Oral problems and Biopsychosocial factors associated with Human Immunodeficiency Virus infection.

Jesús Eduardo Elizondo Ochoa

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Doctor in Dentistry

with the option to International Doctor Mention

Periodontics and Research in Dentistry

Universitat Internacional de Catalunya

July 2017

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Problemas Orales y Factores Biopsicosociales asociados a la Infección por el Virus de la Inmunodeficiencia Humana

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Dedication

Dear María de Jesús Ochoa Ramírez,

It is impossible to thank you adequately for everything you have done, how can I thank you for all your selfless acts of love and tireless devotion. There are not enough words to even describe how important and special you are in my life, but, Mom, I am forever grateful for all that you are and whom you have taught me to be.

I will always love you.

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Preliminary Remarks

The present work is a compendium of five related publications, derived from the thesis research project published between 2015 and 2017. An effort has been made to merge all peer reviewed and indexed scientific publications.

This document has been structured in 6 chapters. Chapter 1 corresponds to the theoretical framework (purpose, problem statements, and scientific literature review and analysis). Chapter 2 includes Hypotheses, Aims, and Objectives. Chapter 3 describes the methodology implemented throughout the research. In turn, Chapter 4 provides published results obtained from the qualitative and quantitative data of the project. To conclude chapter 5 and 6 shows the Discussion, and Conclusion respectively.

The bibliography associated with the chapters can be found in the section bearing the name. The bibliography of each original published article is found in Appendix A section in the requested format by its individual publisher. The thesis was reviewed and approved by the Ethics, Research, and Biosafety Committees at both Universitat Internacional de Catalunya (Spain) and Tecnológico de Monterrey (México), please see Appendix B (Documents in Spanish language). At the end of the thesis, you will notice Appendix C with a short biography of the author.

Please note:

1. Tables have been renumbered. The first number refers to the consecutive order in which they appear in the present work (e.g. 1 for table 1), and the second number to the publication *per se* (e.g. Table 1 Article 2).
2. Bibliographical references format has been unified through all text to provide a single reference list.

Oral problems and Biopsychosocial factors associated with Human Immunodeficiency Virus

By

Jesus Eduardo Elizondo Ochoa

Summary

Introduction

Antiretroviral therapy has transformed the disease caused by the human immunodeficiency virus (HIV) into a chronic condition. Molecular epidemiology and biopsychosocial unique approach systems are required to advance towards a better assessment and understanding of the complex interactions between HIV and its human host. Therefore, it was proposed to establish the biopsychosocial risk factors of oral pathologies in HIV, determining the relationship between oral-systemic health status and antiretroviral treatment.

Material and Methods

Participants were recruited from HIV/AIDS healthcare providers, non-governmental and community-based organizations in Monterrey (México), and adopted a non-probability and snowball sampling. The research involved consenting adult men who have sex with men (MSM [epidemiology], defined by the World Health Organization as one of the Key populations at higher risk of acquiring HIV). Step 1 (Psychosocial research). MSM filled out structured, analytical, self-administered, anonymous questionnaires. Besides the sociodemographic variables, the perception regarding public and private dental services and related professionals there was also evaluated the perceived stigma associated with HIV/AIDS and sexual orientation. Likewise, their perception towards rapid HIV-1/2 testing in the dental practice. All the biopsychosocial aspects were explored by designing psychometric Likert-type scales. Step 2

(Biological research). Gingival crevicular fluid (GCF) and serum samples from HIV-positive adult male subjects (cases) and HIV-negative male subjects (controls) were examined for 17 cytokines using multiplex ELISA.

Results

Psychosocial analyses revealed that most subjects reported omitting their HIV serodiagnosis and agreed that dentists must be trained and qualified to treat patients with HIV/AIDS. The factorial analysis revealed two elements in HIV/AIDS perception: experiences of stigma and discrimination in dental appointments and feelings of concern regarding the attitudes of professionals or their teams concerning patients' HIV serodiagnosis. Most respondents expressed their willingness to take a rapid HIV-1/2 screening test during their dental visit. Nevertheless, most of them considered important that dental professionals must be well trained before applying any rapid HIV-1/2 tests. Factor analysis revealed two factors towards sexual orientation: experiences of sexual orientation stigma and discrimination in dental settings, and feelings of concern about the attitude of dentists and dental staff towards sexual orientation

Biomolecular analyses results of GCF concentrations of IL-6, IL-7, IL-10, IL-12, G-CSF, and MCP-1, as well as serum concentrations of IL-1β, IL-2, and IL-6, showed a statistically significant difference among subgroups. We found a significant effect size correlation on cytokines expression levels. Subjects who were not on antiretroviral therapy (ART) showed significantly higher levels of some of the analyzed cytokines compared to the rest. We found that GCF IL-8 was a significant predictor of the Non-ART HIV status ($p < 0.05$). We observed the same result for GCF G-CSF in the ART Short-term group and serum GM-CSF in the ART Long-term subgroup.

Conclusion

The dental practice may represent a potential location for rapid HIV-1/2 testing contributing in early HIV infection diagnosis. We also observed a low percentage of stigma and discrimination in dental appointments; however, most

MSM with or without HIV/AIDS do not reveal their sexual orientation or HIV serodiagnosis to the dentists out of fear of being rejected. Such fact implies a workplace hazard to dental professionals, but especially to the very own health of HIV/AIDS patients, as dentists will not be able to provide them a proper clinical and pharmaceutical treatment.

Molecular results indicated a high variability of GCF and serum cytokines concentrations and low frequency of their detection in different HIV/ART stages. However, within the limits of the present study, some GCF and serum cytokine concentrations correlated positively. Oral and periodontal innate immunity is affected by HIV viremia and ART. GCF IL-8, G-CSF, as well as serum IL-8, MCP-1, and GM-CSF may be useful biomarkers for the detection of disease presence and its severity due to HIV infection and ART use.

In following years, oral treatment based upon a professional practice focused on specific biological, psychological, social, and environmental (genetic and non-genetic) criteria will contribute to a more ‘precise medicine and dentistry’ accentuating professional practice upon individualized periodontal prevention, diagnosis, and treatment strategies.

Key Words

HIV, AIDS, Biomarkers, Cytokine, Gingival Crevicular Fluid, Periodontal Diseases, Antiretroviral Therapy, Public Health Dentistry, Social Discrimination, Psychometrics, México.

Figures

Tables

Index

Chapter 1: Theoretical Framework

Chapter 1

Purpose and Significance of the Study

Gingivitis and periodontal diseases are modulated by physiological communications, symbiotic relationships, metabolic by-products, and shifts in the constitution of microorganisms in the dental biofilm. Precise mechanisms involved in the initiation and progression of the disease are still unclear. The composition and the interactions between the entire oral microbiome during polymicrobial growth influence the pathogenicity and virulence of the biofilm. Human virome is not an exception and plays an important role in the outcome of periodontal diseases. Latent and active viral infections (e.g. herpes viruses, human papillomaviruses, hepatitis-causing viruses, and HIV) may give rise to an increased prevalence and incidence of periodontal diseases [1].

The paradigm between oral and systemic diseases etiopathogenesis, progression and severity, occur owing to the interplay among a combination of factors such as: microbiome diversity and constitution, immunologic, genetic, environmental, social, psychological, personal behavior, and lifestyle, equally shared by chronic diseases which seem to increase the susceptibility of some individuals to oral, systemic or oral-systemic manifestations.

Diverse systemic conditions may give rise to an increased prevalence and incidence of periodontal diseases, likewise growing evidence indicate that periodontal diseases represent a significant risk factor for systemic diseases. Some theories about common susceptibility, systemic inflammation with increased circulating cytokines and mediators, direct infection and cross-reactivity or molecular mimicry between oral microbiome antigens and self-antigens may explain the periodontal-systemic connection [2–4]. Moreover, industrialization, ethnicity, culture, diet, geographic location, education level, and socioeconomic status may impact the composition and prevalence of some periodontopathogens.

Traditional biomedical models of dentistry and medicine research focus on pathophysiology and other biological approaches to disease. On the contrary, the biopsychosocial approach systematically considers biological, psychological, and social factors and their complex interactions in understanding health, illness, and health care delivery towards the emerging field of precise dentistry and medicine [5–7]. Therefore, both the natural and social sciences are fundamental to dental and medical practice. Psychological and social factors are not merely epiphenomena: they can be understood in scientific ways at their levels as well as regarding their biological correlates [8].

Early research on HIV/AIDS and associated oral diseases were mainly focused on biomedical orientation. However, a more integrated view of the biopsychosocial aspects of HIV/AIDS has been increasingly evident in research. Consequently, in this thesis, an attempt has been made to obtain an insight into the oral and biopsychosocial factors involved in HIV/AIDS infection.

Problem Statements

Is there an existing biopsychosocial relationship and a local-systemic impact of the HIV and the highly active antiretroviral therapy in the oral cavity?

What is the relationship that prevails among people living with HIV, oral health services, and their oral health status in Mexico?

Review of the Literature

The global pandemic of human immunodeficiency virus (HIV) infection is unprecedented in the history of humanity, HIV has expanded from a new disease to one of the world's top 10 causes of death up to the year 2015 [9]. Almost 37 million people are infected worldwide with HIV, the causative agent of AIDS (figure 1). Including about 2.1 million who are newly infected each year according to the Joint United Nations Program on HIV and AIDS [10]. Meanwhile 1.5 million are estimated to be living with HIV in Latin America and the Caribbean, and more

than half of those living with HIV reside in the region's four largest countries: Brazil, México, Colombia, and Argentina [10]. Despite many efforts, no vaccine to prevent HIV infection has been found so far. As the HIV epidemic enters its fourth decade, it is still regarded as an important public health issue worldwide. In turn, the social perception and stigma towards those individuals who live with HIV and AIDS (PLWH) continue to be a negative one [11]. HIV's ways of transmission, its implications regarding the more traditional gender roles, and its association in the social imaginary to socially marginalized groups are the cause of stigma and discrimination in various circles [11].

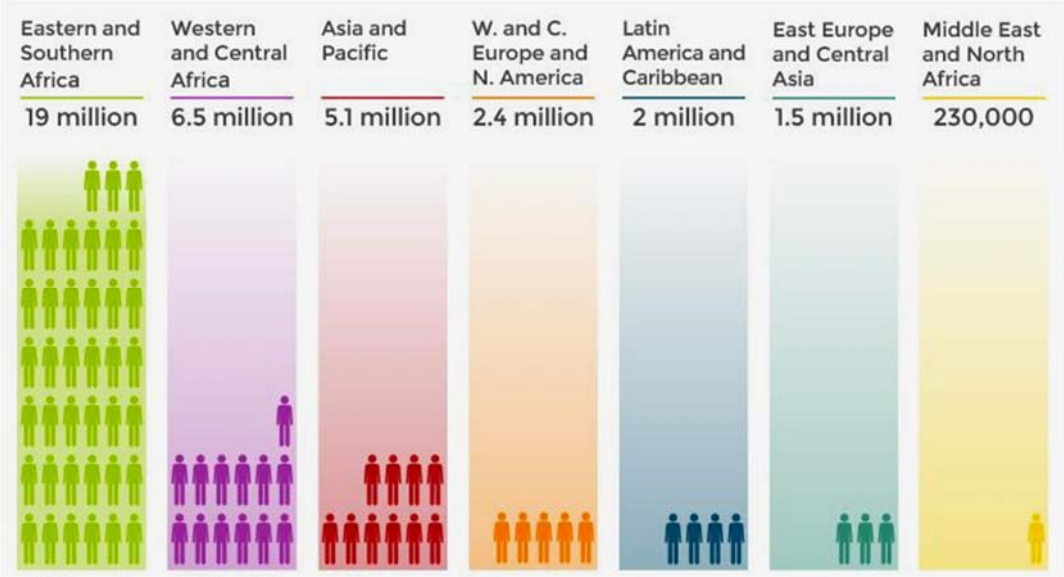

Figure 1. Number of people living with HIV in 2015*. (Source: Averting HIV and AIDS Organization. The Joint United Nations Programme on HIV and AIDS (UNAIDS) 2016 public domain image).*

From a public health perspective HIV- and AIDS-related stigma (HARS) is a major factor that hinders voluntary testing for a timely diagnosis and treatment of HIV infection [12,13]. HARS is also an obstacle for individual's serodiagnosis disclosure to their sexual partners. Thus, prolonging sexual risk behaviors and contributing to HIV transmission [12,14]; particularly in socially stigmatized and discriminated groups such as men who have sex with men (MSM), where social conditions generated by HARS lead MSM to participate in sexual risk behaviors

with a higher risk of acquisition and propagation of HIV [15,16]. Thus, it is not a surprise that globally, gay men and other MSM are 19 times more likely to be living with HIV than the general population [17]. The incidence of HIV among MSM is rising in several parts of the world, and México is not the exception [17–19]. The stigmatization of people living with HIV/AIDS (PLWHA) is an obstacle for their access to health care services and their engagement with the "HIV continuum of care" [20–22]. Evidence-based scientific research shows PLWHA's needs in oral health care, due to the high incidence of HIV-related oral problems that diminish their quality of life [23,24].

HIV is classified by the International Committee on Taxonomy of Viruses (ICTV) within the family Retroviridae, subfamily Orthoretrovirinae and genus Lentivirus. There are two types HIV-1 and HIV-2. Both of them are transmitted sexually, through blood, and from mother to child, and both appear to cause AIDS. However, it seems that HIV type 2 is less easily transmitted, and the period between initial infection and illness is longer in its case. Worldwide, the predominant virus is the HIV-1 type, and generally, when people refer to HIV without specifying the type of virus, they will be referring to HIV-1 (Figure 2). The relatively uncommon HIV-2 type is concentrated in West Africa and is rarely found elsewhere.

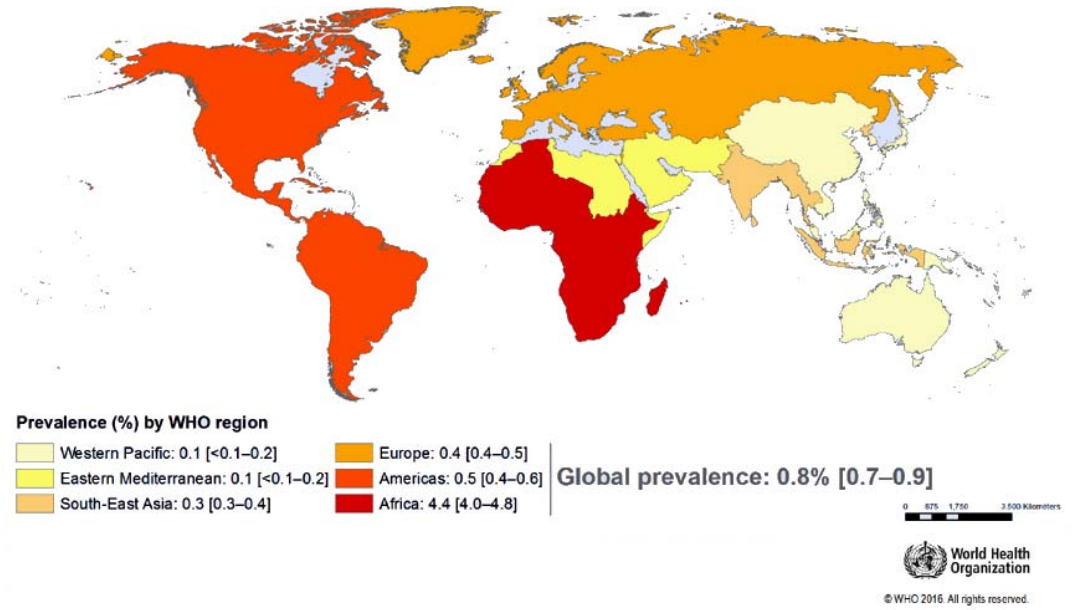

Figure 2. Adult HIV prevalence (15-49 years), 2015 by World Health Organization (WHO) region. *The boundaries and names shown and the designation used on this map do not imply the expression of any opinion whatsoever on the part of the WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement. (Source: WHO 2016 public domain image).*

The strains of HIV-1 type can be classified into four groups with an average of 37.5% diversity among each other [25]. The "major" group M, the "outlier" group O and two new groups, N and P [26–28]. These four groups have been found exclusively in Cameroon within the Congo Basin where the HIV pandemic first emerged and may represent four separate cross-species transmissions of simian immunodeficiency virus into humans in west central Africa [29]. More than 90% of HIV-1 infections belong to HIV-1 group M. However, HIV-1 group O strain has been identified in the US, France, Germany, and Belgium [30], and HIV-1 group N in France [31]. Worldwide group M is the dominant circulating HIV-1 strain. It has been divided into genetically distinct subtypes (or clades), denoted with letters, and sub-subtypes denoted with numerals. Subtypes A1, A2, A3, A4, B, C, D, F1, F2, G, H, J, and K are currently recognized [32].

