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Increased risk of mortality and loss to follow-up among HIV-positive patients with oropharyngeal candidiasis and malnutrition prior to ART initiation – A retrospective analysis from a large urban cohort in Johannesburg, South Africa

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Abstract

Objective—We investigated the effect of oropharyngeal candidiasis (OC) and body mass index (BMI) prior to ART initiation on treatment outcomes of HIV-positive patients.

Methods—Treatment outcomes included failure to increase CD4 count by ≥50 or ≥100cells/mm^3 or failure to suppress viral load (<400copies/ml) at 6- or 12-months in addition to loss to follow-up (LTFU) and mortality by 12-months. Risk and hazard ratios were estimated using log-binomial regression and Cox proportional hazards models, respectively.

Results—Baseline CD4 <100cells/mm^3, low BMI (<18.5 kg/m^2), low hemoglobin and elevated aspartate transaminase were associated with OC at ART initiation. Patients with low BMI with/without OC were at risk of mortality (Hazard Ratio (HR)2.42 95%CI 1.88–3.12; HR1.87 95% CI 1.54-2.28) and LTFU (HR1.36 95%CI 1.02–1.82; HR1.55 95% CI 1.30-1.85).

Conclusion—Low BMI (with/without OC) at ART initiation was associated with poor treatment outcomes. Conversely, normal BMI with OC was associated with adequate CD4 response and reduced LTFU compared to without OC.

Keywords

antiretroviral therapy; body mass index; *Candida*; mortality; oral thrush; resource-limited setting (RLS)

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Introduction

Oropharyngeal candidiasis (OC), a fungal infection of the mouth and/or throat which presents with increasing pain and difficulty in swallowing (dysphagia), has been associated with HIV infection since the advent of the AIDS pandemic.[1] Oral manifestations of HIV/AIDS occur in over 60% of HIV-positive patients and are often the first sign of underlying immune suppression.[1-7] OC is strongly associated with a low CD4 lymphocyte count and a rising HIV viral load.[5,6,8] It is one of the earliest manifestations of HIV disease in high risk individuals not undergoing chemotherapy and is also a strong predictor of the subsequent risk of AIDS-related illness or death.[9,10] OC has been used in resource-limited settings (RLS) as a guide for "when to initiate antiretroviral therapy (ART)" and is a clinical pointer to HIV infection in individuals who do not know their HIV status.[2] The prevalence of OC varies widely among different geographical regions and population groups and in Africa ranges from 34.9% in Cameroon to 80% in Kenya.[1]

Malnutrition refers to a range of conditions that develop when the body does not receive optimal amounts of the vitamins, minerals and other nutrients needed to maintain healthy tissues and organ function. It may be caused by inadequate diet and undernutrition.[11,12,13] Numerous nutrition risk screening or assessment tools have been developed to identify patients at risk of malnutrition.[14,15] These tools offer a simple technique to rapidly identify patients and provide a basis for prompt dietetic referrals however these are underutilized or not readily available in the HIV RLS. However, the measurement of selected anthropometric indices (weight, height, waist-hip ratio, mid-upper arm circumference and body mass index [BMI]),[16] biochemical variables (serum albumin concentration, transferrin, pre-albumin, retinol binding protein, ceruloplasmin, plasma fibronectin and C-reactive protein) and immunological variables (absolute lymphocyte count, lowered CD4 counts and delayed hypersensitivity skin testing) together with clinical judgment can be used to assess nutritional status.[17]

Unplanned weight loss, lipodystrophy, reduced dietary intake or limited access to food together with symptoms (nausea, diarrhoea, vomiting, loss of appetite, fatigue, heartburn, bloating), concomitant drug use (ART or tuberculosis drugs) and the presence/absence/severity of disease (diabetes, cancer, hypertension) are used to identify risk of, and diagnose, malnutrition.[14,16]

Both BMI and weight loss have been used as independent predictors of disease progression and are useful markers to indicate malnutrition.[13] The World Health Organization (WHO) uses BMI to grade nutritional status in the following manner: mild malnutrition (BMI 17.00–18.49), moderate malnutrition (BMI 16.00–16.99), and severe malnutrition (BMI < 16.00).[18]

HIV-positive patients are more vulnerable to malnutrition as they may have impaired nutrient absorption (due to diarrhoea/intestinal tract damage), reduced food intake (due to symptoms such as vomiting or pain on swallowing), food insecurity or poverty as well as functional changes and medication side effects such as loss of appetite, depression or abdominal pain.[12,16,19] Opportunistic infections can affect food intake, absorption and metabolism and so cause weight loss. According to Rollins et al. the populations at greatest risk of HIV infection are also at risk of food insecurity and therefore might already be malnourished before the onset of HIV.[20] Malnutrition in HIV-positive patients causes severe immuno-deficiency with depletion of CD4 cells and increase in HIV viral replication, ultimately increasing susceptibility to opportunistic infections and infectious diseases.[21-23] Hence a cycle of infection, malnutrition and immuno-deficiency has been described (Figure 1).[12,13,19]

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While the statistics in South Africa on the prevalence of OC in the pediatric population ranges from 13.8 – 63%, there is limited data on the prevalence of the condition in HIV-positive adults at ART initiation.[24,25] Additionally, few studies have explored OC in relation to malnutrition among HIV infected persons, and little evidence exists on either topic in RLS.[6] The factors contributing to the development and progression of OC are poorly understood but may include an interrelationship between HIV and *Candida* and/or dysfunction in the local immunity, superimposed on weakened cell-mediated immunity and depletion of CD4 T cells.[1]

OC and malnutrition have been identified as independent predictors of disease progression[9,10,13,26] however the combined effect of OC and malnutrition prior to ART initiation on treatment outcomes has not been described in RLS. This combined effect may lead to poorer treatment outcomes compared to HIV-positive patients with OC or malnutrition alone at ART initiation. Furthermore, as OC has been associated with HIV infection and underlying immune suppression, we anticipate poorer treatment outcomes in patients that present with OC.

