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Self-care intervention to reduce oral candidiasis recurrences in HIV-seropositive persons: a pilot study

Joan F. Hilton[1], Laurie A. MacPhail[2], Laura Pascasio[3], Hervé Y. Sroussi[3], Behnaz Cheikh[3], Maria E. LaBao[3], Katherine Malvin[3], Deborah Greenspan[3] and Marylin J. Dodd[4]

[1]Department of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, CA, [2]Department of Oral and Maxillofacial Pathology, Medicine and Surgery, Temple University School of Dentistry, Philadelphia, PA, Departments of [3]Stomatology, and [4]Physiological Nursing, University of California San Francisco, San Francisco, CA, USA

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Abstract – *Objectives:* This single-blind randomized controlled pilot study evaluated the efficacy of a behavioral intervention program, PRO-SELF: Candidiasis, to reduce time to recurrence of oral candidiasis over 6 months in susceptible HIV-seropositive persons. The intervention involved instruction by dentists on improving oral hygiene, minimizing sugar intake, and self-diagnosing candidiasis. *Methods:* Participants were adults with oral candidiasis responsive to antifungals who presented to the UCSF Stomatology Clinic between 1997 and 2000. At 2–3 weeks of follow-up visits, a dentist 'examiner', masked to group assignment, quizzed participants as to the presence of candidiasis, and assessed candidiasis status. A second, unmasked dentist 'instructor' then delivered the program to intervention participants. Participants recorded dietary and oral hygiene practices in 24-h recall diaries: intervention participants at each visit and controls at initial and final visits. *Results:* At randomization, CD4+ cell counts (cells/mm^3) were 298 ± 188 among 18 intervention participants and 396 ± 228 among 17 controls. The candidiasis recurrence rates at 6 months were 78% among intervention compared with 88% among control participants (hazard ratio 0.72; 95% CI 0.35–1.50). Performing oral hygiene after meals/snacks showed the largest relative improvement: intervention–control difference in proportion of meals/snacks affected was 24% (95% CI −1 to 48%). Self-diagnoses of candidiasis were inaccurate, possibly because of mild episodes. *Conclusions:* The results weakly indicate that regular instruction from healthcare professionals helps patients delay candidiasis recurrence by improving oral hygiene. Among HIV-seropositive persons, those with poor oral hygiene, and high-sugar diets are most likely to benefit.

Key words: HIV; oral candidiasis; oral hygiene; randomized controlled trials; self-care

Laurie A MacPhail PhD, DMD, Temple University School of Dentistry, 3223 North Broad Street, Philadelphia, PA, 19140 USA
Tel: 215-707-7685
Fax: 215-707-5719
e-mail: laurie.macphail@temple.edu

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Many HIV-infected persons develop oral candidiasis during the course of their disease, especially as they become immunosuppressed (1). Untreated oral candidiasis can negatively affect a person's desire and ability to eat, nutritional status and, eventually, general health. Although successful antifungal treatments relieve symptoms, oral candidiasis typically recurs within 1.5 months (2).

The healthy oral cavity supports an ecosystem that includes multiple species of bacteria and, commonly, fungi such as *Candida albicans*. Competition for nutrients normally favors the more rapidly growing bacteria; however, addition of sufficient exogenous glucose stimulates growth of *C. albicans* (3, 4). This suggests that minimizing the presence of exogenous sugars in the mouth by increasing oral hygiene efforts and decreasing dietary sugar may help suppress fungal growth and, in HIV-infected persons, may serve to decrease the frequency of oral candidiasis episodes.

However, with the exception of denture-related candidiasis (5, 6), the efficacy of increased oral hygiene to prevent oral candidiasis has been anecdotal and not subjected to rigorous testing.

Research into the self-care practices of adult oncology patients who were receiving chemotherapy or radiation therapy led to the development of the PRO-SELF© Programs. These are nurse-initiated, informational, interactive programs of self-care intervention. Patients who received the PRO-SELF© targeted intervention programs, when compared with those who did not, were more knowledgeable, performed more self-care behaviors and experienced less morbidity (7–9).

We designed a fourth-generation program, 'PRO-SELF: Candidiasis', to enable HIV-infected adults to avoid the oral discomfort associated with oral candidiasis by empowering them to decrease the frequency of recurrent episodes via a self-help regimen, and when an episode occurs, to recognize its presence early so that treatment may be sought. The PRO-SELF: Candidiasis self-help regimen consists of repeated instruction and training on oral hygiene procedures and diet modifications aimed at minimizing exogenous sugars in the mouth, as well as training in recognition of oral candidiasis. The PRO-SELF: Candidiasis program was designed so that, in addition to dentists, it could be implemented by nurses, dental hygienists, and physicians.

