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Phenylthiocarbamide Taste Perception among HIV-Infected Patients on Highly Active Antiretroviral Therapy

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Authors' contributions

This work was carried out in collaboration between all authors. Author CI designed the study, performed the statistical analysis. Authors CI, TBO and OAA wrote the protocol. Author CI wrote the first draft of the manuscript. Authors CI and JMO managed the analyses of the study. Authors CI and TBO managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: To determine whether phenylthiocarbamide (PTC) taste perception in HIV infection was influenced by highly active antiretroviral therapy (HAART).
Methodology: Study participants were adults (≥16 years) comprising 85 HIV-infected patients on HAART; 83 of whom were on first line of treatment (41 on Lamivudine, Nevirapine and Zidovudine and 42 on Tenofovir, Lamivudine and Efavirenz) and 2 on second line of treatment, 20 asymptomatic HIV-infected persons (and not on any medication) and 100 apparently healthy controls without HIV infection. They were enrolled in this study after clinical examination and informed consent was obtained from each participant. Antibodies to HIV were determined using

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determine HIV 1/HIV 2 test kit and Enzyme linked immunosorbent assay (ELISA) and then confirmed with Western blot (WB) and Real time PCR. Tasters and non-tasters were determined using phenylthiocarbamide (PTC) taste strips (0.0143 mg/strip).

Results: Non-tasters of PTC in the HIV-infected group on HAART (60.0%) were higher than those in the control group (33.0%) ($p < 0.001$). Non-tasters of PTC among the HIV-infected patients on Tenofovir, Lamivudine and Efavirenz (73.8%) were higher than: (i) Non-tasters of PTC among the HIV-infected patients on Lamivudine, Nevirapine and Zidovudine (46.3%) ($p = 0.01$) (ii) Non-tasters in the control group (33.0%) ($p < 0.001$) and (iii) Non-tasters in the asymptomatic HIV-infected group (35.0%) ($p = 0.003$). Non-tasters of PTC among the HIV-infected patients on Lamivudine, Nevirapine and Zidovudine were not significantly different from non-tasters in the control group ($p = 0.13$) or those in the asymptomatic HIV-infected group ($p = 0.40$).

Conclusion: This study showed that bitter taste loss of PTC was significantly associated with HIV-infected patients on Tenofovir, Lamivudine and Efavirenz. Therefore, the choice of HAART for HIV infection can influence PTC taste perception.

Keywords: Phenylthiocarbamide; tasters; non-tasters; HIV infection; asymptomatic; HAART.

1. INTRODUCTION

Phenylthiocarbamide (PTC) taste perception is a classically variable trait both within and between human populations. The ability to taste this compound is generally believed to be a simple Mendelian dominance inheritance, with tasters having genotype TT or Tt and non-tasters genotype tt. The prevalence of taste blindness or inability to taste bitter chemicals varies from one region to another [1,2]. The ability or inability to taste PTC had been associated with some disorders or diseases [2-4]. Non-tasters were said to be more susceptible to epilepsy [3], nodular goiter [5] and dental caries [6] while malaria had been reported to be associated with the ability to taste PTC [4].

Some researchers had reported significant taste losses in HIV-infected patients [7-9] and highly active antiretroviral therapy (HAART) had been implicated as a significant contributory factor to such perversion [10]. Schiffman et al. [9] noted that the taste complaints produced by protease inhibitors could impact negatively on patient compliance to HIV therapy. Graham et al. [7] reported that significant taste and smell losses in HIV-infected patients might be of importance in the development or progression of HIV associated wasting. Also, the pathogenesis of HIV associated wasting had been linked with reduced caloric intake as a principal contributing factor. The perception of taste was known to influence caloric intake and nutrient absorption through cephalic phase reflexes [7].

Although the PTC polymorphism has been regarded as a single locus trait, it is thought that certain individuals' characteristics factors and environmental factors may alter the phenotype [2]. Taste alterations in HIV infection have been reported to be due to both the viral infection and the medication [7-10] but we are not aware of any report on the interaction between PTC taste perception and HIV infection. Against the background that loss of taste could be caused by HAART in HIV infection, we investigated whether or not PTC taste perception in HIV infection was influenced by HAART.

