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Role of oral candidiasis in TB and HIV co-infection: AIDS Clinical Trial Group Protocol A5253

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SUMMARY

OBJECTIVE—To evaluate the association between oral candidiasis and tuberculosis (TB) in human immunodeficiency virus (HIV) infected individuals in sub-Saharan Africa, and to investigate oral candidiasis as a potential tool for TB case finding.

METHODS—Protocol A5253 was a cross-sectional study designed to improve the diagnosis of pulmonary TB in HIV-infected adults in high TB prevalence countries. Participants received an

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oral examination to detect oral candidiasis. We estimated the association between TB disease and oral candidiasis using logistic regression, and sensitivity, specificity and predictive values.

RESULTS—Of 454 participants with TB culture results enrolled in African sites, the median age was 33 years, 71% were female and the median CD4 count was 257 cells/mm³. Fifty-four (12%) had TB disease; the prevalence of oral candidiasis was significantly higher among TB cases (35%) than among non-TB cases (16%, $P < 0.001$). The odds of having TB was 2.4 times higher among those with oral candidiasis when controlling for CD4 count and antifungals (95%CI 1.2–4.7, $P = 0.01$). The sensitivity of oral candidiasis as a predictor of TB was 35% (95%CI 22–48) and the specificity 85% (95%CI 81–88).

CONCLUSION—We found a strong association between oral candidiasis and TB disease, independent of CD4 count, suggesting that in resource-limited settings, oral candidiasis may provide clinical evidence for increased risk of TB and contribute to TB case finding.

Keywords

oral candidiasis; tuberculosis; HIV; acquired immunodeficiency syndrome

THE IDENTIFICATION of human immunodeficiency virus (HIV) infected persons with low CD4+cell count is important in areas of high tuberculosis (TB) prevalence, as this group is at highest risk of having TB disease concomitantly with HIV infection. Several studies have shown that oral candidiasis and TB disease were the most common comorbidities among populations with advanced HIV disease: one study among 356 hospitalized Cambodian patients with the acquired immunodeficiency syndrome (AIDS) revealed that oral candidiasis (51%) and pulmonary and extra-pulmonary TB (44%) were the most frequent opportunistic infections.¹ Another study among 205 HIV-infected adults in Malaysia showed that oral candidiasis was the most common mucocutaneous disease, and significant co-existence was found with the major opportunistic systemic diseases such as TB.²

Early in the HIV epidemic, oral candidiasis was found to be among the strongest clinical predictors of progression to AIDS in various HIV-infected populations.^{3,4} Oral candidiasis has also been shown to be the most common oral manifestation of HIV infection in different parts of the world,^{5–14} and to be closely associated with low CD4+ cell count.^{5,7,8,15–20} A diagnosis of oral candidiasis is usually made by visual examination of the mouth, and non-dental health care providers can be readily trained to perform such an examination.¹⁹ The strong positive association between oral candidiasis and a low CD4+cell count is thus a useful finding with respect to the need for inexpensive surrogate markers of HIV disease progression and related comorbidities in resource-limited countries where measurement of CD4+cell counts is not widely available.

A visual inspection of the soft tissues of the mouth is quick (<5 min), non-invasive, and inexpensive. It could be used as initial screening to identify patients with oral candidiasis who are most likely to have CD4+cell count <200 cells/mm³, and thus at higher risk for TB disease that may or may not yet be symptomatic.

The objective of the present study was to evaluate the value of oral candidiasis as a predictor of TB disease among HIV-infected men and women in resource-limited settings with high TB prevalence.