We analyzed data from a large urban cohort of ART-naïve individuals eligible for initiation of ART to determine the proportion and characteristics of patients who present with OC and/or low BMI. We tested the association between OC and features of malnutrition in HIV-positive patients and investigated the effectiveness of OC and/or low BMI as clinical markers of disease progression. We also estimated the effect of OC and/or low BMI on treatment outcomes which include failure to achieve an adequate viral load or CD4 count response at 6 or 12 months post-ART initiation in addition to mortality and LTFU by 12 months post-ART initiation.

Methods

Study site and subjects

The study was a retrospective analysis of existing data collected from a cohort of HIV-infected adults initiated on ART at Themba Lethu Clinic (TLC), Johannesburg. The TLC is an urban public sector HIV Comprehensive Care Management and Treatment (CCMT) site in Johannesburg, South Africa. Since the start of the National CCMT programme in April 2004 more than 26,000 adults been recruited to the Themba Lethu Clinical Cohort of whom over 16,000 started ART. According to the South African National Department of Health guidelines, patients at TLC are initiated onto a standard public-sector first-line regimen of stavudine (d4T) or zidovudine (AZT) with lamivudine (3TC) and either efavirenz (EFV) or nevirapine (NVP).[27] Patients are eligible for ART initiation if their CD4 cell count is <200 cells/mm^3 irrespective of WHO stage or they have a WHO Stage IV AIDS-defining illness, irrespective of CD4 count.[27] Longitudinal clinical and demographic data is collected and stored on the electronic patient management system, TherapyEdge-HIV™. Use of TLC data was approved by the Human Research Ethics Committee of the University of the Witwatersrand (HREC-Medical M060626/M110140).

Eligibility criteria

Of a total of 16496 HIV-positive individuals initiated on ART, we excluded patients who had a prior ART-drug history (i.e. patients transferred to TLC from another facility or previous clinical trial patients) at presentation to the clinic (n=4146), less than 18 years of age (n=45), pregnant women as BMI and nutrient metabolism vary during pregnancy (n=125)[28] or were initiated on ART outside the study period 01 April 2004 - 01 April 2009 (n=2358). Finally, we excluded patients who did not have a body mass index (BMI; kg/m^2) recorded at initiation (n=1413). The remaining 8409 subjects were included in the analysis.

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Study variables

Individuals were classified as having OC at initiation if a clinical diagnosis of OC (WHO Stage III or IV) was recorded at baseline (defined as any measurement between 90 days prior to seven days after ART initiation).[29,30] This was confirmed if the clinical diagnosis corresponded to a prescription of nystatin or fluconazole (both obtained from medical records).

Since the standard biochemical variables to assess nutritional status[17] are not routinely collected in this cohort, proxies for poor nutritional status or malnutrition such as haemoglobin (<8 g/dL)[31] and aspartate transaminase (>45 IU/L)[32] were included in the analysis. Severe anemia defined as a haemoglobin concentration <8 g/dL has been linked to malnutrition and is an independent predictor of HIV disease progression.[15,31,33] High values of aspartate transaminase (AST; >45 IU/L) have been reported in protein-energy malnutrition and increased liver enzymes have been associated with a high consumption of maize meal and low consumption of meat and vegetables.[34] HIV infection and immune suppression at baseline was determined by an HIV viral load greater than or equal to 20,000 copies/ml[5,35] and a CD4 cell count less than 50 cells/mm^3 or less than 100 cells/mm^3, respectively.[36,37]

Patients were categorized as follows: (i) patients without OC prior to ART initiation and BMI ≥18.5 kg/m^2 (normal), (ii) patients with a diagnosis of OC prior to ART initiation and BMI ≥18.5 kg/m^2, (iii) patients with a BMI <18.5 kg/m^2 and without OC prior to ART initiation and, (iv) patients with a diagnosis of OC prior to ART initiation and a BMI <18.5 kg/m^2.

Outcomes

We assessed failure to achieve an adequate viral load response (defined as a failure to suppress or a detectable HIV viral load ≥400 copies/ml at 6 or 12 months post-ART initiation) and failure to achieve an adequate CD4 count response (defined as failure to increase CD4 count by ≥50 cells/mm^3 at 6 months or failure to increase CD4 count by ≥100 cells/mm^3 at 12 months post-ART initiation).[36,37]

In addition, we compared ART outcomes (loss to follow-up and mortality) by 12 months of follow-up stratified by OC and/or low BMI at ART initiation. Loss to follow-up (LTFU) was defined as having missed a clinic appointment (clinical assessment, antiretroviral drug pickup, counselor visit) by at least 3 months after the scheduled visit date.[38-40] Mortality is ascertained via South Africa's National vital registration system.[38-40] For death or LTFU, person time accrued from ART initiation until the earliest of: (i) death, (ii) LTFU, (iii) completed 12 months of follow-up or (iv) close of dataset on the 01 April 2010. Patients who transferred to another facility were censored at their last clinic visit.

Statistical analysis

Patient characteristics and outcomes were stratified by OC and/or low BMI at ART initiation and summarized as simple proportions. Groups with OC and/or low BMI were compared to the normal group using Student *t* test or Kruskal-Wallis for continuous variables and Chi-square test for proportions.

