

## Selenium deficiency and HIV infection

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### Abstract

Selenium is a non-metallic chemical element of great importance to human health. Low selenium levels in humans are associated with several pathological conditions and are a common finding in HIV infected individuals. We conducted a review of the literature to assess if selenium deficiency or selenium supplementation could play a role in modifying the clinical course of HIV disease.

Several studies investigated the role of selenium in disease progression, morbidity and mortality in HIV infected individuals. Larger studies were conducted in countries with poor economic resources and limited access to HAART. According to the majority of published studies low selenium levels appear to have an association with mortality, and selenium supplementation appears to play a beneficial role on survival or on slowing disease progression among HIV infected individuals. The role of selenium supplementation on preventing hospital admission among HIV outpatients was also noticed. The literature suggests an association between selenium deficiency and development of HIV associated cardiomyopathy and furthermore, selenium supplementation appears to improve the cardiac function in HIV infected individuals with cardiomyopathy. However, there is conflicting evidence regarding the role selenium in modifying HIV viral load and immune status in HIV infection.

### Introduction

Micronutrient supplementation has shown beneficial effects among the human immunodeficiency virus (HIV) infected population<sup>1,2</sup> and there has been increasing interest in supplementation as a therapeutic strategy. Selenium is a non-metallic chemical element deriving from both vegetables and animal products, in particular seafood, liver and cereals.<sup>3</sup> Since the late 1960's, its role on humans' health has been extensively investigated.

Selenium is a key component of several human selenoproteins and mostly involved in redox reactions.<sup>4</sup> It is required for the activity of the enzyme glutathione peroxidase (GPX), a main intracellular antioxidant, that acts to pre-

vent oxidation-induced cellular damage.<sup>5</sup> Chronic exposure to high levels of selenium may be associated with several health problems in humans such as nail and hair loss, gastroenteritis and dermatitis but the most important health effects are related to the deficient state.<sup>6</sup> The normal ranges of serum selenium plasma levels in adults are 1.1 to 2.5  $\mu\text{mol/L}$  in blood and 0.75 to 1.35  $\mu\text{mol/L}$ . The minimum daily intake of selenium is recommended at 30  $\mu\text{g}$ .<sup>7</sup> Selenium deficiency in humans is associated with an increased incidence of cancer, cardiomyopathy (including Keshan disease), a deforming osteoarthropathy (Kashin-Beck disease), male sub-fertility, liver dysfunction, mood disorders, skeletal muscle disorders, impaired thyroid hormone metabolism, impaired immune function, progression of HIV infection and mortality.<sup>8-29</sup>

The first studies were published on the role of selenium in HIV-infected patients in 1989. The aim of this review is to summarise the evidence regarding the relationship between selenium and HIV infection.

### Materials and Methods

We carried out a literature review of published studies that evaluated the relationship between serum/plasma selenium status or selenium supplementation and HIV disease in human subjects. The search was performed through the PubMed database and restricted to full articles published up to September 2009, irrespective of language. No attempt was made to obtain information about unpublished studies.

Index search terms included the Medical Subjects Heading selenium, HIV, AIDS, immunodeficiency, malnutrition, co-infection, opportunistic infections, AIDS progression, AIDS-related neoplasm, viral load, CD4, AIDS stage.

Studies were considered eligible if they presented data pertaining to the relationship between selenium and HIV disease. Reviews, editorials, case reports and literature regarding animal or in vitro studies were excluded.

We did not include results concerning the relationship between selenium and HIV genital shedding.

### Results

Our literature search identified 195 articles. Among these we found 33 studies that met our search criteria. In summary, we found 13 cross-sectional studies, 11 prospective observational studies and 9 clinical trials.

#### Selenium and sero-status of HIV

The possible relationship between serum

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Key words: selenium, HIV, AIDS, micronutrient, mortality.