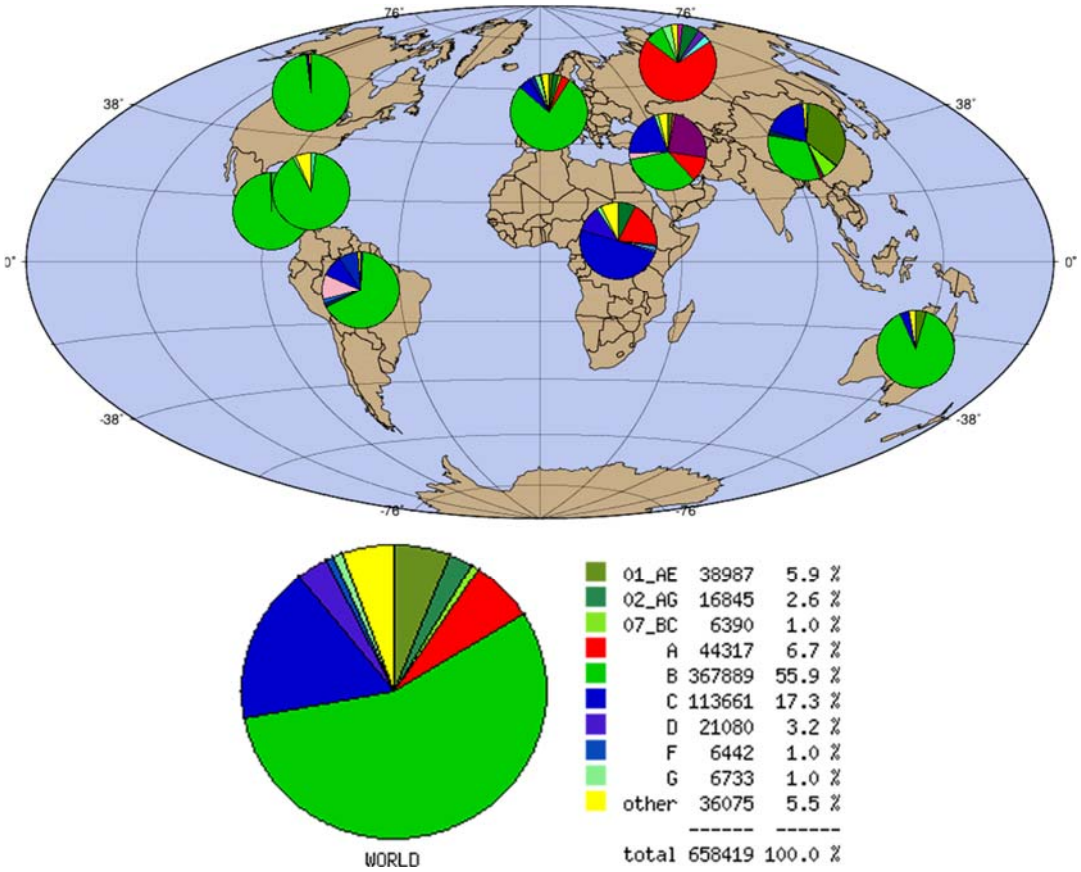

Figure 3. Global geographic distribution of HIV-1 subtypes and recombinant forms*. Distributions derived from the relative frequency of subtypes among >500,000 HIV genomic sequences. (Source: Los Alamos National Laboratory HIV Sequence Database 2015 public domain image. Additional information available at www.hiv.lanl.gov/components/sequence/HIV/geo/geo.comp).*

HIV-1 recombination can lead to further viral diversity; it occurs when one person is coinfected with two separate strains of the virus that are multiplying in the same cell [33]. Accordingly, to HIV sequence compendium 2011, the HIV sequence database is replete with 414,398 sequences. Advances in HIV full-genome sequencing have led to the identification of Circulating and unique recombinant forms (CRFs and URFs, respectively). These are the result of recombination between subtypes within a dually infected person, from whom the recombinant forms are then passed to other people. The recombinant progenies are classified as circulating recombinant forms if they are identified in three or more individuals with no direct epidemiologic linkage; otherwise, they are described as unique recombinant forms. CRFs account approximately for 16% of worldwide HIV-1 [34]. This extensive genetic diversity has limited the ability to

rapidly and cost-effectively sequence HIV-1 genomes from different populations and geographical regions. Proof of the continual divergent evolution of the virus is its approximate 1% per year rate of evolution, and this phenomenon *per se* poses a tremendous challenge for vaccine development against HIV/AIDS. The worldwide distribution of subtypes and circulating recombinant forms reflects the complexity of the molecular epidemiology of HIV-1 [25,34–37]. Subtype B is predominant in Latin America with an overall prevalence of 10.2% [32,38]. Subtype B has an initial tropism to CCR5 during initial infection. Acquisition of CXCR4 use increases with time after infection and as the disease becomes more severe [39].

HIV has several inherent mechanisms that ensure rapid viral evolution and acquisition of drug resistance. The HIV reverse transcriptase lacks proofreading activity, the ability to confirm that the DNA transcript it makes is an accurate copy of the RNA code, and confers a mutation rate of approximately 3.4×10^{-5} mutations per base pair per replication cycle [40]. The estimated average total HIV-1 production is $10.3x10^{9}$ virions per day [40]. Highly active antiretroviral therapy (HAART) is one of the most potent selective pressures on the HIV-1 genome.

HIV most often targets a type of white blood cell, called CD4+ T-cell. Infected HIV cells release newly formed viruses in a semi-synchronous wave pattern and are also thought to spread HIV through direct contact with their neighbors via virological synapses and by pools of free virus [41]. The oral cavity appears to be a site of HIV-1 pathogenesis, and a potential reservoir for HIV progression as HIV RNA and DNA forms are present in the gingival crevicular fluid as well as in saliva, and oral epithelial cells are susceptible to either cell-free or cell-associated HIV infection [42,43]. The clinical and biological basis of probable associations between chronic oral inflammatory disorders, such as periodontal disease, and exacerbation of HIV viremia have received little attention [42]. Oral lesions associated with HIV/AIDS affect patients' quality of life. Nonetheless, they are useful markers of HIV disease progression and immunosuppression. Oral lesions in HIV infection have been well-documented in developed countries, but there are fewer reports on oral lesions in individuals

from developing countries. Oral manifestations are the first and most important indicators of HIV infection. Seven cardinal lesions: oral candidiasis, hairy leukoplakia (EBV), Kaposi sarcoma (HHV8), linear gingival erythema, necrotizing ulcerative gingivitis, necrotizing ulcerative periodontitis and non-Hodgkin lymphoma are strongly associated with HIV infection and have been identified [44]. Oral candidiasis is the most frequent opportunistic infection seen in all regions. Kaposi's sarcoma has been reported in adult Latin-Americans. HIV-associated salivary gland disease has a high prevalence in Latin America, especially in the pediatric group [45].

Caspase-3-mediated apoptosis accounts for the death of only a small fraction of CD4+ T cells corresponding to those that are both activated and productively infected by HIV. The remaining over 95% of quiescent lymphoid CD4+ T cells die by caspase-1-mediated pyroptosis triggered by an abortive viral infection. This death pathway links the two signature events in HIV infection-CD4+ T-cell depletion and chronic inflammation that in turn creates a vicious pathogenic cycle in which dying CD4+ T cells release inflammatory signals that attract more cells to die [46,47]. HAART regimen have proved to be effective in decreasing HIV viral load, improving CD4+ T-cell counts, and have considerably altered the natural history of HIV-1 infection. As a result, substantial improvements in HIV-related morbidity and mortality have been documented, and HIV infection is increasingly being considered as a chronic and manageable illness in many areas of the world. Nevertheless, controversial data regarding the association between immunosuppression and prevalence/ severity of periodontal diseases in HIV infection have been reported [48,49]. Recent scientific evidence has shown that HIV-infected patients with more current periodontal diseases such as chronic periodontitis may have increased gingival recession and attachment loss when compared to HIV-uninfected individuals. This loss of periodontal support may be due in part to a diffuse invasion of opportunistic microbial infections into the periodontal tissue, leading to a higher and more diffuse destructive inflammatory response in the periodontal soft and hard tissues [49]. Growing evidence also shows significant immunological changes at an oral level in HIV-1 positive individuals compared with healthy controls, which appear

to be substantial risk factors for more rapid progression of aggressive forms of periodontal diseases in the HIV-1-infected population [50,51].

In the presence or absence of local bleeding, especially in subjects with advanced HIV infection and increased loss of clinical attachment, mononuclear cells present in gingival crevicular fluid and harboring proviral HIV-1 DNA could represent a potential source of HIV [52]. One of the first findings that drew attention in immunocompromised patients with HIV-1 is the susceptibility to opportunistic infections [53]. Although CD4+ T cells appear to be the primary targets of HIV, other immune and non-immune cells with or without CD4+ receptor on their surfaces can also be infected. Thus, macrophages, dendritic cells, CD8+ T cells, endothelial cells, epithelial cells, and fibroblasts also can harbor HIV proviruses in their genome [54]. Research with tissue samples from HIV-1 positive patients with opportunistic infections or co-infected with one or more pathogens, found a significant increase in HIV-1 within macrophages, suggesting that not only HIV-1 increases susceptibility to opportunistic infections but equally, opportunistic pathogens promote replication of HIV-1 in a reciprocal relationship [55]. Clearly, the immune activation in inflammatory or co-infection sites provides key signals that not only promote permissiveness to infection of macrophages by HIV-1 but also enhance viral replication.

The chemokines and their receptors have been receiving exceptional attention in recent years following the discoveries that some chemokines could specifically block human immunodeficiency virus type 1 (HIV-1) infection and that certain chemokine receptors were the long-sought co-receptors which, along with CD4+ T-cell, are required for the productive entry of HIV-1. Both inhibition and enhancement chemokines and their receptor signaling events elicit on the HIV-1 entry, and replication processes have once again highlighted the intricate and complex balance of factors that govern the pathogenic process.

Elizondo et al. [56], examined whether the levels of IL-2, IL-4, IL-6, IL-8, IL-10, GM-CSF, IFN-γ, and TNF-α, in gingival crevicular fluid (GCF) were altered in patients with HIV/AIDS and no periodontal disease, and whether CD4+ T lymphocyte count, viral load, and HAART, affected those levels. Complete

medical history including risk factors such as intravenous drug abuse and smoking was taken. Clinical measurements including plaque index, gingival index, bleeding on probing, probing depth, attachment loss, and GCF samples were taken from the upper right posterior sextant of each patient using sterile paper strips. They used the Bio-Plex® suspension array system and xMAP technology, licensed from Luminex Corp., which enables the simultaneous multiplexing quantitative measurement of different cytokines within a single sample of GCF.

Results showed a difference ($p<0.05$) in the expression of the 8-cytokine panel profile in the GCF of HIV-infected patients compared to HIV-negative healthy controls. However, IL- 6, IL-8, IFN-ɣ, IL-10, and TNF-α levels among HIV-1 infected patients with a high viral load (> 10,000 copies/ml) were higher than those from patients with a low viral load (< 40 copies/ml). HIV-1 infected patients with or without HAART, at different stages of HIV disease, showed enhanced IL-6, IL-8 and IFN-ɣ. IL-6 induces HIV-1 viral replication *in vitro* of T cells and macrophages by activation of NF-kB. IL-8 regulates the expression of the HIV Tat protein, in a cell cycle-dependent manner, playing an important role in virus production and infection. INF-γ is a potent modulator of HIV expression in persistently infected U1 promonocytic cells, in which viral production is characterized by a constitutive state of relative latency; it is also augmented in immunological responses to efavirenz-based HAART regimen. In contrast, same patients showed in GCF decreased IL-2, IL-10, TNF-α, and GM-CSF. IL-2 is critical in HIV disease since this cytokine acts as an important T-cell growth factor.

The balance between IL-10/TNF-α has been suggested to be of importance in the pathogenesis of HIV infection, and HAART therapy induces a significant gradual decrease in IL-10. GM-CSF is linked to pro-inflammatory effects, but the possible mechanism by which GM-CSF might affect HIV-1 replication in macrophages remains unclear. Meanwhile, IL-4 was undetectable in HIV+ individuals as compared to the healthy controls. IL-4 induces differentiation of naive helper T cells (Th0 cells) to Th2 cells; its function is to inhibit the propagation of non-syncytia-inducing, and to increase the propagation of syncytia-inducing HIV-1 isolates; also, IL-4 genes appear to influence host

response to microbial challenge. Results above suggest that patients with HIV/AIDS have an increased inflammatory balance, a high susceptibility to develop periodontal diseases, and a possible alteration in the oral microbiome. Thus another cause of periodontal breakdown may be an increase in the pro-inflammatory cytokines levels in the gingival crevicular fluid of HIV-positive patients [56–58].

Progression of periodontal disease in the presence of HIV infection is dependent on the immunologic competence of the host and the local inflammatory response to typical and atypical subgingival microorganisms. Periodontal diseases may participate in the wound healing process, and tissue destruction via the inflammatory process [59], and various dental plaque biofilm periodontopathogens induce different cytokine response profiles in gingival epithelial cells that may reflect their individual virulence or commensal status [60]. Aforementioned suggests that the inflammatory and infectious components of periodontal disease as a global oral infection in HIV-1 positive patients might have the capacity to induce HIV viral reactivation and recrudescence contributing to HAART treatment failure [42,43].

Chapter 2: Hypothesis and Aims

Chapter 2

Hypothesis

Ho: Progression and severity of HIV/AIDS associated oral pathologies are closely related to the individuals' psychological and social environment, HIV viral load, CD4+ T-lymphocyte count, highly active antiretroviral therapy, and the overexpression of proinflammatory cytokines.

H1: There is no relationship among oral pathologies present in people living with HIV, their psychosocial environment, HIV viral load, CD4+ T-cell count, highly active antiretroviral therapy type and time, and their expression of proinflammatory cytokines in serum or gingival crevicular fluid.

General Aims

Clinical Aim. Search for HIV/AIDS associated oral pathologies prevalence and risk factors within our study population. Also, determine a probable relationship among local health status (oral and periodontal), systemic health status (viral load, CD4+ T-lymphocytes) and highly active antiretroviral therapy, to identify a systemic causal inference (HIV/HAART) in oral diseases.

Molecular Biology Aim. Determine a probable systemic-oral bidirectional causal inference (the relationship between local oral health status, systemic health status, and HAART) in people living with HIV and AIDS, through different molecular diagnostic tools, to contribute to an early detection of secondary infectious diseases, and long-term control of the HIV infection.

Specific Aims

The above aims will be accomplished by fulfilling the following specific aims:

1. Establish how a select cohort of HIV-infected individuals determine their oral health status, the level of importance they give to oral diseases as HIV opportunistic diseases, whether they reveal their serological status to dental professionals on attending a dentist, and if they have perceived any form of stigma or discrimination by dental health providers.
2. To identify qualitatively and quantitatively the oral pathologies present in HIV-infected individuals relative to their viral load, CD4+ T-lymphocyte count, at different stages of HIV infection, and the types and time of HAART.
3. To identify qualitatively and quantitatively the oral pathologies present in a control group of subjects not infected by HIV-1, paired by sex, age, lifestyle and same sexual risk behaviors.
4. Analyze a panel of 17 human cytokines and chemokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, G-CSF, GM-SCF, IFN-γ, MCP-1, MIP-1β, TNF-α) by multiple immunochemical analysis and flow cytometry essay in gingival crevicular fluid and serum samples collected from HIV-infected and HIV-uninfected individuals.
5. To compare the overexpression or subexpression of the analyzed cytokines in the gingival crevicular fluid and serum, with their systemic health status in different stages of HIV infection, periodontal health status, viral load, CD4+ T lymphocytes, types and time of HAART.
6. Identify and establish predictive periodontal and systemic HIV/AIDS risk biomarkers by objective methods and measures in the gingival crevicular fluid to contribute to the development of a more precise medicine and dentistry.

Chapter 3: Methodology

Chapter 3

Research Design

Cross-sectional study of the oral and biopsychosocial characteristics of HIV/AIDS infection.

Ethics

The study protocol was reviewed and approved by the ethics, research and biosafety committees at Tecnologico de Monterrey (México) and Universitat Internacional de Catalunya (Spain). Subjects were given both verbal and written information about the nature of the study (Appendix B, documents in Spanish language). The study procedures were undertaken with the written consent of each participant and according to the Declaration of Helsinki [61]. Subjects could leave the study at any time during the procedures. All information about the participants and their identity were anonymous.

Recruitment and participants

Participants were recruited from HIV/AIDS healthcare providers, non-governmental and community-based organizations in Monterrey, México and adopted a non-probability and snowball sampling. The research involved consenting adult men who have sex with men (MSM).

Step 1 (Psychosocial research). Data collection occurred during 60 days, and eligible participants were those 18 years or older and who had engaged in sex - anal or oral - with another male at least once within the past 12 months. Participants were first grouped based on their HIV status disclosure and later on regrouped based on the inclusion and exclusion study criteria.185 MSM filled out structured, analytical, self-administered, anonymous questionnaires.

Besides the sociodemographic variables, the perception regarding public and private dental services and related professionals there was also evaluated the perceived stigma associated with HIV/AIDS and sexual orientation. Likewise, their perception towards rapid HIV-1/2 testing in the dental practice. All the biopsychosocial aspects were explored by designing psychometric Likert-type scales. Following the procedure recommended by Lynn [62], a group of reviewers assessed how well the items of each scale evaluated the concepts of HIV/AIDS- and sexual orientation-related stigma and discrimination regarding their accuracy and relevance of both concepts. Such scales consisted of five alternatives that ranged from “never” to “very often.”

A digital survey database was created and submitted to a dual quality control to assure reliability of information. The subjects accessed the survey website (www.encuestas.no-ip.org) to answer the online questionnaire. No log-in data (e.g., internet protocols) were stored in the electronic access. After the survey was completed (average of 25 minutes), and as a benefit to all participants, voluntarily, informed, and consented oral examination and oral prophylaxis were offered free by qualified, certified, and sensitized dentists.

Exclusion criteria

The following criteria allowed us to select candidates for the molecular study.

1. A medical condition that makes it inappropriate for the patient to be enrolled or that may interfere with the patient's participation in the study and with the end of treatment.
2. Medical history of severe or uncontrolled psychiatric illness especially depression, history of hospitalization or attempted suicide or history of moderate psychiatric illness within the last 5 years.
3. Two-way related diseases with cardiovascular periodontal disease, stroke, diabetes, chronic obstructive pulmonary disease, and pneumonia

4. Anemia, Osteoporosis, Coagulation disorders, Rheumatic fever, Cardiac diseases, Circulatory diseases, Respiratory diseases, Endocrine diseases, Cancer, Organ transplant patient.
5. Medical history or present tuberculosis.
6. Uncontrolled arterial hypertension, e.g. patients with systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥ 100 mmHg.
7. Hemoglobinopathies (thalassemia major, sickle cell anemia or sickle cell disease).
8. Prior application of any previous vaccine ≤ four weeks.
9. Prior use ≤ six weeks of any antibiotic, antimycotic or antiviral (except for HBV and HCV).
10. Previous periodontal treatment or procedure ≤ six months.
11. Use of ≤6 weeks of chlorhexidine mouth rinse, oral antiseptics or electrolyzed superoxidation solution.
12. Use of orthodontic or prosthetic devices (oral fixed and removable).

Step 2 (Biological research). HIV-positive subjects were diagnosed in advance of the study as HIV antibody positive by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western Blot [63]. All self-declared non-HIV subjects were provided with an opportunity to undergo voluntary counseling and testing for HIV infection (at screening and if enrolled, 3 months after all study samples were taken), detected by a simplified visual immunochromatographic rapid HIV-1/2 test based on oral fluid (OraQuick Advance HIV-1/2 assay [OraSure Technologies, Inc., Bethlehem, PA]) with a 99.3% sensitivity and 99.8% specificity.

MSM who voluntarily decided to participate and tested HIV negative served as controls. All rapid tests were performed accordingly to manufacturer's instructions and were conducted by a trained counselor certified in STI/HIV/AIDS prevention counseling, testing, and referral. Tests results were obtained in10-20 minutes. Rapid HIV testing and streamlined counseling increase rates of testing and receipt of test results and is cost-effective compared with traditional HIV testing strategies [64].