We estimated the strength of association of an oral lesion prior to ART initiation with features of malnutrition, HIV infection and immune suppression.[23] Log-binomial regression analysis was used to estimate the Relative Risk (RR) and 95% confidence interval (CI) of prevalent OC lesions at ART initiation with the following factors: (i) CD4 cell count <100

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cells/mm^3 or <50 cells/mm^3, (ii) HIV viral load ≥20,000 copies/ml,[5,35] (iii) BMI <18.5 kg/m^2,[11,12,16,18] (iv) hemoglobin (Hb) <8.0 g/dL[31] and (v) AST >45 IU/L at ART initiation.[32]

We used log-binomial regression models to estimate the Relative Risk (RR) and 95% confidence interval (CI) of OC and/or low BMI on failure to achieve an adequate viral load or CD4 count response at 6 or 12 months post-ART initiation.

We compared ART outcomes (mortality and LTFU) by 12 months follow-up using Cox proportional hazard models, Kaplan-Meier curves and log-rank tests. Factors such as age, gender, CD4 count, hemoglobin (Hb), AST and tuberculosis (TB) at initiation of ART were included in models where appropriate. All analyses were performed with SAS version 9.1 (SAS Institute Inc., Cary, NC).

Results

Table 1 summarizes the characteristics and outcomes of the 8409 patients stratified by OC and BMI at ART initiation. Overall patients had a median age of 36.2 years (interquartile range (IQR) 31.3–42.5), median CD4 count of 82.0 cell/mm^3 (IQR 31–150), median hemoglobin of 11.5 g/dL (IQR 9.9–12.9), were predominantly female (62%) and on standard first-line regimen of d4T, 3TC and EFV (90%).

Of the 8409, 5442 (65%) patients were normal (no OC and BMI ≥18.5 kg/m^2), 1112 (13%) had OC and BMI ≥18.5 kg/m^2, 1401 (17%) had a BMI <18.5 kg/m^2 and no OC while 454 (5%) had OC with BMI <18.5 kg/m^2. Median total follow-up time on ART for the abovementioned groups were 27.6 months (IQR 13.8–44.9), 32.1 (IQR 16.6–48.2), 20.4 (IQR 7.2–38.4) to 23.7 (6.8–44.6), respectively. Patients with low BMI, irrespective of OC, at ART initiation showed a decrease in hemoglobin, increase in AST and increase in TB at ART initiation compared to those with normal BMI (≥18.5 kg/m^2). Patients with normal or low BMI with OC showed elevated AST (>45 IU/L) levels compared to patients without OC (normal 31% vs. 24% and low 41% vs. 35%) but also showed a decline in immune competence with 44.3% and 59.6% having a CD4 cell count <50 cell/mm^3, respectively (Table 1).

Association of OC with features of malnutrition, HIV infection and immune function

A prior diagnosis of OC was associated with several features of malnutrition at initiation of ART. Risk of prevalent OC lesions at ART initiation included low BMI <18.5 kg/m^2 (RR 1.27 95% CI 1.16–1.40), severe anemia (<8.0 g/dL) (RR 1.60 95%CI 1.23–2.06) and elevated liver transaminase – AST (>45 IU/L) (RR 1.25 95%CI 1.13–1.39) at ART initiation. OC at ART initiation was strongly associated with a low CD4 cell count (<50 cells/mm^3; RR 1.49 95%CI 1.38–1.62 or <100 cells/mm^3; RR 1.31 95%CI 1.25–1.38) but not with a high viral load (≥20,000 copies/ml; RR 0.96 95%CI 0.86–1.07).

Outcomes by 6 and 12 months of follow-up

Among 8409 patients, 6549 (77.9%) were alive and in care, 661 (7.9%) died, 878 (10.4%) were LTFU and 321 (3.8%) were transferred out during the 12 months of follow-up. Median follow-up time for patients who died or were LTFU was 2.98 months (IQR 1.21–6.26) and 5.0 months (IQR 4.0–7.7), respectively. The number of OC lesions decreased from 18.6% (1566/8409) at initiation, to 2.7% (175/6549) at 0–12 months, to 1.1% (67/5838) at 13–24 months post-ART initiation (Table 1).

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Viral load and CD4 response

Adjusted log-binomial regression models showed that patients with OC at initiation were more likely to achieve an adequate CD4 response (RR 0.72 95%CI 0.61–0.85 at 6 months; RR 0.83 95%CI 0.71–0.96 at 12 months) and viral load response (RR 0.76 95%CI 0.56–1.03 at 6 months) compared to normal patients. Additionally, patients with low BMI and no OC (RR 1.60 95%CI 1.11–2.29) or a combination of OC and low BMI (RR 1.10 95%CI 0.84–1.45) at initiation were at increased risk of having a detectable viral load at 12 months compared to normal patients (Table 2).

Mortality and loss to follow-up

Rates of death and LTFU were highest amongst patients with low BMI and no OC (death-16.1/100 person years (pys); LTFU 18.2/100 pys) or those with OC and low BMI (death-22.2/100 pys; LTFU 16.1/100 pys). Adjusted hazard models showed that patients with low BMI and no OC or those with OC and low BMI at ART initiation were at increased risk of LTFU (Hazard Ratio (HR) 1.55 95%CI 1.30 – 1.85; HR 1.36 95%CI 1.02–1.82) and mortality (R 1.87 95%CI 1.54 – 2.28; HR 2.42 95%CI 1.88–3.12), respectively. Predictors of LTFU included, males (1.29 95%CI 1.11 – 1.49), those with CD4 cell count <50 cells/mm^3 (HR 1.19 95%CI 1.02 – 1.38), hemoglobin <8.0 g/dL (HR 1.64 95%CI 1.28 – 2.10) and elevated AST levels >45 IU/L (HR 1.16 95%CI 0.99 – 1.35). Predictors of mortality included patients ≥40 years of age (HR 1.29 95%CI 1.10–1.53), males (HR 1.17 95%CI 0.99–1.37), those with CD4 cell count <50 cells/mm^3 (HR 2.27 95%CI 1.92–2.67), hemoglobin <8.0 g/dL (HR 1.77 95%CI 1.37–2.27) and elevated AST levels >45 IU/L (HR 1.55 95%CI 1.32–1.83). TB did not contribute to an increased risk of LTFU (HR 0.91 95%CI 0.75-1.10) or mortality (HR 0.89 95%CI 0.72-1.10) (Table 3).