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selenium levels and the sero-status of HIV has been analysed in 12 studies.<sup>18,30-40</sup> The majority of these reported a significant association between HIV infection and low serum selenium levels.<sup>30-38</sup> However, three studies comparing HIV-positive to HIV-negative subjects did not find a significant relationship between HIV-infection and selenium deficiency.<sup>18,39-40</sup> It is possible that these studies failed to demonstrate a significant association due to small sample sizes<sup>39,40</sup> and the inclusion of severely malnourished subjects in both the HIV-positive and HIV-negative study groups.<sup>18</sup>

#### Selenium and HIV disease stage/disease progression

An association between selenium levels and HIV disease stage (including CD4 cell counts, opportunistic infections, AIDS-related neoplasm and viral load) has been reported by seven authors.<sup>14-17,19-21</sup>

Cirelli *et al.* measured serum selenium concentration in four groups of HIV-infected patients: symptom-free subjects, persistent generalized lymphadenopathy (PGL), AIDS related complex (ARG) and AIDS. Serum selenium concentrations were significantly higher in symptom-free HIV positive subjects as compared to the other three groups.<sup>14</sup> Similarly, Constans *et al.* observed that serum levels of selenium were lower in patients with a count

Table 1. Relevant studies on selenium and HIV infection published in the literature.

Author/year	Study population	Objectives and/or End Points	Results
Cirelli 1991**14	67 HIV+ male pts Group 1: 23 pts symptom-free subjects Group 2: 7 pts with PGL Group 3: 7 with ARC Group 4: 30 AIDS patients Group 5: 15 HIV- controls 12 HIV+ received Se supplementation	To assess the Se status of HIV+ pts; the relationship between different stages of HIV disease and Se deficiency; to verify if Se supplementation improves immunological function.	Se was normal in Group 1 pts and lower in Groups 2-3-4 pts Group 4 showed a positive correlation between Se levels and Hb and ESR Positive increase of Se levels in pts receiving Se [80 µg/day] supplementation
Constans 1993 <sup>15</sup>	77 HIV+ Group 1: CD4 <50 Group 2: CD4 50-200 Group 3: CD4 200-400 Group 4: CD4 >400 20 HIV- controls	To investigate Se role on oxidative metabolism in HIV+ pts	Se levels were low in Groups 1-2-3 Se was correlated with body mass index (BMI)
Constans 1995 <sup>16</sup>	95 HIV- followed for 1 year - 84 died - 47 had an AIDS-defining OI	To investigate the role of selenium in predicting outcome among HIV+ pts	Serum Se correlated with CD4 cell count (univariate) Serum Se correlated with p24 antigenemia (univariate) Death was correlated with serum Se (univariate) Occurrence of OI correlated with serum Se (univariate) Death correlated with serum Se (multivariate) OI correlated with serum Se (multivariate)