Clinical examination

Medical and dental files were recorded for HIV-positive individuals as cases and non-HIV subjects as matched controls. Data included history or current manifestation of any systemic diseases, autoimmune diseases, infectious diseases, or other than HIV/AIDS, likewise diabetes, concurrent psychiatric or psychological treatment, illicit drug use, current alcohol abuse, chronic usage of anti-inflammatory drugs, chronic or intermittent use of antibiotics and chlorhexidine digluconate, antidepressant drugs, application of any previous vaccine (≤ 4 weeks), presence of oral lesions, periodontal treatment or procedure prior ≤ 6 months and current use of prosthetic or orthodontic appliances (fixed or removable), that could affect periodontal or systemic cytokine expression. The smoking habit was recorded and not excluded due to the prevalence of smoking among MSM with that among other men [65,66]. In like manner, obesity could not be avoided, and body mass index (BMI) was taken into account due to the rapid growth in its prevalence among Mexican adult population [67].

Oral examination

All participants underwent a standardized oral examination at the baseline visit carried out by a single calibrated examiner (ACT) to ensure consistency of measurements (intra-examiner reproducibility ranged from 89% to 91%). Gingival recession (REC), probing pocket depth (PPD), clinical attachment level (CAL) and bleeding on probing (BOP) were measured using a computerized constant pressure probe i.e., Florida Probe® (Florida Probe Corporation, Gainesville, FL, USA) with a constant force of 15 g (pressure-154 N/cm2), tip diameter of 0.40 mm, precision of 0.2 mm and a probe length of 11 mm.

Six sites (distobuccal, midbuccal, mesiobuccal, distolingual, midlingual, and mesiolingual) were measured in each tooth present per subject, except third molars (a maximum of 168 sites/subject). RECs, PPDs, and CALs were measured considering a fixed reference point on the occlusal surface of the teeth,

and cementoenamel junction and BOP was calculated as the percentage of positive sites per subject. BOP was considered positive if bleeding was elicited within 30 seconds following insertion of the probe to measure the PPD. Plaque score was recorded by using Turesky modification of the Quigley-Hein plaque index (PI) [68].

No radiographs were taken. Periodontitis was defined by the presence of at least one site with PPD ≥ 4 mm and CAL ≥ 3 mm on at least 4 different teeth with or without BOP. HIV-related oral lesions in case subjects were recorded according to the classified criteria EC-Clearinghouse on Oral Problems Related to HIV Infection [69], and the Oral HIV/AIDS Research Alliance case definitions of oral disease endpoints [48].

Samples and laboratory tests

Prior sampling all subjects were tested for the presence of anti-HBc, HBsAg and anti-HCV, detected by visual immunochromatographic rapid diagnostic stick tests (One step HBV test [six tests profile HBsAg, HBsAb, HBeAg, HBeAb, HBcAb and HBcIgM, Intec, Xiamen, China] and Rapid Anti-HCV Test [Intec, Xiamen, China]), both with 99% sensitivity and specificity. In addition, non-fasted blood glucose levels (BGL) were determined in all participants (OneTouch Ultra2 System [LifeScan, Inc., Milpitas, CA]). All of the aforementioned tests were performed in capillary blood (100μl per test) obtained by finger puncture.

To avoid drug-related cytokine changes a non-invasive method was used to determine drug abuse in all subjects by one-step chromatographic immunoassay device employed for the qualitative simultaneous detection of multiple drugs: cocaine, methamphetamine/MDMA, tetrahydrocannabinol (THC), amphetamine, opiates, and benzodiazepines. (Oratect III Oral Fluid Drug Screen Device [Branan Medical Corp., Irvine, CA]). All rapid tests were performed according to manufacturer's instructions and were conducted at the dental clinic

by a trained counselor certified in STI/HIV/AIDS prevention counseling, testing, and referral.

Based on inclusion and exclusion criteria the study sample comprised 117 voluntary MSM. Descriptive statistics were used to analyze breakdown of subjects by the status of HIV test. 78 HIV-positive subjects as cases and 39 HIV-negative subjects as controls match in the race, sex, sexual orientation, and sexual behavior. All 39 HIV-negative subjects were retested three months after all study samples were taken and remained HIV negative.

Gingival crevicular fluid collection

Oral sampling site selection for all subjects was performed by one examiner, and the samples were collected on a subsequent day. This was undertaken to prevent the contamination of GCF with blood associated with the probing of inflamed sites. The participants were told not to eat or drink anything or chew gum, neither smoking, teeth brushing, nor using any mouthwash or toothpaste at least 2 hours before GCF samples were taken.

Maxillary teeth including first molars, second premolars, and canines or central incisors (three teeth for each subject) were selected to avoid possible saliva contamination during sampling. Sampled teeth were free of gingival inflammation, caries, prosthetic reconstruction, and root canal therapy. After supragingival plaque was removed from each tooth, the individual tooth site was gently air-dried and isolated with cotton rolls. A saliva ejector was used to avoid salivary contamination of the samples. Samples of GCF were collected from buccal aspects of two interproximal sites around the three selected teeth in each individual participating in the study. Paper strips (PerioPaper Strips, OraFlow, Plainview, New York, USA) were gently inserted into the crevice at the mesial or distal midpoints until slight resistance was met, and the strip was kept in the selected site for 30 seconds.

GCF volume was measured using a calibrated Periotron 8000 (OraFlow, Plainview, New York, USA) which was calibrated using known volumes of phosphate-buffered saline (PBS), pH 7.4. Paper strips with traces of blood were discarded, and sampling was replicated from another site of the natural tooth that was not sampled. The GCF was measured electronically in Periotron units, which were converted to microliters (µl) by MCCONVRT software (Software version 2.52, Oraflow Inc., Amityville, NY, USA). Six strips of each patient were immediately placed in a labeled tube containing 500µl PBS and transported at 4°C to the laboratory. Following 10s vortexing and 20min shaking, the strips were removed and the eluates centrifuged for 5min at 5800 x g at -4°C to remove plaque and cellular elements. The eluate was divided into aliquots and stored at -80°C until assayed.

Serum and plasma samples

All subjects were asked to refrain from eating and drinking at least 8 hours before sampling. All samples were collected from subjects between 7:00 and 10:00 a.m. Peripheral blood was drawn from both groups by a trained healthcare professional using a sterile 20-guage needle with 5-ml syringes. About 5ml of blood was collected from the antecubital fossa by venipuncture into Vacutainer test tubes without additives for the control group. The same procedure was employed to collect 10ml of blood from case subjects, distributed 5ml into Vacutainer test tubes without additives and 5ml in test tubes with EDTA as an anticoagulant.

Following the standard operating procedures for serum and plasma collection for biomarker discovery and validation [70], collected samples were preserved at 4°C and immediately transferred to the laboratory. Within 30 minutes of sample collection, 50 µL of whole blood from HIV+ subjects were separated (for the determination of CD4+ T-cell count and percentage within 2 hours of collected), then serum and plasma were separated from the rest of the blood

samples by centrifuging at 1,000 x g for 15 minutes and were immediately transferred to label plastic vials and stored at -80°C until assayed for cytokine and HIV-1 RNA.

CD4+-T-cell counting

Blood samples were stained and analyzed by FACSCount (Becton Dickinson, San Jose, CA) within 2 hours and all measures were performed in triplicate according to the manufacturer's instructions. The FACSCount is a fully equipped single platform (SP) FCM equipped with a green laser. It is combined with built-in software and two-colour monoclonal antibodies (mAb) reagents in a twin-tube containing calibrated beads, with additional control beads. Briefly, 50 µL of EDTA anti-coagulated whole blood was added to the FACSCount reagent tubes containing anti-CD3-PE, and anti-CD4-PE-Cy5 or anti-CD8-PE-Cy5. The tubes were capped, vortexed and incubated in the dark at room temperature for 60 minutes. After incubation, 50 µL of fixative solution was added to reagent tubes, and samples were run on the FACSCount instrument.

Cytokine assay

Levels of cytokines in serum and GCF samples from all subjects were determined using the Bioplex Pro Human Cytokine 17-Plex Assay (Bioplex, Bio-Rad Lab., Inc., Hercules, CA, USA), which is a multiplex biometric ELISA-based immunoassay involving dyed microspheres conjugated with a monoclonal antibody specific for a target protein. The standard 17-plex cytokine detection kit includes human IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, G-CSF, GM-CSF, IFN-γ, MCP-1, MIP-1β, and TNF-α.

The manufacturer reports that the assay accurately measures cytokine values in the range of 1–2, 500 pg/ml and shows less than 1% cross-reactivity among cytokines or with other molecules. All serum and GCF samples used in

this study were examined for cytokines according to the manufacturer's protocol at the same time in duplicate. Serum and GCF levels of all proteins were determined using a Bio-Plex array reader (Luminex, Austin, TX, USA) at 405 nm wavelength. The analyte concentration in each (serum 5ml and GCF 0.5ml) sample was calculated using a standard curve, with software provided by the manufacturer (Bio-Plex Manager Software). Samples with cytokine concentrations below the detection limit were assigned an averaged value between 0 and the lowest detectable level in each assay plate before log transformation so that all samples were retained in the dataset. Concentrations of the cytokines were corrected for serum and GCF volume and were defined as $\mathrm{pg}/\mu\mathrm{l}$, for the GCF the total amounts of cytokines were expressed as pg/6 sites. The technician who performed the ELISA was unaware of the study groups.

HIV-1 RNA assay

Plasma samples from HIV-1 infected individuals were analyzed using real-time PCR technology for detection and quantification of HIV RNA by Cobas Ampliprep/Cobas TaqMan HIV-1 test, version 2.0 assay (Roche CAP/CTM-48 V2) on the TaqMan 48 analyzer (Roche Molecular Systems, Branchburg, NJ). This RT-PCR assay uses primers targeting both gag and long terminal repeat regions of the HIV genome and has a reportable range of 20 to 1.0E+7 HIV RNA copies/ml. Assay was performed according to the manufacturers' instructions. The reported viral load represented the value determined on the day of gingival crevicular fluid collection. Each patient record was also reviewed to ensure that two previous viral load measurements would have placed them in the same group.

Gingival crevicular fluid (GCF) and serum samples from HIV-positive adult male subjects (cases) and HIV-negative male subjects (controls) were examined for 17 cytokines using multiplex ELISA. HIV-positive subjects were grouped according to the Center for Disease Control (CDC) classification for HIV infection [71]. Included stage, and duration of HIV infection (calculated from HIV

serodiagnosis date), use of ART, Anti-HIV drug classes, México's ART guideline (first, second or salvage) [72], duration of ART, CD4+ T-cell count, and HIV RNA viral load. The cohort was then divided into subgroups, six HIV-infected subjects were not on antiretroviral therapy (Non-ART subgroup) at the time of the study, and seventy-two were receiving different combinations of ART, mainly one non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors.

Statistical analysis

An exploratory factor analysis was performed to empirically synthesize the psychosocial variables concerning the perception of HIV/AIDS- and sexual orientation-related stigma and discrimination. In this analysis, the inclusion of variables was conditioned by a matrix that validates the presence of marked correlations among all of them and ensures that their application is fitting. Items with no statistical significance were disregarded in each scale. The analytical criterion to determine the number of covered factors included the ones whose values were shown to have proper internal consistency index through Cronbach's alpha [73]. Principal components analysis was used to extract core factors. Before the extraction, Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity were used to assess the suitability of the respondent data for factor analysis. A Varimax rotation method with Kaiser Normalization was performed to facilitate the interpretation of the factor loadings. A k-means clustering procedure was performed after the factor analysis. Once those clusters had been outlined, each of the factors that were used in their differentiation was proven to be statistically significant by an analysis of variance (ANOVA).

Biological data were tested for normal distribution using the Kolmogorov-Smirnov test [74] and Levene's test to assess differences in distribution and variance of samples. Grubbs' test (maximum normalized residual test) [75] was used to determine significant outliers from data set. Outliers were winsorized from the analysis [76], and normality was reconfirmed with the above-mentioned

normality test. Results for parameters based on normality and outlier tests were followed by repeated measures Multivariate Analysis of Variance (MANOVA) to test for group differences in changes in the dependent variables. Differences within groups are presented as means ± standard deviation (SD) for continuous variables and as proportions for categorical variables.

Additionally, all data were analyzed with a series of follow-up ANOVA, the homogeneity of variance assumption was tested for all analyzed variables. Based on a series of Levene's *F* test, the homogeneity of variance assumption was considered satisfied, suggesting that the ANOVA will be robust in this case. Paired *"t"* test was used to compare the means of data from two related samples. A series of posthoc Scheffé's test were performed to examine individual mean difference comparisons (control of the type I error) and determine the exact nature of group differences.

Pearson's correlation and multivariate linear regression analyses were used to compare means of immunological parameters among independent groups. The assumptions of independence and homoscedasticity for multivariate linear regression was checked using the Durbin-Watson test [77] and Breusch-Pagan test, [78] respectively. Heteroscedasticity-consistent standard error estimators [79] were used to correct any presence of spatial non-stationarity or heteroscedasticity and to avoid type I errors in the multivariate linear regression models. All data were analyzed with SPSS® (version 22.0), and all test were performed considering $\alpha = 0.05$ to indicate statistical significance.

Chapter 4: Published Peer Reviewed and Indexed Journal Articles

Chapter 4

Published Article #1

Title. Contribution of multi “-OMICS” to the future of oral health

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Main text

Editorial

The scientific “-OMICS” turmoil began at the end of the last century, leading to a new and deeper level of complex biological insights that completely change the way scientist understand the molecular mechanisms of the diseases. Health professionals in the post -omics era will use thousands of disease-associated biomarkers provided by high-throughput technology. Thus, clinical practice will grant the adaptation of multiomics data to personal health care.

Multiomics biomedical approach resides on wide profiling methods that haul considerable amounts of -omics data. “-OMICS” technologies including epigenomics, genomics, exomics, transcriptomics, proteomics, metabolomics, and nascent fields such as viromics -the study of virus in our body and how they might cause certain conditions- coupled with bioinformatics and biostatistics to generate and process massive biological data. Nevertheless, multiomics gained results and knowledge are assessed individually rather than conjointly. In this manner, interactomics deals with studying both the interactions and the consequences of those interactions. Recent studies of metagenomes have opened the door to characterize the size and diversity of the human 'virobiota' and to identify its associated genes (the 'virome'), promoting the emerging field of host-virobiota interactions.

Viruses prevail on or in just about every species and every ecological niche [80], and although viral structure differs considerably among different types of viruses, many of them can colonize the human oral cavity as well as other microbes such as oral bacteria [81,82]. The mouth offers a splendid portal to a new host. Viruses in the oral cavity are most commonly acquired in early childhood, from mother to infant via infected saliva or in adulthood transmitted by the oral-oral, oral-genital, or oral-anal route, but other factors such as environmental, developmental, social, behavioral, or others may also play a major role (‘exposomics’). Novel findings had highlighted the role of the immune system in shaping the composition of the oral virobiota and consider how resident viruses may impact host immunity [83]. Many viruses have ‘highly’ mutation rates

and constantly shift as means of eluding the host's immune system. Evidence suggests a bi-directional association with a range of oral and systemic diseases [84,3].

Leading-edge scientific research has revealed the possible role that latent and active viral infections have in the etiopathogenesis, progression and severity of periodontal diseases (PDs) [81]. After dental caries, PDs are the second most prevalent oral diseases affecting up to 90% of the worldwide population, contributing to the global burden of chronic disease, and meeting criteria as a public health problem [85,86]. Essentially PDs are poly-periodontopathogenic and multifactorial infectious diseases which trigger chronic inflammatory and immune responses that lead to tissue destruction of the supporting structures of the teeth, also known as periodontium -gingiva, periodontal ligament, and alveolar bone -. Periodontal disease is a chronic oral infection associated with numerous oral microbial species organized in planktonic or biofilms communities.

Specific microorganisms are believed to play an essential role in PDs, so far their relative numbers and significant contribution to the initiation and progression of the disease is still unclear [87,88]. The collection of microorganisms found in the oral cavity has been referred to as the oral microflora, the oral microbiota, or currently as the oral microbiome. The ultimate diversity of the oral microbiome was estimated to be around 19,000 phylotypes. Notwithstanding, viruses surpass microbial cells 10:1 in most environments, as far as viruses inhabit oral tissues, saliva, gingival crevicular fluid, and the subgingival and supragingival biofilms, little is still known about how oral viruses are spread throughout the oral cavity and their role as constituents of the human microbiome. However, viral sequence databases have considerably expanded since the beginning of the viromics era, and particular species are detected now and then in the oral cavity [89].

Human viruses may occur in periodontal lesions with relatively high prevalence; common conditions are the different herpes viruses, human papillomaviruses, hepatitis-causing viruses, and HIV [1]. Viruses that replicate or not in the oral tissue but that are capable of infecting and impairing immune

mediated response, resulting in proinflammatory signaling events or bacteriophages that predate upon cellular oral microbiota rather than the human host may contribute in shifting oral microbiome diversity and constitution, causing an increased pathogenicity of the periodontal microbiota [81,82]. Viral infection of certain cell types, upregulate cellular surface receptors enhancing polymicrobial adhesion. Therefore, viral coinfection with other polymicrobial pathogens may lead to immunomodulatory effects that repress more than one microorganism clearance mechanisms and therefore increasing colonization, being a key issue in host–symbiont evolutionary dynamics where hosts and their symbionts speciate in parallel, by cospeciation, or through host shifts.

Periodontal viral-polymicrobial interactions initiate various and distinct mechanisms. For example, virus-induced alteration in epithelial cells, reduced cellular functions, cell death/decreased junctional epithelium or epithelial barrier function, virus-upregulated cellular surface receptors for polymicrobial adhesion, virus-enhanced polymicrobial colonization, virus-mediated inhibition of innate immune cells, suppressed phagocytosis, impaired polymicrobial killing, depressed leukocyte migration, antiviral immune molecules, suppressed innate immunity, inhibited IL-17 responses, dysregulated inflammation, enhanced periodontal tissue injury from increased inflammation (e.g., chemokines) and increased susceptibility from induction of anti-inflammatory cytokines. Wherefore, viral-polymicrobial interactions may explain in part the etiopathogenesis and progression of periodontal disease [81].

Progression of PDs in the presence of virus-induced infection is dependent on the immune competency of the host and the local inflammatory response to typical and atypical subgingival microorganisms [90]. Periodontal diseases may participate in the wound healing process, and tissue destruction via the inflammatory process and various dental plaque biofilm periodontopathogens induce different cytokine response profiles in gingival epithelial cells that may reflect their particular virulence or commensal status. The aforementioned suggests that the inflammatory and infectious components of periodontal disease as an oral infection might have the capacity to prompt viral reactivation and recrudescence. Nowadays has become evident that cytokines have a major

relevance in immune responses to persistent viral infections and that the functional impact of a specific cytokine can be strikingly distinct or even opposite in chronic versus acute contexts of infection [90,91].

Some theories about common susceptibility, systemic inflammation with increased circulating cytokines and mediators, direct infection and cross-reactivity or molecular mimicry between oral microbiome-virome antigens and self-antigens try to explain periodontal etiopathogenesis and disease progression. Thus, understanding the molecular interactions in the microbiome-virome and host's immune system using 'molecular profiling' and 'molecular perturbation' approaches through a combination of multiomics [92] is one of the main challenges towards discerning among the convoluted diverging and converging signaling pathways between human oral physiological and pathological states.

