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Oral and Systemic Health Correlates of HIV-1 Shedding in Saliva

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Abstract

The relationship among oral and systemic health and HIV shedding in saliva is not well understood. We hypothesized that oral and systemic health are associated with HIV shedding in saliva of HIV-infected women. Saliva from 127 participants enrolled in the Women's Interagency HIV Study (WIHS) was collected at repeated visits over a 5-1/2 year study period (October 1998 through March 2004) and was evaluated for HIV-1 RNA. Demographic, lifestyle, systemic and oral health characteristics were evaluated as possible correlates of salivary HIV-1 shedding. Multivariate models showed significantly increased risk of HIV-1 shedding in saliva as blood levels of CD4 cell counts decreased ($p<0.0001$) and HIV RNA increased ($p<0.0001$). Diabetes ($p=0.002$) and high proportion of gingival bleeding sites ($p=0.01$) were associated with increased likelihood, while antiretroviral therapy ($p=0.0003$) and higher levels of stimulated saliva flow rates ($p=0.02$) were associated with a lower likelihood of HIV-1 RNA shedding in saliva.

KEYWORDS (3-5)

HIV-1 Shedding; Saliva; Oral Health

INTRODUCTION

In 2007, about 33 million people globally were infected with HIV-1. The number of HIV-infections worldwide has been stable since 2000; however, new cases continue to increase in resource-limited nations. The source of infection differs by country, and includes intercourse (vaginal or anal), injected drugs, transmission from mother to child including breast milk and unsafe injections or other nosocomial sources (Cohen et al., 2008). The estimated incidence of HIV in the United States in 2006 was 56,300 affecting primarily Blacks (45%) followed by Whites (35%), Hispanics (17%), Asian/Pacific Islanders (2%) and American Indian/Alaska Natives (1%). Of these, 15,000 (27%) occurred in females (Hall et al., 2008). HIV transmission in females is predominantly attributed to high-risk heterosexual contact, accounting for 80% of new infections.

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Blood, semen, vaginal and cervical secretions, and breast milk are established sources of HIV transmission (Schacker et al., 1996). While HIV is detected in saliva in varying numbers with different techniques (Freel et al., 2003; Liuzzi et al., 1996; Shugars et al., 2000), the possibility of HIV transmission via saliva is remote (Scully and Porter, 2000), a finding explained by relatively low viral load in saliva, hypotonic disruption of mononuclear leukocytes, low numbers of CD4-positive target cells, anti-HIV antibodies, and inhibition of virus by salivary carbohydrate moieties and proteins such as secretory leukocyte protease inhibitor (SLPI) (Baron et al., 1999; Habte et al., 2006; Lin et al., 2004; Shugars and Wahl, 1998; Shugars et al., 2002; Yeung et al., 1993). However, the possibility of transmission of HIV and other viruses from saliva remains feasible if oral and systemic health is compromised (Gandhi et al., 2004; Greenspan et al., 2000).

Possible sources for viral particles, HIV virions and proviral HIV-1 DNA, include serum exudate and migration of HIV-1 containing mononuclear cells from gingival crevicular fluid (GCF) (Maticic et al., 2000). Other potential sources include oral ulcerations or erosions, inflamed gingiva and oral herpes (Campo et al., 2006). The impact of oral and systemic health on HIV shedding in saliva is not well understood and few studies have addressed this (Liuzzi et al., 1996; Maticic et al., 2000; Shugars et al., 2000). In addition, most studies have been cross-sectional in design with limited data for a short period of time and there is a paucity of such data in HIV infected women.

We hypothesized that oral and systemic health factors are associated with HIV shedding in saliva of infected women. The objective of the study was to correlate the presence of HIV-1 RNA in saliva samples from participants of the Women's Interagency HIV Study (Barkan et al., 1998; Mulligan et al., 2004) with demographic, lifestyle, medical and oral health characteristics. We believe this is the first longitudinal study to assess the effects of oral and systemic health on HIV-1 shedding in saliva of HIV-positive women in the United States.

