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AIDS 2015, **29**:745–753

Protein-losing enteropathy in an HIV-infected pediatric patient with previous disseminated *Mycobacterium genavense* infection

Disseminated *Mycobacterium genavense* infection accounts for 4–13% of nontuberculous mycobacteria infections in patients infected with HIV [1,2]. Those with poorly controlled HIV infection and $CD4^+$ cell counts below $100/mm^3$ are currently at the highest risk of acquiring this disease [3]. The clinical presentation is similar to that of infection by *Mycobacterium avium* complex (MAC) [4], although *M. genavense* has a greater affinity for the gastrointestinal tract [5]. New clinical conditions involving the gastrointestinal tract in HIV are emerging, such as retractile mesenteritis, described in 2013 [3], but there are no reports of intestinal lymphangiectasia due to *M. genavense* in HIV patients. Cases caused by MAC infection have been described [6,7], but they are uncommon since the introduction of highly active antiretroviral therapy (HAART) [8]. Furthermore, there are no reported cases of protein-losing enteropathy associated with nontuberculous mycobacteria infection in pediatric HIV patients.

We present the case of a 13-year-old boy diagnosed with HIV infection in 2008 after consulting for persistent diarrhea, weight loss, and abdominal and mediastinal lymphadenopathy due to disseminated *M. genavense* infection. At the time of the diagnosis, $CD4^+$ lymphocyte count was $1/mm^3$ and viral load was 47 000 copies/ml. The patient was simultaneously started on primary prophylaxis against *Pneumocystis* jirovecii with trimetoprim-sulfametoxazol, A antiretroviral therapy (ART) with abacavir, lamivudine, and efavirenz, and mycobacteriosis treatment with azithromycin, ethambutol, and rifabutin. At 8 months, failure of mycobacteriosis treatment was evidenced by persistent diarrhea, and treatment was changed to levofloxacin, ethambutol, rifabutin, and amikacin. This regimen was maintained for 22 months (amikacin for 10 weeks) and at completion, secondary levofloxacin prophylaxis was started, with a satisfactory clinical and radiologic response. At the same time, the patient experienced virologic failure (viral load, 8100 copies/ml) and the ART components were changed to ritonavir-boosted didanosine, zidovudine, and lopinavir, with a good response. Since the start of that regimen to the time of writing, viral load has been undetectable (<50 copies/ml) and $CD4^+$ lymphocyte count always above $300/mm^3$.

In September 2011, severe hypogammaglobulinemia [immunoglobulin G (IgG) 167 mg/dl, IgA 145 mg/dl, and IgM 20 mg/dl] and moderate hypoalbuminemia (2.8 g/dl) were detected on routine 3-month follow-up testing. Three months later, the patient presented facial and lower limb edema, viral load was undetectable, and $CD4^+$ lymphocyte count was $1007/mm^3$. Proteinuria was ruled out, and an alfa-1-antitripsin level of 4.76 mg/g in stool samples (later confirmed) established the diagnosis of protein-losing enteropathy. Abdominal MRI showed signs consistent with intestinal lymphangiectasia: dilation of lymphatic vessels, small intestinal wall thickening, and ascites, as well as retroperitoneal and mesenteric adenopathy. Video capsule endoscopy and intestinal biopsy confirmed the diagnosis (Fig. 1). Smear microscopy findings and mycobacteria detection by molecular biology techniques were negative in biopsied tissue. Scintigraphy with ^{99m}Tc-labeled albumin showed no abnormalities. In March 2012, a low-fat diet with medium chain triglyceride supplementation and high-protein shakes was established. Periodic intravenous infusion of nonspecific serum albumin and gamma globulin was also started. Despite a progressive decrease in fecal α-1 antitrypsin values on serial monitoring (currently 1.29 mg/g), the patient continued to experience intermittent edema and gastrointestinal discomfort, whereas adherence to ART and immunovirologic control were both good.