Look 1997 <sup>17</sup>	104 HIV+ (28 coinfecting with HCV): - 33 CDC I pts - 34 CDC II pts - 37 CDC III pts (among these 21 pts with either acute OI and/or AIDS defining tumors) 72 healthy controls	To investigate antioxidant defence status and surrogate markers of HIV disease in HIV-infected patients	Se levels were lower in CDC II-III pts vs CDC I pts Se levels were lower in CDC II-III pts vs healthy controls Se levels were lower in CDC III pts vs CDC II pts Se levels were positively correlated with CD4 count CD4 was not independently correlated with Se (multivariate) Se levels of coinfecting pts (HIV/HCV) were lower than HIV infected only pts Se levels were lower in CDC III pts with OI or AIDS defining tumors than in the remaining CDC III pts
Ndagije 2007 <sup>18</sup>	112 severely malnourished Rwandan children: 52 HIV+ (none on ART) 60 HIV-	To determine levels of CD4 cells and micronutrients in HIV+ and HIV- severely malnourished Rwandan children	One third in both groups (HIV+ and HIV-) had low Se levels No significant difference in Se levels between HIV+ and HIV- children Correlation between Se and regression of CD4 in HIV- children (multivariate) Correlation between Se and regression of CD4 in HIV- children (multivariate)
Burbano 2002**19	186 HIV+ - 89 Se supplemented group - 97 plb supplemented group	To evaluate the impact of Se chemoprevention (200 µg/day) on hospitalizations in HIV+ individuals.	Plb-group had higher CD4 decline than Se-receiving group Se group had lower admission rate than plb group Se group had lower % of hospitalization than plb group Cost for hospitalization was lower in Se group than in Plb group Se is an independent factor for ↓ risk of hospitalization
McClelland RS 2004**20	400 HIV+ ART-naive pregnant Kenyan women: - 200 multivitamin + Se (200 µg) supplemented pts - 200 placebo supplemented pts	To evaluate CD4, VL and cervical and vaginal shedding of HIV-1 infected cells and RNA in women treated or not treated with micronutrient supplementation for 6 weeks	Micronutrient group had ↑ CD4 vs plb group Micronutrient group had ↑ CD8 vs plb group No relationship between micronutrients and VL
Hurwitz 2007**21	174 HIV+ (9-month FU assessment): - Se group = 91 pts - Plb group = 83 pts	To evaluate the effect of Se supplementation [200 µg/d for 9 months] on serum Se levels and the subsequent impact on HIV-1 viral load and CD4 count.	Se group had greater change in serum Se at the 9-months assessment. Se responders (50/91) had greater increases in serum Se concentration than plb and nonresponders Se responders (50/91) had less viral load increase than plb and nonresponders Se responders (50/91) had greater CD4 count increase than plb and nonresponders