The purpose of this single-blind randomized controlled trial was to evaluate the efficacy of the PRO-SELF: Candidiasis program based on oral candidiasis recurrence rates in susceptible HIV-infected persons. We also examined the intervention's effect on intermediate outcomes: changes in oral hygiene and dietary practices and in plaque and gingival indices. Finally, we determined if participants in the PRO-SELF: Candidiasis study arm self-reported the recurrence of oral candidiasis more accurately than did participants in the control arm. The study was reviewed and approved by the institutional review board of University of California, San Francisco.

Methods

Study design

Following recruitment (January 1997 to June 2000), determination of eligibility, and randomization, study procedures were conducted at an initial 'baseline' visit and periodic follow-up visits (every 2–3 weeks) over 6 months. To minimize bias in the assessment of oral candidiasis, each participant was seen by two study dentists, an 'examiner' and an 'instructor'. The examiner, who remained masked to the participant's group assignment throughout the trial, diagnosed the presence or absence of oral candidiasis. Subsequently, the unmasked instructor performed study indices and provided intervention participants with individualized PRO-SELF: Candidiasis dietary and oral hygiene instruction. All participants had the same instructor throughout the trial. Five dentists experienced in the oral care of HIV-infected patients served as examiners or instructors. They were trained to conduct clinical assessments and indices in accordance with the written study protocol. Participants who completed the study were compensated $155 and received two professional teeth cleanings, one following the baseline visit and a second after completing the study.

Eligibility criteria and enrollment procedures

HIV-infected persons who presented at the UCSF Stomatology Clinical Center (an oral medicine referral clinic) with clinical oral candidiasis, either because of oral soft tissue problems or in response to study advertisements, were informed of the risks and benefits of the study. If interested, they were screened for eligibility.

Eligible persons were male or female over 18 years of age with documented HIV-infection (by test results from a state-certified, licensed laboratory or a written note from a referring physician) who were able to read English and sign an informed consent document. All medications except antifungals and systemic or topical oral corticosteroids were allowed. Ineligible persons were those who were unable to alter their diet, to follow oral hygiene instructions, to execute the manipulations required of brushing and flossing, or to see well enough to perform an oral self-examination. Persons with esophageal candidiasis or oral candidiasis unresponsive to antifungal therapy, those allergic to the erythrosine dyes in plaque disclosing fluid, those wearing dentures that could not be cleaned by ultrasonic treatment, and those who, by American Heart Association criteria (10), required prophylaxis prior to dental treatment but were unable to take the recommended oral antibiotics were also excluded.

All potential participants were required to have an episode of oral candidiasis that was observed by study dentists. They were prescribed antifungals

(nystatin vaginal tablets, clotrimazole troches, itraconazole suspension, amphotericin B suspension, or fluconazole tablets) and instructed to remain on the antifungal until they were re-examined 2–3 weeks later. Those who returned clinically clear of oral candidiasis and signed informed consent forms were enrolled.

Baseline procedures

At the baseline visit, a study dentist documented the participant's demographic and HIV-related characteristics, and all medications. The participant's stated oral hygiene practices and food preferences, requirements and allergies were also documented. Participants were given a recall diary on which to enter what they had eaten at meals (breakfast, lunch, dinner) or snacks (morning, afternoon, evening) during the previous 24 h. They were also asked to indicate oral hygiene procedures (brushing, flossing, or rinsing) that they had performed following each meal or snack.

A study dentist determined the tooth count; the number of decayed, missing, and filled coronal tooth surfaces (DMFS score); and whether the participant wore a denture and its condition and cleanliness. The examiner performed the oral soft-tissue examination, ascertained the absence of oral candidiasis by clinical examination and KOH smear. The instructor then randomized half the participants to the control and the other half to the intervention group following a scheme prepared by the study biostatistician. The instructor documented the Gingival Index (11), disclosed the participant with Red-Cote® (John O Butler Co., Chicago, IL, USA), and performed the Turesky modification of the Quigley and Hein Plaque Index (12).

To avoid masking of improved oral hygiene efforts by preexisting stains and calculus deposits and to make the groups as comparable as possible at randomization, participants had their teeth and dentures professionally cleaned by a dentist or dental hygienist after the baseline visit. All received standard oral hygiene and denture care instructions by the hygienist or dentist who cleaned their teeth. This was the only oral hygiene instruction that control participants received during the 6-month study.

Follow-up visits

Candidiasis assessments

At the start of a visit, each participant in both groups was quizzed regarding the presence/absence of oral candidiasis in his/her mouth. Each was handed a slip of paper on which was written, 'Do you think you have oral candidiasis (thrush) today?' and was asked to circle 'Yes' or 'No'. Also on the slip was a reminder not to reveal the group assignment to the examiner and to hold any questions for the instructor.

The examiner assessed the presence/absence of clinical candidiasis based on definitions and diagnostic criteria developed by the USA Oral AIDS Collaborative Group (13), prescribed antifungals as necessary, and left the room. The instructor solicited current medications, most recent CD4 counts and HIV-1 RNA levels at each visit. The instructor also performed the plaque and gingival indices for all participants and provided intervention participants with PRO-SELF: Candidiasis instructions and training, as described below.