2. METHODOLOGY

This study was carried out in Osogbo, the State capital city of Osun State, Southwestern Nigeria. It is about 88 km Northeast of Ibadan and its inhabitants are mainly members of the Yoruba ethnic group. HIV-infected participants on HAART were drawn from patients attending HIV clinics at Osun State General Hospital, Asubiaro, Osogbo while the asymptomatic HIV-infected individuals were enrolled from apparently healthy persons who visited the health facility for blood donation or routine investigation. A total of 105 HIV-infected persons (29 males and 76 females) and 100 controls (25 males and 75 females) of age ≥ 16 – 63 years participated in this study after clinical examination. Of the 105 HIV-infected individuals, 85 (80.9%) were on HAART: 41 (39.0%) on first line combination therapy of Lamivudine, Nevirapine and Zidovudine, 42 (40%) on first line combination therapy of Tenofovir, Lamivudine and Efavirenz, 2 (2.0%) on second line of treatment) and 20 (19.1%) were asymptomatic HIV-infected individuals not on any medication. They were apparently healthy persons who tested positive to HIV test when they visited for blood donation or routine investigation. The 100 control individuals were apparently healthy students and staff from the Teaching Hospital without HIV infection as of the

time of investigation. HIV-infected patients who had been HAART compliant were included in this study. HIV-infected patients on HAART who were not HAART compliant and those who had tuberculosis in addition were excluded from this study. Verfication of patients' adherence to antiretrovirals was done using patients' self-reports, CD_4^+ cell counts, Pharmacy records and pill counts. Questionnaire was administered to each participant to obtain relevant information including duration of HIV diagnosis, type and duration of medication for HIV-infected patients.

Antibodies to HIV were determined using determine HIV 1/HIV 2 test kit and Enzyme linked immunosorbent assay (ELISA) and then confirmed with Western blot (WB) and Real time PCR. Phenylthiocarbamide (PTC) taste strips (0.0143 mg of PTC/strip) were obtained from Carolina Biological Supply Company, North Carolina, USA. Each participant was given a PTC taste strip and a filter paper (as control) and was asked to put each on their tongue and allow to be soaked in their saliva before describing their perception to each strip. Taste description of each participant was recorded. The most recent CD_4^+ cell counts of the HIV-infected patients on HAART were obtained at the clinic and used to classify them according to Centers for Disease Control and WHO staging systems [11].

The statistical package for social sciences software package (SPSS version 14) was used for statistical analysis. Differences between percentages and proportions were tested by Chi-square test. Sample means were compared by Student's t test. A p-value of < 0.05 was considered to be significant.

3. RESULTS

A total of 105 HIV-infected persons (29 males and 76 females) and 100 controls (25 males and 75 females) of age ≥16 years participated in this study. The sex and age distributions of the study participants are given in Table 1. The distributions of males and females in the test and control groups were not significantly different (χ^2 = 0.18, df= 1, p = 0.67) and there was no significant difference in the distribution of age between the HIV-infected persons and the controls (χ^2 = 0.56, df = 3, p = 0.91). Similarly, the mean ages of the HIV-infected persons (40.12±11.05) and the controls (39.18±11.30) were not significantly different (t = 0.60, p = 0.55).

Of the 105 HIV-infected persons, 20 were asymptomatic and not on any medication, 13 (65.0%) of whom were tasters and 7 (35.0%) non-tasters; 85 were on HAART, 34 (40.0%) of whom were tasters and 51 (60.0%) non-tasters. The distribution of phenylthiocarbamide tasters and non-tasters among the test and control groups are given in Table 2. Phenylthiocarbamide taste perception varied significantly among the three groups (χ^2 = 14.36, df = 2, p < 0.001). Further Chi-square tests showed that non-tasters were significantly higher in the HAART group (60.0%) than in the control group (33.0%) (p < 0.001; OR 3.05; 95% CI 1.68-5.53) and than in the asymptomatic HIV-infected group (35.0%) (p = 0.043; OR 2.79; 95% CI 1.03-7.54). However, non-tasters in asymptomatic HIV-infected group (35.0%) and control group (33.0%) were not significantly different (p = 0.86; OR 1.09; 95% CI 0.41-2.89).

Table 1. Distribution of the study population by sex and age

Variable	Test group (%)	Control group (%)	Total (%)	p
Sex[a]				0.67
Female	76 (72.4)	75 (75.0)	153 (73.6)	
Male	29 (27.6)	25 (25.0)	55 (26.4)	
Total	105 (52.5)	100 (47.5)	205 (100.0)	
Age[b] (years)				0.91
16-25	9 (8.6)	11 (11.0)	20 (10.6)	
26-40	50 (47.6)	49 (49.0)	99 (47.6)	
41-60	41 (39.0)	35 (35.0)	76 (37.0)	
>60	5 (4.8)	5 (5.0)	10 (4.8)	
Total	105 (52.5)	100 (47.5)	205 (100.0)	