Oral multiomics milieu will be transformed by the evolution of high-throughput techniques and bioinformatics resources, facilitating novel approaches, rapid analysis, and interpretation of large datasets. Thus, providing health care professionals with new insights into oral health and disease, potentiating multiomics clinical application and advancing towards the implementation of a 'precise medicine and dentistry' within the next decade. In the interim further and better designed large-scale longitudinal studies in various populations, with the application of nouveau multiomics sciences and technologies; the use of molecular determinants for assessing potential targets for the inhibition of co-adhesion, biofilm development and regulation of the ecological balance in the oral cavity; may ultimately provide the means to modify microbiome-virome colonization and thus reduce the impact of oral diseases on human health. In following years, oral treatment based upon multiomics - genetic and non-genetic - criteria will contribute to a more 'precise medicine and dentistry' accentuated upon individualized periodontal prevention, diagnosis, and treatment strategies, along with a professional practice focused on specific biological, psychological, social, and environmental contexts.

Published Article #2

Title. Perceived HIV-associated stigma among HIV-seropositive men: psychometric study of HIV stigma scale

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Full reference

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Abstract

Objectives

To assess the internal consistency and factor structure of the abridged Spanish version of the Berger HIV Stigma Scale (HSS-21), to provide evidence for its convergent and discriminant validity, and to describe perceived stigma in an urban population from northeast México.

Methods

Seventy-five HIV-positive men who have sex with men (MSM) were recruited. Participants answered the Spanish versions of three Likert-type scales: HSS-21, Rosenberg's self-esteem scale, and the abbreviated version of the Zung's Depression Scale.

Results

HSS-21 showed high reliability and validity; its factor structure included four components: concern with public attitudes; negative self-image; disclosure concerns; and enacted stigma. The level of stigma was high in 27 out of 75 (36%) participants; nevertheless, the score found in the component related to disclosure concerns indicated a high level of stigma in 68% of participants. The score of HSS-21 was positively correlated with the score of depression and negatively correlated with the score of self-esteem.

Conclusion

Results demonstrated high reliability for the HSS-21; correlations with other scales supported its validity. This scale demonstrated to be a practical tool for assessing stigma among Mexican HIV-positive MSM. High level of stigma was found only in the factor related to disclosure concerns.

Policy implications

Identifying HIV-associated stigma through a short, reliable, and validated instrument will allow the development of interventions that cope and manage stigma in HIV-positive MSM. HSS-21 distinguishes between different dimensions of stigma and will contribute to a better understanding of this phenomenon.

Keywords: HIV, AIDS, social stigma, men who have sex with men, public health, validation studies, psychometrics, México

Main text

Introduction

As the human immunodeficiency virus (HIV) epidemic enters its fourth decade, it is still regarded as an important public health issue worldwide. In turn, the social perception toward those individuals who live with HIV and AIDS (PLWH) continues to be a negative one. HIV's ways of transmission, its implications regarding the more traditional gender roles, and its association in the social imaginary to socially marginalized groups are the cause of stigma and discrimination in various circles [11]. Stigma can be conceptualized as a "mark" (attribute) linking an individual with a set of undesirable characteristics (stereotypes) [93,94]. Three main sub-types of stigma have been described: acted stigma refers to the actual experience of acts of discrimination. Perceived stigma refers to the fear experienced by an individual in the presence of negative attitudes of society toward a given attribute considered as undesirable, for example, an ethnic group, a disease, some personal behaviors, etc. A third sub-type is internalized stigma (self-stigma), a term which includes the negative beliefs, opinions, and feelings that an individual holds toward a given attribute and toward himself/herself as a result of an internalization process of the societies' opinions and beliefs toward such attribute [95].

The term HIV- and AIDS-related stigma (HARS) makes reference to the negative appraisal that society as a whole give to any person who lives, or is believed to live with HIV and AIDS. In the psychosocial model developed by Berger et al. [96], the term "perceived stigma" is conceptualized as the perception of PLWH of social disqualification (incomplete social acceptance or even rejection), denial or limitation of opportunities (e.g., housing and employment offers, access to medical services, etc.), as well as negative changes to their social identity as a result of their HIV serostatus. This stigmatization process is also associated with other factors involved in judgment formation, such as sexual orientation, diversity of sexual partners, and use of illegal substances. This "blame the victim" attitude increases the isolation sensation and the interiorized sense of shame by the HIV-infected individual [11].

From a public health perspective, HARS is an important factor that hinders voluntary testing for a timely diagnosis and treatment of HIV infection [11–13]. HARS is also an obstacle for individual's serodiagnosis disclosure to their sexual partners, thus prolonging sexual risk behaviors and contributing to HIV transmission [12,14]; particularly in socially stigmatized and discriminated groups such as gay men and men who have sex with men (MSM), where social conditions generated by HARS lead MSM to participate in sexual risk behaviors with a higher risk of acquisition and propagation of HIV [15,16]. Thus, it is not a surprise that worldwide gay men and other MSM are 19 times more likely to be living with HIV than the general population [17]. The incidence of HIV among MSM is rising in several parts of the world, and México is not the exception [17,19,97].

Likewise, HARS can also lead PLWH to postpone the use of medical, public health services [12,98], to a suboptimal adherence to antiretroviral therapy [99–101], and to a poor overall health [13,102]. Furthermore, HARS is associated with stress, anxiety, depressive symptomatology, and a decreased quality of life [103,104]. Aforementioned, HARS and its multiple consequences have a deep impact on the HIV epidemic development by reinforcing existing social inequalities with serious implications for public health policies.

Several instruments have been developed and validated to evaluate HARS in PLWH [96,105,106]. One of the best known is the HIV Stigma Scale (HSS-40) developed by Berger et al. [96]. This scale has been used to assess perceived stigma among adult PLWH [107–110]. Likewise it has been adapted for PLWH children [111], and as well to assess perceived stigma of other diseases [112].

The HSS-40 scale assesses how PLWH feel in regards to four dimensions of stigma: (a) personalized stigma (or acted stigma), (b) individuals' concerns related to disclose his/her own HIV serostatus, (c) negative self-image (self-stigma), and (d) individuals' concerns related to public attitudes toward PLWH. The instrument has shown evidence of construct validity and high internal consistency for a set of 40 items ($\alpha = 0.96$), as well as for its factors ($\alpha = 0.90$–

0.93) [104]. The HSS-40 Spanish language translation, adaptation, and validation were done by Franke et al. [113], who also developed a shorter version (HSS-21). Likewise, as the complete scale version, the HHS-21 also showed evidence of construct validity (α = 0.84 as a total score), and an adequate-to-high internal consistency (α = 0.68–0.80) in assessing the four dimensions of stigma.

Since HARS not only represents one of the greatest obstacles in preventing new HIV infections but also deeply and negatively affects multiple aspects of HIV treatment, as well as the physical, mental, and emotional well-being of the PLWH [114], it becomes important to assess perceived stigma among PLWH. Considering the lack of adapted and validated instruments for HARS assessment that could improve current HIV and AIDS public health policies in México (e.g., Healthy Border 2010/2010 initiative), this study aims to evaluate the internal consistency, factorial structure, convergent, and discriminant validity of the HSS-21, as well as to describe HARS in a sample of HIV-positive MSM in Nuevo León (Mexican border state with U.S. Texas state).

Materials and Methods

Participants

The research involved 185 MSM and who collaborated with non-governmental and community-based organizations members of Nuevo Leon's Multisectoral STI/HIV/AIDS Response Board (MEMUREVIH). Inclusion criteria involved only male subjects who had had sexual experiences with other men, HIV-positive, aged 18 years or more, and who resided in Nuevo León, a Mexican state. Taken into account that most HIV-positive MSM does not disclose their serological HIV status, this study adopted a non-probability sampling and a respondent-driven sampling. The sample consisted of 75 MSM who voluntarily declared to have an HIV-positive serodiagnosis, and who responded to a written or an online survey.

Recruitment

The data collection process lasted 60 days. Prior to the data collection process, collaboration was requested to the different non-governmental and

community-based organizations members of MEMUREVIH to implement the survey in their office location and to their MSM affiliates. Four properly qualified surveyors visited all sites and applied the written or online surveys on the previously agreed dates and time with the aforementioned organizations.

Procedure

In order to guarantee information input reliability, a digital survey database was created and submitted to a double-quality control check. All subjects were given both verbal and written information about the nature of the study, prior to responding to either the written or online questionnaire. The study procedures were undertaken according to ethical principles with the understanding and written consent of each subject. The study protocol was reviewed and approved by the ethics and research committee at the Tecnologico de Monterrey. Anonymity was guaranteed throughout the process, as well as the confidentiality of both physical and electronic data. To access the online questionnaire, respondents accessed the survey via the website – (www.encuestas.no-ip.org), and none of the log-in data (IP address, etc.) was stored in the electronic access. Completion of either the written or online survey took an average of 25 min.

Instrument

The study used an analytical-type structured questionnaire (closed-ended questions and multiple response alternatives) in either written or online formats. The questionnaire explored socio-demographic characteristics, the perception of HARS, self-esteem, and depression by means of the following Likert-type scales:

HIV Stigma Scale (HSS-21)

The abridged and Spanish-adapted version of the HIV stigma scale (HSS-21) used in this study was developed by Franke et al. [112]; it is composed of 21 positively keyed items that are evaluated on a 4-point Likert-type scale (from 1 = strongly disagree to 7 = strongly agree), and was shown to be internally consistent. The sum of these items yields a total score, with higher scores representing a greater degree of perception of stigma.

Rosenberg Self-Esteem Scale (RSS-10)

It is composed of 10 items rated on a 4-point Likert-type scale. Possible scores range from 10 to 40, with higher ones indicating greater self-esteem. Among men, scores lower than 28 indicate low self-esteem [115].

Zung Depression Scale (ZDS-10)

Zung depression scale constituted of 20 items that involve affective, psychological, and somatic symptoms. Respondents indicate the frequency with which any symptom is experienced: the higher the score, the greater the degree of depressive symptoms. Diaz et al. [116], developed and validated a short, Spanish-adapted version of this scale (ZDS-10); the cut-off point to distinguish the presence of clinically significant depressive symptoms is 22 (sensitivity = 92.3%, specificity = 71.4%).

Statistical analysis

Two psychometric properties of the items in HSS-21 were estimated: discrimination and internal consistency. Discrimination was estimated by the ability to differentiate in a statistically significant manner the high score group (percentile equal or >73) and the low score group (percentile equal or <27) in the sum score of the 21 items. A mean difference higher than two was considered to be significant, as well as a reliable discriminant property for each one of the assessed items. The internal consistency of the items was estimated by means of corrected correlation, estimation of Cronbach's alpha excluding the item, and communalities. It was sought that the corrected correlation values were >0.30, that a non-decrease value of Cronbach's coefficient alpha after eliminating the item could demonstrate a reliable internal consistency, and that the communalities values were >0.20. Consistency was interpreted as high when it expressed a value equal or >0.70. The distribution fitting to a normal curve was contrasted using Kolmogorov–Smirnov test or Shapiro–Wilk test (34). All data were analyzed with SPSS® software (version 20.0).

The dimensional structure was studied by means of exploratory factor analysis; considering appropriate factoring characteristics: (a) that the

determinant of the correlation matrix would tend to 0 ($|R| < 0.01$), (b) KMO > 0.6, and (c) that the null hypothesis of equivalence of the correlation matrix to an identity matrix by Bartlett's sphericity test would be rejected (34). The extraction was executed by generalized least squares (GLS) and the Promax rotation method of the factor matrix, adjusting the solution to four factors in agreement with the structure found in other studies [96,113].

The correlations between factors were calculated by Pearson's correlation coefficient. The correlations between the HSS-21 scores and the EDZ-10 and RSS-10 scores were established by Spearman's rho. The significance of the score difference in the scales ZDS-10 and RSS-10 among the respondents who expressed or did not expressed HARS was carried out by the Mann–Whitney U test. The effect size was calculated by Cohen's d [117].

Results

Respondents

The 75 HIV-positive MSM respondents had an average age of 35 (SD = 7.38) years old. Median time since HIV infection diagnosis was 18 months. Average years in school was 13.93 (SD = 3.73) years. At the time of the survey, 81.9% of men were working full time, while 10.6% worked part-time, and 7.4% were unemployed. Moreover, despite employment status, 69.2% indicated that they received a monthly income of ≤15,000 MXN ($ 1.146/867.45 €). Regarding sexual orientation, 88% of participants defined themselves as homosexual, 9.23% as bisexual, and 2.67% as heterosexual.

HSS-21' descriptive statistics

The HSS-21 mean total score was 76.28 (SD = 21.522), and its distribution was fitted to a normal curve (ZK-S = 0.67, p = 0.20). Considering the whole scale items, its mean can be transformed into a continued value between 1 and 7 or equal to 3.63. Using the same procedure, most items means scores were also between 2.5 and 4. However, eight items (V2, V6, V11, V12, V14, V15, and V17) had a mean value ≥4 (Table 1).

Discrimination, internal consistency, and validity of HSS-21 items

HSS-21 presented a high internal consistency (α = 0.88). Items expressed reliable internal consistency values since deletion of none of them increased Cronbach's alpha coefficient. Items' corrected correlations ranged from 0.32 to 0.68 (except item V12, whose corrected correlation was 0.06). Initial communalities varied between 0.44 and 0.77, except for item V12 (MD = 0.05). Thus, with the exception of item V12, the remaining 20 items had reliable psychometric properties (Table 1).

HSS-21' dimensional structure

The correlation matrix of the 21 items of the HSS-21 scale showed adequate properties for factor extraction. Its determinant tended to 0 ($|R| < 0.01$), the KMO index was >0.6 (KMO = 0.777), and the null hypothesis of equivalence of the correlation matrix to an identity matrix by Bartlett's sphericity test was rejected [$\chi 2$ (210, N = 75) = 752.413, $p < 0.001$]. Four components were extracted, which accounted for 60.51% of the total variance.

After rotating the factor component matrix by the Promax method and performing the extraction by GLS, four factors were found with a high internal consistency; they were constituted by positive indicators and factor loadings >0.32 (Table 2). The first factor (self-stigma, VNS) integrated by six items (V1, V4, V7, V8, V10, and V16) related to feelings of not being as good as others and emotion of guilt or shame (α = 0.81). The second factor (acted stigma, VES) integrated by five items (items V13, V18, V19, V20, and V21) related to the consequences of others finding out the individuals' serodiagnosis and personal experiences of rejection (α = 0.83). The third factor (concern about public attitude toward HIV and AIDS, VPA) integrated by five items (V5, V6, V9, V11, and V14) related to what PLWH believe that other people could think of them if they knew their serostatus (α = 0.83). The fourth factor (PLWH concern about HIV serodiagnosis disclosure, VDC) integrated by five items (V2, V3, V12, V15, and V17) related to the perceived need of controlling HIV serodiagnosis information (α = 0.76). Item 21 had a high factor loading in two factors. Nevertheless, including it in the second factor increased its internal consistency from 0.80 to 0.83, due to its content item 21 is highly related to acted stigma. The correlations

between factors were medium (r = 0.32–0.46), with the exception of the correlation between factors 3 and 4, which was small (r = 0.21).

HSS-21 factors' descriptive statistics

The score range for all items is from 1 to 7, and the higher score results are correlated to a high stigma. Considering the number of items in each of the four factors, their mean can be transformed into a continuous value within 1 and 7. Such value can be interpreted as the answer label for each item, dividing the answer range value by four intervals of constant amplitude. Table3 exposes factor descriptive statistics.

HSS-21 factors' descriptive statistics.

The mean of VNS can be interpreted as a non-definitive disagreement with HARS dimension. Means comparison among the 36 (48%) respondents who expressed stigma [M = 5.04, SD = 0.59; 95% IC = (4.85, 5.24)] and the 39 (52%) respondents who did not express stigma [M = 3.02, SD = 0.74; 95% IC = (2.78, 3.26)] were statistically significant (p < 0.01).

Also, VES mean can be interpreted as a non-definitive disagreement with HARS dimension. The comparison of means among the 23 (30.7%) respondents who expressed stigma [M = 4.96, DE = 0.69; 95% IC = (4.66, 5.26)] and the 52 (69.3%) respondents who did not express stigma [M = 2.34, SD = 0.91; 95% IC = (2.09, 2.60)] was statistically significant (p < 0.01).

The VPA mean can be interpreted as a non-definitive disagreement with HARS dimension. The comparison of means among the 40 (53.3%) respondents who expressed stigma [M = 4.99, DE = 0.65; 95% IC = (4.78, 5.20)] and the 35 (36.7%) respondents who did not express stigma [M = 2.74, SD = 0.75; 95% IC = (2.48, 3.00)] was statistically significant (p < 0.01).

Likewise, VDC mean can be interpreted as a non-definitive disagreement with HARS dimension. Means comparison among the 51 (68%) respondents who expressed stigma [M = 5.59, DE = 0.94; 95% IC = (5.32, 5.85)] and the 24 (32%)

respondents who did not express stigma [M = 3.10, SD = 0.74; 95% IC = (2.79, 3.41)] were statistically significant ($p < 0.01$).

ZDS-10 descriptive statistics

ZDS-10 scale had an average score of 20.48 (SD = 4.82) with a non-normal distribution curve (ZK-S = 0.11, p = 0.02). Likewise, scores among the 48 respondents who did not express stigma showed a non-normal distribution curve (ZS-W = 0.93, p = 0.01). Whereas, distribution among the 27 respondents who expressed stigma was adjusted to a normal curve (ZS-W = 0.95, p = 0.17).

After running the Mann–Whitney U test, it was found that the respondents with HARS had significantly higher scores in ZDS-10 [M = 22.41, SD = 4.40, n = 27; 95% IC (20.67, 24.15)] than the scores of the respondents without HARS [M = 19.40, SD = 4.74, n = 48; 95% IC (18.02, 20.77)], with a medium size effect of stigma on the total ZDS-10 score; Z = −2.37, $p < 0.02$, d = 0.65, 95% IC (0.16, 1.13).

Of the 48 HIV-positive MSM respondents who did not express HARS, 14 (29.17%) presented clinically significant symptoms of depression, while 34 (70.83%) did not show such symptoms. Of the 27 respondents who expressed HARS, 16 (59.26%) showed clinically significant symptoms of depression, while 11 (40.74%) did not show such symptoms.

RSS-10 descriptive statistics

The mean in the total score of the RSS-10 was 34.43 (SD = 4.78) with a non-normal distribution curve (ZK-S = 0.20, $p < 0.0.001$). Similarly, the distribution of the scores between the respondents who did not express stigma (ZS-W = 0.87, p = 0.001) and those who did express stigma (ZS-W = 0.88, p = 0.007) presented a non-normal distribution curve.