We present the first reported case of intestinal lymphangiectasia due to *M. genavense* in a pediatric patient with HIV infection. The parallel pathogenesis and symptoms of this condition with those of MAC suggest that the mesenteric and retroperitoneal lymphadenopathy is related to chronic obstruction of lymphatic flow to the intestinal territory, which would lead to a loss of substances due to excessive pressure in the intestinal lumen [9]. Other studies have provided ^{99m}Tc-labeled albumin scintigraphy findings to support this idea [9,10], but this test yielded normal results in our patient.

Management of this entity is difficult because the disruption of lymphatic vessels is currently irreversible and the treatments attempted (somatostatin analogues) have not been effective [6]. Dietary supplementation with medium chain triglyceride may attenuate the symptoms [7] because they avoid the lymphatic system, thereby reducing pressure in the lymphatic vessels. Replacement therapy by periodic infusion of nonspecific serum albumin and gamma globulin is the only option at this time [6,7,9,10].

To date, there are no data regarding a possible association of *M. genavense* with intestinal lymphangiectasia; hence,

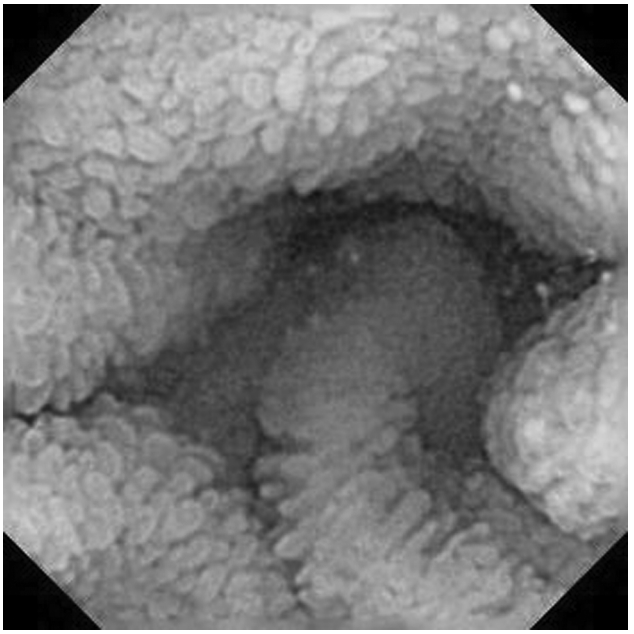

Fig. 1. Accumulations of PAS-positive histiocytes. Edematous villi with mild lymphangiectasia.

the approach used was extrapolated from the treatment for MAC. We believe it is important to make this association known so that suspicion will be raised when hypoproteinuria occurs in an HIV-infected pediatric patient with previous intestinal mycobacteriosis, despite resolution of this condition and good immunovirologic control.

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Proximal tubular dysfunction in a HIV-1 patient with coadministered tenofovir disoproxil-fumarate and ibuprofen

Tenofovir disoproxil-fumarate (TDF) is recommended for the treatment of HIV-1 as part of combination antiretroviral therapy. TDF is excreted by glomerular filtration and active secretion in the proximal tubulus. Long-term TDF exposure may accelerate renal function decline, and cause proximal tubulopathy in HIV-1 patients [1]. Toxic intracellular TDF concentrations lead to dysfunction of the proximal tubulus, characterized by the impaired ability to reabsorb solutes including bicarbonate, phosphate, glucose, and low-molecular weight proteins.

The multidrug-resistance-protein 4 transporter (MRP-4), an active transporter in proximal tubulus cells, coordinates the secretion of TDF at the apical side. Commonly used medicines can impair the function of MRP-4 *in vitro*, including nonsteroidal anti-inflammatory drugs (NSAID), salicylates, and phosphodiesterase-5 inhibitors [2–4]. Whether the concomitant use of TDF and these MRP-4 inhibitors is associated with renal dysfunction *in vivo* is unknown. We describe a patient with proximal tubulopathy following the concomitant exposure to TDF and ibuprofen, a known MRP-4 inhibitor *in vitro*.