[a] χ^2 = 0.18, df = 1, p = 0.67; [b] χ^2 = 0.56, df = 3, p = 0.91

The distributions of phenylthiocarbamide tasters and non-tasters among HIV-infected patients on highly active antiretroviral therapy are given in Table 3. Of the 85 HIV-infected patients on HAART, 83 were on first line of treatment; 41 (48.2%) of whom were on combination therapy of Lamivudine, Nevirapine and Zidovudine and 42 (49.4%) on combination therapy of Tenofovir, Lamivudine and Efavirenz. The other 2 were on second line of treatment. The mean duration of HIV-infected patients on Lamivudine, Nevirapine and Zidovudine (62.24±33.72 months) and that of the HIV infected patients on Tenofovir, Lamivudine and Efavirenz (63.15±32.65 months) were not significantly different (p = 0.90). The mean CD_4^+ count of the HIV-infected persons on Lamivudine, Nevirapine and Zidovudine was 455 ± 306 cells/µL and that of the those on Tenofovir, Lamivudine and Efavirenz was 390 ± 223 cells/µL (p = 0.27). The proportion of HIV-infected patients on Lamivudine, Nevirapine and Zidovudine who were PTC non-tasters (46.3%) was significantly lower than the proportion of those on Tenofovir, Lamivudine and Efavirenz who were PTC non-tasters (73.8%) (p = 0.01; OR 3.26; 95% CI 1.32-8.08) but not significantly different from non-tasters in the asymptomatic HIV-infected group (35.0%) (p = 0.40; OR 1.60; 95% CI 0.53-4.81) or those in the control group (33.0%) (p = 0.13; OR 1.75; 95% CI 0.84-3.65). The proportion of HIV-infected patients on Tenofovir, Lamivudine and Efavirenz who were non-tasters was significantly higher than non-tasters in the asymptomatic HIV-infected group (p = 0.003; OR 5.23; 95% CI 1.73-15.85) or those in the control group (p < 0.001; OR 5.72; CI 2.66-12.30). Therefore, the inability to taste PTC was significantly more associated with HIV-infected patients on Tenofovir, Lamivudine and Efavirenz than with those on Lamivudine, Nevirapine and Zidovudine. The distribution of phenylthiocarbamide (PTC) Taste Perception of the HIV-infected patients on HAART by CD_4^+ Count is given in Table 4. There was no significant association between the level of CD_4^+ count and PTC taste perception (p = 0.45).

Table 2. Distribution of phenylthiocarbamide (PTC) taste perception among the HIV-infected patients and controls

Subjects	Taster (%)	Non-taster (%)	Total (%)	p
				<0.001
HIV on HAART	34 (40.0)	51 (60.0)	85 (40.9)	
Asymptomatic HIV	13 (66.7)	7 (33.3)	20 (9.6)	
Control	67 (67.0)	33 (31.0)	100 (48.1)	
Total	114 (55.6)	91 (44.4)	205 (100.0)	

$\chi^2 = 14.36$, df = 2, p < 0.001

Table 3. Phenylthiocarbamide (PTC) taste perception among HIV-infected patients on highly active antiretroviral therapy (HAART)

HAART	Taster (%)	Non-taster (%)	Total (%)
Nevirapine, Lamivudine, Zidovudine	22 (53.7)	19 (46.3)	41 (48.2)
Tenofovir, Lamivudine, Efavirenz	11 (26.2)	31 (73.8)	42 (49.4)
Tenofovir, Lamivudine, Atazanavir, zidovudine	1 (50.0)	1 (50.0)	2 (1.2)
Total	34 (40.0)	51 (60.0)	85 (100.0)

Table 4. Distribution of phenylthiocarbamide (PTC) taste perception of HIV-infected patients on HAART by CD_4^+ count

Level	CD_4^+ count (cells/µL)	Taster (%)	Non-taster (%)	Total (%)	p
					0.45
1	≥500	6 (28.6)	15 (71.4)	21 (24.7)	
2	200-499	15 (45.5)	18 (54.5)	33 (38.8)	
3	<200	13 (41.9)	18 (58.1)	31 (36.5)	
Total		34 (40.0)	51 (60.0)	85 (100.0)	

$\chi^2 = 1.6$, df = 2, p = 0.45

4. DISCUSSION

The incidence of PTC tasters among the control group in this study was in line with that of previous study carried out in the same region [4]. This implied that the result of the control group was a true reflection of the distribution of PTC tasters and non-tasters in the general population. Also, the frequency distribution of the PTC tasters and non-tasters in the asymptomatic HIV-infected group tallied with that of the control group. This implied that HIV infection had no influence on the distribution pattern of tasters and non-tasters; in other words, PTC taste perception was not significantly associated with HIV infection since both tasters and non-tasters of PTC could equally come down with the infection. Nevertheless, a larger sample size of asymptomatic HIV-infected persons is required for analysis to confirm if PTC taste status is indeed independent of HIV infection. We are presently gathering more data that will enable us confirm this initial finding.