MATERIALS AND METHODS

Study Sample

The Women's Interagency HIV Study was established to investigate the impact of HIV infection on women in the United States. The Women's Interagency HIV Study initially enrolled 2059 HIV-seropositive and 569 demographically similar HIV-seronegative women between October 1994 and November 1995. A second recruitment enrolled 737 HIV-seropositives and 406 HIV-seronegatives between 2001 and 2002. The current sub-study is based on data on HIV-positive women from both recruitments. Oral and systemic health data and saliva were collected at baseline and at follow-up evaluations every 6 months at Los Angeles and Chicago sites. A total of 127 participants donated saliva from October 1998 through March 2004. Of these 127 subjects, 32 contributed data on 1 visit, 34 had 2 visits, 25 had 3 visits, 14 had 4 visits, and 22 had between 5 and 7 visits, for a total of 354 subject-visits. A complete description of the Women's Interagency HIV Study design and participants was reported (Barkan et al., 1998). The study was approved by institutional review boards and informed consent was obtained from all participants.

Study Outcome Measures

Unstimulated and chewing stimulated whole saliva were collected under standardized conditions (Navazesh and Christensen, 1982). The stimulated saliva collection involved subjects chewing on a standard-sized gum base for 2 minutes; saliva generated was discarded. Saliva was collected for additional 3 minutes and saved for further analysis.

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HIV-1 RNA in saliva was measured using a commercial NASBA/NucliSens® assay (Nucleic Acid Sequence Based Amplification Assay; BioMerieux, Durham, NC, USA). The binary response variable used in data analysis was the detection of HIV-1 RNA in saliva, with the limit of detection ≥25 copies per ml. The NASBA/NucliSens® assay's software reports a quantitative result if the sample's HIV-1 RNA is within the range of 25 to approximately 5 million copies per ml. The performance of the assay is linear from 51 to 5.39×10^6 copies/ml HIV-1 RNA. The detection rate diminishes below 176 copies/ml (>95% detection rate) to approximately 50% detection rate at 40 copies/ml and below (Nowicki et al., 2001).

Other Data Collection

Demographic, lifestyle, medical and oral health characteristics were evaluated as possible correlates of salivary HIV-1 shedding. Sociodemographic variables included age, race/ethnicity and education. Lifestyle measures were alcohol use, smoking, recreational and illicit drug use, frequency of oral sex and HIV exposure category. Health measurements included body mass index, self-reported diabetes, hepatitis C serostatus, AIDS status, CD4+ cell count and HIV-1 RNA in plasma. Antiretroviral therapy use was modeled in two ways: type of antiretroviral therapy currently used (monotherapy, combination therapy or highly active antiretroviral therapy), and as an indicator of highly active antiretroviral therapy use relative to prior visits (never on; initiated; continued on; or terminated highly active antiretroviral therapy). Oral health characteristics included the following: Enlarged parotid and submandibular glands; unstimulated and stimulated salivary flow rates; hard, tender or >1cm lymph nodes; plaque; gingival banding; proportion of bleeding sites; papilla with cratering; pocket depth >4mm; proportion of teeth with loss of attachment >2mm; proportion of teeth with recession; number of decayed missing filled teeth, decayed missing filled surfaces, and decayed filled root surfaces. We evaluated proportion rather than absolute numbers of teeth/sites affected, as the number of teeth present for evaluation varied across subjects. Stimulated and unstimulated saliva flow rates were also evaluated as correlates of HIV shedding. Independent variables except for age, race, education and HCV status were time-dependent (using data collected at each visit). A description of methodologies for oral and systemic health parameters are published (Alves et al., 2006; Gandhi et al., 2004; Greenspan et al., 2004; Mulligan et al., 2000; Mulligan et al., 2004; Navazesh et al., 2000; Navazesh et al., 2009; Phelan et al., 2004).

Statistical Analysis

Univariate and multivariate analyses used logistic regression with generalized estimating equations (GEE) to account for the correlated data arising from repeated measurements from subjects over multiple visits. The dependent variable was the presence of detectable HIV-1 RNA in saliva. Independent variables with univariate p-values<0.10 were included in multivariate modeling; variables significant at p<.05 on multivariate modeling were retained. Due to the possible collinearity due to the high negative correlation between CD4+ cell counts and plasma HIV-1 RNA ($r = -0.54$, $p<0.0001$), two multivariate models were evaluated, one with CD4+ cell counts included (CD4 model), and the other with HIV-1 RNA in plasma included (RNA model). To determine if associations with salivary shedding were constant over the study follow-up, interactions between all variables in the final model and study visit were tested. To consider the quantitative nature of the HIV RNA data we also employed an ordinal logistic regression approach, categorizing the salivary HIV RNA outcome at each visit as: not detectable, 26–499, 500–4999, and ≥5000 copies/ml. As HIV RNA was not detected in saliva in 60% of subject visits and very few displayed very high RNA levels, the results did not substantially differ from the dichotomous analysis. We therefore present only the dichotomous results. A two-sided alpha level for the final model was set at 0.05. All analyses used SAS Version 9.0.