A 57-year-old Caucasian man had a longstanding well controlled HIV-1 infection (<20 copies/ml) on coformulated rilpivirine/emtricitabine/TDF 25/200/245 mg. His medical history was unremarkable. The estimated glomerular filtration rate (by the Modification of Diet in Renal Disease formula) of this patient was more than 90 ml/min and his urinalysis has always been normal. During routine control, the patient mentioned that he has taken ibuprofen 600 mg TID since a tooth extraction 2 weeks earlier. The urinalysis during this follow-up showed new onset +1 proteinuria, and normoglycemic glycosuria. The urine protein-to-creatinine ratio was increased to 31.28 mg/mmol and the albumin-to-protein ratio was 0.11. Despite hypophosphatemia, the fractional excretion of phosphate was above 5% and therefore abnormal. The glomerular filtration rate was slightly decreased (87 ml/min). Serum potassium and bicarbonate were normal. A potential NSAID-related TDF-associated proximal tubulopathy was suspected. The discontinuation of ibuprofen resulted in a protein-to-creatinine ratio reduction to normal values (9.30 mg/mmol) with the disappearance of glycosuria, 1 week later. Full renal recovery was noted during subsequent visits, and TDF was continued throughout the course of the proximal tubulopathy.

This case illustrates that frequently used medicines, acting as MRP-4 inhibitors *in vitro*, may also exacerbate TDF-associated renal toxicity *in vivo*. Ibuprofen coadministration with TDF appeared to be a contributor to the observed proximal tubulopathy in our patient. Of notice, the patient did not have a history of renal impairment while on TDF, and developed the signs of tubular injury after ibuprofen administration. Therefore, the renal injuries likely represent a drug interaction between TDF and ibuprofen.

The active transport of TDF in the proximal tubulus cell can be impaired by MRP-4 inhibitors, resulting in tubular toxicity *in vitro* [2]. Large observational cohort studies have identified demographical and HIV-related predictor variables for accelerated renal function decline on TDF [1,5,6]. However, exposure to MRP-4 inhibitors was not examined in these studies, and may be an important unmeasured confounder.

Only one small case series has retrospectively evaluated the influence of physician-prescribed diclofenac on the occurrence of TDF-related proximal tubulopathy. Although the authors described high rates of tubular injury following diclofenac administration (13/89 patients), their study did not include an evaluation of other potential MRP-4 inhibitors, including ibuprofen [7].

This case study is the first to highlight the possible toxic effects of coadministrating other MRP-4 inhibitors than diclofenac to HIV-1 patients on TDF containing regimens. Not only NSAIDs, but also sildenafil and salicylates have been associated with MRP-4 inhibition *in vitro*. Especially the inhibitory effect of sildenafil *in vivo* could be of interest in HIV-1-infected MSM because a very substantial part of HIV positive men use sildenafil often in supratherapeutic dosage. Also, most of these potential MRP-4 influencing drugs are freely available or ordered via the internet [8]. The inhibitory effect may even be more pronounced in patients with genetic variations in ABCC4 (the gene encoding for MRP-4) associated with its impaired function [9,10]. A study to address the additional influence of these compounds on the potential of TDF to cause proximal tubulopathy, and the subgroups at risk, should therefore be done.

In sum, this case indicates that commonly used and freely available drugs that inhibit MRP-4 may have additional renal tubular toxicity in HIV-1 patients taking TDF as part of their combination antiretroviral therapy. Although not all parameters associated with proximal tubular dysfunction (specific low-molecular weight proteins, uric acid) were assessed in this patient, the recovery of tubular dysfunction after NSAID interruption strongly suggests a causal relation. HIV physicians and patients should be aware that NSAID coadministration, and other potential MRP-4 inhibitors, with TDF may be associated with TDF-related proximal tubulopathy until a well designed study has shown otherwise.