METHODS

Study design and population

This study was conducted as part of the AIDS Clinical Trial Group (ACTG) Protocol A5253 in collaboration with the Oral HIV/AIDS Research Alliance (OHARA).²¹ Protocol A5253 was a cross-sectional study designed to construct a standardized diagnostic evaluation (SDE) that improves diagnosis of pulmonary TB as compared to standard-of-care (SOC) TB screening in HIV-infected participants not currently receiving antiretroviral therapy (ART).²²

The target population for Protocol A5253 was HIV-infected males and females aged 13 years living in high TB prevalence regions in sub-Saharan Africa, India and South America. In addition to being HIV-infected, eligibility criteria included not having received ART, or a diagnosis of pulmonary TB, or medications to treat TB within 90 days before study entry. Participants were recruited between 5 February and 30 November 2010 from 11 clinical trials units of the ACTG by clinical site investigators using a convenience sampling strategy. Sites were required to be in a country with a TB incidence of >60 per 100 000 population per year according to the World Health Organization (WHO) Global Health Atlas country profiles.²³ The institutional review boards or ethics committees of the participating institutions approved the study, and each participant gave written informed consent. The present report focuses on the African sites only, as 96% of the TB cases were observed in these sites.

Clinical data collection

All participants in Protocol A5253 were screened according to SOC and candidate SDE elements.²² Sputum culture in either solid or liquid culture was used as the gold standard to define a participant as TB-positive. SOC screening algorithm components were cough, fever, weight loss and/or night sweats occurring within the previous 30 days, Ziehl-Neelsen sputum smear and chest radiography (CXR) for non-pregnant participants. SDE screening included additional symptoms and clinical signs, and sputum smear using fluorescence microscopy. All participants underwent all evaluations. A detailed description of these methods has been published elsewhere.²²

All participants also underwent a standardized oral soft tissue examination performed by a nurse or a physician who had been trained and calibrated in the diagnosis of common HIV-related oral mucosal diseases using a protocol developed by the Clinical Science Unit of OHARA. Examiners were trained by watching a 1-h presentation that described how to perform an oral soft tissue examination, and how to diagnose pseudomembranous candidiasis, erythematous candidiasis and angular cheilitis, which are all part of the spectrum of oral candidiasis, as well as other common oral lesions. We used published case definitions of these oral endpoints.²⁴ Examiners were considered calibrated if they obtained

80% correct answers to a post-test of clinical slides administered after the training. Participants found to have clinical signs of oral candidiasis had a swab (BBL™ Culture-Swab™ kit, BD, Sparks, MD, USA) collected from a well-defined area for culture confirmation of the clinical diagnosis. If a participant had more than one form of oral candidiasis, the examiner was instructed to preferentially collect a swab from a pseudomembranous candidiasis lesion if present. If pseudomembranous candidiasis was not present, but angular cheilitis was observed together with erythematous candidiasis, then the examiner was instructed to collect the swab from the angular cheilitis.

Oral swab specimen processing

Collection supplies were distributed to clinical trial sites from the OHARA/ACTG *Candida* repository at the Center for Medical Mycology, Case Western Reserve University, Cleveland, OH, USA. These consisted of culturette swabs containing Amies Transport Media (Becton Dickinson, Franklin Lakes, NJ, USA), dehydrated potato dextrose agar (PDA) (BD) and 4 ml Wheaton vials for preparing agar slants (Wheaton Industries, Millville, NJ, USA). After collection, oral swabs were forwarded to a local laboratory for processing onto PDA (potato dextrose agar) plates for *Candida* colony count, which were recorded. A subculture of each distinct colony type suspected of being a *Candida* isolate was then prepared on an agar slant and forwarded to the Case repository for speciation.