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RESULTS

At baseline, 48 (38%) of the 127 women had detectable HIV-1 RNA in saliva. Over all visits, 141 (40%) of 354 specimens had detectable virus (Table 1). Independent variables associated on univariate analysis with salivary shedding at $p<0.10$ (Table 2) were included in multivariate modeling (Tables 3 and 4).

In the multivariate model including CD4 cell count (Table 3), the risk of HIV-1 shedding in saliva increased significantly with decreasing level of CD4 cell counts ($p<0.0001$). History of diabetes ($p=0.002$) and high proportion of gingival bleeding sites ($p=0.01$) were associated with increased likelihood of HIV-1 RNA shedding while antiretroviral therapy ($p=0.0003$) and higher stimulated salivary flow rates ($p=0.02$) were associated with a lower likelihood of HIV-1 RNA shedding.

In the multivariate model including HIV-1 RNA in plasma (Table 4), the risk of HIV-1 shedding in saliva increased significantly with increasing HIV RNA ($p<0.0001$). The Spearman correlations between baseline plasma and saliva HIV RNA was 0.60 (unadjusted, $p<0.0001$) and 0.61 (adjusted for variables in Table 4, $p<0.001$). History of diabetes ($p<0.0001$), high proportion of gingival bleeding sites ($p=0.001$) and decayed/filled root surfaces ($p=0.002$) were associated with increased likelihood of HIV-1 RNA shedding in saliva while antiretroviral therapy ($p=0.002$) was associated with a lower likelihood of HIV-1 RNA shedding. In both multivariate models, study visit number (i.e., longer duration of follow-up) was associated with higher likelihood of HIV shedding in saliva ($p<0.0001$), indicating increasing prevalence of HIV shedding over follow-up (baseline prevalence = 38%, median prevalence visits 1–3 = 30%; median prevalence visits 4–6 = 44%; median prevalence visits 7–9 = 62%).

DISCUSSION

Forty-eight (38%) of the 127 women had detectable HIV-1 RNA in saliva in all study visits, whereas overall 141 (40%) of 354 specimens had detectable salivary viral load. This was comparable to an earlier study where 42% of subjects had HIV-1 RNA shedding in saliva (Shugars et al., 2000). However, this is incomparable to other studies which reported very high (96%) (Liuzzi et al., 1996) or very low (1%) (Barr et al., 1992) prevalence of salivary HIV-1 RNA shedding. The use of different collection methods, and/or molecular techniques for measuring salivary viral shedding may explain these differences.

Higher HIV-1 RNA viral load in plasma was strongly associated with a higher likelihood of salivary viral shedding. This was noted in earlier studies (Liuzzi et al., 1996; Shugars et al., 2000) and reinforces the idea that saliva may be a useful, non-invasive source for estimating plasma viral load (Shugars et al., 2000). In addition, decreased CD4+ cell count and positive AIDS status (in univariate models only) increased the risk of HIV-1 shedding in saliva suggesting an effect of immunosuppression on salivary viral shedding.

The advent of highly active antiretroviral therapy has significantly reduced HIV viral load systemically in plasma and other body fluids including saliva (Shugars et al., 2000). This was evident in Women's Interagency HIV Study where subjects on highly active antiretroviral therapy were less likely to have detectable HIV-1 RNA in saliva than participants not on antiretroviral therapy.

Diabetes increased the likelihood of salivary HIV-1 shedding. Alteration in saliva composition is noted in diabetics with otherwise normal oral and systemic health. The mechanism by which diabetes increased HIV-1 shedding in saliva is unknown and deserves further investigation (Yavuzyilmaz et al., 1996).

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We previously reported the association between salivary gland hypofunction, HIV-1 infection and highly active antiretroviral therapy in Women's Interagency HIV Study (Navazesh et al., 2003; Navazesh et al., 2009). The current investigation revealed a significant association between lower volume of chewing-stimulated saliva and higher risk for HIV-1 shedding in saliva. This could imply that endogenous viral inhibitors suppress HIV-1 shedding in saliva.