After running the Mann–Whitney U test, it was found that the HIV-positive MSM respondents who did not express HARS had significantly higher RSS-10 scores [M = 35.53, SD = 3.62, 95% IC (34.50, 36.60)] than those of the respondents who did express HARS [M = 32.48, SD = 5.93, 95% IC (30.14,

34.83)], with a medium size effect of stigma on the total RSS-10 score; $Z = -2.26$, $p < 0.03$, $d = -0–67$, 95% IC (−1.14, −0.18).

Of the 48 respondents who did not express HARS, one (2%) respondent presented a low self-esteem, and 47 (98%) presented a high self-esteem. Of the 27 respondents who expresses HARS, six (22.2%) respondents presented a low self-esteem, and 16 (77.8%) presented a high self-esteem.

Validity evidences

The total HSS-21 score expressed convergent validity with a significant and direct correlation to the ZDS-10 total score. The factors that expressed a high correlation were VNS ($\rho = 0.336$, $p < 0.001$) and VES ($\rho = 0.252$, $p < 0.01$). Also, the total HSS-21 score demonstrated discriminant validity with significant and reverse correlation to RSS-10 total score. HSS-21 factors showed correlations from small (VNS, VDC, and VES) to trivial (VPA) with the RSS-10, but did not reach a statistical significance.

Discussion

Stigma can be conceptualized as a deeply degrading attribute that binds an individual with one or more undesirable characteristics and finally diminish socially his/her self-image. Concern about stigma is widely extended among PLWH, although this is not universal [118]. The results of the study determined that the Spanish-adapted version of the HSS-21 scale developed by Franke et al. [113] has good overall internal consistency, reliability, and psychometric characteristics among the subpopulation studied (HIV-positive MSM).

From the HSS-21 total scores, more than half (64%) of the HIV-positive MSM respondents did not express HARS. However, VDC factor scores showed that 68% of the respondents perceived HARS. The HSS-21 score had a significant and direct correlation with the ZDS-10 total score, showing evidence of convergent validity. Likewise, it also presented a significant and reverse correlation with the RSS-10 total score, demonstrating evidence of discriminant validity. The respondents who perceive HARS had significantly higher scores

($p < 0.02$) in ZDS-10 and significantly lower scores ($p < 0.03$) in RSS-10 than the respondents who do not perceive HARS.

There are only a small number of published studies on interventions and programs designed to reduce HARS. Given the difficulties in defining and measuring stigma, few such interventions and programs described in the literature have been rigorously evaluated in developing countries [16,105]. One of the limitations of this study – typically found in other HIV-related studies – is the fact that it was conducted with a small and convenience sample. For this reason, the study does not offer sufficient data to assess the true meaning of the stigma scores of the scale, and herein reported results and derived conclusions should be considered as hypothetical for similar social groups, which limits the ability to apply it to the general PLWH population, or to draw conclusions about the impact of perceptions of HARS in México. Moreover, HARS data were obtained through a self-reported evaluation and therefore they can be different from those obtained through an interview, projective tests, or psychophysiological tests, etc. Also, sexual orientation, gender identity, social, economic, and cultural differences need to be assessed. Nevertheless, the findings can serve as the basis for HARS measurement research with Spanish-speaking populations in México and other countries.

To improve our understanding of HARS, it is necessary to focus on a series of distinguishable variables across different societies. Implementing HARS evaluation in PLWH is important, as it can lead to identifying clinically significant symptoms of depression which could have a negative influence on treatment adherence [99–101], it could also limit the use of public health services [119,120], and limit social support seeking due to fear of rejection [121,122]. Identifying perceived stigma among PLWH through a short, reliable, and validated instrument provides data that will help governments make efficient and effective use of resources spent on stigma and discrimination reduction as well as the opportunity to develop public health interventions that help PLWH to cope and manage stigma. The implementation and evaluation of these strategies will benefit from the availability of a widely validated and user-friendly psychometric instruments to assess the HARS.

This study was the first to use the Spanish-adapted version of the HSS-21 scale in HIV-positive MSM in México, and the findings help move from evaluating HARS to implementing reduction interventions to mitigate the impact of HARS and promote empowerment among HIV-positive men and to enhance the sexual health of gay and bisexual men through a community-based process involving the MEMUREVIH (program developed by a consortium of members who represent four sectors: academia, government, key population, non-governmental and community-based organizations in Nuevo León state). Through study results, the MEMUREVIH intervention aimed to diminish HARS, create greater support for HIV-positive men, make disclosure safer and easier, discourage reliance on disclosure on preventing HIV transmission and encouraging testing. The contact hypothesis suggests that facilitating social interaction between PLWH and others (e.g., healthcare providers, friends, family, co-workers, etc.) may help to reduce prejudice, stereotypes, and discrimination among others via the mechanisms of increased knowledge of HIV, reduced social anxiety regarding PLWH, and increased empathy toward PLWH [123]. The corresponding author is currently working on MEMUREVIH intervention data.

As HARS places people at a substantial social disadvantage, it increases their exposure to risks and limits access to protective factors, potentially adding to their burden of disease or disability. Stigma not only predisposes PLWH to greater HARS and discrimination but also critically reinforces stereotyping and status loss of all them, regardless of how they may have acquired the infection. In such manner, underestimating the insidious power of stigma jeopardizes the success of public health programs aimed to prevent, timely detect, and treat HIV and AIDS. HSS-21 scale distinguishes different dimensions of stigma and contributes to better understand HARS impact in public health-related issues. Furthermore, the intention is also to encourage researchers to consider additional ways to reduce stigma and discrimination, acknowledging and addressing HARS challenges with research methodology; thereby, creating a sense of timeliness and urgency for the development and testing of HARS, and thus, contributing to discrimination reduction efforts. It is only with stronger, more nuanced understandings of HARS that we will be able to break the associations between

HIV stigma and indicators of poor affective, behavioral, and physical health and well-being among PLWH within interventions.

Tables

Table 1, Article 2. *Descriptive statistics, interpretation, homoscedasticity, discrimination, and internal consistency of the items*

Item	*Descriptive statistics*						*K-S*			*Homoscedasticity*		*Discrimination*				*Consistency*		
	M	*Mdn*	*Mo*	*SD*	*Sk*	*K*	Z	*p*	I	*F*	*p*	*MD*	*t*	*df*	*p*	$r_{i,t\text{-}i}$	$\alpha_{t\text{-}i}$	*hi*
V1	2.95	3	1	2.18	0.63	-1.03	0.29	.00	2	1.67	.20	2.7	-4.75	38	.00	.48	.88	.62
V2	4.73	5	5	1.84	-0.69	-0.17	0.30	.00	3	18.10	.00	2.5	-4.54	26.66	.00	.52	.87	.70
V3	3.85	3	3	2.23	0.16	-1.33	0.21	.00	2	0.79	.38	2.6	-3.86	38.00	.00	.38	.88	.70
V4	2.73	3	1	1.95	0.81	-0.47	0.28	.00	2	2.10	.15	2.2	-4.41	38.00	.00	.36	.88	.44
V5	3.21	3	1*	1.96	0.14	-1.36	0.25	.00	2	0.05	.82	2.4	-4.22	38.00	.00	.43	.88	.56
V6	4.07	5	5	1.65	-0.55	-0.39	0.33	.00	3	3.63	.06	2.6	-5.81	38.00	.00	.55	.87	.74
V7	2.52	1	1	1.83	0.83	-0.50	0.32	.00	2	9.62	.00	2.6	-5.64	30.76	.00	.56	.87	.71
V8	2.20	1	1	1.68	1.16	0.28	0.36	.00	1	12.10	.00	2.5	-5.54	29.67	.00	.55	.87	.62
V9	3.53	3	5	1.72	-0.16	-9.98	0.26	.00	2	0.21	.65	2.3	-5.04	38.00	.00	.40	.88	.64
V10	1.99	1	1	1.48	1.35	0.97	0.39	.00	1	20.14	.00	2.3	-5.68	23.89	.00	.56	.87	.68
V11	4.44	5	5	1.70	-0.52	-0.16	0.31	.00	3	8.37	.00	2.5	-5.15	32.44	.00	.55	.87	.73
V12	6.31	7	7	1.21	-1.94	4.45	0.42	.00	4	3.35	.07	0.5	-1.12	38.00	.27	.06	.88	.65
V13	3.00	3	1	2.00	0.67	-0.23	0.23	.00	2	15.31	.00	2.5	-4.86	26.32	.00	.41	.88	.60

V14	4.44	5	5	1.56	-0.50	0.55	0.32	.00	3	0.02	.90	2.7	-6.76	38.00	.00	.58	.87	.59
V15	4.23	5	7	2.39	-0.28	-1.48	0.21	.00	3	9.30	.00	4.4	-8.63	25.59	.00	.68	.87	.76
V16	2.16	5	5*	2.16	0.33	-1.12	0.21	.00	1	6.81	.01	2.7	-4.34	32.67	.00	.44	.88	.64
V17	4.84	5	7	2.13	-0.53	-0.99	0.23	.00	3	6.73	.01	3.3	-5.96	28.57	.00	.63	.87	.67
V18	3.87	3	3	2.07	0.44	-0.95	0.23	.00	2	8.25	.00	2.2	-3.47	31.76	.00	.32	.88	.77
V19	2.97	3	3	1.72	0.55	-0.36	0.24	.00	2	2.25	.14	2.1	-4.58	38.00	.00	.38	.88	.74
V20	3.37	3	1	2.02	0.26	-1.10	0.20	.00	2	6.75	.01	2.9	-5.22	29.50	.00	.53	.87	.62
V21	3.03	3	3	1.82	0.64	-0.30	0.25	.00	2	9.76	.00	3.1	-6.94	27.84	.00	.64	.87	.73

Table 1. *M*: mean, *Mdn:* median, *Mo:* Mode, *SD:* standard deviation, *Sk:* skewness *K:* kurtosis, K-S: Kolmogorov-Smirnov test, *p:* probability, I: Interpretation, 1: Totally in disagreement, 2: In disagreement, 3: In agreement, 4: Totally in agreement, *MD:* Mean difference between the group with high scores and the group with low scores on the scale, *df*; degrees of freedom, $r_{i,t-i:}$ Correlation between the item and the scale, $\alpha_{t-i:}$ Cronbach's alpha coefficient after removing the item, *hi*: Communality

Table 2, Article 2. *Descriptive statistics of the score of the four factors of HSS-21 in the total sample*

	Item	*Factor*			
		1	2	3	4
V6	Most people believe a person who has HIV is dirty	.88			
V11	Most with HIV are rejected when others learn I have HIV	.77			
V9	Most people think a person with HIV is disgusting	.73			
V5	People with HIV are treated like despicable persons	.71			
V14	Most people are uncomfortable around someone with HIV	.59			
V21	People seem afraid of me because I have HIV	.53			.44
V7	Having HIV makes me feel unclean		.93		
V8	I feel set apart, isolated from the rest of the world		.71		
V10	Having HIV makes me feel I'm a bad person		.68		
V1	I feel guilty because I have HIV		.67		
V4	I feel I'm not as good as others because I have HIV		.36		
V16	Having HIV in my body is disgusting to me		.32		
V2	Telling someone, I have HIV is risky			.77	
V15	I worry that people may judge me when they learn I have HIV			.76	
V17	I worry people who know I have HIV will tell others			.69	
V3	I work hard to keep my HIV a secret			.65	
V12	I am very careful whom I tell that I have HIV		-.39	.50	
V18	I regret having told some people that I have HIV				.93
V19	As a rule, telling others has been a mistake				.92
V20	Some people act as though it's my fault I have HIV				.51
V13	Some people who know have grown more distant	.37			.48

Extraction method: GSL. Rotation method: Promax with Kaiser normalization.

Table 3, Article 2. *Descriptive statistics of the score of the four factors of HSS-21 in the total sample*

Factor	*Descriptive statistics*					*K-S*			*Interpretation*
	M	*Mdn*	*Mo*	*SD*	*Sk*	*K*	*Z*	*p*	
VNS	3.99	3.83	3.83	1.22	-0.17	-0.66	0.10	.07	In disagreement
VES	3.15	3	1	1.48	0.56	-0.40	0.10	.07	In disagreement
VPA	3.94	4.2	5	1.33	-0.22	-0.71	0.18	.01	In disagreement
VDC	4.79	4.6	4.6	1.46	.81	-.47	0.10	.07	In agreement

M: mean, *Mdn*: median, *Mo*: Mode, *SD*: standard deviation, *Sk*: skewness *K*: kurtosis, K-S: Kolmogorov-Smirnov test, *p*: probability, VNS: negative self-image, VES: enacted stigma, VPA: public attitude, VDC: disclosure concerns.

Published Article #3

Title. Dentistry and HIV/AIDS-related stigma

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Abstract

Objective

To analyze HIV/AIDS positive individual's perception and attitudes regarding dental services.

Methods

One hundred and thirty-four subjects (30.0% of women and 70.0% of men) from Nuevo León, México, took part in the study (2014). They filled out structured, analytical, self-administered, anonymous questionnaires. Besides the sociodemographic variables, the perception regarding public and private dental services and related professionals was evaluated, as well as the perceived stigma associated with HIV/AIDS, through a Likert-type scale. The statistical evaluation included a factorial and a non-hierarchical cluster analysis.

Results

Social inequalities were found regarding the search for public and private dental professionals and services. Most subjects reported omitting their HIV serodiagnosis and agreed that dentists must be trained and qualified to treat patients with HIV/AIDS. The factorial analysis revealed two elements: experiences of stigma and discrimination in dental appointments and feelings of concern regarding the attitudes of professionals or their teams concerning patients' HIV serodiagnosis. The cluster analysis identified three groups: users who have not experienced stigma or discrimination (85.0%); the ones who have not had those experiences but feel somewhat concerned (12.7%); and the ones who underwent stigma and discrimination and feel concerned (2.3%).

Conclusions

We observed a low percentage of stigma and discrimination in dental appointments; however, most HIV/AIDS patients do not reveal their serodiagnosis to dentists out of fear of being rejected. Such fact implies a workplace hazard to dental professionals, but especially to the very own health of HIV/AIDS patients, as dentists will not be able to provide them a proper clinical and pharmaceutical treatment.

Descriptors

HIV Long-Term Survivors. Dental Health Services. Health Knowledge, Attitudes, Practice. Prejudice. Social Discrimination. Health Inequalities. Psychometrics. México.

Main text

INTRODUCTION

HIV epidemic is about to reach its fourth decade. It is considered a relevant public health care problem worldwide, regardless of antiretroviral therapy advances, which has made of this infection a chronic illness. Life quality and expectancy rates of people living with HIV/AIDS (PLWHA) may be compared to those of the general population [124,125]. Nevertheless, social perception towards PLWHA remains a negative one [11,21]. Its transmission routes, its implications regarding the most traditional gender roles, and its association in the social imaginary to socially marginalized groups are the cause of stigma and discrimination at different levels [11,21].

Stigma is a degrading social evaluation or label that is attached to people that exhibit socially undesirable characteristics.[93] Stigmatization is the social process by which such evaluations or labels and the consequent negative emotional and behavioral responses are generated and sustained. Therefore, originating and shaping social exclusion [126].

Stigma is sustained by a complex set of factors difficult to address. An existing duality is observed between the social rejection and approval of attitudes and behaviors of people with certain characteristics. In addition, factors such as beliefs and the environment in which stigma is developed, impose the intensity of the rejection or the acceptance of individuals in a certain context [127].

HIV/AIDS-related stigma and discrimination have multiple consequences that affect HIV epidemic development and reinforce existing social inequalities, especially those related to gender roles, sexuality, and ethnicity. The stigma PLWHA go by is an obstacle in their access to health care services and their engagement into the “HIV continuum of care” [20–22].

Evidence-based scientific research shows PLWHA’s needs in oral health care, due to the high incidence of HIV-related oral problems that diminish their

quality of life [23,24]. This study intends to analyze HIV/AIDS positive individual's perception and attitudes towards the received oral health care.

METHODS

One hundred and thirty-four subjects (30.0% of women and 70.0% of men) from Nuevo León, México, took part in the study (2014). They filled out a written or online format questionnaire at the non-governmental and community-based organizations members of Nuevo Leon's Multisector Response Board to HIV, AIDS, and other sexually-transmitted infections (MEMUREIVH). A non-probabilistic and convenience sample including HIV-positive men and women was adopted.

The data collection process lasted 60 days. Prior to the data collection, collaboration was requested to the different non-governmental and community-based organizations members of the MEMUREIVH, to implement the survey in their office location and to their HIV/AIDS positive affiliates. Four properly qualified surveyors visited all sites and applied the written or on-line surveys on the previously agreed dates and time with the aforementioned organizations. There were no cancellations.

An analytical-type structured questionnaire was used (closed-ended questions and multiple response alternatives) in either written or online formats. Self-administered questionnaires have been shown to be proper methods to collect several data, since they are fully anonymous and, unlike interviews, do not involve a face-to-face confrontation, which could possibly lead to false answers.[128] The following topics were covered: sociodemographic characteristics, perception regarding public and private dental professionals and services, and that regarding the received HIV-related oral health care. Perception of HIV-AIDS-related stigma in the dental office was analyzed through a Likert-type scale.[129] Following the procedure recommended by Lynn,[62] a group of reviewers assessed how well the 11 items evaluated the concepts of stigma and discrimination in terms of their accuracy and relevance of both concepts. Such scale consisted of five alternatives that ranged from "never" to "very often."

A digital survey database was created and submitted to a double-quality control to assure reliability of information. The subjects accessed the survey website (www.encuestas.no-ip.org) to answer the online questionnaire. No log-in data (e.g., internet protocols) were stored in the electronic access. After the survey was completed (average of 25 minutes), and as a benefit to all participants, voluntarily, informed, and consented oral examination and oral prophylaxis were offered free by qualified, certified and sensitized dentists.

An exploratory factor analysis was performed to empirically synthesize the variables concerning the perception of HIV/AIDS-related stigma and discrimination. In this analysis, the inclusion of variables was conditioned by a matrix that validates the presence of marked correlations among all of them and ensures that their application is fitting. Items with no statistical significance were disregarded. The analytical criterion to determine the number of covered factors included the ones whose values were shown to have proper internal consistency index through Cronbach's alpha.[73] Principal components analysis was used to extract core factors. Prior to the extraction, Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity were used to assess the suitability of the respondent data for factor analysis. A Varimax rotation method with Kaiser Normalization was performed to facilitate the interpretation of the factor loadings. A k-means clustering procedure was performed after the factor analysis. Once those clusters had been outlined, each of the factors that were used in their differentiation was proven to be statistically significant by an analysis of variance (ANOVA).