Statistical analyses

Summary statistics were used to describe participant characteristics (sex, age, region of residence and CD4 cell count) by TB disease status. We computed the prevalence of the three types of oral candidiasis and of other oral mucosal lesions, and used the χ^2 test (or Fisher's exact test for smaller cell sizes) to explore whether an association existed between these oral outcomes and TB. We fit a stepwise logistic regression model to investigate the association between oral candidiasis and TB disease while controlling for potential confounders. We started by fitting a model in which we included all variables that were suspected confounders of the association between oral candidiasis and TB: CD4 cell count, sex, age and receipt of antifungal medication at the time of study examination. We then performed backward elimination analysis to remove variables that were not associated with TB at a significance level of 0.2. The model yielded adjusted odds ratios (aORs) with 95% confidence intervals (CIs). We initially also included an interaction term in the logistic regression model to detect whether a possible effect modification existed between CD4 cell count and oral candidiasis, but found no significant interaction effect ($P = 0.33$). To investigate the role of oral candidiasis as a predictor of TB, we estimated the sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) in relation to TB.

RESULTS

Among 521 participants enrolled in Protocol A5253 in African sites, 455 had an interpretable TB sputum culture result, and 454 underwent an oral examination (and are included in the present report). The majority were Black non-Hispanic (99%) and female (71%); 54 had culture-confirmed TB disease (12%; Table 1); 18% had a clinical diagnosis of oral candidiasis. The median age was 33 years, and the median CD4+ cell count was 257

cells/mm³. As previously reported, participants with and those without TB were similar with regard to age and sex; however, the median CD4 cell count was significantly lower among TB cases (202 cells/mm³, range 2–699) than in non-cases (270 cells/mm³, range 1–1796, $P = 0.003$).²² Among participants with TB, 2% were using an antifungal medication at the time of study entry compared to 9% among those without TB ($P = 0.10$).

The prevalence of oral candidiasis was significantly higher among TB cases (35%) than among non-cases (16%; $P < 0.001$), predominantly pseudomembranous candidiasis (Table 2). Among 77 cases with a clinical diagnosis of oral candidiasis who had a swab collected for culture (4 cases did not have a confirmatory swab), 62 (81%) were culture-confirmed. The proportion of confirmation using culture differed by type of candidiasis, with angular cheilitis and pseudomembranous candidiasis having the highest level of culture confirmation (100% and 85%, respectively), and erythematous candidiasis the lowest (72%).

Other types of oral lesions had low prevalence (4% for each type of condition), and included hairy leukoplakia ($n = 7$), recurrent herpes simplex infection ($n = 6$), necrotizing ulcerative gingivitis/periodontitis ($n = 6$), oral Kaposi's sarcoma ($n = 3$), oral warts ($n = 2$) and recurrent aphthous ulcers ($n = 1$).

Among those with oral candidiasis, 68% had a CD4 cell count < 200 cells/mm³, while among those without oral candidiasis 74% had a CD4 cell count > 200 cells/mm³ (Table 3). We found a strong positive association between low CD4 cell count and the presence of oral candidiasis, using a contingency table approach or a non-parametric analysis.

A multivariate logistic regression model exploring the association between TB (outcome) and oral candidiasis revealed that the odds of having TB was 2.4 times higher among those with oral candidiasis when controlling for CD4 count and antifungal medication (95%CI 1.2–4.7, $P = 0.01$; Table 4).

The proportion of participants with TB who also had oral candidiasis (sensitivity) was 35% (95%CI 22–48). The specificity was 85% (95%CI 81–88). Both PPV and NPV of oral candidiasis in relation to TB are presented as functions of TB prevalence in the Figure. For example, for a TB prevalence ranging from 10% to 15%, the PPV would range from 20% to 29%, and if TB prevalence was as high as 20%, the PPV of oral candidiasis would be 37%.