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Management guidelines for non-AIDS morbidity result in increased screening but no change in primary prevention implementation

We read with interest the report from De Socio *et al*. [1] in the AIDS February edition, which described decreasing cardiovascular risk (CVR) amongst Italian HIV-positive patients from two large multicentre surveys between 2005 and 2011. The authors attribute this finding to decreased smoking rates, the more metabolically friendly profile of newer antiretroviral agents and the impact of medical education programs aimed at improving CVR management implemented across the centres from which the cohorts were recruited. Unfortunately, our local experience of the impact of education programmes on CVR management is more sobering.

In April 2013, we developed local education tools and guidelines for CVR management in HIV-positive patients. They were easy-to-read, colour-coded flow charts that included advice on the type and frequency of screening tests, thresholds for the initiation of primary prevention therapy and triggers for referral to specialists. The guidelines were released in concert with an intensive education programme that consisted of 6 weeks of weekly physician training sessions along with internet and E-mail based promotion and distribution of the new guidelines, which were available in electronic and hard copy formats in clinic review rooms.

An audit of compliance with recommendations for the screening and management of CVR was performed prior to and 1 year after the implementation of the education tools to determine the impact on practice. Two unique groups of 100 consecutive HIV-positive outpatients who attend the Department of Infectious Diseases, Alfred Hospital, for routine HIV care pre- and postintervention were compared. Data were collected retrospectively from the electronic medical record and pathology systems with all results from the last 2 years included.

The results were summarized by group, using Fisher's exact or chi-squared tests as appropriate to evaluate differences in proportions, or the Mann–Whitney *U*-test for continuous data with all statistical analyses performed using Stata 11.0/IC (College Station, Texas, USA). The project was approved by the Alfred Ethics committee (Project number: 167/13).

Table 1 details patient characteristics and CVR parameters pre- and postintervention. As expected and given the nature of the epidemic in Australia, the majority of patients were male (90.5%) with a median age of 49 years. Prior to the intervention, surprisingly high numbers of patients had not had a blood pressure recorded in the previous 2 years nor been screened for diabetes. Despite awareness of the strong association between cigarette smoking and a number of medical conditions, smoking status had not been documented in one-third of patients.

The intervention led to a significant improvement in screening for diabetes, hypertension and cigarette smoking (Table 1). Yet, although the number of patients

Table 1. Patient demographics and cardiovascular risk parameters pre- and postintervention.

	Pre-intervention	Postintervention	*P*
N	100	100	–
Male	93 (93%)	88 (88%)	0.230
Age (years)	49 (21–72)	49 (22–78)	0.635
Smoking status			
Never smoked	24 (24%)	44 (44%)	0.002
Ex-smoker	5 (5%)	9 (9%)	0.269
Current smoker	38 (38%)	37 (37%)	0.884
Not documented	33 (33%)	10 (10%)	<0.001
Diabetic status			
Nondiabetic	58 (58%)	74 (74%)	0.016
Diabetic	6 (6%)	12 (12%)	0.139
Not screened	36 (36%)	14 (14%)	<0.001
History of cardiovascular disease[a]	7 (7%)	8 (8%)	0.789
Framingham risk score, mean[b]	10 (1–53)	8 (1–53)	0.537
Blood pressure recorded	65 (65%)	88 (88%)	<0.001
Systolic blood pressure (mmHg)	125 (90–170)	122.5 (90–180)	0.742
Fasting lipids performed	81 (81%)	83 (83%)	0.714
Fasting lipid parameters[c]			
Total cholesterol	4.5 (2.6–9)	4.7 (2.2–7.2)	0.912
HDL-cholesterol	1.0 (0.1–2.0)	1.0 (0.4–2.2)	0.153
LDL-cholesterol	2.6 (1.2–5.0)	2.9 (0.8–5.1)	0.544
Triglycerides	1.6 (0.7–10.9)	1.6 (0.6–14.6)	0.573
eGFR[d]	85.5 (8–99)	86.5 (35–99)	0.481