Intervention procedures

Each PRO-SELF: Candidiasis participant completed a 24-h recall diet and oral hygiene diary at every follow-up visit. The instructor reviewed and discussed the diary with the participant and provided individualized advice on how the participant could modify his/her eating and oral hygiene habits with the intent of reducing the duration of daily exposure of his/her oral cavity to exogenous sugars. Dietary advice was patterned after that developed to prevent dental caries, i.e. to decrease the duration and the frequency of eating, to eliminate between-meal sugary snacks, and to perform some oral hygiene procedure after each meal/snack (14–16). If between-meal salivary stimulation was desired in order to alleviate xerostomia, sugar-free gum or candies were recommended (15, 17). In contrast, control participants completed 24-h recall diet/hygiene diaries at the first and last follow-up visits only, and did not receive advice based on these data. The strategy of repeated recording of dietary/hygiene data by intervention participants was meant to prompt these participants to modify their sugar intake and its duration in the mouth, whereas recording by control participants was limited to avoid such prompting.

The major thrust of the intervention program was intensive oral hygiene to remove debris and dissolved sugars remaining after meals or snacks in order to reduce the daily exposure time to exogenous sugars. Each intervention participant was instructed to clean excess food from his/her mouth after *every* feeding by brushing, flossing or rinsing vigorously. They were also instructed to thoroughly brush for 2 min and floss after at least the

first and last times they ate for the day. Instructions and guided practice were given in flossing techniques and the modified Bass technique for tooth brushing (18). Handouts included written PROSELF: Candidiasis instructions and standard dental pamphlets on brushing and flossing techniques (19, 20). Oral hygiene instruction was tailored to the participant's mouth by using the results of the gingival and plaque index to illustrate problem areas. Any oral hygiene aids needed such as toothpaste, fluoride gel, toothbrush, floss, floss aid, floss threader, interproximal and end-tuft brushes, disclosing tablets, denture cleaner and soak, and mouth mirror were provided.

The instructor reviewed the examiner and participant's findings regarding presence or absence of oral candidiasis with the participant and used them as a teaching aid. The intervention participant was taught to recognize oral candidiasis by guided inspection of his/her own mouth and by use of color photographs of oral candidiasis types before and after treatment. Each intervention participant was asked to perform an oral self-examination every morning before eating. He/she was instructed to first rinse with water and then to use a flashlight to examine his/her mouth in the bathroom mirror.

Verification that groups are balanced by baseline covariates

We described the demographic baseline, HIV-related, and oral health characteristics of the study population, within and between groups, using means or proportions and 95% confidence intervals (CI). The 24-h recall diary data were entered by one dentist into 'The Food Processor' software (version 7.9; ESHA Research, Salem, OR, USA) and the nutrient content of the stated foods was analyzed with emphasis on dietary sugars that could serve as food sources for *C. albicans* (i.e. glucose, sucrose, or fructose, but not xylitol). Diets were summarized via total sugar intake (grams consumed) and carbohydrate intake (percentage of total calories). Oral hygiene practices were summarized via percentage of meals/snacks that were followed by hygiene. Oral health was summarized via plaque and gingival indices, DMFS scores and tooth counts.

Effect of the intervention on candidiasis recurrence

Because of the small number of participants and candidiasis episodes, all clinically diagnosed candidiasis types were combined for analyses. To compare the groups with respect to candidiasis recurrence, we used the Kaplan–Meier method to estimate 6-month rates of recurrence and used a two-sided log-rank statistic to test for a significant reduction in the hazard ratio (HR) among intervention participants. Hazard ratios <1.0 indicate that the intervention protects against recurrence of candidiasis. Using Cox proportional hazards models, we determined if the intervention's effect on candidiasis recurrence rate depends on baseline demographic and HIV-related factors, dietary and oral hygiene practices, or other measures of oral health. Within each level of these characteristics, with the characteristics subdivided into roughly equal-sized groups or split at natural break points, we estimated 6-month candidiasis recurrence rates via the Kaplan–Meier method. Using logistic regression models, we also examined the effects of changes in sugar intake and oral hygiene practices on the intervention's effect on candidiasis recurrence during the study period. These results were inconclusive – the wide confidence intervals on the estimates reflected the small sample sizes – and are not shown.