DISCUSSION

This analysis among HIV-infected participants in ACTG Protocol A5253 revealed that oral candidiasis was the most common type of oral mucosal disease. Furthermore, as reported in other studies in sub-Saharan Africa, there was a strong positive association between the presence of oral candidiasis and low CD4 cell count.¹⁹ Clinical diagnoses of oral candidiasis made by nurses and physicians at various ACTG sites, which were confirmed by a positive culture in more than 80% of the cases, were strongly associated with TB even after adjusting for CD4 count. The sensitivity was only 35%, while the specificity was 85%. The sensitivity of oral candidiasis was somewhat similar to that of other clinical symptoms described in the primary A5253 paper, such as fever, night sweats and fatigue, which were 43%, 48% and 50%, respectively.²² The specificity for these symptoms was lower than that of oral

candidiasis: 71%, 61% and 60%, respectively. Furthermore, while a history of cough in the last 30 days had the highest sensitivity of all clinical symptoms (82%), specificity was low (39%). In the A5253 primary paper, performance characteristics were assessed for multiple combinations of clinical symptoms, CD4 cell count, CXR and/or lymphadenopathy. None of these combinations improved upon the predictive values of symptoms of cough, fever, night sweats and fatigue, which are used in TB case finding. The present analysis reveals that due to its strong association with TB disease and high specificity, and despite its modest sensitivity, oral candidiasis should also prompt further evaluation for TB disease among HIV-infected adults.

The strength of the present study is that it specifically explored the association between oral candidiasis and TB by including a systematic oral examination among all participants, regardless of oral symptoms. Furthermore, the clinical diagnosis of oral candidiasis was confirmed by an oral swab culture, and revealed a high proportion of correct clinical diagnoses. Oral examinations were performed by nurses/physicians who had received the same standardized training on the diagnosis of the various forms of oral candidiasis.²⁴ The standardized oral examination training module has been evaluated within ACTG clinical research sites (CRS) as part of a recent study to assess the accuracy of oral diagnoses made by CRS examiners (non-dental health care professionals). Among 328 HIV-infected participants, the sensitivity and specificity for the diagnosis of oral candidiasis by trained CRS examiners as compared to Oral Medicine specialists as reference standard was 90% and 92%, respectively, with 153 cases of oral candidiasis diagnosed in this cross-sectional study (unpublished data). The limitations of our study include a potential lack of power, as there were only 54 cases of TB. Use of sputum culture as reference standard excluded cases of extra-pulmonary disease. The proportion of participants currently taking an antifungal medication (8%) may have slightly diluted the magnitude of the association, although there was no evidence of preferential bias as these participants were evenly distributed by TB status.

The WHO, the Joint United Nations Programme on HIV/AIDS and the Stop TB Partnership have set a target of halving TB mortality rates among HIV-positive people by 2015 compared to 2004.²⁵ WHO recommendations on the interventions needed to prevent, diagnose and treat TB in people living with HIV have been available since 2004.²⁶ The plan recommends that all people living with HIV should be regularly screened for TB using a clinical symptom-based algorithm consisting of current cough, fever, weight loss or night sweats at the time of initial presentation for HIV care and at every visit to a health care facility or contact with a health care worker afterwards. Oral candidiasis is strongly associated with TB disease, and can be assessed by a quick visual examination of the mouth. Like other clinical symptoms, it therefore represents a useful clinical marker to identify a high-risk population who must be screened for TB disease. While many studies have reported on the strong association between oral candidiasis and low CD4 cell count, the present study is among the first to detect a strong association between oral candidiasis and TB disease after controlling for CD4 cell count. It is consistent with findings from a study of 2086 adults with HIV disease in South Africa that revealed that TB and oral candidiasis were the only opportunistic infections to commonly occur among those with CD4 cell counts < 200 cells/mm³.²⁷ Among those with CD4 cell count between 201 and 350

cells/mm³, the incidence rate of TB and oral candidiasis was 5.7 (95% CI 3.7–7.8) and 15.2 (95% CI 11.6–18.8) per 100 person-years, respectively, while all other opportunistic infections had an incidence rate of <2.5.