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Table 1. Continued from previous page.

Author/Year	Study population	Objectives and/or End Points	Results
Allavena 1995 <sup>22</sup>	80 HIV + at stage IV (CDC) - Group 1: 19 pts who died one yr later - Group 2: 61 pts who remained alive	To evaluate relationship between trace elements, $\beta 2$ microglobulin and HIV infection progression	Group 1 had lower Se levels than Group 2, pts Se levels in all HIV pts of the study were lower than normal values of Se
Baum 1997 <sup>25</sup>	125 HIV + drug users	To evaluate nutritional status and immune parameters in HIV+ who abuse drugs	HIV+ women had lower Se than the HIV+ men HIV+ women had higher proportion of Se deficiency than the HIV+ men Among pts with CD4 < 200, Se levels were lower in women vs men
Campa 1999 <sup>6</sup>	24 HIV + children observed for 5 yrs (12 died over the course of the study of HIV-related causes)	To determine the contribution of specific nutritional factors on disease progression and survival in HIV + children	Se deficiency was significantly and independently related to mortality Survival time was shorter in selenium deficient children Among the children who died, those with low Se died at younger age
Kupka 2008 <sup>**27</sup>	913 HIV pregnant Tanzanian women (mostly HAART-naïve) treated with Se or placebo from recruitment until 6 mo after delivery	Effect of Se [200 µg] on CD4, viral load, pregnancy outcomes, maternal and infant mortality	Se had no effect on maternal CD4 cell count or VL Se had no effect on maternal mortality
Djinhi 2009 <sup>30</sup>	- 30 HIV asymptomatic HAART-naïve Ivorian (CD4 > 200) - 30 HIV - controls	To evaluate the oxidative stress and Se status and the antioxidant capacity of asymptomatic HIV+	Se levels were significantly lower in HIV+ subjects
Beck 1990 <sup>31</sup>	59 HIV+ (male) 26 healthy controls (male)	To compare serum concentrations of selected elements in HIV+ pts vs healthy controls	In HIV+ pts direct correlation between serum Zn and Se HIV + pts had significantly lower Se than the controls No significant correlations between stage of the disease and Se
Delmas-Beauvieux 1996 <sup>**33</sup>	45 HIV+ pts with CD4<400: - 18 placebo group - 14 Se group (100 µg/d) - 13 $\beta$ -carotene group 26 healthy adults (control group)	To investigate (1 year) the effect of Se (100 µg/d) and $\beta$ -carotene supplementation in HIV + pts	Plasma Se at baseline was lower in HIV+ than in controls
Allard 1998 <sup>33</sup>	49 HIV+ 15 HIV- controls	To compare HIV + and HIV - plasmatic antioxidants levels	Se concentrations were significantly lower in HIV+ than in HIV- pts
Ogunro 2006 <sup>34</sup>	62 HIV+ (before beginning ART) 30 healthy HIV + controls 11 HIV- controls	To investigate a relationship between plasma Se concentration and erythrocyte activity in HIV+ pts with the progression of the disease	Plasma Se ↓ in HIV with CD4 < 200 vs controls Plasma Se ↓ in HIV with CD4 200-499 vs controls
Tohill 2007 <sup>35</sup>	369 HIV + women 184 HIV- women	To assess nutritional biomarkers associated with several gynecological conditions in women with or at risk of HIV infection	HIV+ women had ↓ Se values vs population median values HIV+ women had Se concentration lower than HIV - women
Khalili 2008 <sup>36</sup>	100 HIV+ 100 healthy controls	Compare nutritional status of Iranian subject newly diagnosed with HIV infection with control healthy subjects	Serum Se was significantly lower in HIV group vs control group Serum Se in IVDU was significantly lower than in sexually infected individuals Serum Se in HIV pts positively correlated with malnutrition levels
Forrester 2009 <sup>37</sup>	300 US Hispanic adults (4 groups): - HIV+ drug users - HIV- drug users - HIV+ who do not use drugs - healthy persons who denied drug use	To examine the effects of HIV, HCV and drug use on micronutrients in HIV+ pts	HIV infection was associated with ↓ Se Low Se levels (<85 µg/L) were more prevalent in co-infected (HIV/HCV) pts ART, CD4 count, VL were not predictors of micronutrient status in HIV+ pts No interaction effect between HIV and HCV for any micronutrient (including Se)
Stephensen 2007 <sup>38</sup>	244 HIV+ adolescents 121 HIV- adolescents	To determine if HIV infection is associated with poor Se status and low antioxidant protection	HIV status was a significant negative predictor of plasmatic Se Mean Se concentrations were lower in women than in men Plasma Se was not associated with VL

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Table 1. Continued from previous page.