Effect of the intervention on diet, oral hygiene, and candidiasis recognition

Finally, we examined whether the intervention was associated with reduced sugar intake, better oral hygiene practices, and ability to identify oral candidiasis lesions. We calculated within-participant changes between the baseline and final study visits in dietary and oral hygiene practices, and summarized the mean difference between groups as above. We used mixed effects models, with a random participant factor and an autoregressive covariance matrix (one-visit lag), to determine if intervention participants experienced greater improvements than controls in plaque and gingival indices over the 6-month study. For candidiasis recognition, we calculated individual's sensitivities (i.e. among study visits at which a candidiasis episode was diagnosed by a clinician, the proportion that were recognized by the participant) and specificities (i.e. proportion of candidiasis-free study visits that were recognized as such by the participant) and compared mean levels of these variables across groups via *t*-tests and 95% CIs. We did not examine whether sensitivity improved over the study period (i.e. with the number of candidiasis diagnoses) because few episodes were diagnosed per participant.

Results

Baseline characteristics of study participants

Of 43 participants randomized between January 1997 and June 2000, eight dropped out for various reasons after one (three participants) or two (five participants) study visits, and were excluded from analyses. The remaining 35 participants (control, 17; intervention, 18) completed at least six study visits each (median, 8; maximum, 13) over the course of 6 months.

Participants ranged from 35 to 63 years of age, and women were on average 6.0 ± 6.2 years younger than men were. Male participants represented 83% of the intervention group and 65% of the control group (Table 1). Among both men and women, more intervention than control participants were Caucasian. The majority of participants reported being infected with HIV through sexual contact. Two of 26 men reported being intravenous drug users, compared with three of nine women; all five were nonusers during the study period, were housed, and were actively under the care of primary care providers experienced in the management of HIV disease. Most patients were taking antiretrovirals (three-drug regimens, 63%; two-drugs, 6%); however, a third were taking no anti-HIV medications (31%). Women reported shorter durations of HIV infection, higher CD4 counts, and higher HIV RNA levels than men did.

Mean baseline sugar intake of 90 g/day was higher than the WHO recommended daily allowance for refined sugars (10% of total calories, or 50 g/day for a 2000-cal diet and 63 g for 2500-cal diet) (21). Calories from carbohydrates represented about half of participants' diets. Participants typically ate four times a day, including at least one high-sugar (>25 g) meal/snack. They reported performing oral hygiene after 60% of all meals/snacks, but after only 20% of high-sugar meals/

Table 1. Baseline characteristics

Characteristic	Control group ($n = 17$)	Intervention group ($n = 18$)	Mean difference[a] (95% CI)
Demographic and HIV-related characteristics			
Age (years)	44.9 ± 6.8	48.4 ± 6.2	3.4 (−1.0 to 7.9)
Sex/ethnicity (%)			
Male/Caucasian	47.1	72.2	25.1 (−6.3 to 56.7)
Male/non-Caucasian	17.6	11.1	−6.5 (−29.7 to 16.7)
Female/Caucasian	5.9	16.7	10.8 (−9.7 to 31.3)
Female/non-Caucasian	29.4	0.0	−29.4 (−51.1 to −7.7)
Sex/HIV transmission mode (%)			
Male/gay-bisexual	58.8	77.8	19.0 (−11.3 to 49.3)
Male/heterosexual-IDU	5.9	5.6	−0.3 (−15.7 to 15.1)
Female/heterosexual	23.5	11.1	−12.4 (−37.2 to 12.4)
Female/IDU	11.8	5.6	−6.3 (−24.9 to 12.5)
Duration of HIV infection (years)	10.4 ± 4.5	12.0 ± 4.8	1.6 (−1.7 to 4.9)
CD4 count (cells/mm^3)	396 ± 228	298 ± 188	−98.0 (−241 to 45)
HIV-1 RNA (log_{10} copies/ml)	3.5 ± 1.2	3.5 ± 1.4	0.0 (−1.0 to 1.0)
Dietary practices			
Total meals/snacks	4.4 ± 1.0	4.2 ± 1.0	−0.2 (−0.9 to 0.5)
High-sugar meals/snacks	1.2 ± 0.9	1.4 ± 1.5	0.1 (−0.7 to 1.0)
Sugar intake (g/day)	90.0 ± 52.6	92.0 ± 56.7	2.0 (−36.2 to 40.4)
Calories from carbohydrates (%)	49.9 ± 13.4	50.2 ± 11.7	0.3 (−8.5 to 9.0)
Oral hygiene (OH) practices			
Meal/snack + OH (%)	60.2 ± 34.9	62.4 ± 36.4	2.2 (−22.8 to 27.2)
High-sugar meal/snack + OH (%)	19.4 ± 19.2	21.5 ± 28.3	2.1 (−15.0 to 19.2)
Brushing (times per day)	2.0 ± 1.3	1.8 ± 1.0	−0.2 (−1.0 to 0.7)
Flossing (times per day)	0.7 ± 1.1	0.7 ± 1.1	0.0 (−0.8 to 0.7)
Rinsing (times per day)	1.8 ± 1.8	1.7 ± 1.9	0.1 (−1.4 to 1.2)
Oral health measures			
Plaque Index (scale 0–5)	2.1 ± 1.1	2.0 ± 0.8	−0.1 (−0.8 to −0.5)
Gingival Index (scale 0–3)	1.0 ± 0.2	1.0 ± 0.3	−0.02 (−0.2 to 0.2)
DMFS (scale 0–148)	73.7 ± 46.8	67.0 ± 34.7	−6.7 (−34.9 to 21.5)
Tooth count (number)	20.6 ± 10.9	23.8 ± 7.6	3.2 (−3.3 to 9.6)
Wearing dentures (%)	35.3	22.2	−13.1 (−42.8 to 16.6)

