions.

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Received: 27 October 2008; accepted: 27 October 2008.

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DOI:10.1097/QAD.0b013e32831fc6a5