Based on the modest sensitivity and PPV reported by our study, oral candidiasis cannot be used as a diagnostic test for TB disease. However, the strong association found between the presence of oral candidiasis and TB disease independently of CD4 cell count, and the high specificity of oral candidiasis in relation to TB, suggest that it could be used to identify those who should be screened for TB disease, for example with culture and/or nucleic acid amplification tests. Consideration may also be given to use of the urine lipoarabinomannan assay, which has high sensitivity among patients with advanced immunodeficiency.²⁸ In resource-limited countries, it is useful to have a clinical tool that may help identify those at highest risk for TB, and we recommend that TB screening be performed on all HIV-infected patients with a diagnosis of oral candidiasis.

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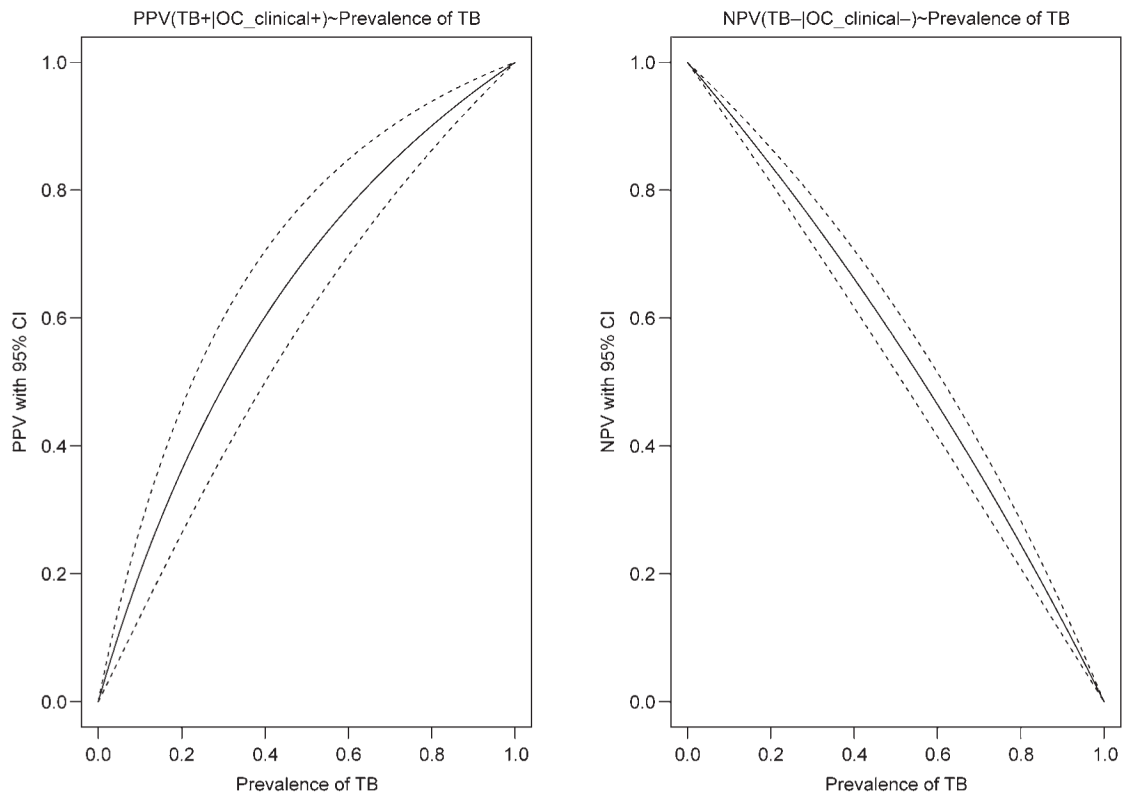
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**Figure.**

PPVs and NPVs of clinical diagnosis of oral candidiasis in predicting TB in the Africa sites participating in Protocol A5253. PPV = positive predictive value; OC = oral candidiasis; TB = tuberculosis; NPV = negative predictive value; CI = confidence interval.