Additionally, crude Kaplan-Meier survival curves showed that patients with low BMI and no OC were at highest risk for LTFU (log-rank test $p < 0.001$) (Figure 2A) while those with low BMI and OC at initiation were at highest risk for mortality by 12 months of follow-up (log-rank test $p < 0.001$) (Figure 2B).

Discussion

Malnutrition is associated with many adverse outcomes including depression of the immune system, impaired wound healing, muscle wasting, longer lengths of hospital stay, higher treatment costs and increased mortality – in elderly, hospitalized, diabetic patients and not just HIV-positive patients.[14]

We demonstrate that patients with low BMI (with or without OC) at initiation of ART have poorer treatment outcomes in terms of LTFU and mortality compared to patients with no OC and normal BMI. Patients with a BMI <18.5 kg/m^2 at ART initiation were more likely to have a detectable viral load (≥400 copies/ml) and were at increased risk of mortality and LTFU at 12-months post-ART initiation compared to normal patients. Since a cycle of infection, malnutrition and immuno-deficiency has been described[12,13,19] (Figure 1) it is important to identify and treat these patients early to reduce viral replication and disease progression, limit drug resistance due to ongoing viral burden and improve treatment outcomes. Furthermore, we demonstrate that OC at ART initiation is associated with immune suppression and features of malnutrition including (i) a low BMI, (ii) low hemoglobin and (iii) elevated AST levels.

The number of undernourished people of all ages in sub-Saharan Africa increased from about 90 million in 1970 to 225 million in 2008 and is projected to add another 100 million by 2015.[41] Both malnutrition and opportunistic infections can worsen HIV disease progression and prognosis and may be a cause as well as a result of immunologic

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dysfunction.[11,19,42] Nutritional deficiencies from HIV-related metabolic changes can contribute to anemia, malnutrition (loss of body weight, low BMI and low CD4 cell count) and opportunistic infections.[34] Maize meal or pap (smooth maize meal porridge) is the staple diet of many people, especially black African's in South Africa. Considering a diet consisting mainly of carbohydrates,[16] with a poor nutritional intake, then it is feasible that proxies for nutritional status (high AST, low BMI and low hemoglobin) indicate malnutrition as a consequence of poor nutrition and altered nutrient absorption or metabolic changes related to HIV-infection. Severe anemia is common amongst people with low incomes or low socio-economic backgrounds, probably due to malnutrition.[31] Increased liver enzymes signify poor nutritional status associated with a high consumption of maize meal and lower consumption of meat and vegetables which results in an inadequate intake of nutrients and poor nutritional status.[34] High levels of AST have been reported in HIV positive patients not on ART therapy[43] however it has also been reported with protein-energy malnutrition,[44] where levels increase according to the severity. The single most important factor that leads to malnourishment is poverty.[45] Employment status, a proxy for social class, indicates that more than 50% of this cohort has a low socio-economic status.

Other factors may also contribute to malnutrition. Active TB is associated with wasting, low BMI, micronutrient deficiencies and anemia. Since a higher rate of TB co-infection was reported in patients presenting with OC, it is feasible that TB may aggravate malnutrition. There is limited data on the relationship between malnutrition and the incidence of TB but it has been suggested that general malnutrition reduces the expression of mycobactericidal substances which may compromise cell-mediated immunity and lead to active TB.[46] Despite the high prevalence of TB at ART initiation in this cohort, TB did not contribute to an increased risk of LTFU or mortality.

The prevalence of HIV-related oral lesions and malnutrition in developing countries remains high as ART use is limited.[47,48] The prevalence of OC (18%) in this cohort was similar to that reported for pediatric HIV-positive orphans from Gauteng, South Africa[25] but lower than those reported for other regions in Africa.[1] Multiple studies on the prevalence of HIV-related oral lesions conducted in industrialized countries before and after the availability of ART have shown that OC is the most common and frequent HIV-related oral condition.[7,49,50] Results from this study are consistent with previous findings that ART can help to dramatically decrease the number of OC lesions by 12 and 24 months post-ART initiation.[6,7,9,51,52]

According to the South African ART treatment guidelines, adults and adolescents are initiated on ART if they have a WHO Stage IV AIDS-defining illness, irrespective of CD4 count.[27] As patients with OC are initiated regardless of CD4 count some of these patients may present at the clinic sooner in search of treatment for their symptoms. In a sub-analysis of all patients with OC at ART initiation, patients with OC were initiated onto ART quicker (fast tracked) than patients that presented without OC ($p = 0.002$). This may be responsible for the improved outcomes after initiation and explain why these patients are more likely to achieve an adequate viral load and CD4 response after ART initiation. Results suggest that ART dramatically decreases OC and promotes immune reconstitution – improving survival and LTFU rates. Additionally, two studies have shown that patients with a history of opportunistic infections have increased adherence.[53,54] The authors of these studies postulate that experience with illness motivates adherence and healthy behavior.

Patients with OC and normal BMI are at the lowest risk for death and LTFU by 12 months of follow-up while patients with low BMI and no OC or those with a combination of OC and low BMI are at a higher risk for LTFU and mortality when compared to normal patients. Patients with low BMI and no OC at initiation were more likely to have a detectable viral

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load and were at increased risk of mortality and LTFU by 12 months post-ART when compared to normal patients.