Author/Year	Study population	Objectives and/or End Points	Results
Henderson 1997 <sup>39</sup>	10 HIV <sup>+</sup> with growth retardation 18 HIV <sup>+</sup> 10 HIV <sup>-</sup>	Evaluate Se, plasma protein and micronutrient levels in HIV children with or without growth retardation	No significant differences between groups in the frequency of deficiency for any nutrient studied (Se included).
Mahy 1994 <sup>40</sup>	- 10 HIV <sup>+</sup> haemophilic children (Gr. A) Controls: - 10 HIV <sup>-</sup> haemophilic children (Gr. B) - 20 healthy boys (Gr. C)	To evaluate the relationship of plasma malondialdehyde, vitamin E and antioxidant micronutrients to HIV-1 seropositivity	No differences in Se levels between Group A, Group B, Group C
Look 1998 <sup>**41</sup>	Two groups: A (13 pts), B (11 pts): - A: HIV <sup>+</sup> treated from wk 0 to wk 24 - B: HIV <sup>+</sup> treated from wk 12 to wk 24 [group B served as untreated control during the first 12 weeks]	To evaluate effects of NAC [600 mg i.i.d.] and Se [500 µg/d] on plasma GSH, erythrocyte GSH-Px activity, GSSG, lymphocytes subpopulations and HIV-VL in asymptomatic HIV ART-naive pts	Increase in CD4 percentage at week 6 in Group A vs Group B CD4/CD8 ratio was increased after 6-12 weeks in Group A vs Group B Decrease in the absolute CD8/CD38 count after 6 weeks in Group A vs Group B Decrease in the absolute CD8/CD38 count after 12 weeks in Group A vs Group B Decrease in the CD8/CD38 percentage after 6 weeks in Group A vs Group B No CD4% changes in Group B after 6 and 12 weeks No changes in VL after 12 wks of NAC/Se treatment (both Group A and B)
Constans 1996 <sup>**42</sup>	15 HIV <sup>+</sup> supplemented with Se 15 HIV <sup>+</sup> supplemented with -carotene 22 HIV <sup>+</sup> non supplemented (controls)	To assess the effect on Se supplementation [100 µg/day for one year] on HIV <sup>+</sup> pts	No effect of Se supplementation on CD4 cell counts
Jones 2006 <sup>44</sup>	188 HIV <sup>+</sup> on HAART: - 171 HIV <sup>+</sup> men - 17 HIV <sup>+</sup> women	To determine the prevalence of micronutrients in HIV <sup>+</sup> on HAART and to assess the association of micronutrient levels with HIV disease status	No association between Se levels and CD4 count No association between Se supplements and HIV disease status
Drain 2006 <sup>45</sup>	400 HIV <sup>+</sup> ART-naive women	To evaluate relationship between serum Se and CD4, VL, serum albumin and ACR	Serum Se was not significantly associated with CD4, VL and ACR
Baeten 2001 <sup>46</sup>	318 HIV <sup>+</sup> women (Kenya)	To assess the relation between Se deficiency and vaginal or cervical shedding of HIV-1-infected cells	CD4 not significantly different between Se deficient and Se not-deficient women. No significant correlation between CD4 and Se concentration
Rousseau 2000 <sup>47</sup>	44 HIV <sup>+</sup> (77% IVDU) Group A: pts with CD4 < 250 Group B: pts with CD4 >250	To assess micronutrient variations in HIV/AIDS patients before and after HAART (data collected in 1995 when no pts received HAART and 1998 when most patients received HAART)	In 1995 Pts wit CD4 < 250 had lower Se vs pts with CD4 >250 In 1995 Se in group A men was lower than in group A women In 1995 77% pts had low Se levels in 1998 10% pts had low Se levels In 1998 (after HAART introduction) no differences between Se concentration in Group A and B
Kelly 1999 <sup>**48</sup>	135 HIV <sup>+</sup> pts: - 66 micronutrients-treated group - 69 placebo-treated group	To evaluate micronutrient supplementation (containing Se) for 2 weeks in the AIDS diarrhoea-wasting syndrome in Zambia	No difference between micronutrient-treated and plb-treated on diarrhoea No difference in mortality between the treatment groups
Shor-Posner 2002 <sup>**49</sup>	12 HIV with mycobacterial disease 32 HIV controls	To investigate the impact of Se status on the development of mycobacterial diseases in HIV <sup>+</sup> drug users (2 yrs observation)	Se ≤135 g/L was associated with 13x risk of mycobacterial disease vs Se > 135 g/L (univariate analyses) Low Se increases risk of mycobacterial diseases in HIV (multivariate analyses)
Zazzo 1988 <sup>50</sup>	10 AIDS pts with nonobstructive cardiomyopathy	To prospectively evaluate the effect of Se supplementation (800 µg/day during 15 days and 400 µg/day during 8 days) on 10 AIDS pts by echocardiography	8 out of 10 patients had low plasmatic selenium 6 out of 8 patients with cardiomyopathy and low plasmatic selenium returned to normal ventricular shortening fraction within 21 days
Twagrumukizza 2007 <sup>51</sup>	416 HIV <sup>+</sup> Rwandan pts (71 affected by DCMP)	To assess the prevalence of DCMP in HIV not on HAART and to investigate risk factors associated with its development	Low Se associated with development of DCMP