There was a significant difference between asymptomatic HIV-infected persons and medicated HIV- infected patients with respect to inability to taste PTC as the latter group had a higher proportion of non-tasters. We were not able to enroll sufficient symptomatic HIV-infected persons that were not on HAART in this study for statistical analysis as only 2 persons were in this category. Comparing the PTC taste perception of the symptomatic HIV-infected patients on HAART with their counterparts not on HAART would allow us to assess the effect of progression of HIV infection on PTC taste perception. This can be further investigated. Nevertheless, early progression of HIV had been reported to bring about degeneration of chorda tympani and leaving the glossopharngeal nerve unhindered in relaying bitter sensory input to the CNS which could consequently result in increase in taste perception [12]. Also, studies had shown that continued progression of HIV infection not only reduced the quantity of taste buds and papillae in the upper orodigestive tract [13,14] but also predisposed infected persons to oral candidiasis and lesions which might cause taste dysfunction [15].

HIV medications had been reported as a source of dysgeusia; Mattes [16] reported that HIV infected persons in 'real world' case studies were on medications when they first reported taste alterations. Schiffman [17] reported that antimicrobial drugs such as metronidazole, ampicillin, amphotericin B and tetrapentamidine could cause a loss or distortion of taste. Taste impairments in HIV infection contributed to HIV associated wasting [7]. According to Graham et al. [7] progression of HIV virus was associated with peripheral neural, taste receptor atrophy together with degeneration of CNS neurons in the prefrontal cortex where sensory input was received and processed and these taste losses and subsequent malnourishment might be increased by medications which would distort saliva secretion or penetrate the blood-brain barrier affecting CNS information processing in the nucleus of solitary tract (NST). Also, it had been reported that the number of medications that HIV-infected individuals were currently taking was an accurate predictor of taste complaints as a patient on more medications was more likely to report taste disturbances and signs of taste receptor atrophy than a patient with fewer medications [7].

HAART improves CD_4^+ cell count [18]; the destruction of which leads to progressive replication of HIV and susceptibility to opportunistic infections. It therefore lowers HIV disease stage and improves quality of life. However, losses of taste had been reported as one of its side effects and studies had shown that a high number of HIV-infected patients on HAART presented with taste complaints [8-10, 19]. For instance, one major drawback that had been associated with protease inhibitors was that they had metallic taste causing a prolong taste abnormalities [9] which had a severe negative impact on patients' compliance and quality of life.

One way to ensure patients' compliance, prevent HIV wasting and thereby enhance their quality of life is flavour enhancement which increases the appeal for nutritional foods and reduces nutritional deficiencies. It increases the concentration of odor and taste compounds thereby initiating a greater preference for nutritious foods in HIV-infected patients. Since recovery from dysgeusia is slow and incomplete in HIV-infected patients [16], specific chemicals that initiate recovery can be isolated and their synthetic forms developed and administered to them in order to restore normal gustatory detection thresholds. In addition, the possibility of these chemicals allowing for the development of medications which will bypass the gustatory system should be explored.

In this study, we examined how PTC taste perception was influenced by choice of HAART.

The PTC tasting sensitivity of the HIV-infected patients on Nevirapine, Lamivudine, Zidovudine combination therapy was not significantly different from that of the control group. However, the PTC tasting sensitivity of the HIV-infected patients on Tenofovir, Lamivudine, Efavirenz was significantly different from that of the control group. These implied that while the use of Nevirapine, Lamivudine, Zidovudine combination therapy did not tamper with PTC tasting significantly, the use of Tenofovir, Lamivudine, Efavirenz combination therapy considerably affected PTC tasting sensitivity. Since a significant higher proportion of those on Tenofovir, Lamivudine, Efavirenz combination therapy turned out to be non-tasters of PTC, it is possible that non-tasters might find the Tenofovir, Lamivudine, Efavirenz combination therapy more compatible to their body chemistry compared to Nevirapine, Lamivudine, Zidovudine combination therapy. This is open to investigation and may help in the determination of the choice of combination therapy to adopt for newly HIV-infected cases. In addition, further investigation, preferably a longitudinal one (conducted before and after initiation of HAART) can further help to clarify if it is the medication or the HIV infection itself that is responsible for the alteration in PTC taste perception.

5. CONCLUSION

While PTC tasting ability of HIV infected persons on Tenofovir, Lamivudine, Efavirenz is changed significantly, that of those on Nevirapine, Lamivudine, Zidovudine is not significantly affected. Therefore, PTC taste losses in HIV-infected individuals may or may not be significant depending on the combination therapy employed.

CONSENT

Written informed consent was obtained from each of the participants recruited for this study.

ETHICAL APPROVAL

Ethical approval for this study was obtained from the Ethical Committee of the College of Health Sciences, Ladoke Akintola University of Technology, Osogbo, Nigeria. Therefore, all procedures were performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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