All data were analyzed using SPSS software, version 20.0.

The study protocol was approved by the Ethics Committee at the Tecnologico de Monterrey (BIO-ELB-2012-01). Participants signed informed consent forms. The anonymity and confidentiality of written or electronic data were guaranteed.

RESULTS

The sample consisted of 134 PLWHA (30.0% of women and 70.0% of men). The mean age of women was 41.7 years (standard deviation [SD] = 10.9; range: 22 to 57 years). The median time of HIV diagnosis was five years. The average education level was 8.4 (SD = 4.1), and all female subjects reported being heterosexual. The mean age of male participants was 34.9 years (SD = 9; range: 22 to 57), and their median time of HIV diagnosis was two years. In regards to men's education levels, the average was 14 years (SD = 3.5), and most of them (88.4%) reported being homosexual (Table 4).

Forty percent of the women included reported working full time, and the remaining ones were unemployed. However, regardless of their job statuses, their monthly incomes exceeded the minimum wage in northeastern México (≤ 15,000 MXN or 1,146 USD) In the case of men, 81.9% of them reported working full time, whereas 10.6% reported working part-time and the remaining 7.4% were unemployed. Out of the total, 69.2% men earned a monthly income of ≤ 15,000 MXN (1,146 USD).

Out of all women, 44.7% reported having had dental appointments at least once a year. On the other hand, half of the men reported having them once a year and the remaining half reported having them two times or more a year. (Table 5).

In regards to the modalities of services, 39.5% of women used public dental services and 74.5% of men reported using private ones. Whilst 37.1% of women reported not knowing whether they received a general or specialist oral health care service, 40.4% of the men reported having the general one and 33.0%, the specialist oral health service.

The main reasons the women pointed out for choosing a certain dentist were their professional knowledge (32.4%) and good chairside manner (18.9%). Conversely, most men (29.8%) based their choices on the professionals' length of experience, followed by their knowledge (26.6%).

Regarding the women, 72.5% of them reported they considered the dental offices they went to as being neither safe, clean, nor complying with infection control rules required by health care authorities. The perception from most men (91.5%) regarding their elected offices was another one entirely. Besides that, 84.6% of the women and 91.5% of the men considered that dentist have to be specifically trained to deal with PLWHA (Table 6).

In 58.3% of the cases involving women and in 68.1% of cases involving men, dentists were said to be reliable concerning the confidentiality of the information in their dental records. However, only 48.7% of the women and 30.9% of the men reported disclosing their HIV serodiagnosis to dental professionals. Despite PLWHA (61.5% of the women and 78.7% of the men) considered it was important that their dentists were aware of their HIV-positive condition, they did not disclose it, since they (63.5% of women and 68.1% of men) were concerned they would be denied oral health care or that inconveniences would arise during dental appointment (in this last case, 62.5% of women and 43.6% of men). In turn, 65.0% of the women and 70.3% of the men believed they were entitled to keep from disclosing their HIV/AIDS serodiagnosis to their dentists. (Table 6).

Most women (54.1%) considered that their dentists do not take professional ethics into account, and that is why they thought they would not receive the same care a non-HIV patient would receive. Such perception regarding the dental professionals ran contrary to the women by most men (80.9%).

Most PLWHA (66.7% of women and 54.3% of men) do not believe HIV can be transmitted in dental office environments; 85.0% of the women and 83.0% of the men do not believe the dental professionals can transmit the virus to their patients, or vice versa (74.4% of women and 53.2% of men) during appointments. Most PLWHA (77.5% of the women and 79.7% of the men) does not believe they can transmit HIV to other people going to the same office or clinic. The same way, 61.5% of the women and 77.7% of the men do not find it necessary for them to go to specific dental offices or clinics due to their HIV-positive status.

In spite of most PLWHA (71.8% of the women and 42.6% of the men) considering they have good oral and dental health, they do not believe (61.5% of the women and 60.7% of the men) they can come down with a secondary infection during or after dental care, due to the fact they are infected with HIV. Nonetheless, they stated (87.5% of the women and 67.0% of the men) that their general state of health could be affected by the lack of dental care if they will suffer from any HIV-related oral manifestations.

Most PLWHA (69.4% of the women and 84.0% of the men) reported never having experienced any discrimination from dentists, nor that dental professionals had denied them care due to their HIV-positive status (79.5% of the women and 90.4% of the men). Most subjects (76.9% of the women and 83.0% of the men) were never given excuses to denied their oral health care service, nor did most of them (69.2% of the women and 86.2% of the men) had their oral care purposefully delayed due to their PLWHA condition, as compared to the other patients. (Table 7).

Most subjects (81.6% of the women and 83.0% of the men) never felt being the target of whispers, glances, or laughter during their dental appointments. The majority of them (81.6% of the women and 88.2% of the men) have never received negative opinions about their lifestyles or sexual behaviors either, nor have they been belittled by their dentists or by their staff (74.4% of the women and 87.2% of the men).

Among the subjects, 78.4% of the women and 89.4% of the men reported that never had noticed that dentists or their staff avoided direct contact with them, neither have most of them (74.4% of the women and 87.2% of the men) noticed fear or insecurity by dental professionals during their appointments. Finally, 76.3% of the women and 88.3% of the men reported never having heard any request to discard materials used in their appointments under the argument that they are highly risky patients due to HIV.

The 11 items have shown evidence of proper internal consistency,[73] as none of them were discarded. A Cronbach’s alpha of 0.942 was obtained. The

first factor consisted of variables related to stigma and discrimination experiences perceived by participants during dental appointments; the second one, for variables related to participants' concern towards dentists or their staff attitudes regarding their HIV serodiagnosis. After factor analysis, a non-hierarchical clustering analysis was conducted. The first group included subjects identified as "users who have not experienced HIV-related stigma and discrimination in dental appointments" (85.0%). The second group was characterized by a group of subjects referred to as "users who have not experienced stigma and discrimination, but feel slightly concerned about dentists or their staffs' reaction if they knew about their HIV-positive status" (12.7%). The third group comprised "users who had experienced stigma and discrimination, and feel concerned about dentists or their staffs' reaction if they knew about their HIV-positive status" (2.3%). (Table 8).

DISCUSSION

Most PLWHA went to a dental office once or more times a year in search of oral health care, as they recognize that oral diseases affect their overall state of health. The socioeconomic and education-related determinants revealed social inequalities in HIV care.[130] The women who took part in this study tended to seek general and public dental health care services, whereas male participants in this study, as they were observed to have a higher income, tended to seek for dental private and specialized services.

Even though, men and women agreed that (i) dentists must be qualified to treat PLWHA; (ii) it is important to inform dental professionals about one's HIV-positive diagnose; and (iii) that dentists are believed to keep their patient's dental record information confidential. In the end, both men and women decline to disclose their HIV-positive status to dental professionals. Stigma is a social process or personal experience which influences all aspects in one's life. Thus, the HIV/AIDS diagnose is omitted by people suffering from it, in order to avoid being excluded socially. That is what Goffman calls "concealment."[93]

Similar to what was shown globally in other studies[131–133] with different population groups affected by HIV/AIDS pandemic, among the main reasons why

PLWHA do not disclose their HIV status to dentists are fear of being shunned, inconveniences that may arise in the dentist-patient relationship, and one's right not to disclose their diagnose.

One of the limitations of this study – typically found in other HIV-related studies – is the fact that it was conducted with a small sample, as most patients do not disclose their HIV-positive status.[132] Nonetheless, the obtained results provide an overview of opinions and problems that PLWHA have undergone concerning their dentists.

Although the results of this study have shown a low percentage of perceived stigma and discrimination in dental appointments, most PLWHA reported (through their answers to the questionnaire) not disclosing their HIV status to dental professionals, whether because of previous experiences of stigma and discrimination these people were submitted to in other situations or due to their social collective identity within a given context. Such omission may lead to workplace hazards for dentists and their staff, not only in the case of HIV transmission (and the provision of post-exposure prophylaxis) but also in the case of infection with other blood-borne pathogens, such as hepatitis B and C viruses.[134,135] Likewise, such fact jeopardizes the very health of PLWHA, as dental professionals will not be able to provide proper clinical care,[136] and might prescribe a drug that could enhance or antagonize with antiretroviral therapy.[137–139]

According to the Global Report 2013 of the Joint United Nations Programme on HIV/AIDS, 61.0% of the countries reported the existence of laws against discrimination that protect PLWHA. In México – based on the provisions of the first article of its federal constitution and on the first article, second paragraph, section II of the federal law for preventing and eliminating discrimination – it is illegal to stigmatize and deny rights that are afforded to all other citizens. Consequently, denying oral health care to PLWHA and other patients with infectious diseases is considered to be discrimination, as it violates the Universal Declaration of Human Rights, such as the right to adequate health.

Nonetheless, the lack of accessible legal services leads to the frequent neglect of many HIV-related discrimination cases.

Both realities (individuals who chose not to disclose their HIV status and dental professionals who deny care to people with infectious diseases) do not ensure that dental professionals or their patients avoid being exposed to HIV and other pathogens, as individuals living with HIV or other infectious diseases may not be aware of being infected. For that reason, dentists and all health care professionals are responsible for and ethically bound to seek training concerning the treatment of HIV and other diseases in its category. They also have to keep up-to-date regarding gender studies, diversity, and human rights, to keep high professional standards and to ensure all patients are provided dignified and egalitarian care.

Tables

Table 4, Article 3. *Sociodemographic characteristics of the subjects. Nuevo León, México, 2014.*

Variable	Women			Men			
	Mean	SD	Median	Mean	SD	Median	p[a]
Age (years)	41.7	10.9	41[b]	34.9	8	34[b]	< 0.0001
HIV (years of diagnose)	6.10	5.51	5[d]	3.19	4.18	2[d]	< 0.001
Education level (years of schooling)	8.4	4.1	9[b]	14	3.5	15[b]	< 0.0001
Sexual orientation	n		%	n		%	
Homosexual	0		0	83		88.3[b,c]	< 0.0001
Bisexual	0		0	9		9.6	
Heterosexual	40		100[b,c]	2		2.2	
Workload							
Full-time	16		40.0	77		81.9[b,c]	< 0.0001
Part-time	0			10		10.6	
Does not work	24		60.0[b,c]	7		7.4	
Monthly income							
≤ 15,000 MXN (1,146 USD)	40		100[c]	65		69.2[b,c]	< 0.0001
≤ 30,000 MXN (2,292 USD)	0		0	22		23.4	
≤ 30,000 MXN (2,292 USD)	0		0	7		7.5	

[a] Through ANOVA.

[b] ($p < 0.001$) intergroups

[c] ($p < 0.001$) intragroups

[d] ($p < 0.001$) intergroups

Table 5, Article 3. *Perception regarding private and public oral health care professionals and services. Nuevo León, México, 2014.*

Variable	Women		Men		
	n	%	n	%	p[a]
How many times a year do you have dental appointments?					
None	11	28.9	0	0	
Once a year	17	44.7[c]	47	50.0	< 0.001
Twice or more a year	10	26.3	47	50.0	
Do you have appointments in public or in a private dental office?					
None	11	28.9	0	0	
Public	15	39.5[b]	24	25.5	
Private	12	31.6	70	74.5[b,c]	< 0.001
Do you have appointments with a general or with a specialty dentist?					
None	2	5.7	0	0	
I do not know	13	37.1[b]	25	26.6	
General	11	31.4	38	40.4[b,c]	< 0.001
Specialty	9	25.7	31	33.0	
Among the following options, which is the most similar to the main reason why you select a certain dentist?					
Knowledge	12	32.4[b,c]	25	26.6	
Experience	5	13.5	28	29.8[b,c]	< 0.001
Formality	3	8.1	6	6.4	
Price	5	13.5	11	11.7	
Good chairside manner	7	18.9	7	7.4	
Office appearance	1	2.7	6	6.4	
Office hygiene	2	5.4	8	8.5	
Dentist's personal appearance	2	5.4	3	3.2	

[a] Through ANOVA.

[b] ($p < 0.001$) intergroups.

[c] ($p < 0.001$) intragroups.

Table 6, Article 3. *Perception regarding HIV care in dental appointments. Nuevo León, México, 2014.*

Variable	Women		Men		
	n	%	n	%	p[a]
Is the dental office you have appointments in safe, clean, and complying with infection control regulations?					
Yes	11	27.5	86	91.5[b,c]	< 0.001
No	29	72.5[b,c]	8	8.5	
Do you trust your dentist to keep the confidentiality of the information in your dental record?					
Yes	21	58.3[c]	64	68.1[c]	< 0.001
No	15	41.7	29	30.9	
Do you believe it is important that your dentist is qualified to treat HIV patients?					
Yes	33	84.6[c]	86	91.5[c]	< 0.001
No	6	15.4	8	8.5	
Have you informed your dentist of your HIV status?					
Yes	19	48.7	29	30.9	
No	20	51.3	65	69.2[c]	< 0.001
Do you think it is important that you tell your dentist you live with HIV?					
Yes	24	61.5[c]	74	78.7[c]	< 0.001
No	15	38.5	20	21.3	
I have a right not to disclose my HIV status, and that is why I do not tell it to my dentist:					
Yes	26	65.0[b]	66	70.3[c]	< 0.001
No	14	35.0	28	29.8	
I am afraid to be denied dental care, and that is why I do not tell my dentist I live with HIV:					
Yes	25	62.5[c]	64	68.1[c]	< 0.001
No	15	37.5	30	31.9	
I am afraid of the inconveniences that may arise in dental care, and that is why I do not tell my dentist I have HIV:					
Yes	25	62.5[b,c]	41	43.6	< 0.001
No	15	37.5	53	56.4[b,c]	
Do you think dentists, in general, are health care professionals who follow ethical principles, and because of that, they treat you like any other patient, regardless of whether you are HIV positive or not?					
Yes	16	43.2	76	80.9[b,c]	< 0.001
No	20	54.1[b]	18	19.1	
I do not know	1	2.7	0	0	
Do you believe HIV/AIDS can be transmitted in dental offices?					
Yes	13	33.3	42	44.7	
No	26	66.7[b]	51	54.3[c]	< 0.001
I do not know	0	0	0	0	

Do you believe your dentist may transmit HIV?					
Yes	5	12.5	16	17.0	
No	34	85.0[c]	78	83.0[c]	< 0.001
I do not know	1	2.5	0		
Do you believe you can transmit HIV to your dentist?					
Yes	10	25.6	31	33.0	
No	29	74.4[c]	50	53.2[c]	< 0.001
I do not know	0	0	13	13.8	
Do you believe you can transmit HIV to other people going to the same dental office or clinic?					
Yes	9	22.5	18	19.1	
No	31	77.5[c]	75	79.7[c]	< 0.001
I do not know	0	0	0	0	
Do you believe you can catch a secondary infection during or after being treated in a dental office or clinic because you have HIV?					
Yes	13	33.3	37	39.4	
No	24	61.5[c]	57	60.7[c]	< 0.001
I do not know	2	5.1	0	0	
Do you believe people living with HIV must only seek care in dental offices or clinics which are exclusive to HIV patients?					
Yes	15	38.5	21	23.3	
No	24	61.5[c]	73	77.7[c]	< 0.001
I do not know	0	0	0	0	
Do you believe oral illnesses affect your general state of health?					
Yes	35	87.5[c]	63	67.0[c]	< 0.001
No	5	12.5	31	33.0	
I do not know	0	0	0	0	
How do you appraise your overall oral health?					
Excellent	8	20.5	6	6.4	
Good	28	71.8[c]	40	42.6[c]	< 0.001
Fair	1	2.6	36	38.3	
Poor	2	5.1	12	12.8	
I do not know	0	0	0	0	

HIV: human immunodeficiency virus

[a] Through ANOVA.

[b] ($p < 0.001$) intergroups.

[c] ($p < 0.001$) intragroups.

Table 7, Article 3. *Perception of the HIV/AIDS-related stigma and discrimination Nuevo León, México, 2014.*

Items		Never n (%)		Rarely n (%)		Occasionally n (%)		Often n (%)		Very often n (%)	
		W	M	W	M	W	M	W	M	W	M
a.	Have you ever been discriminated by a dentist because you live with HIV?	25 (69.4)	79 (84.0)	4 (11.1)	8 (8.5)	4 (11.1)	5 (5.3)	2 (5.6)	1 (1.1)	1 (2.8)	1 (1.1)
b.	Over the last 12 months, how often were you denied dental care for being HIV positive?	31 (79.5)	85 (90.4)	3 (7.7)	7 (7.4)	5 (12.8)	1 (1.1)	0	1 (1.1)	0	1 (1.1)
c.	When you go to a dental office or clinic, has anyone given you a reason for denying you dental care services cos you are HIV positive?	30 (76.9)	78 (83.0)	2 (5.1)	10 (10.6)	4 (10.3)	3 (3.2)	3 (7.7)	2 (2.1)	0	1 (1.1)
d.	When you go to a dental office or clinic, does it take you longer to be treated than other patients?	27 (69.2)	81 (86.2)	3 (7.7)	5 (5.3)	6 (15.4)	5 (5.3)	2 (5.1)	2 (2.1)	1 (2.6)	1 (1.1)
e.	When you go to a dental office or clinic, do you notice whispers, glances, or laughter towards you?	31 (81.6)	78 (83.0)	0	9 (9.6)	4 (10.5)	5 (5.3)	3 (7.9)	2 (2.1)	0	0
f.	Have you ever been made to fell blamed, undermined, or belittled for having HIV whilst being treated in a dental office or clinic?	31 (81.6)	83 (88.2)	1 (2.6)	4 (4.3)	3 (7.9)	5 (5.3)	1 (2.6)	0	2 (5.3)	2 (2.1)
g.	Have you ever been given negative opinions about your lifestyle or sexual behaviors whilst being treated in a dental office or clinic?	30 (78.9)	82 (87.2)	0	6 (6.4)	5 (13.2)	5 (5.3)	2 (5.3)	1 (1.1)	1 (2.6)	0
h.	Have you ever been treated with disdain, indifference, or criticism whilst being treated in a dental office or clinic?	29 (74.4)	82 (87.2)	3 (7.7)	6 (6.4)	4 (10.3)	6 (6.4)	1 (2.6)	0	2 (5.1)	0
i.	Has anyone ever avoided getting in contact with your skin whilst being treated in a dental office or clinic?	29 (78.4)	84 (89.4)	1 (2.7)	7 (7.4)	3 (8.1)	2 (2.1)	2 (5.4)	1 (1.1)	2 (5.4)	0
j.	Has anybody ever behaved in a way to display fear or insecurity at the time they had to dress wounds, apply sutures, injections, or other dental procedures during treatment in a dental office or clinic?	29 (74.4)	82 (87.2)	0	7 (7.4)	7 (17.9)	2 (2.1)	1 (2.6)	2 (2.1)	2 (5.1)	1 (1.1)
k.	Whilst being treated in a dental office or clinic, has anybody ever requested that the materials used in your treatment be discarded, based on the argument that your HIV-positive status offered a higher risk?	29 (76.3)	83 (88.3)	1 (2.6)	7 (7.4)	2 (5.3)	0	2 (5.3)	1 (1.1)	4 (10.5)	3 (3.2)