Interestingly, we observed an increase in prevalence of HIV-1 shedding in saliva with longer follow-up (higher subject visits). The mean plasma viral loads were elevated beyond the baseline level in later study visits (beyond visit 5) in some patients which could increase the HIV-1 shedding in saliva (results not shown here). We speculate that this could be due to non-compliance with HIV medication intake or development of resistance to medications.

We observed a significant association between the proportion of bleeding sites and the risk of HIV-1 shedding in saliva. Similarly, increased linear gingival banding and visible plaque (only in univariate model) were associated with increased HIV shedding that was similar to a previous observation (Maticic et al., 2000; Shugars et al., 2000). Inflammatory conditions such as linear gingival banding or erythema may increase viral shedding through ulcerated surfaces or via gingival crevicular fluid (Shugars et al., 2000). However, these findings conflict with earlier reports indicating no significant association between infectious HIV-1 in whole saliva and periodontal disease (Barr et al., 1996). These differences could be attributed to differences in populations and different sensitivities of the HIV assays. Among the other dental variables, presence of decayed/filled root surfaces increased the risk of HIV-1 shedding in saliva.

Limitations of this study include the fact that some independent variables were based on patient self-report and hence could be subject to higher measurement error. Despite obtaining multiple systemic and oral health measures from the same cohort, the comprehensive nature of measures examined, as well as the longitudinal study design, make it more challenging to obtain objective assessments of all the variables. Given the large number of associations tested, it is possible that some of our findings may have arisen by chance; however, the highly significant associations noted in our multivariate models make this possibility unlikely. Nonetheless, these findings should be replicated in an independent sample.

To our knowledge this is the first comprehensive evaluation of HIV-1 shedding in saliva of HIV-infected women. We observed specific oral and systemic health parameters to be associated with HIV-1 RNA shedding in saliva of HIV-infected women in Women's Interagency HIV Study.

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LIST OF ABBREVIATIONS

HIV	Human Immunodeficiency Virus

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AIDS	Acquired Immunodeficiency Syndrome
WIHS	Women's Interagency HIV Study
RNA	Ribonucleic Acid
HAART	Highly active anti-retroviral therapy
SLPI	Secretory Leukocyte Protease Inhibitor
GCF	Gingival Crevicular Fluid
GEE	Generalized Estimating Equations
IDU	Injection Drug Use

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Table 1

Baseline demographics and frequency of salivary HIV-1 shedding (n=127 WIHS participants)

Characteristic	
All subjects, baseline salivary shedding	48/127 (38)[a]
Age (median, 35; IQR, 29–43)	
<30	14/32 (44)
30 – 39	18/43 (42)
40 – 49	13/45 (29)
50+	3/7 (43)
Race	
White	1/5 (20)
Black	22/55 (40)
Hispanic	25/66 (38)
Others	0/1 (0)
AIDS	
No	35/98 (36)
Yes	13/29 (45)
CD4+ cells (median, 400; IQR, 246–551)	
500+	7/38 (18)
350–499	10/38 (26)
200–349	19/30 (63)
<200	12/21 (57)
HIV-1 RNA in plasma (median, 1055; IQR, 80–13000)	
<1,000	5/63 (8)[b]
1,000 – 9,999	16/30 (53)
10,000+	26/33 (79)
ARV therapy	
None	25/42 (60)
Mono/Combo	5/16 (31)
HAART	18/69 (26)

[a]No. with salivary shedding/total no. in demographic category (percent with salivary shedding)

[b]One subject with missing viral load at baseline

Viral load in plasma was censored at 80 copies/ml.