ACR, acute phase response (the presence of C-reactive protein  $\geq 1$  mg/dL and/or l-acid glycoprotein  $\geq 100$  mg/dL); AIDS, acquired immune deficiency syndrome; ARC, AIDS-related complex; ART, antiretroviral therapy; DCMP, dilated cardiomyopathy; FU, follow-up; GSH, glutathione; GSH-Px, glutathione peroxidase; GSSG, glutathionedisulphide; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IL, interleukin; IVDU, intravenous drug users; mo: months; NAC, N-acetylcysteine; OI, opportunistic infections; PGL, persistent generalized lymphadenopathy; Plb, placebo; Pts, patient; Se: selenium; TB, tuberculosis; US, United States; VL, viral load; Zn, zincum. \* Clinical trials are marked.

of CD4 less than 400 cells/mm<sup>3</sup>.<sup>15</sup> Another study reported that opportunistic infections occurred more frequently among patients with lower serum selenium concentration.<sup>16</sup> In a cross-sectional study on 104 HIV-infected individuals Look *et al.* reported that mean serum selenium levels were significantly lower in patients at CDC HIV stage II and III as compared to healthy subjects and to HIV stage I patients.<sup>17</sup>

In addition, three clinical trials reported a slower decline in CD4 or an increase in CD4 cell counts in patients receiving oral selenium supplementation and these are briefly described below.<sup>19,21</sup>

Burbano *et al.* conducted a randomized, double-blind, placebo-controlled trial on 186 HIV-infected individuals and showed that the placebo group had a more rapid decline in CD4 count than the selenium-supplemented group.<sup>19</sup> A further randomized, double-blind, placebo-controlled supplementation trial (micronutrients + 200 µg/day of selenium) designed by McClelland *et al.*, involving 400 pregnant HIV positive women in Kenya, showed that the selenium-supplemented group had higher CD4 levels than the placebo group.<sup>20</sup>

Hurwitz *et al.* administered either supplementation with selenium (200 µg/day) or placebo to 174 HIV subjects for 9 months. At the end of the follow-up period, an higher increase in CD4 count was observed among selenium responders (individuals whose mean serum selenium concentration changed more than 3 standard deviations above the mean serum selenium concentration change of the placebo group) than that recorded in the placebo and selenium non-responder groups. Authors performed an analysis to examine if the effect on CD4 count was mediated by the viral load change. Interestingly, a model with several covariates (including HIV disease stage, antiretroviral treatment and adherence to it) confirmed that, in this study, selenium treated patients had a significant decrease in HIV viral load.<sup>21</sup>

Seven studies did not demonstrate a significant relationship between selenium levels or supplementation and CD4 cell count or disease status.<sup>27,41-45</sup> However, Rousseau *et al.* failed to find a relationship between selenium levels and CD4 cell count or disease status in a study which looked at patients treated with highly active antiretroviral therapy (HAART). This may suggest that the rapid improvement in the immune status of the patients taking antiretroviral therapy, may be masking any effect of selenium supplementation or adequate plasma selenium levels.<sup>46</sup>

The majority of studies that investigated for a relationship between either plasma or serum selenium concentration or selenium supplementation and plasma HIV viral load, failed to find a significant association.<sup>20,27,38,44,47</sup> Only one supplementation trial reported that selenium-

responders had slower progression of HIV viral burden than the placebo or selenium non-responders group.<sup>21</sup>

### Selenium and mortality in HIV-infected subjects

Five studies evaluated the role of selenium on mortality in HIV-infected subjects.<sup>15,22, 25, 26, 48</sup>

Allavena *et al.* analyzed the relationship between serum selenium levels in 80 HIV seropositive patients at stage IV of infection (CDC classification) treated with zidovudine (AZT) and mortality within one year. They observed that the patients who died had significantly lower selenium values.<sup>22</sup> In a one-year prospective study on 95 HIV positive subjects, Constans *et al.* found that death was significantly associated with low serum selenium levels.<sup>15</sup> Baum *et al.* longitudinally evaluated 125 HIV positive intravenous drug users for 3.5 years: selenium deficiency was significantly associated with mortality.<sup>25</sup> In another study, Campa *et al.* observed 24 HIV positive children, for a five-year period and found that selenium deficiency was an independent risk factor for HIV-related mortality.<sup>26</sup>