Median (range) or *n* (%) as appropriate.
[a]Documented diagnosis of coronary heart disease, stroke or peripheral vascular disease.
[b]Framingham risk score calculated using the online equation available at: http://old.mdcalc.com/framingham-coronary-heart-disease-risk-score-si-units/. Complete data necessary to calculate a Framingham risk score were available on 60 patients pre-intervention and 77 patients postintervention.
[c]Total cholesterol available in 81 pre- and 83 postintervention; high-density lipoprotein (HDL)-cholesterol available in 67 pre- and 74 postintervention; low-density lipoprotein (LDL)-cholesterol available in 61 pre- and 71 postintervention, triglycerides available in 81 pre- and 82 postintervention, all mmol/l.
[d]Estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI equation (chronic kidney disease epidemiological collaboration), ml/min available on all participants pre- and postintervention.

having routine blood pressure monitoring increased (88% post compared with 65% pre-intervention), this did not translate into increased antihypertensive prescription or improvements in systolic blood pressure (SBP). Pre-intervention 23 participants were on an antihypertensive compared with 17 postintervention ($P = 0.291$). Twelve participants pre- and 19 postintervention had an SBP at least 140 mmHg, of whom five (41.6%) and 13 (68.0%) participants, respectively, were not receiving any antihypertensive treatment ($P = 0.151$).

Compliance with guidelines for statin use was high in both periods (94 and 92%, respectively) and there was no change in the number of patients receiving a statin (24% in both periods) or the type of statin prescribed (atorvastatin, rosuvastatin or pravastatin in equal use). Of patients receiving a statin, only eight (17%) had a total cholesterol level less than 4.0 mmol/l (the target currently recommended by the Australian National Vascular Disease Prevention Alliance) [2]. There was also a persisting small percentage of patients who fit criteria for statin therapy but who were not receiving it (6% pre- and 8% postintervention).

Although representing only a small sample of patients from a single centre, our findings are consistent with an audit performed in HIV-positive patients attending General Practices in Australia, which notably found that 25% of hypertensive patients were not on an antihypertensive treatment [3].

As the incidence of AIDS-related complications continues to decrease, the life-expectancy and quality of life of HIV-positive patients will increasingly be determined by the adequacy of the prevention and management of serious non-AIDS events and in particular cardiovascular and renal disease [4]. Our data show that improvements in screening for CVR factors can be achieved with education tools, but these alone were not sufficient to improve the implementation of primary prevention therapies. Perhaps because in this modern era, we are expecting infectious diseases physicians to also be expert cardiologists, endocrinologists and nephrologist when, in truth, a change in the model of HIV care provision may be needed.

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Response to: the relationship of physical performance with HIV disease and mortality: a cohort study

We would like to congratulate the Journal of *AIDS* for the publication of the study entitled 'The relationship of physical performance with HIV disease and mortality: a cohort study', by Greene *et al.* [1]. It is a cohort study with a large sample size that reported findings about the impact of HIV infection on physical performance, and consequently, on mortality rates. The results presented are of utmost importance to science because of their clinical and social relevance.

However, some methodological aspects need clarification and should be discussed further.

Although the authors reported that the methodology of the ALIVE project has been described previously by Vhahov *et al.* [2], some data regarding the characteristics of the study participants are missing. Greene *et al.* [1] do not present the results related to the period and frequency of injecting drug use by the surveyed population. There is a lack of information about the current use of drugs, pharmacological treatment and average time since diagnosis of HIV infection. These data could provide a better interpretation of the findings, as these variables may be associated with the outcome.

The method used to verify the physical performance, restricted to the balance and activities of the lower limbs, The Short Physical Performance Battery (SPPB), has been validated for the elderly population, but the median age within the study population was 51 years. The authors stated that there was no consensus on the best method to assess physical performance in people infected with HIV and that the SPPB method was suited for young adults. However, this can compromise the findings, as the method was not validated for that population [3].