HIV: human immunodeficiency virus; W: women; M: men

Table 8, Article 3. *Factorial analysis of the perception of the HIV and AIDS- related stigma and discrimination in dental appointments. Nuevo León, México, 2014.*

Means and correlation matrix											
Items	Mean	1	2	3	4	5	6	7	8	9	10
a	0.338										
b	0.185	0.583									
c	0.308	0.661	0.589								
d	0.346	0.514	0.305	0.579							
e	0.323	0.574	0.462	0.658	0.663						
f	0.431	0.522	0.523	0.567	0.545	0.758					
g	0.285	0.540	0.484	0.541	0.596	0.822	0.713				
h	0.262	0.456	0.431	0.537	0.525	0.776	0.676	0.790			
i	0.238	0.516	0.432	0.554	0.541	0.803	0.741	0.802	0.880		
j	0.308	0.539	0.506	0.543	0.555	0.804	0.747	0.771	0.823	0.819	
k	0.308	0.529	0.405	0.469	0.491	0.470	0.613	0.472	0.495	0.472	0.636

Rotated component matrix			
Items	Factor 1. Non-personal disparagement experiences from dentists or their staff	Factor 2. Non-concern with dentists or their staffs' attitudes	Commonalities
a	0.286	0.821	0.756
b	0.207	0.785	0.659
c	0.368	0.768	0.725
d	0.552	0.458	0.514
e	0.822	0.402	0.838
f	0.719	0.456	0.726
g	0.834	0.337	0.809
h	0.890	0.239	0.849
i	0.891	0.271	0.868
j	0.831	0.378	0.833
k	0.422	0.569	0.502
Eigenvalues	7.049	1.030	

Percentage of explained variance	64.079	9.361

Distances between final cluster centers

Cluster	1. Users who have not experienced HIV-related stigma and discrimination in dental appointments.	2. Users who have not experienced stigma and discrimination, but feel slightly concerned about dentists or their staffs' reaction regarding their HIV+ serodiagnosis.	3. Users who have experienced HIV-related stigma and discrimination, and feel concerned about dentists and their staffs' reaction regarding their HIV+ serodiagnosis.
	85.0% (n = 114)	12.7% (n = 17)	2.3% (n = 3)
1		9.434	5,292*
2	9.434		4,394*
3	5.292	4.394	

Rotation method: Varimax with Kaiser Normalization. Kaiser-Meyer-Olkin measure of sampling adequacy: 0.904. Bartlett's sphericity test $p < 0.0001$; it converges to three iterations. Non-hierarchical clustering analysis (K-means Cluster).

* $p < 0.001$ through ANOVA.

Published Article #4

Title. [Men who have sex with men and human immunodeficiency virus testing in dental practice.] Article in Spanish language.

Authors

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Abstract

Objectives

Explore attitudes of men who have sex with men (MSM) towards the implementation of rapid HIV-1/2 testing in the dental practice, and evaluate MSM's perceptions of stigma and discrimination related to sexual orientation by dental care professionals.

Methods

Analytic structured questionnaire, self-administered and anonymously answered by 185 MSM in México. The survey included socio-demographic variables, MSM's perceptions towards public and private dental providers, and dental services. As well as their perception towards rapid HIV-1/2 testing in the dental practice. In addition, the perception of stigma and discrimination associated with sexual orientation was explored by designing a psychometric Likert-type scale. The statistical analysis included factor analysis and non-hierarchical cluster analysis.

Results

86.5% of the respondents expressed their willingness to take a rapid HIV-1/2 screening test during their dental visit. Nevertheless, 91.9% of them considered important that dental professionals must be well trained before applying any rapid HIV-1/2 tests. Factor analysis revealed two factors: experiences of sexual orientation stigma and discrimination in dental settings, and feelings of concern about the attitude of the dentist and dental staff towards sexual orientation. Based on these factors and cluster analysis, three user profiles were identified: users who have not experienced stigma and discrimination (90.3%); users who have not experienced stigma and discrimination, but feel a slight concern (8.1%), and users who have experienced some form of discrimination and feel concern (1.6%).

Conclusion

The dental practice may represent a potential location for rapid HIV-1/2 testing contributing in early HIV infection diagnosis.

Keywords

AIDS Serodiagnosis; HIV/AIDS prevention; Public Health Dentistry; Dental Staff; Men who have sex with men; Health promotion; Psychometrics; México.

Main text

Introducción

El virus de la inmunodeficiencia humana (VIH) sigue siendo uno de los más
graves problemas de salud pública en Latinoamérica y el Caribe.[140] El Centro Nacional para la Prevención y el Control del VIH y el Sida en México (CENSIDA) reportó que una de cada tres personas con VIH desconoce su estado serológico frente a la infección.[18,141] El índice de transmisión de las personas con VIH pero que aún no han sido diagnosticadas es de 6.6 transmisiones por 100 personas-año.[142]

Con el fin de lograr las metas de salud pública 90-90-90 del Programa Conjunto de las Naciones Unidas sobre el VIH y el Sida (ONUSIDA),[143] México y muchos países consideran prioritario que la prueba rápida para la detección de anticuerpos VIH-1/2 (PR-VIH) se ofrezca y realice en los centros de servicios médicos y en las instalaciones de las organizaciones comunitarias de la sociedad civil, a los adolescentes y adultos de 13 a 64 años al menos una vez a lo largo de sus vidas, a los que tienen factores de riesgo (ej. usuarios de drogas inyectables, hombres que tienen sexo con hombres, entre otros.) cada 3 a 6 meses, así como a las mujeres embarazadas, incluyendo las que se presentan en labor de parto y cuyo serodiagnóstico al VIH se desconozca.[144–147]

Por su parte, la declaración de Phucket promueve la integración de los odontólogos en la prevención, detección y atención del VIH.[148] Sin embargo, a pesar de que el VIH puede ser detectado mediante métodos no invasivos en el suero, plasma, sangre total o líquido crevicular-saliva,[145] los odontólogos aun hoy en día debaten no solo en México sino en el resto del mundo si deberían o no ofrecer la PR-VIH en la consulta privada y escuelas de odontología.[149–154]

Por contraste, se han realizado algunos estudios concernientes a la opinión de la población en general para la realización de la PR-VIH durante la consulta odontológica.[152,155–159] No obstante, nada en cuanto a conocer la opinión de los grupos considerados como de alto riesgo en la adquisición y

transmisión del VIH; tal es el caso de los hombres que tienen sexo con hombres (HSH), en donde las condiciones sociales generadas por el estigma y la discriminación asociados a la orientación sexual (EDAOS) favorecen que éstos incurran en conductas sexuales de riesgo, fomentando así una mayor incidencia en la adquisición y propagación del virus.[16–18,141]

Desde una perspectiva de salud pública, el EDAOS es un factor importante que obstaculiza a los HSH la divulgación de su orientación sexual y prácticas sexuales a los trabajadores de la salud,[160] por ende, obstruye el acceso a los servicios de salud y al modelo del "*Continuo del diagnóstico-atención del VIH*".[161,162] La investigación científica demuestra que más del 70% de los individuos que reportan comportamientos sexuales de alto riesgo y que nunca se han realizado un análisis de detección del VIH, han estado en contacto reciente con un proveedor de servicios odontológicos.[163] Por consiguiente, el objetivo principal del presente estudio fue analizar la percepción y las actitudes de los HSH hacia la implementación de la PR-VIH y del EDAOS en la consulta odontológica.

Método

Participantes y Reclutamiento

En este estudio transversal participaron 185 HSH. Como criterios de inclusión se tuvo en cuenta que los participantes fueran hombres mayores de 18 años que hubieran tenido relaciones sexuales - anal u oral - con otro hombre.
Los participantes fueron reclutados mediante la técnica de muestreo por cadena de referencia para el estudio de poblaciones de difícil acceso,[164] con la colaboración de las organizaciones no gubernamentales y de base comunitaria de HSH en Monterrey, México. La recogida de datos ocurrió durante 10 semanas de marzo a mayo del 2015 en un consultorio odontológico privado, de fácil acceso en el centro de la ciudad. Después de la encuesta (duración media de 25 min) a los HSH participantes se les ofreció como beneficio la realización de la PR-VIH en saliva (OraSure Technologies, Inc., Bethlehem, PA), así como una exploración y profilaxis oral de forma voluntaria, informada, consentida y gratuita, por 2 odontólogos capacitados, sensibilizados y certificados. No hubo pérdidas o rechazos.

Ética

El protocolo del estudio fue revisado y aprobado por los comités de ética e investigación del Tecnológico de Monterrey y de la Universitat Internacional de Catalunya. Los procedimientos del estudio se realizaron con el consentimiento por escrito de cada sujeto y de acuerdo con la Declaración de Helsinki.[61]

Instrumento

Se utilizó un cuestionario auto-administrado de tipo estructurado analítico (de pregunta cerrada y alternativas múltiples) mediante la recopilación de datos asistida por ordenador.[165] Los temas explorados fueron: características sociodemográficas, percepción hacia los prestadores y servicios odontológicos públicos y privados, y hacia realizar el diagnóstico del VIH-1/2 en la consulta odontológica. Consulte las Tablas 2 y 3 para las preguntas de la encuesta. Además, se exploró mediante el desarrollo de una escala psicométrica tipo Likert[129] siguiendo el procedimiento recomendado por Lynn,[62] la percepción del EDAOS en la consulta odontológica. Esta escala constó con cinco alternativas en gradiente, desde “nunca” hasta “muy a menudo”. Consulte la Tabla 4 para los ítems de la escala. En todo momento se garantizó el anonimato y la confidencialidad. No se almacenó ningún registro de datos (dirección y protocolo de internet, entre otros) en el acceso electrónico.

Análisis estadístico

Se analizaron los datos en el programa de análisis estadístico SPSS® versión 20.0. Se realizó análisis factorial exploratorio para sintetizar empíricamente las variables relacionadas con el EDAOS. La inclusión de las variables fue condicionada por la matriz de correlaciones que convalida la presencia de una notable correlación entre las mismas y garantiza la idoneidad de la aplicación de un análisis factorial. Ítems sin significación estadística no se incluyeron en el análisis factorial. Se conservaron los factores cuyos valores mostraran índices adecuados de consistencia interna mediante la estimación del coeficiente alfa de Cronbach.[73] El método de extracción de los factores fue el de los componentes principales. Se calculó la medida de adecuación muestral de Kaiser, Meyer y Olkin (KMO) y se realizó la prueba de esfericidad de Barlett para comprobar la conveniencia de este análisis. Se realizó una rotación por el

método Varimax con Kaiser para facilitar la interpretación de los resultados. Después del análisis factorial, se realizó un análisis de *clusters* no jerárquico (K-Means Cluster) para detectar el número óptimo de grupos y su composición a partir de la similaridad existente entre los casos. Una vez delimitados estos grupos o *clusters,* se comprobó que cada uno de los factores utilizados en la diferenciación de los grupos fuera estadísticamente significativo mediante el análisis de la varianza (ANOVA).

Resultados

La muestra estudio la conformaron 185 HSH. La mediana de edad de los encuestados fue de 34 años (rango intercuartílico [RQ=11]). La mediana de escolarización fue de 15 años (RQ=4). En relación a la orientación sexual la mayoría (86%) se definió como homosexual. No obstante, el 85,4% prefiere no expresar de manera abierta su orientación sexual. Por otra parte, solo el 76,8% de los participantes trabajan de tiempo completo. Sin embargo, independientemente de su situación laboral, recibían un ingreso económico mensual de ≤15.000 MXN (1.146 USD), (Tabla 9).

Percepción de servicios odontológicos

El 50,8% acudió a la consulta odontológica al menos una vez al año y el 49,2% restante asistió dos o más veces en un año. La mayoría (74,6%) asistía a los servicios odontológicos del sector privado. El 40,5% recibía atención odontológica general, mientras el 31,9% de especialidad. Entre las razones principales por la que los encuestados elegían un determinado odontólogo fueron la experiencia (30,8%) y los conocimientos (24,9%) de éste. (Tabla 10).

Percepción a la PR-VIH en la consulta odontológica

La mayor parte (91,9%), consideraba que el consultorio al que acudía era seguro, limpio y contaba con las normas de control de infección requeridas por las instancias de salud pública. El 69,2% creía en la confidencialidad del expediente odontológico y el 82,2% consideró que el odontólogo se rige por la ética profesional y por ende no discriminaría a sus usuarios, independientemente del resultado de la PR-VIH. Además, el 86,5% desearía que en el consultorio o clínica odontológica a la que acude se le ofreciera la PR-VIH de manera

voluntaria, mediante consejería, consentimiento informado y firmado. Sin embargo, el 91,9% creía que era necesario que el odontólogo estuviese capacitado y sensibilizado para realizar dicha prueba.

Entre los participantes el 48,1% indico que no se había realizado una PR-VIH (Tabla 11). Dos participantes resultaron reactivos (tasa de prevalencia de VIH sin detectar de 1,08%). Por otra parte, el 62,2% (n=115) de los HSH encuestados tuvo un familiar, amigo o pareja con VIH, a su vez, el 46,5% (n=86) comentó que esta persona falleció a causa de alguna enfermedad o padecimiento asociado al virus. La asociación entre ambas variables de riesgo relativo (RR) e intervalo de confianza del 95% (IC) de muerte por el VIH fue RR 3,9; 95% IC 2,17-7,01.

Precepción del EDAOS en la consulta odontológica

El 90,3% señaló que nunca ha experimentado alguna situación de discriminación por parte de algún odontólogo. Tampoco el odontólogo le ha negado la atención odontológica debido a su orientación sexual (93,5%). A la mayoría (86,9%) nunca le han dado excusas para negarle la atención, ni tampoco a la mayor parte (83,2%) nunca le han demorado el servicio odontológico por su orientación sexual, con relación al resto de los usuarios. Finalmente, el 74,6% de los HSH encuestados nunca se han sentido discriminados por la forma en la que expresan su orientación sexual (Tabla 12).

En relación a la evaluación estadística de la escala psicométrica del EDAOS en la consulta odontológica, los 11 ítems mostraron índices adecuados de consistencia interna (alfa de Cronbach de 0,938),[73] por lo que ninguno fue eliminado. El determinante de la matriz de correlaciones tendió a cero ($|R|<0,01$), el índice KMO fue 0,885 y se rechazó la hipótesis nula de equivalencia de la matriz de correlaciones a una matriz identidad por la prueba de esfericidad de Bartlett ($p < 0.001$). Tras rotar la matriz de componentes factoriales por el método Varimax con Kaiser se extrajeron dos componentes, los cuales explicaron el 73,24% de la varianza total. El primer factor estuvo compuesto por aquellas variables relacionadas con las experiencias de estigma y discriminación percibidas por los usuarios en la consulta odontológica; y el

segundo, por aquellas relacionadas con la preocupación de los usuarios por la actitud del odontólogo o su personal hacia su orientación sexual (Tabla 13).

Tras el análisis factorial se realizó un análisis de clusters no jerárquico. En el primer grupo se identificó a los individuos como “usuarios que no han experimentado estigma ni discriminación en la consulta odontológica” (90,3%). El segundo grupo se caracterizó por el conglomerado de individuos denominados “usuarios que no han experimentado estigma ni discriminación, pero sienten una ligera preocupación hacia la reacción del odontólogo o su personal al enterarse de su orientación sexual” (8,1%). El tercer grupo se caracterizó como “usuarios que han experimentado algún tipo de estigma y discriminación, y sienten preocupación por la reacción del odontólogo o su personal al enterarse de su orientación sexual” (1,6%) (Tabla13).

Discusión

Esta investigación es la primera que ha evaluado en México la receptividad del colectivo HSH para la implementación de la PR-VIH en la consulta odontológica de manera voluntaria, informada y consentida. Además, es la primera en desarrollar y evaluar una escala psicométrica de la percepción del estigma y la discriminación asociados a la orientación sexual en la consulta odontológica. Al igual que en otras investigaciones,[149–152,154,159] nuestros resultados sugieren que la consulta odontológica podría ser una ubicación potencial para realizar la PR-VIH y un sitio favorable para realizar el diagnóstico temprano del VIH-1/2 en una de las poblaciones clave más afectadas por la pandemia del VIH.[163]

Aunque la composición sociodemográfica de nuestra población difiere de estudios anteriores, la alta tasa global (n= 160, 86,5%) de aceptación a la PR-VIH en la consulta odontológica es coherente con los resultados realizados por Durall et al. (71%),[155] Dietz et al. (73%),[159] VanDevanter et al. (74%),[156] Greenberg et al. (80%),[157] Nassry et al. (88%)[152] y Blackstock et al. (97%).[158] Sin embargo, a diferencia del presente estudio (n=185, 100%) solo algunas de estas investigaciones encuestaron a los HSH sobre la PR-VIH, Durall

et al. (n= 19, 5%),[155] Blackstock et al. (n=93, 2,6%)[158] y Dietz et al. (n=3, 12,5%).[159]

Es indispensable considerar que la mayor parte de las personas diagnosticadas con VIH cada año son HSH y que una tercera parte de las nuevas infecciones se les atribuye a quienes desconocían que estaban infectados.[16–18,141] El 48,1% de los HSH encuestados en el presente estudio respondió que no se había realizado la PR-VIH, lo que significa que desconocían su diagnóstico serológico frente al VIH. Aunado a lo anterior, el riesgo relativo percibido (RR 3,9; 95% IC 2,17-7,01) por los encuestados en torno a la muerte por un padecimiento asociado al VIH podrían ser los factores por los cuales la mayoría de los HSH favorecieron la implementación de la PR-VIH en la consulta odontológica.

A diferencia del estudio de Blackstock et al.[158] quienes reportaron una tasa de prevalencia del VIH no diagnosticada de 0,5% en población general, nuestro estudio obtuvo una prevalencia del virus sin detectar en HSH de 1,08%. Relacionado a lo anterior, al igual que Pollack et al.,[163] encontramos que los individuos con alto riesgo de infección por VIH, han estado en contacto reciente con un proveedor de servicios odontológicos (51% y 70% respectivamente). Por tanto, la alta tasa de prevalencia en los HSH y su contacto frecuente con los proveedores de servicios odontológicos podrían ser indicativos de que la implementación de la PR-VIH en la consulta odontológica contribuiría al alcance de las metas de salud pública 90-90-90,[18,141,143] al brindarse un servicio de detección oportuna y de vinculación al "*Continuo del diagnóstico-atención del VIH*" [161,162] con énfasis en las poblaciones clave y vulnerables.