Following ART initiation, patients with OC and normal BMI are more likely to achieve an adequate viral and CD4 response (although not all these estimates were precise) and less likely to be LTFU compared to those that present without OC – possibly as a result of ART and improved adherence to ART.[53,54] Patients presenting with low BMI (with or without OC) have an increased risk of mortality and LTFU confirming that low BMI is a strong predictor of LTFU and mortality.

Our findings should be considered in light of the study limitations. Firstly, we had no micronutrient or macronutrient data to confirm the assumption that there are nutritional deficiencies. Deficiencies in vitamin A, B_{12}, E, C, selenium, zinc and iron need to be confirmed in this study population. Secondly, the study represents patients from one large government ART site and thus results may not be generalizable to other regions or clinics. However, the demographics of patients in this study are similar to the HIV/AIDS patient profile in South Africa (i.e. black-African, female, between 15-49 years of age, unemployed, with a low socio-economic status.[38,45] Also malnutrition in a rural setting may be different to that in an urban setting as additional risk factors such as socio-economic status, environmental conditions and hygiene conditions (i.e. inadequate housing, absence of water and sanitation) and food availability may be poorer. Thirdly, 1413/16496 (8.6%) of patients, without baseline BMI, were excluded from the analysis which may introduce selection bias. However, the baseline clinical and demographic characteristics of this group such as age at initiation 36.5 (IQR 31.5–42.3); female 63.6%; CD4 cell count 69 (IQR 22–142) and hemoglobin 11.3 (IQR 9.5–12.8) were similar to those included in the analysis (Table 1). Fourthly, OC is a WHO Stage III/IV condition where a presumptive and definitive diagnosis is made on the basis of clinical signs/macroscopic appearance and where confirmatory diagnostic testing or laboratory studies are not necessary according to these guidelines. A relatively simple way to confirm the suspected diagnosis is to scrape the plaques with a tongue blade to reveal an inflamed and/or bleeding base. In this study patients were classified as having OC at ART initiation if a clinical diagnosis was recorded in our patient database (TherapyEdge-HIV™) so the prevalence of OC (18%) may be under/overestimated in this population. According to guidelines applicable to this setting, OC is diagnosed clinically and lesions are not smeared or cultured routinely which may be a potential weakness in this study. However, clinicians are intensively trained in the history, clinical appearance, examination and treatment of infections such as OC and ultimately each clinician uses their discretion in making such a clinical diagnosis. The clinical team at this site is supported and assisted by highly experienced specialist HIV and infectious diseases consultants. As nystatin and fluconazole are also commonly used to treat OC,[55] this was included to support a diagnosis of OC at ART initiation. 519 patients were prescribed nystatin or fluconazole at ART initiation however a clinical diagnosis of OC could not be confirmed. These antifungal drugs can be prescribed for cutaneous, vaginal, mucosal and esophageal *Candida* infections. If these individuals are included in the analysis as having OC at ART initiation the prevalence increases to 24.8%. The estimate (compared to normal) for LTFU for those with OC and normal BMI, low BMI and no OC and OC with low BMI at initiation is then HR 0.73 (IQR 0.63-0.86), HR 1.30 (1.08-1.57) and HR 2.01 (IQR 1.63-2.48), respectively while the estimate for mortality is then HR 1.47 (IQR 1.29-1.68), HR 1.22 (IQR 0.97-1.53), HR 2.37 (1.87-3.01), respectively. Fifthly, the *Candida* isolates or the resistance profile to antifungal drugs in these HIV-infected patients is not known and this may contribute to morbidity and mortality.[49]

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Lastly, although opportunistic infections affect food intake which places people living with HIV/AIDS at a high risk of developing malnutrition, the authors are not suggesting a causal link but rather report an association between OC and malnutrition.

Conclusion

Malnutrition is considered a major underlying factor in the full clinical expression of AIDS in HIV infected individuals.[56,57] We demonstrate that patients with OC and normal BMI at ART initiation are more likely to achieve an adequate CD4 response and less likely to be LTFU whereas patients with a combination of OC and low BMI have the highest risk of mortality and are at increased risk of LTFU compared to normal patients. Patients presenting with low BMI (with or without OC) have poorer treatment outcomes and markedly diminished survival rates highlighting the need for early recognition with subsequent ART and micronutrient supplementation to help reduce mortality. Studies validating these data are important for demonstrating that the combination of OC and malnutrition at initiation of ART could be used as a clinical marker of HIV disease progression.