[a]Intervention group minus control group.

snacks. On average, sugar content of snacks was not statistically significantly greater than that of meals (24.0 g versus 19.5 g; paired t-test $P = 0.30$).

The median baseline plaque index was 2.1 (range 0.4–4.1) on a five-point scale. The median gingival index was 1.1 (range 0.4–1.4) on a three-point scale. The correlation between baseline plaque and gingival indices was low (Pearson's correlation coefficient 0.06). The mean DMFS score was 70.2 (range 4–148). Women in the control group ($n = 6$) had relatively high baseline plaque indices and DMFS scores, and five of six wore dentures.

Effect of the intervention on candidiasis recurrence

In both groups, the rates of candidiasis recurrence within 6 months were high (control group 88%; intervention group 78%). More subjects were diagnosed with erythematous candidiasis lesions ($n = 28$) than with pseudomembranous candidiasis ($n = 16$). Although control participants had a slightly greater rate and shorter median time until recurrence (control group 1.4 months; intervention group 2.0 months), there was no statistically

Table 2. Predictors of recurrence of oral candidiasis within 6 months

Subgroup (no. participants)	Recurrence within 6 months (%)	Intervention effect hazard ratio (95% CI)	Interaction P-value
Overall intervention effect			–
Control (17)	88.2	–	
Intervention (18)	77.8	0.72 (0.35 to 1.50)	
Dietary intake at baseline			
Sugar			0.56
>99 g (13)	92.3	0.41 (0.13 to 1.34)	
50–99 g (12)	83.3	1.10 (0.31 to 3.91)	
<50 g (9)	66.7	0.59 (0.12 to 2.91)	
Calories from carbohydrates			0.3
>59% (8)	100.0	1.12 (0.26 to 4.67)	
50–59% (11)	63.6	0.36 (0.08 to 1.61)	
40–49% (6)	83.3	3.20 (0.52 to 7.23)	
<40% (9)	88.9	0.57 (0.14 to 2.33)	
Oral hygiene (OH) practices at baseline			
Meals followed by oral hygiene			0.93
<2/3 meals per day (19)	78.9	0.75 (0.27 to 2.07)	
≥2/3 meals per day (15)	86.7	0.70 (0.11 to 4.30)	
High-sugar meals followed by OH			0.44
<1/2 meals per day (11)	90.9	0.48 (0.13 to 1.75)	
≥1/2 meals per day (23)	78.3	0.89 (0.35 to 2.28)	
Brushing frequency			0.88
Once a day (9)	77.8	0.83 (0.19 to 3.70)	
More than once a day (24)	83.3	0.72 (0.58 to 1.73)	
Flossing frequency			0.26
Once a day (29)	82.8	0.82 (0.37 to 1.83)	
More than once a day (4)	75.0	0.16 (0.01 to 1.93)	
Rinsing frequency			0.88
Once a day (16)	87.50	0.78 (0.27 to 2.24)	
More than once a day (17)	76.50	0.69 (0.23 to 2.08)	
Oral health at baseline			
Plaque Index			0.24
2.5–5.0 (13)	92.3	0.41 (0.12 to 1.34)	
1.5–2.4 (8)	75.0	0.58 (0.11 to 3.22)	
0.0–1.49 (12)	78.6	1.18 (0.36 to 3.87)	
Gingival Index			0.89
1.0–3.0 (19)	79.0	0.75 (0.27 to 2.09)	
0.0–0.99 (14)	87.5	0.68 (0.24 to 1.94)	
Tooth count and denture status			0.62
>25 teeth, no dentures (19)	84.2	0.88 (0.33 to 2.38)	
<26 teeth, dentures (10)	80.0	0.68 (0.16 to 2.79)	
<26 teeth, no dentures (6)	83.3	0.46 (0.08 to 2.79)	
DMFS			0.61
>96 (11)	72.7	0.65 (0.14 to 2.99)	
38–96 (16)	87.5	0.58 (0.09 to 3.71)	
<38 (8)	87.5	1.51 (0.33 to 6.95)	

significant difference between groups in the risk of recurrence (HR 0.72; 95% confidence interval 0.35–1.50; $P = 0.37$; Table 2). Furthermore, the effect of CD4 count added to this model was nonsignificant ($P = 0.7$). The 6-month candidiasis recurrence rate tended to be higher among women than men (89% versus 77%) and among non-Caucasians than Caucasians (90% versus 80%), but did not vary with age.