There are several benefits provided by regular physical activity to HIV-infected people, such as increased lean body mass, bone mineral density and muscle strength, fat percentage reduction and aerobic fitness improvement. These results suggest that physical activity contributes to the development of physical performance [4]. The authors did not measure the level of physical activity and exercise of the study participants.

The BMI was used as a method for assessing obesity in research participants; however, this is not the most appropriate method, given that the BMI does not take into account body composition. The prevalence of HIV-associated lipodystrophy is significant in this population, especially among those individuals receiving antiretroviral therapy [5]. By the way, this is an important information that was not presented by the authors, that is the percentage of participants receiving antiretroviral therapy, including the treatment regimens used and the time of use of antiretroviral drugs. Some classes of antiretroviral drugs – such as the protease inhibitors and reverse transcriptase inhibitors – can cause the loss of peripheral subcutaneous fat (lipoatrophy) and/or central fat accumulation (lipohypertrophy), as well as metabolic changes such as insulin resistance and metabolic syndrome, leading to an increased risk for cardiovascular disease [6]. For this reason, other methods should be used to assess obesity and body-fat distribution. Establishing the diagnosis of lipodystrophy in

research participants would be very interesting to examine the effects of this variable on mortality.

In summary, these contributions serve to clarify some points that may interfere in the interpretation of the data. The suggestions are intended to contribute to the study improvement and inclusion in the ALIVE protocol that will possibly continue to be used by new studies resulting from this project.

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The relationship of physical performance with HIV disease and mortality: authors' response

We appreciate the comments of Trevisol *et al*. [1] regarding the significance of our recent article on the relationship of physical performance with HIV infection and with mortality [2]. Below, we provide additional information in response to their specific inquiries regarding other potential confounding exposures (e.g. injection drug use, HIV duration and treatment), the outcome measure of physical performance used, and the potential effects of physical activity and body composition on our observed association between HIV and reduced physical performance.

The AIDS Linked to the Intra Venous Experience (ALIVE) cohort follows injection drug users (IDUs) both with and without HIV infection collecting detailed risk behavior data at each 6-month follow-up visit. During 27 years of observation in our cohort, the prevalence of active injection drug use has notably declined from 81% at cohort entry to only 23% of current participants. Table 1 in the article [1] provides the proportion of participants who had recently injected drugs both at the baseline physical performance assessment and across all study visits included in this analysis. As illustrated in the Supplemental Table, recent injection drug use was associated with better rather than reduced physical performance in univariate analysis. Previously, we have noted a 'healthy drug user effect' [3] whereby individuals that are able to maintain active illicit drug use are often free of debilitating disease with lower prevalence of multimorbidity and relatively better physical function. Given this known effect in our cohort, we decided *a priori* not to include injection drug use as a variable in our multivariable analyses, and hence did not provide more details in the article.

However, it should be noted that this 'healthy drug user effect' reflects our internal comparison of current injectors to former injectors. It is plausible that in an analysis performed in other settings, IDUs will actually have reduced physical performance compared with other non-IDU populations. Finally, even when active injection status was incorporated into our models, our findings were not substantially altered. For example, the association of HIV infection with reduced physical performance was identical with an odds ratio of 1.30 irrespective of whether current infection was included in models [95% confidence interval (CI), 1.11−1.51] or not (95% CI, 1.12−1.52).