Only one supplementation trial did not observe an effect of selenium on mortality.<sup>48</sup>

### Selenium and HIV co-infections

Only two studies have been carried out to investigate the relationship between selenium levels and co-infected HIV positive individuals.<sup>17,49</sup>

Look *et al.*, in a cross-sectional study, compared serum selenium levels among HIV-infected patients co-infected with hepatitis C virus (HCV) and subjects infected with HIV only. HCV co-infected patients showed significantly lower selenium concentrations.<sup>17</sup>

Finally, Shor-Posner *et al.* demonstrated that lower levels of selenium significantly increased the risk of developing mycobacterial disease among HIV-infected individuals.<sup>49</sup>

### Selenium and cardiovascular involvement in HIV-infected subjects

Selenium seems to also play a role in the development of cardiac dysfunction among HIV-positive subjects. Two studies investigated this relationship and are described below.<sup>50,51</sup>

Zazzo *et al.* prospectively evaluated the effect of selenium supplementation in 10 consecutive patients with both acquired immune deficiency syndrome (AIDS) and non-obstructive cardiomyopathy. Each patient received sodium selenite orally, 800 µg/day for 15 days and 400 µg/day for 8 days. Eight of these patients were found to have low plasma selenium levels before treatment yet six showed a return to a normal left ventricular shortening fraction within 21 days. One patient died on the 15<sup>th</sup> day of treatment and one had a thiamin

deficiency.<sup>50</sup>

Twagirumukiza *et al.* conducted a prospective multicenter study of 416 HIV positive Rwandan patients who were not receiving HAART and did not have a previously documented history of cardiovascular disease. Clinical examination, biochemical tests and echocardiography was carried out on all those enrolled in the study. Investigations showed that 71 (17.7%) patients had dilated cardiomyopathy and a low plasma level of selenium was significantly associated with the development of cardiomyopathy.<sup>51</sup>

### Selenium and hospital admissions in HIV infected subjects

A randomized, double-blind, placebo-controlled study evaluated the role of selenium supplementation on preventing hospital admission in patients with HIV infection, attending outpatient clinics.<sup>19</sup> The trial showed a decrease in total hospital admission rates, percent of hospitalization and cost for hospitalization in the selenium-receiving group compared with the placebo group.<sup>19</sup>

## Discussion

Selenium is recognized to have an important role in both immunologic function and antioxidant defense mechanisms. Evidence suggests that oxidative stress contributes to the pathogenesis of HIV infection; in fact several studies have indicated that the apoptosis of CD4 cells contributing to HIV progression does not result solely from HIV infection, but largely from antioxidant imbalances in the host.<sup>52-54</sup> It has been reported that selenium supplementation has a positive effect on oxidative stress in HIV-infected individuals.<sup>32</sup> Moreover, studies show that selenium is vital to cell-mediated immunity and B-cell function.<sup>55</sup>

According to the majority of published studies, HIV infection is associated with lower serum selenium concentration.<sup>30-38</sup> Nutritional deficiencies are common in HIV-infected individuals<sup>56,57</sup> and are caused by several factors: the oxidative state induced by the virus, malabsorption, altered metabolism, gut infection, altered gut barrier function, and the hypermetabolic state produced by chronic HIV infection.<sup>58-60</sup> It has also been suggested that a possible cause of selenium depletion among HIV positive subjects is the utilization of selenium by HIV-1 virus to produce its own selenoenzymes.<sup>51,62</sup>

In our literature review, three studies did not find a significant relationship between blood selenium concentrations when HIV seropositive and HIV seronegative subjects

were compared.<sup>18,39,40</sup> It is interesting to note that in a study conducted by Look *et al.*, when comparing advanced stage HIV subjects with uninfected subjects, the former group had significant lower selenium levels. Whereas there was no difference in blood selenium levels if asymptomatic HIV-positive subjects were compared with uninfected subjects.<sup>17</sup> These findings suggest that HIV infection alone is not the sole factor involved but perhaps it is the stage of disease that has a larger impact on selenium level.