Table 2 presents associations between risk factors and recurrence of oral candidiasis. The level of each risk factor is presented in decreasing order of expected risk of oral candidiasis (e.g. *a priori* we expected the 6-month rate of recurrence to be higher in the control group than the intervention group). Our expectations were borne out for several risk factors, including sugar intake, high-sugar meals followed by oral hygiene, flossing and rinsing, and plaque index (column 2; recurrence within 6 months).

When we examined whether the overall intervention effect (HR 0.72) led to improvements within any risk group (columns 3 and 4), we found that patients with very high sugar intake (>99 g/day) and/or very high plaque scores at baseline were successfully motivated by the intervention efforts; their HR dropped to 0.41 (95% CI 0.13–1.34). Patients already consuming lower levels of sugar (<50 g/day) or already flossing more than once per day at baseline also appeared to benefit from the intervention, perhaps representing highly compliant patients willing to do even better. Further, the four frequent flossers also had excellent oral hygiene habits at baseline, brushing their teeth after almost every meal/snack. None of the confidence intervals excluded 1, which was consistent with the statistically nonsignificant tests of interactions between the intervention assignment and the risk group.

Effect of the intervention on diet, oral hygiene, and candidiasis recognition

Finally, we examined whether the targeted behaviors and oral hygiene parameters changed more among intervention group than among control group participants (Table 3). In the 15 of 18 intervention participants and nine of 17 control participants who completed recall diaries at first and last visits, slight reductions in sugar intake (intervention −9 ± 19 g; control −6 ± 19 g) were reported. Oral hygiene following meals/snacks changed little among control participants, but among intervention participants, it increased by 26 ± 32% overall and by 12 ± 25% for high-sugar meals/snacks. There were no statistically significant differences between intervention and control groups with respect to improvements in plaque and gingival indices over the course of the study.

The average prevalence of candidiasis during follow-up was 26% in the intervention group and 31% in the control group (odds ratio 0.76; 95% CI 0.35–1.61; $P = 0.47$). Of the 10 participants

Table 3. Changes in diet, oral hygiene, oral health, and candidiasis recognition by intervention group

Intervention component	Control group ($n = 17$)	Intervention group ($n = 18$)	Mean difference[a] (95% CI)
Dietary changes (final visit–baseline visit)[b]			
Sugar intake (g)	−6.3 ± 18.9	−9.3 ± 18.6	−3.0 (−38.3 to 32.3)
Calories from carbohydrates (%)	−2.4 ± 9.2	5.5 ± 12.0	7.0 (−2.6 to 16.7)
Changes in oral hygiene (OH) practices (final visit–baseline visit)			
Meal/snack + OH (%)	2.0 ± 18.9	25.6 ± 31.5	23.5 (−1.0 to 47.6)
High-sugar meal/snack + OH (%)	−2.0 ± 18.4	12.2 ± 25.4	14.3 (−5.9 to 34.4)
Brushing (times per day)	0.50 ± 1.19	0.27 ± 1.39	−0.18 (−1.31 to 0.96)
Flossing (times per day)	−0.63 ± 1.60	0.20 ± 1.32	0.64 (−0.60 to 1.89)
Rinsing (times per day)	−0.75 ± 1.80	0.07 ± 2.0	0.73 (−0.94 to 2.41)
Changes in oral health measures (final visit–baseline visit)			
Plaque Index (mean)	−0.21 ± 0.25	−0.21 ± 0.25	0.00 (−0.68 to 0.67)
Gingival Index (mean)	−0.017 ± 0.09	−0.049 ± 0.09	−0.03 (−0.27 to 0.20)
Diagnosis of oral candidiasis (OC)			
Clinician diagnosed OC-positive (mean no. visits)	2.7 ± 2.0	2.6 ± 1.4	−0.1 (−1.7 to 1.5)
Patient assessed OC-positive among OC-positive visits (%)	31 ± 39	29 ± 33	−2% (−73 to 69)
Clinician diagnosed OC-free (mean no. visits)	6.2 ± 1.9	7.0 ± 2.8	0.8 (−1.4 to 3.0)
Patient assessed OC-free among OC-free visits (%)	62 ± 27	67 ± 24	5% (−46 to 56)

[a]Intervention group minus control group.
[b]Among participants with at least two diaries (nine control, 15 intervention).

wearing dentures, eight had candidiasis under their dentures on at least one occasion. Patients identified lesions (Table 3) in 30 ± 35% of visits at which a clinician diagnosed candidiasis (sensitivity), and they identified themselves as lesion-free in 64 ± 15% of visits at which a clinician did not diagnose candidiasis (specificity). There was no statistically significant difference between groups in either measure of diagnostic accuracy.