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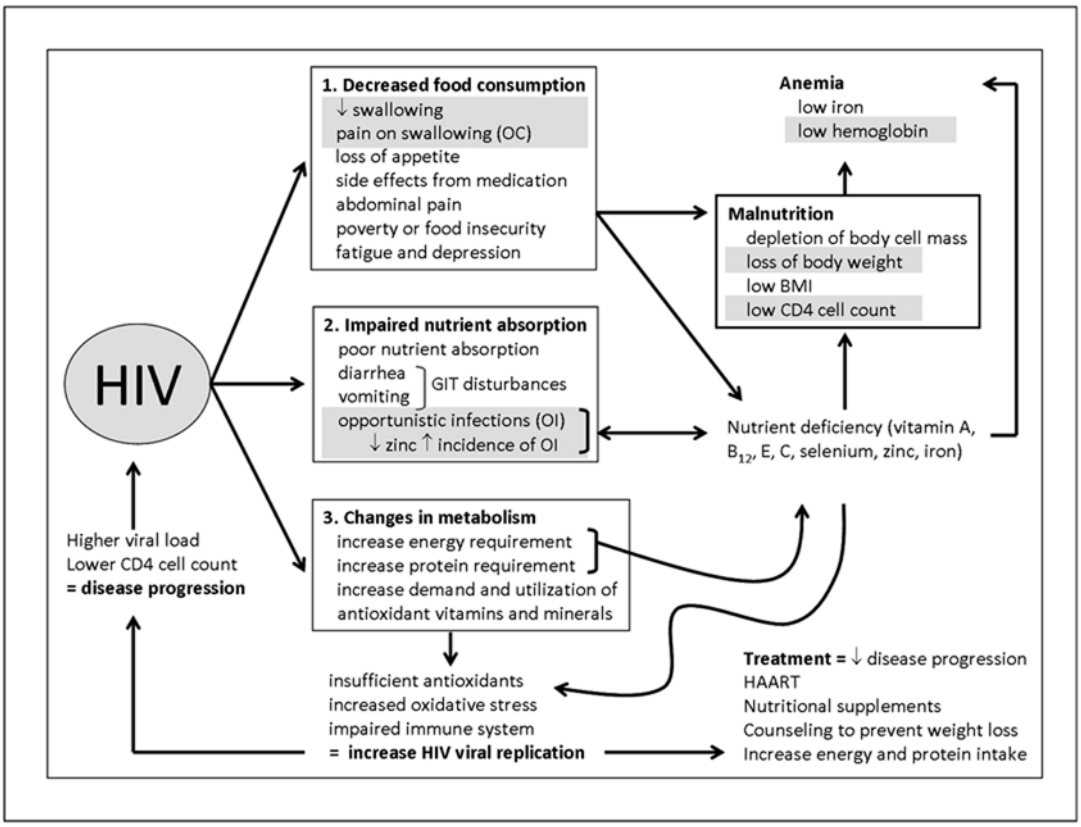

Figure 1.

Interaction between nutritional status and HIV disease progression - a cycle of infection, malnutrition and immuno-deficiency has been described. Opportunistic infections are responsible for reduced intake and place people living with HIV/AIDS at a high risk of developing malnutrition. Nutritional deficiencies are responsible for HIV disease progression as insufficient antioxidants and increased oxidative stress leads to increased HIV viral replication and depletion of CD4 cells.

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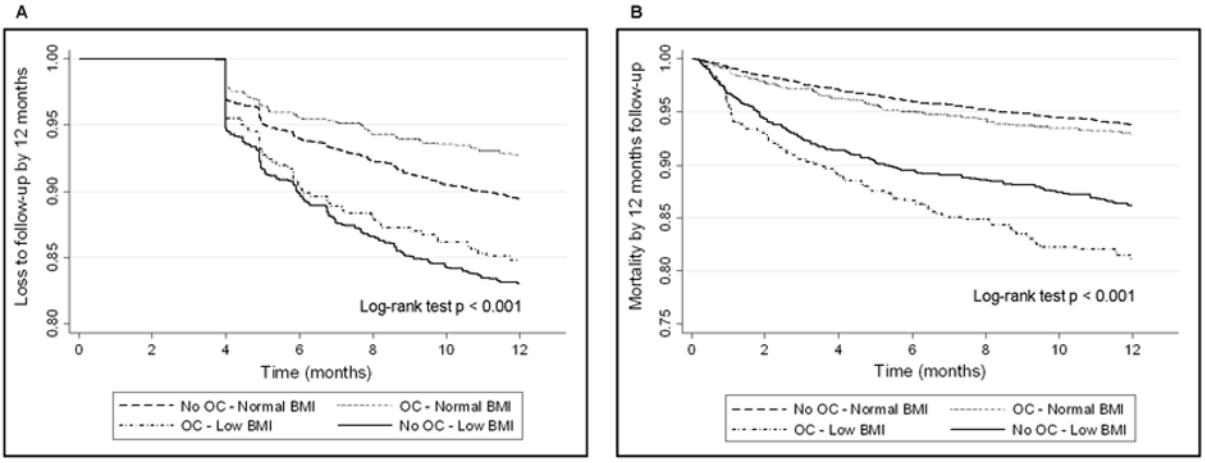

Figure 2.

Crude Kaplan-Meier survival curves of loss to follow-up (A) and mortality (B) by 12 months post-ART initiation, stratified by OC and BMI status at ART initiation (n = 8409). Patients with a diagnosis of OC and normal BMI, patients with no OC a BMI <18.5 kg/m^2 and patients with a diagnosis of OC prior to ART initiation and a BMI <18.5 kg/m^2 were compared to normal (without OC and BMI ≥18.5 kg/m^2) patients. Log-rank test for loss to follow-up (A) and mortality (B) was $p < 0.001$.

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Table 1

Baseline demographic and clinical characteristics of 8409 patients, stratified by oropharyngeal candidiasis (OC) and body mass index (<18.5 kg/m^2 vs. ≥18.5 kg/m^2), initiated on ART from an urban site (Themba Lethu Clinic, Johannesburg, South Africa).