Table 1

Baseline characteristics among 454 participants with an interpretable sputum culture in Protocol A5253 (sub-Saharan Africa sites)*

Characteristic	n (%)
Categorical variables	
Race/ethnicity	
Black Non-Hispanic	451 (99)
Hispanic (any race)	2 (<1)
Asian/Pacific Islander	1 (<1)
Sex	
Female	321 (71)
Male	133 (29)
Sputum culture-positive for tuberculosis	54 (12)
Oral candidiasis	
Clinical diagnosis	81 (18)
Culture-confirmed diagnosis [†]	62 (14)
Currently on antifungal medication	36 (8)
Continuous variables, median (range)	
Age	33 (18–65)
CD4 cell count	257 (1–1796)

* Among 455 participants with interpretable sputum culture in Africa sites in Protocol A5253, 454 underwent an oral examination.

[†] n = 77 underwent an oral swab culture to confirm the clinical diagnosis of oral candidiasis.

Table 2

Prevalence of oral candidiasis and other oral mucosal lesions by TB status (as determined using sputum culture) among 454 participants in Protocol A5253

Oral lesion (clinical diagnosis)	TB-positive (n = 54) n (%)	TB-negative (n = 400) n (%)	P value
Candidiasis			
Any oral candidiasis	19 (35)	62 (16)	<0.001*
Pseudomembranous candidiasis	18 (33)	48 (12)	<0.001*
Erythematous candidiasis	2 (4)	16 (4)	1.00†
Angular cheilitis	0 (0)	5 (1)	1.00†
Other oral mucosal lesions			
Hairy leukoplakia	1 (2)	6 (2)	0.59†
Necrotizing ulcerative gingivitis/periodontitis	2 (4)	4 (1)	0.15†
Recurrent oral/labial herpes simplex infection	2 (4)	4 (1)	0.15†
Kaposi's sarcoma	0 (0)	3 (<1)	1.00†
Oral warts	0 (0)	2 (<1)	1.00†
Ulceration not otherwise specified	0 (0)	1 (<1)	1.00†

* χ^2 test.

† Fisher's exact test.

TB = tuberculosis.

Table 3

Baseline characteristics by diagnosis of oral candidiasis among 454 participants with an interpretable sputum culture in Protocol A5253 (sub-Saharan Africa sites)*

Characteristic	Oral candidiasis (n = 81) n (%)	No oral candidiasis (n = 373) n (%)	P value [†]
Categorical variables			
Race/ethnicity			
Black non-Hispanic	81 (100)	370 (99)	1.000
Hispanic (any race)	0 (0)	2 (1)	
Asian/Pacific Islander	0 (0)	1 (<1)	
Sex			
Female	53 (65)	268 (72)	0.250
Male	28 (35)	105 (28)	
CD4 cell count, cells/mm ³			
<200	55 (68)	96 (26)	<0.001
200–500	22 (27)	202 (54)	
>500	4 (5)	75 (20)	
Currently on antifungal medication	8 (10)	28 (8)	0.496
Continuous variables, median (Q1, Q3) [‡]			
Age	35 (29, 40)	32 (28, 39)	0.108
CD4 cell count	151 (46, 228)	287 (190, 463)	<0.001

* Among 455 participants with interpretable sputum culture result in African sites in Protocol A5253, 454 underwent an oral examination.

[†]Fisher's exact test for race and CD4 cell count; χ^2 test for sex.

[‡]P values using Wilcoxon's rank-sum test.

Q = quartile.

Table 4

Multivariate model exploring the association between tuberculosis (outcome) and oral candidiasis controlling for CD4 cell count, and antifungal medication among 454 Protocol A5253 participants recruited from African sites

Independent variables	aOR (95%CI)	P value
Clinical diagnosis of oral candidiasis (vs. no oral candidiasis)	2.38 (1.22–4.66)	0.01
CD4 cell count, cells/mm ³ (per 50 unit increase)	0.92 (0.84–0.99)	0.04
Antifungal medication (yes vs. no)	0.16 (0.02–1.19)	0.07

aOR = adjusted odds ratio; CI = confidence interval.