Discussion

HIV primarily targets CD4 lymphocytes, and the resultant decrease in number and function of these cells leads to a constellation of immune system imbalances and opportunistic infections. Many normally well-balanced host–parasite interactions are shifted to favor the parasite. One of the most common of these involves the commensal yeast species of the oral cavity and their human hosts (1, 22, 23). The disease state, oral candidiasis, is predominantly caused by overgrowth of *C. albicans* (2). Untreated patients have inflamed patches that may become raw or ulcerated and/or have masses of cheesy-white fungal growths throughout the mouth. They can experience an intense burning sensation or pain in the mouth, adverse alterations or loss of taste, and adverse emotional responses related to having masses of mold in the mouth. This negatively affects their desire and ability to eat, nutritional status and, eventually, their general health. Whereas oral candidiasis usually responds well to antifungal therapy, it recurs; thus, episodic or continuous antifungal treatment may be needed from the first occurrence until the patient dies. Adjunct self-care behaviors that reduce the severity and frequency of episodes would be beneficial to the patient's health and potentially work synergistically with antifungal agents to increase their effectiveness. In addition, patients who are able to recognize the first signs of oral candidiasis could seek help from health-care providers before symptoms become pronounced.

Although, oral candidiasis is common among HIV-seropositive persons, the candidiasis types differ as to their association with CD4 cell counts: studies of HIV-seropositive women found that low CD4 cell counts are associated with pseudomembranous candidiasis, but not with erythematous candidiasis or denture stomatitis (24, 25). We studied the recurrence rather than incidence of oral candidiasis because these lesions are not observed in all HIV-infected persons (26) and we required participants who were likely to experience candidiasis during the course of the study (2).

Availability of sugars (especially glucose) in saliva appears to be an important predisposing factor for oral candidiasis. Laboratory studies have shown that competition for nutrients in nonsterile saliva favors rapid-growing bacteria over slower-growing *Candida* species resulting in inhibition of candidal growth. If bacterial competition is negated by use of filter-sterilized saliva or by the addition of antibiotics or exogenous glucose to nonsterile saliva, growth of *C. albicans* is stimulated (3, 4, 27). Exogenous sugars may also enhance adherence of *Candida* to epithelial cells (27, 28). Clinical evidence for the importance of dietary sugars comes from several sources. The landmark Turku sugar studies (17) conducted on Finnish dental students and dental school personnel in the 1970s followed up persons in three study groups who were carriers of *C. albicans*. The study groups were those on sucrose, fructose or xylitol diets. After 4 months on sucrose or fructose diets, there was no significant difference in the percent of persons with saliva samples culture positive for *Candida*. In contrast, persons on the xylitol diet showed a significant decrease (50 to 18%) in culture-positive samples. Another line of evidence is that good oral hygiene, including denture cleanliness, has been shown to be fundamental to the control of denture-related candidiasis (5, 6, 29–31). In addition, erythematous candidiasis in HIV-seropositive women is significantly associated with high plaque index scores, but not with CD4 counts (24).

General factors influencing the supplies of exogenous glucose and other sugars available in the mouth are diet, host usage and oral hygiene. The diet determines the amount that enters the mouth, swallowing determines the amount used by the host and oral hygiene influences the amount that remains, and its duration in the mouth. In developing a self-help intervention program, PRO-SELF: Candidiasis to reduce the prevalence of candidiasis, we reasoned that the oral hygiene methods and dietary advice established for preventing dental caries – another oral infection influenced by exogenous sugar supply – might be effectively applied in the management of oral candidiasis.

The program was designed to encourage and enable patients to reduce exogenous sugars in the mouth by addressing oral hygiene and dietary sugar intake. In general, improved oral hygiene to reduce the duration of the daily sugar exposure

was emphasized over dietary modifications. It was reasoned that HIV-positive persons might need high-calorie supplements to prevent HIV-related wasting or require frequent smaller meals because of medication regimens. If so, making major alterations in their diets or eating habits (other than encouraging them to not prolong the time taken to eat meals/snacks) could have negative consequences. The program also provided instruction to enable a patient to recognize candidiasis episodes in his/her own mouth to enable them to seek treatment as early as possible.

The 24-h recall diary format was selected instead of a food frequency questionnaire because the diary would give current information as to food items eaten, as well as oral hygiene efforts, that were used for participant instruction in the PRO-SELF: Candidiasis program. A limitation of the 24-h recall format is that no single diary entry might be representative of a participant's usual practices. However, the longitudinal design of this study compensated for this limitation and allowed estimation of changes in eating and hygiene habits between the start and end of the study.