		No OC lesion Normal BMI	OC lesion Normal BMI	No OC lesion Low BMI	OC lesion Low BMI
Baseline Characteristics					
	N (%)	5442 (65%)	1112 (13%)	1401 (17%)	454 (5%)
Age at initiation	Median (IQR)	36.7 (31.6 – 42.7)[i,t]	36.2 (31.6 – 42.6)	34.9 (29.7 – 41.5)[i]	34.9 (30.7 – 42.7)[t]
	>40 years	1918 (35%)	374 (34%)	415 (30%)	157 (35%)
Gender	Female	3505 (64%)[j,u]	727 (65%)	724 (52%)[j]	248 (55%)[u]
	Male	1937 (36%)	385 (35%)	677 (48%)	206 (45%)
Employed	Yes	2583 (47%)[k,v]	513 (46%)	517 (37%)[k]	159 (35%)[v]
Ethnic group	African	5196 (95%)	1062 (96%)	1316 (94%)	425 (94%)
BMI (kg/m^2)	Median (x, IQR)	22.5 (20.5 – 25.5)[a,l,w]	21.8 (20.1 – 24.1)[a]	17.1 (16.0 – 17.9)[l]	17.0 (15.7 – 17.8)[w]
Hemoglobin	Median (x, IQR)	11.8 (10.3 – 13.2)[b,m,x]	11.2 (9.9 – 12.7)[b]	10.5 (9.0 – 12.1)[m]	10.4 (9.0 – 11.8)[x]
	<8.0 g/dL	216 (4%)	74 (7%)	164 (12%)	52 (12%)
Liver transaminase	AST (1 – 45 IU/L)	33 (26 – 45)[c,n,y]	36 (27 – 51)[c]	37 (28 – 55)[n]	41 (30 – 58)[y]
	AST >45 IU/L	1204 (24%)	324 (31%)	457 (35%)	174 (41%)
	ALT (1 – 50 IU/L)	23 (17 – 33)[d,o,z]	24 (17 – 37)[d]	24 (16 – 37)°	24 (18 – 38)[z]
CD4 count	Median (x, IQR)	100 (42 – 163)[e,p,A]	58 (22 – 120)[e]	55 (18 – 118)[p]	37 (11 – 87)[A]
	<50 cells/mm^3	1529/5333 (28.7%)	486/1096 (44.3%)	660/1374 (48.0%)	268/450 (59.6%)
	51 - 100 cells/mm^3	1152/5333 (21.6%)	260/1096 (23.7%)	288/1374 (21.0%)	87/450 (19.3%)
	101 - 200 cells/mm^3	2136/5333 (40.0%)	310/1096 (28.3%)	367/1374 (26.7%)	72/450 (16.0%)
	>201 cells/mm^3	516/5333 (9.7%)	40/1096 (3.7%)	59/1374 (4.3%)	23/450 (5.1%)
Viral load (copies/ml)	Median (x, IQR)	21000 (8300 – 41300)	19500 (10000 – 38000)	21000 (11000 – 43000)	24500 (12500 – 43550)
Clinical stage	Stage I and II	2829 (67%)	323 (36%)	501 (45%)	81 (22%)
	Stage III and IV	1416 (33%)[f,q,B]	569 (64%)[f]	612 (55%)[q]	287 (78%)[B]
First-line ART regimen	AZT/3TC/EFV	153 (2.8%)	19 (1.7%)	32 (2.3%)	11 (2.4%)

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		No OC lesion Normal BMI	OC lesion Normal BMI	No OC lesion Low BMI	OC lesion Low BMI
	AZT/3TC/NVP	21 (0.4%)	-	3 (0.2%)	-
	d4T/3TC/EFV	4831 (88.8%)^{g,r,C}	1008 (90.7%)^{g}	1293 (92.3%)^{r}	423 (93.2%)^{C}
	d4T/3TC/NVP	437 (8.0%)	85 (7.6%)	73 (5.2%)	20 (4.4%)
TB at initiation	n (%)	718 (13%)^{h,s,D}	212 (19%)^{h}	328 (23%)^{s}	105 (23%)^{D}
Patient follow-up and outcomes					
New diagnosis of OC					
0 – 12 months	n (%)	119/4370 (2.7%)	16/921 (1.7%)	31/950 (3.3%)	9/308 (2.9%)
BMI 6 months before	Median (IQR)	23.3 (20.5 – 26.6)	23.0 (21.7 – 25.4)	16.6 (14.9 – 18.4)	17.2 (15.5 – 18.5)
BMI 6 months after	Median (IQR)	23.9 (20.9 – 28.0)	22.9 (22.0 – 24.3)	18.1 (16.9 – 21.1)	18.4 (15.6 – 20.3)
13 – 24 months	n (%)	36/3933 (0.9%)	15/830 (1.8%)	15/814 (1.8%)	1/261 (0.4%)
BMI 6 months before	Median (IQR)	22.0 (19.2 – 24.9)	21.7 (18.8 – 24.0)	19.1 (17.0 – 22.2)	22.4 (22.4 – 22.4)
BMI 6 months after	Median (IQR)	22.5 (20.8 – 26.7)	22.0 (15.9 – 24.1)	20.2 (17.5 – 22.0)	22.6 (22.6 – 22.6)
Outcomes by 12 months of follow-up					
Alive and in care	n (%)	4370 (80.3%)	921 (82.8%)	950 (67.8%)	308 (67.8%)
Loss to follow-up$^{\$}$	n (%)	538 (9.9%)	75 (6.8%)	206 (14.7%)	59 (13.0%)
Transferred out	n (%)	212 (3.9%)	40 (3.6%)	63 (4.5%)	6 (1.3%)
Death$^{\&}$	n (%)	322 (5.9%)	76 (6.8%)	182 (13.0%)	81 (17.9%)
Time on ART (months)	Median (IQR)	27.6 (13.8 – 44.9)	32.1 (16.6 – 48.2)	20.4 (7.2 – 38.4)	23.7 (6.8 – 44.6)

ART = antiretroviral therapy, BMI = body mass index, AST = aspartate transaminase, OC = oropharyngeal candidiasis, IQR = interquartile range

Variables are proportions (n, %) unless otherwise specified.

$^{\$}$Loss to follow-up defined as ≥3 months since last visit.

$^{\&}$Mortality obtained from South African National Vital Registration Infrastructure Initiative.

a,b,c,d,e,i,l,l,m,n,o,p,t,w,x,y,z,A $p < 0.05$ by T-test (parametric or normally distributed data) or Kruskal-Wallis (non-parametric or non-normally distributed data)

f,g,h,j,k,q,r,s,u,v,B,C,D $p < 0.05$ by Chi-square test for proportions

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Table 2

Outcomes after initiation on ART.