Many authors report a significant relationship between CD4 cell count, opportunistic infections, HIV stage and selenium levels, whereas the association with HIV viral load is much more controversial.

Regarding the role of selenium in HIV-HCV co-infection, co-infected subjects usually have a higher levels of oxidative-stress which could explain the progressive lack of endogenous antioxidants and the subsequent decrease in selenium levels. As such, infection with more than one virus may cause an higher selenium depletion.

Data from the literature, indicates that cardiac tissue selenium levels are lower in AIDS patients with cardiomyopathy as compared to non-AIDS controls.<sup>51</sup> Indeed, low plasma levels of selenium are associated with the development of cardiomyopathy in HIV positive individuals who are not receiving HAART.<sup>63,64</sup> Two further studies showed an improvement of the patient's left ventricular shortening fraction after selenium supplementation.<sup>50,65</sup>

The role of selenium in the pathogenesis of cardiac diseases has been suggested yet. Selenium deficiency has been strongly implicated in the pathogenesis of Keshan disease, a dilated congestive cardiomyopathy endemic to certain mountainous areas of China.<sup>9,29</sup> A similar cardiomyopathy has been described in patients on long-term total parenteral nutrition who became selenium deficient.<sup>10,56,57</sup> In conclusion, although HAART has remarkably improved the survival of HIV-infected individuals, selenium supplementation could yet have a role in slowing the disease progression, by reducing the incidence of opportunistic infections and HIV-associated mortality. This may have a particularly useful application in patients living in countries with poor economic resources. However, it is not possible to give an exact indication on the use of selenium in clinical practice.

The role of selenium in cardiovascular diseases seems interesting and deserve further investigations. Since the oxidative stress from free radicals may promote heart disease, selenium, because of its antioxidant properties, may help limit the oxidation of LDL cholesterol and thereby help to prevent coronary artery disease. A recent meta-analysis showed that selenium concentrations were inversely asso-

ciated with coronary heart disease risk in observational studies but findings from randomized trials that addressed the cardiovascular efficacy of selenium supplementation are still inconclusive.<sup>66</sup> HIV-positive patients, especially those living in resource replete settings, are now at greater risk of cardiovascular diseases, due to the effects of HAART and to the longer life-expectancy. The evaluation of the effect of selenium supplementation on cardiovascular risk among HIV-positive subjects, especially among those taking HAART, would be useful.

It is important to underscore that our study simply reviewed the available evidence on the effect of selenium in HIV infected subjects. Since we have not performed any statistical analysis we are not able neither to state the exact relationship between selenium and HIV disease nor to clearly define the role of selenium in the disease progression and the HIV-related mortality. Moreover published studies on this topic have several limitations. First, regarding selenium supplementation, only three randomized trials aimed to assess its effect on HIV viral load or CD4 count were performed. Most of included studies were cohort or case-control studies, with the known limitation of these studies. Second, in two trials, selenium was administered in association with other supplements, hampering the assessment of the effect due to selenium. Third, in most of included studies, an adjustment for principal confounders (i.e. CD4 mean count, HIV viral load, antiretroviral therapy, presence of factors that could reduce selenium adsorption) was not performed. Finally, several studies were performed in the era that preceded the introduction of highly active antiretroviral therapies or were conducted in resource-poor settings, involving populations with limited or no access to HAART or patients taking non-standardised antiretroviral regimens.

Further randomized clinical trials, enrolling an adequate number of HIV infected subjects, are needed to clarify the role of selenium supplementation both in HIV naïve-patients and in those treated with HAART.

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