We tested the efficacy of the PRO-SELF: Candidiasis program in decreasing oral candidiasis recurrence rates in susceptible HIV-infected persons and in teaching them to recognize oral candidiasis and found the program only mildly effective. However, the study had a much smaller sample size than planned, primarily because of the advent of highly active antiretroviral therapy (HAART) (32) and attendant drop in candidiasis prevalence (33) that coincided with the start of the trial. Between 1988 and 1993 about 120 persons per year presented to our clinic with oral candidiasis. In contrast, since January 1997 when our first participant was enrolled, the number has dropped to 45 or fewer per year. This otherwise welcome decrease in the prevalence of candidiasis negatively affected accrual and the study was terminated after enrolling 43 participants over 3 years. The requirement that participants have candidiasis responsive to antifungal therapy did not affect recruitment, as it did not result in the exclusion of any potential participants.

Several trends in the data nonetheless support the hypothesis that reduction of exogenous sugars in the mouth can help control growth of *Candida*. There was a reduction in the 6-month rate of oral candidiasis recurrence (HR 0.72) in the intervention group. Because the percentage of meals/snacks followed promptly by oral hygiene procedures increased to a statistically significantly greater extent among intervention participants (by 26%) than among control participants (by 2%), it is possible that the reduction in recurrence rate was a result of the major thrust of the intervention program, improved oral hygiene practices. The intervention effect is especially strong considering that the prophylaxes at baseline may have attenuated it. However, as our intervention was hygiene related and it was not possible to obtain accurate hygiene histories, these prophylaxes ensured that the groups were as comparable as possible at randomization with respect to this prognostic variable. In addition, participants who benefitted most from the intervention were those whose practices put them at high risk of candidiasis; specifically, those with high sugar intake (>100 g/day), relatively high plaque indices (PI > 2.5 on a five-point scale), and moderate-to-high DMFS scores (>37). Further support for our hypotheses comes from the tendency for the candidiasis recurrence rate to be highest among those with high baseline plaque index and sugar intake, and lower among those flossing more than once a day. The four frequent flossers also had excellent oral hygiene habits at baseline, brushing their teeth after almost every meal/snack.

Patient compliance with dental or medical healthcare workers' instructions may be low (50% or less) and typically declines with time (34). Particularly if the instructions involve time intensive or complicated procedures designed for long-term control of a generally chronic, asymptomatic condition such as periodontal disease (34, 35). Recognizing this, our self-care program was tailored for each patient to minimize the number and complexity of behavior changes requested (35, 36). Each participant's diet/hygiene diaries and plaque indices was reviewed and a selection of simple procedures was proposed that could help reduce the amount and duration of exogenous sugar in the mouth. For example, if a participant habitually drank morning coffee with sugar over a period of 1 h, suggested alternatives would be to use a sugar substitute or no sweetener and/or to drink the sugared coffee more quickly and perform oral hygiene afterwards. The idea was that if the behaviors were easy to adopt, the participant would be more likely to make a change. The significant increase in hygiene after meals/snacks in the intervention when compared with the control group indicates that, at least during the

course of the study, our self-care intervention was successful in inducing desired behavior changes.

In contrast to the improvements in hygiene, the intervention-associated reduction in daily sugar intake was minimal, perhaps in part reflecting the intervention program's lesser emphasis on diet alterations in deference to the participants' nutritional needs. However, among persons who are not at risk for wasting or malnutrition, increased emphasis on daily sugar reduction should be considered as a means of reducing exogenous sugars in the mouth.

Despite repeated attempts to train intervention-group participants over a 6-month study period, improvement in candidiasis-specific diagnostic skills were minimal. Training may have been unsuccessful because the number of episodes per participant during the study was low so that they had little practice in recognizing candidiasis in their mouths. In addition, the frequent study visits (established to capture and treat all episodes) resulted in 43% (32/74) of the episodes being mild (less than five white removable plaques or red spots on one to three locations in the mouth), and therefore challenging to diagnose. Only 31% (10/32) of the mild episodes were correctly identified by participants, compared with 71% (10/14) of the severe episodes (plaques or red spots too dense to count on multiple locations in the mouth). Although the intention was to teach the participants to recognize early signs of candidiasis, the result was a very tough course in oral diagnosis that few passed. Thus, we recommend that patients not be relied upon for early self-diagnosis of candidiasis, but rather that they see their healthcare providers on a regular basis.

Intervening to reduce recurrence of candidiasis via diet and oral hygiene may be unnecessary now in areas where effective antiretroviral medications are commonly available; nonetheless, this goal remains worthwhile in areas where they are not. Despite our study's small sample size, the biologic plausibility and consistency of the trends in our findings suggest that self-care behaviors, supported by advice from dentists, dental hygienists and other healthcare providers, may aid those at risk of candidiasis recurrences. However, further study with a larger sample size is necessary to validate the trends observed in this pilot study. If such a study is performed, it is recommended that participants be selected from among persons who have frequent episodes of oral candidiasis, poor oral hygiene practices, and high-sugar diets, in order to maximize differences among control and intervention participants. Such a study might be most readily completed in geographic regions where substantial numbers of HIV-seropositive persons are not on effective antiretroviral medications.

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