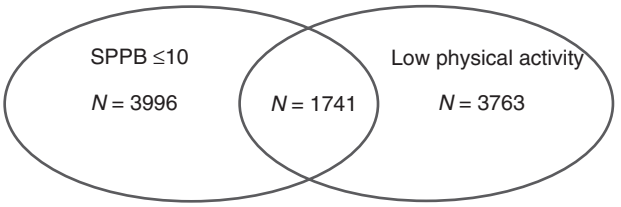
Although we collect data on when HIV infection was originally diagnosed among our participants, we consider

this estimate to be unreliable and did not include in our analysis. Estimated duration of HIV infection is wholly dependent on when an HIV diagnosis is made; substantial variability exists in how and when individuals seek HIV testing or enter care in response to symptoms. Alternatively, we incorporated $CD4^+$ nadir as a measure of the severity of HIV disease progression prior to treatment and reported an increased likelihood of reduced physical performance associated with lower $CD4^+$ cell count nadir. By performing routine HIV testing on HIV-uninfected participants, we do have estimated dates of seroconversion for 131 individuals. In the analysis of this subset, we failed to observe a dose–response increase in the likelihood of reduced physical performance with increasing years since seroconversion compared with HIV-uninfected participants. An estimated 15 years or more since seroconversion was associated with reduced physical performance (odds ratio 1.41; 95% CI, 1.01–1.96); associations with age, sex, education, depressive symptoms, and comorbidities persisted in this model.

Table 1 in the article [1] also includes the proportion of participants on antiretroviral therapy (ART) at baseline (56.2%) and across all visits (65.6%). As further context, the distribution of ART regimens by class reported across study visits included 62% protease inhibitors, 22% nonnucleoside reverse transcriptase inhibitors, 10% combination of protease inhibitors/nonnucleoside reverse transcriptase inhibitors, and 6% other classes; nucleoside analogs were used almost uniformly. The median duration of ART for participants during the study period analyzed was 2.7 years. Compared with other 'in-care' clinic-based cohorts, we follow participants in and out of care and have observed frequent treatment interruptions and inability to maintain viral suppression [4,5]. However, our limitation in comparison to clinic-based cohorts is that we do not prescribe ART and rely on participant self-report of ART usage. Instead, we emphasize examination of effective ART as measured by viral suppression. We observed a strong association of detectable HIV RNA levels with reduced physical performance.

As Trevisol *et al*. [1] point out, the short physical performance battery (SPPB) was originally developed and validated in populations substantially older than our study population. Physical function has been assessed using varying approaches relying on both subjective and objective measurements. To date, there remains considerable debate on what approach constitutes the 'gold' standard. In the absence of a clear gold standard, we sought to apply the SPPB as a standardized, objective measure of physical performance. Our findings do demonstrate strong criterion validity of SPPB in our younger population with the observation of expected associations of lower SPPB scores with factors previously associated with reduced physical function (age, female gender, comorbidities) and independent, dose–response increases in mortality risk associated with lower SPPB scores.

We strongly agree that physical activity is an important construct that merits further investigation in HIV-infected populations. In terms of evaluating physical activity in ALIVE, we did not have any standardized measures available during this study period. As a surrogate, we evaluated health-related limitations in physical activity from the Medical Outcomes Survey-HIV ('Does your health now limit the kinds or amounts of vigorous activities you do, like lifting heavy objects, running, or participating in strenuous sports?' [6]), which has previously been incorporated as a marker of limited physical activity in frailty phenotype assessments [7,8]. As illustrated in the Venn diagram, there was only limited overlap in the proportion of study visits wherein persons were characterized both with low physical activity (defined as severe limitation to above question) and with reduced physical performance.



When this measure of low physical activity was included in multivariable models, it was significantly associated with reduced physical performance but this did not impact the association of other covariates (e.g., HIV, age, sex) with reduced physical performance. Recent studies from the general population have shown that the physical performance-to-mortality relationship in midlife is robust to adjustment for physical activity [9]. Similarly, in our study including low physical activity in the survival analysis did not substantially attenuate the associations of reduced physical performance or of HIV infection with mortality; low physical activity was not associated with increased mortality in multivariable analysis.

Although abnormalities in fat distribution would be interesting to examine in relation to physical performance, we currently do not have these data available in ALIVE. Lipodystrophy is a particularly difficult construct to reliably and efficiently measure in our observational cohort setting.

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Conflicts of interest

There are no conflicts of interest.

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