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Table 2

Univariate Logistic Regression of HIV Shedding in Saliva

Variable	Salivary HIV-1 Shedding	OR (95% CI)	p-value
Alcohol use in last 6 months			
No	71/207 (34)[a]	1.00	
Yes	68/143 (48)	1.57 (0.97 – 2.54)	0.07
Drug use in last 6 months (crack, cocaine, heroin, IDU)			
No	117/318 (37)	1.00	
Yes	22/34 (65)	2.87 (1.08 – 7.63)	0.03
Diabetes			
No	131/338 (39)	1.00	
Yes	9/15 (60)	2.75 (0.95 – 7.99)	0.06
AIDS			
No	90/247 (36)	1.00	
Yes	51/107 (48)	1.59 (0.95 – 2.68)	0.08
ARV therapy at study visit			
None	57/96 (59)	1.00	0.0002[b]
Mono/Combo	17/45 (38)	0.32 (0.14 – 0.75)	
HAART	66/212 (31)	0.28 (0.16 – 0.48)	
CD4+ cell count			
500+	37/139 (27)	1.00	<.0001[b]
350–499	27/84 (32)	1.38 (0.75 – 2.53)	
200–349	37/65 (57)	3.56 (1.76 – 7.20)	
<200	39/62 (63)	4.72 (2.46 – 9.06)	
HIV-1 RNA in plasma			
<1,000	39/202 (19)	1.00	<.0001[b]
1,000 – 9,999	34/67 (51)	4.16 (2.15 – 8.08)	
10,000+	67/81 (83)	19.6 (10.3 – 37.3)	
Plaque			
No or probe only	17/57 (30)	1.00	
Visible	111/273 (41)	1.57 (0.93 – 2.68)	0.09
Average gingival banding			
None	111/303 (37)	1.00	
Present	17/27 (63)	2.22 (0.97 – 5.10)	0.06
Decayed filled root surfaces			
None	103/278 (37)	1.00	
Present	29/57 (51)	1.64 (0.91 – 2.96)	0.10
Stimulated salivary flow rate, mL/min [c]			
Positive for shedding [d]	0.67 (0.67) [d]	0.67 (0.46 – 0.98)	0.04
No shedding	0.83 (0.75)		
Proportion of teeth with plaque visible [c]			

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Variable	Salivary HIV-1 Shedding	OR (95% CI)	p-value
Positive for shedding [d]	0.25 (0.40) [d]	2.08 (0.93 – 4.66)	0.08
No shedding	0.19 (0.39)		
Proportion of bleeding sites [c]			
Positive for shedding [d]	0.20 (0.30) [d]	4.28 (1.59 – 11.5)	.004
No shedding	0.14 (0.24)		
Visit [c]		1.16 (1.07 – 1.25)	0.0003 [b]

Table includes independent variables associated with salivary shedding at p≤0.10. Parameter estimates and significance tests are from logistic regression with generalized estimating equations.

[a]No. of visits with salivary shedding/total visits (percent)

[b]P-value for trend

[c]ORs for continuous variables are based on a one unit change in the predictor; for study visit, one unit change = 6 months

[d]Median(IQR) by salivary shedding status

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Table 3

Multivariate Logistic Regression (CD4 model)[a]

Variables	OR (95% CI)	p-value
Visit [b]	1.23 (1.11 – 1.37)	<.0001
Diabetes		
No	1.00	
Yes	3.93 (1.64 – 9.38)	0.002
ARV therapy		
None	1.00	0.0003[c]
Mono/Combo	0.35 (0.12 – 1.01)	
HAART	0.23 (0.12 – 0.46)	
CD4+ cell count		
500+	1.00	<.0001[c]
350–499	1.58 (0.78 – 3.21)	
200–349	3.78 (1.65 – 8.58)	
<200	4.90 (2.17 – 11.1)	
Stimuated salivary flow rate, mL/min	0.57 (0.36 – 0.91)	0.02
Proportion of bleeding sites	1.42 (1.10–1.84)[d]	0.01

[a] Logistic regression with generalized estimating equations (319 visits, 119 subjects), using exchangeable correlation

[b] OR per one unit change in study visit = 6 months

[c] P-value for trend.

[d] OR based on a one standard deviation change in the independent variable

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Table 4

Multivariate Logistic Regression (RNA model)[a]

Variables	OR (95% CI)	p-value
Visit [b]	1.37 (1.21 – 1.54)	<.0001
Diabetes		
No	1.00	
Yes	5.86 (2.45 – 14.0)	<.0001
ARV therapy		
None	1.00	0.002[c]
Mono/Combo	0.67 (0.22 – 2.10)	
HAART	0.30 (0.15 – 0.63)	
HIV-1 RNA in plasma		
<1,000	1.00	<.0001[c]
1,000 – 9,999	5.47 (2.61 – 11.5)	
10,000+	43.4 (18.8 – 100)	
Decayed filled root surfaces		
None	1.00	
Present	2.84 (1.45 – 5.56)	0.002
Proportion of bleeding sites	1.65 (1.22 – 2.24)[d]	0.001

[a]Logistic regression with generalized estimating equations (321 visits, 120 subjects) using exchangeable correlation

[b]OR per one unit change in study visit = 6 months

[c]P-value for trend.

[d]OR based on a one standard deviation change in the independent variable