	N (%) with outcome	Crude RR (95% CI)	Adjusted RR (95% CI)*
A. Failure to increase CD4 count by ≥50 cells/mm^3 at 6 months post-ART initiation$			
No OC – Normal BMI	970 (24.7%)	1.0	1.0
OC - Normal BMI	137 (16.8%)	0.70 (0.59 – 0.82)	0.72 (0.61 – 0.85)
No OC - Low BMI	192 (22.0%)	0.94 (0.83 – 1.08)	1.07 (0.86 – 1.33)
OC - Low BMI	69 (25.1%)	1.09 (0.88 – 1.34)	0.92 (0.80 – 1.06)
B. Failure to increase CD4 count by ≥100 cells/mm^3 at 12 months post-ART initiation$			
No OC – Normal BMI	1020 (29.4%)	1.0	1.0
OC - Normal BMI	176 (23.6%)	0.82 (0.71 – 0.93)	0.83 (0.71 – 0.96)
No OC - Low BMI	193 (26.6%)	0.93 (0.82 – 1.06)	0.92 (0.65 – 1.05)
OC - Low BMI	60 (24.5%)	0.86 (0.69 – 1.08)	0.95 (0.83 – 1.09)
C. Detectable HIV viral load ≥400 copies/ml at 6 months post-ART initiation#			
No OC – Normal BMI	332 (8.9%)	1.0	1.0
OC - Normal BMI	57 (7.4%)	0.79 (0.61 – 1.04)	0.76 (0.56 – 1.03)
No OC - Low BMI	79 (9.5%)	1.05 (0.84 – 1.31)	1.31 (0.91 – 1.90)
OC - Low BMI	28 (10.8%)	1.20 (0.84 – 1.71)	1.02 (0.79 – 1.32)
D. Detectable HIV viral load ≥400 copies/ml at 12 months post-ART initiation#			
No OC – Normal BMI	281 (8.6%)	1.0	1.0
OC - Normal BMI	59 (8.6%)	0.93 (0.72 – 1.21)	0.98 (0.74 – 1.30)
No OC - Low BMI	68 (10.2%)	1.13 (0.88 –1.43)	1.60 (1.11 – 2.29)
OC - Low BMI	33 (14.7%)	1.64 (1.18 – 2.28)	1.10 (0.84 – 1.45)

OC = oropharyngeal candidiasis, ART = antiretroviral therapy, BMI = body mass index (kg/m^2), RR = Relative Risk, CI = confidence interval, No OC – Normal BMI = patients without OC prior to ART initiation and BMI ≥18.5 kg/m^2, OC – Normal BMI = patients with a diagnosis of OC prior to ART initiation and BMI ≥18.5 kg/m^2, No OC – Low BMI = patients with a BMI <18.5 kg/m^2 and without OC prior to ART initiation, OC – Low BMI = patients with a diagnosis of OC prior to ART initiation and a BMI <18.5 kg/m^2

$Failure to achieve an adequate CD4 count response was defined as failure to increase CD4 count by ≥50 cells/mm^3 at 6 months or failure to increase CD4 count by ≥100 cells/mm^3 at 12 months post-ART initiation.

#Failure to achieve an adequate viral load response was defined as a failure to suppress HIV viral load below 400 copies/ml, in other words a detectable viral load (≥400 copies/ml) at 6 or 12 months post-ART initiation.

*Adjusted for hemoglobin, CD4 count, AST, TB, age and gender at ART initiation.

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Table 3

Cox proportional hazards ratio for death and LTFU by 12 months post-ART initiation.

		Person time (years)	Rate/100 pys[†]	Crude HR (95% CI)	Adjusted HR (95% CI)[*]
Loss to follow-up by 12 months post-ART initiation[$]					
No OC – Normal BMI	Normal	4868.1	11.0	1.0	1.0
OC -Normal BMI	OC – Normal BMI vs. normal	1002.2	7.5	0.59 (0.47 – 0.75)	0.69 (0.54 – 0.88)
No OC -Low BMI	No OC -Low BMI vs. normal	1129.5	18.2	1.71 (1.46 – 1.99)	1.55 (1.30 – 1.85)
OC -Low BMI	OC -Low BMI with OC vs. normal	365.6	16.1	1.39 (1.07 – 1.81)	1.36 (1.02 – 1.82)
Mortality by 12 months post-ART initiation[&]					
No OC – Normal BMI	Normal	4868.1	6.6	1.0	1.0
OC -Normal BMI	OC – Normal BMI vs. normal	1002.2	7.6	0.84 (0.66 – 1.06)	1.00 (0.77 – 1.29)
No OC -Low BMI	No OC -Low BMI vs. normal	1129.5	16.1	2.05 (1.73 – 2.43)	1.87 (1.54 – 2.28)
OC -Low BMI	OC -Low BMI with OC vs. normal	365.6	22.2	2.64 (2.09 – 3.33)	2.42 (1.88 – 3.12)

OC = oropharyngeal candidiasis, ART = antiretroviral therapy, BMI = body mass index (kg/m^2), HR = Hazard Ratio, CI = confidence interval

[†]pys = person years, No OC – Normal BMI = patients without OC prior to ART initiation and BMI ≥18.5 kg/m^2, OC – Normal BMI = patients with a diagnosis of OC prior to ART initiation and BMI ≥18.5 kg/m^2, No OC – Low BMI = patients with a BMI <18.5 kg/m^2 and without OC prior to ART initiation, OC – Low BMI = patients with a diagnosis of OC prior to ART initiation and a BMI <18.5 kg/m^2

[*]Adjusted for hemoglobin, CD4 count, AST, TB, age and gender at ART initiation.

[$]Loss to follow-up defined as 3 months since last visit

[&]Mortality obtained from South African National Vital Registration Infrastructure Initiative