No obstante, el EDAOS es un factor importante que obstaculiza a los HSH la divulgación de su orientación sexual y prácticas sexuales a los trabajadores de la salud,[160] nuestros resultados mostraron una baja percepción del mismo en la consulta odontológica. Lo anterior puede deberse a que medir el EDAOS resulta complicado porque las personas son más propensas a reconocer la discriminación contra los colectivos sociales, que a reconocer la discriminación contra ellos mismos como individuos.[166] Asimismo, puede existir un sub-

registro del EDAOS debido a la «*homonegatividad internalizada*», en donde el individuo se auto-vigila para no realizar ninguna acción que pueda evidenciar su orientación sexual.[167]

Orientaciones Futuras: Implicaciones y retos de la intervención

Antes de la implementación de la PR-VIH en el ámbito odontológico, deben resolverse importantes cuestiones éticas, legales y económicas. Igualmente, se debe realizar un énfasis educativo dentro del plan de estudios de las escuelas de odontología con el fin de ampliar la cobertura, promover e incorporar la aplicación de la PR-VIH en la consulta odontológica. A su vez, deben fomentarse programas de capacitación, sensibilización y certificación en los conocimientos científicos detrás del VIH, la consejería e implementación de la PR-VIH, así como en estudios de género, diversidad sexual y derechos humanos, para asegurar que todos los usuarios reciban un trato digno y equitativo en la consulta odontológica.

De igual forma, existe una serie de cuestiones logísticas relacionadas con la implementación de la detección rápida del VIH, en las que se incluyen: la obtención de resultados reactivos de la prueba; la necesidad de consejería profesional y los protocolos de confirmación, vinculación y retención de los casos reactivos a los servicios de salud en coordinación con las autoridades locales; el suministro de insumos de prevención e información focalizada del VIH; y la confidencialidad de los resultados de la PR-VIH y del expediente odontológico.

Fortalezas y debilidades

En el presente estudio, se deben considerar las limitaciones al haberse implementado con un tamaño modesto de muestra, lo que imposibilita realizar cualquier tipo de subanálisis y afirmaciones generales con peso estadístico sobre la población. Al diseñar estudios de intervención en poblaciones ocultas y específicamente en HSH, hay que considerar que al ser un grupo estigmatizado se desconoce su tamaño real, que no todos se reconocen como homosexuales o bisexuales y que no pueden ser alcanzados por las metodologías de muestreo tradicionales. Por ende, los estudios realizados hasta el momento no permiten un conocimiento certero de la realidad epidemiológica de esta población ni la

estandarización de los resultados. Los resultados y conclusiones obtenidos deben ser considerados como hipotéticos para otros grupos sociales, lo que limita la capacidad de la utilización de la escala en la población general o sacar conclusiones sobre el impacto del EDAOS percibido en la consulta odontológica. Sin embargo, el presente estudio proporciona un panorama sobre las actitudes y percepciones de una de las poblaciones de mayor riego en adquirir el VIH en México.

Conclusión

Desde nuestro particular punto de vista, es indispensable generar programas que incluyan la participación del odontólogo en los esfuerzos de salud pública, más allá de la lucha contra la caries o padecimientos de las encías, sino también en otras enfermedades crónico-degenerativas como la respuesta global al VIH. Sumar al odontólogo a esta respuesta coadyuvaría en concientizar a sus usuarios de la infección por VIH a través de la PR-VIH, a la vez ofrecería una ubicación más para la detección oportuna como un primer paso esencial para vincular a las personas al "*Continuo del diagnóstico-atención del VIH*", lo que contribuiría a la reducción de la incidencia de nuevos casos de VIH y en un avance importante en la salud pública. No obstante, es poco probable que dentro de la consulta odontológica se ofrezca la PR-VIH a todos los usuarios. Un enfoque específico parecería más adecuado, pero la logística de cómo esto sería ofrecido requiere un poco de pensamiento crítico para evitar prácticas discriminatorias. Por ende, se requiere realizar investigación futura a mayor escala para verificar los hallazgos del presente estudio y para conocer los principales obstáculos que se anteponen a la aplicación de la PR-VIH en la consulta odontológica.

Tables

Table 9, Article 4. *Características sociodemográficas de los participantes*

Variable	Mediana	RQ
Edad (años)	34	11
Escolarización (años cursados)	15	4
	n	%
Orientación Sexual		
Homosexual	159	86
Bisexual	23	12,4
Hombres que tienen sexo con hombres que no se definen como homosexual o bisexual	3	1,6
Trabajo		
Tiempo completo	142	76,8
Medio tiempo	26	14
No trabaja	17	9,2
Ingresos mensuales		
≤15.000 MXN (1.146 USD)	124	67
≤30.000 MXN (2.292 USD)	43	23,3
>30.000 MXN (2.292 USD)	18	9,7

RQ: Rango intercuartílico

Table 10, Article 4. *Percepción hacia los prestadores y servicios de salud oral públicos y privados*

Variable	*n*	%
¿Cuántas veces al año acudes a consulta odontológica?		
Ninguna	0	
Una vez al año	94	50,8
Dos o más veces al año	91	49,2
¿Acudes con un odontólogo(a) del sector público o privado?		
Ninguno	0	
Público	47	25,4
Privado	138	74,6
¿Acudes con un odontólogo(a) de práctica general o de especialidad?		
Ninguno	0	
No sé	51	27,6
General	75	40,5
Especialidad	59	31.9
De las siguientes opciones marca la que más se asemeje a la razón principal por la que elijes a un odontólogo(a).		
Conocimientos	46	24,9
Experiencia	57	30,8
Formalidad	10	5,4
Precio	27	14,6
Trato amable	15	8,1
Aspecto del consultorio	10	5,4
Higiene del consultorio	15	8,1
Aspecto personal del odontólogo(a)	5	2,7

Table 11, Article 4. *Percepción hacia realizar la detección de anticuerpos VIH-1/2 en la consulta odontológica*

Variable	*n*	%
¿El consultorio o clínica dental al que acudes es seguro, limpio y cuenta con las normas de control de infección?		
Si	170	91,9
No	15	8,1
No sé	0	0
¿Te has realizado en alguna ocasión la prueba de VIH?		
Si	96	51,9
No	87	47,0
No sé	2	1,1
¿Te gustaría que en el consultorio o clínica dental al que acudes, te ofrezcan la prueba rápida de detección de VIH de manera voluntaria, bajo consentimiento informado y firmado?		
Si	160	86,5
No	25	13,5
No sé	0	0
¿Crees que sea importante que el odontólogo(a) esté capacitado(a) para hacer la prueba anti VIH?		
Si	170	91,9
No	15	8,1
No sé	0	0
¿Crees en la confidencialidad de los expedientes odontológicos?		
Si	128	69,2
No	55	29,7
No sé	2	1,1
¿En general los odontólogos(as) son profesionistas de la salud que se rigen por la ética profesional y por consiguiente te atenderán como a cualquier otro usuario independientemente del resultado de la prueba anti VIH?		
Si	152	82,2
No	33	17,8
No sé	0	0
¿Algún familiar cercano, amigo o pareja falleció por causa de alguna enfermedad asociada al VIH?		
Si	86	46,5
No	99	53,5

VIH: Virus de Inmunodeficiencia Humana

Table 12, Article 4. *Percepción del estigma y discriminación asociados a la orientación sexual en la consulta odontológica.*

Ítems		Nunca	Casi nunca	De vez en cuando	A menudo	Muy a menudo
		n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
a.	*¿Has experimentado alguna situación de discriminación por parte de algún odontólogo(a) por tu orientación sexual*	167 (90,3)	11 (6)	5 (2,7)	1 (0,5)	1 (0,5)
b.	*¿Con qué frecuencia se te ha negado la atención odontológica debido a tu orientación sexual?*	173 (93,5)	8 (4,3)	0	2 (1,1)	2 (1,1)
c.	*¿Cuándo has asistido a un consultorio o clínica odontológica dan o te dieron excusas para negarte el servicio debido a tu orientación sexual?*	160 (86,9)	15 (8,1)	6 (3,2)	2 (1,1)	2 (1,1)
d.	*¿Cuándo has asistido a un consultorio o clínica odontológica se demoran o han demorado más en atenderte que al resto de los usuarios?*	154 (83,2)	18 (9,7)	6 (3,3)	4 (2,2)	3 (1,6)
e.	*¿Cuándo has asistido a un consultorio o clínica odontológica realizan o han realizado murmullos, miradas o risas sobre tu persona?*	160 (86,4)	15 (8,1)	6 (3,3)	4 (2,2)	0
f.	*¿Cuándo has asistido a un consultorio o clínica odontológica opinaron negativamente sobre tu vida y comportamientos sexuales?*	169 (91,3)	8 (4,3)	6 (3,3)	2 (1,1)	0
g.	*¿Cuándo has asistido a un consultorio o clínica odontológica te atendieron con disgusto, indiferencia o de manera despectiva?*	168 (90,8)	9 (4,9)	8 (4,3)	0	0
h.	*¿Cuándo has asistido a un consultorio o clínica odontológica evitaron el contacto con tu sudor o con tu piel?*	172 (92,9)	9 (4,9)	2 (1,1)	2 (1,1)	0
i.	*¿Cuándo has asistido a un consultorio o clínica odontológica mostraron temor o inseguridad al momento de realizarte curaciones, suturas, aplicarte inyecciones u otros procedimientos odontológicos?*	171 (92,4)	8 (4,3)	2 (1,1)	2 (1,1)	2 (1,1)
j.	*¿Cuándo has asistido a un consultorio o clínica odontológica solicitaron que se desechen los materiales que utilizaron contigo, argumentando el alto riesgo que se tiene debido a tu orientación sexual?*	172 (92,9)	6 (3,3)	0	4 (2,2)	3 (1,6)
k.	*¿Te has sentido discriminado por la forma en la que expresas tu orientación sexual?*	138 (74,7)	27 (14,6)	18 (9,7)	1 (0,5)	1 (0,5)

Table 13, Article 4. *Análisis factorial de la percepción del estigma y discriminación asociados a la orientación sexual en la consulta odontológica*

	Medias y matriz de correlaciones										
Ítems	Medias	1	2	3	4	5	6	7	8	9	10
a	0,266										
b	0,149	0,652									
c	0,277	0,759	0,579								
d	0,266	0,636	0,411	0,694							
e	0,266	0,748	0,468	0,655	0,704						
f	0,202	0,709	0,562	0,558	0,593	0,760					
g	0,191	0,747	0,544	0,584	0,569	0,801	0,847				
h	0,149	0,856	0,622	0,646	0,746	0,850	0,848	0,842			
i	0,223	0,804	0,656	0,542	0,611	0,790	0,801	0,787	0,894		
j	0,234	0,635	0,518	0,446	0,435	0,496	0,550	0,501	0,633	0,746	
k	0,309	0,192	0,164	0,203	0,137	0,206	0,287	0,228	0,192	0,202	0,190

Ítems	Matriz de componentes rotados		
	Factor 1. Sin experiencias personales de rechazo por parte del odontólogo(a) o su personal	Factor 2. Sin preocupación por la actitud del odontólogo(a) o su personal	Comunalidades
a	0,902	0,082	0,820
b	0,701	0,105	0,503
c	0,767	0,066	0,592
d	0,777	-0,026	0,605
e	0,873	0,097	0,772
f	0,846	0,240	0,773

g	0,856	0,168	0,762
h	0,952	0,087	0,915
i	0,906	0,130	0,839
j	0,689	0,154	0,499
k	0,111	0,982	0,977
Auto-valores	7,101	0,954	
Porcentaje de la varianza explicada	64,553	8,677	

Distancias entre los centros de los conglomerados finales

Conglomerado	1. Usuarios que no han experimentado estigma y discriminación en la consulta odontológica.	2. Usuarios que no han experimentado, pero sienten una ligera preocupación por lo que el odontólogo(a) o su personal opinen sobre su orientación sexual.	3. Usuarios que han experimentado algún tipo de discriminación y sienten preocupación por lo que el odontólogo(a) o su personal opinen sobre su orientación sexual.
	90,3% (n=167)	8,1% (n=15)	1,6% (n=3)
1		7,104	11,061[a]
2	7,104		4,401[a]
3	11,061	4,401	

Método de rotación: normalización Varimax con Kaiser. Medida de adecuación muestral Kaiser-Meyer-Olkin: 0,885.
Prueba de esfericidad de Bartlett p<0,001; converge en tres iteraciones. Análisis de cluster no jerárquico (K-means Cluster).
[a] ($p < 0,001$) mediante ANOVA.

Published Article #5

Title. Potential Gingival Crevicular Fluid and Serum Biomarkers by Stage of HIV Infection

Authors

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Abstract

Objective

This study evaluates the potential of gingival crevicular fluid and serum cytokines as HIV stage biomarkers.

Methods

Gingival crevicular fluid (GCF) and serum samples from 78 HIV-positive adult male subjects (cases) and 39 HIV-negative male subjects (controls) from México were examined for 17 cytokines using multiplex ELISA. Participants were divided into five subgroups by HIV stage of infection on age-specific CD4+ T-lymphocyte count and antiretroviral therapy (ART), and further correlated to the cytokine levels.

Results

GCF concentrations of IL-6, IL-7, IL-10, IL-12, G-CSF, and MCP-1, as well as serum concentrations of IL-1β, IL-2 and IL-6 showed a statistically significant difference among subgroups. We found a significant effect size correlation on cytokines expression levels. Subjects who were not in ART showed significantly higher levels of some of the analyzed cytokines compared to the rest. We found that GCF IL-8 was a significant predictor of the Non-ART HIV status ($p < 0.05$). We observed the same result for GCF G-CSF in the ART Short-term group and serum GM-CSF in the ART Long-term subgroup.

Conclusion

Results indicate a high variability of GCF and serum cytokines concentrations and low frequency of their detection in different HIV/ART stages. However, within the limits of the present study, some GCF and serum cytokine concentrations correlate positively. Oral and periodontal innate immunity is affected by HIV viremia and ART. GCF IL-8, G-CSF, as well as serum IL-8, MCP-1, and GM-CSF may be useful biomarkers for the detection of disease presence and/or its severity due to HIV infection and ART use.

Keywords: Biomarkers, Cytokine, HIV, Gingival Crevicular Fluid, Periodontal Diseases, Antiretroviral Therapy, México.

Main text

1. Introduction

Viruses and other periodontopathogens are risk factors in many oral and systemic diseases, and human immunodeficiency virus (HIV) is not the exception. Co-pathogenesis is characterized by numerous complex interactions between the co-infecting pathogens and their host, inducing disruption of physical barriers, dysregulation of immune responses and arrears to achieve immune homeostasis. HIV targets and infects CD4+ T-cells by binding to cell surface glycoprotein CD4 and then to chemokine coreceptors CCR5 or CXCR4. Infected HIV cells release newly formed virions in a semi-synchronous wave pattern and are also thought to spread them through direct contact with their neighbors via virological synapses and by pools of free virions [41]. The oral cavity seems to be a potential reservoir of HIV, as its RNA and DNA can be detected and quantified in the subgingival biofilm, gingival crevicular fluid (GCF) and saliva of HIV-infected individuals [43,168,169]. Therefore, the oral epithelial cells are susceptible to either cell-free or cell-associated HIV infection.

The biological and clinical basis of the probable relationship between oral chronic inflammatory disorders, such as periodontal disease and the exacerbation of HIV viremia have received limited attention [42]. Nevertheless, controversial data regarding the association between immunosuppression and prevalence/severity of oral and periodontal diseases in HIV-infected individuals had been reported [49,170].

The cytokines, chemokines, and their receptors have been receiving notable consideration afterward the discoveries that some of them could specifically block HIV infection and that some specific chemokine receptors were the long-sought co-receptors which, along with CD4+ T-cell, are required for the productive entry of HIV [171]. The intricate and complex balance of factors that regulate the HIV-1 pathogenic process is highlighted by both the inhibition and enhancement that cytokines, chemokines and their receptor signaling events elicit on the HIV entry and replication processes.

Extending our prior work, where we examined whether the levels of interleukin (IL)-2, IL-4, IL-6, IL-8, IL-10, granulocyte-macrophage-colony-stimulating factor (GM-CSF), interferon-gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) in GCF were altered in HIV-infected individuals with non-periodontal disease, and whether CD4+ T-cell count, HIV viral load and antiretroviral therapy (ART), affected those levels [56]. We decided to explore the possible association between GCF and serum levels of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, GM-CSF, IFN-γ, granulocyte colony-stimulating factor (G-CSF), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1β (MIP-1β), tumor necrosis factor alpha (TNF-α), with CD4+ T-cell count, HIV viral load and ART, as well as their association with HIV/ART status, in an effort to identify and quantify periodontal and systemic risk biomarkers by objective methods and measures.

2. Material and methods

2.1 Recruitment and participants

Participants were recruited from HIV/AIDS healthcare providers, non-governmental and community-based organizations in Monterrey, México and adopted a non-probability and snowball sampling [164]. The research involved 202 consenting adult men who have sex with men (MSM). Eligible participants in the cross-sectional study were those 18 years or older and who had engaged in sex - anal or oral - with another male.

HIV-infected subjects were diagnosed in advance of the study as HIV-positive by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western Blot [63]. All self-declared non-HIV subjects were provided with an opportunity to undergo voluntary counseling and testing for HIV (at screening and if enrolled, 3 months after all study samples were taken), detected by rapid HIV-1/2 test (OraSure Technologies, Inc., Bethlehem, PA).

2.2 Ethics

The study protocol was reviewed and approved by the ethics, research and biosafety committees at Tecnologico de Monterrey and Universitat

Internacional de Catalunya. The study procedures were undertaken with the written consent of each subject and according to the Declaration of Helsinki [61].

2.3 Clinical examination

2.3.1 Anamnesis

All participating patients were offered a general health survey, and baseline electronic medical/dental records were collected. Exclusion criteria included history or current manifestation of any systemic, autoimmune, and infectious diseases, or other than HIV/AIDS. Likewise, diabetes, concurrent psychiatric or psychological treatment, illicit drug use, current alcohol abuse, chronic or intermittent usage of anti-inflammatory or antidepressant drugs, antibiotics, chlorhexidine digluconate, previous vaccination (≤4 weeks), previous periodontal treatment (≤6 months) and current use of prosthetic or orthodontic appliances (fixed or removable), that could affect periodontal or systemic cytokine expression. Smoking habit was recorded and not excluded due to its prevalence among MSM with that among other men [65,66]. In like manner, obesity could not be avoided, and body mass index (BMI) was taken into account due to obesity prevalence among Mexican adult population [67].

2.3.2 Oral examination

All participants underwent a standardized baseline oral examination. Gingival recession (REC), probing pocket depth (PPD), clinical attachment level (CAL) and bleeding on probing (BOP) were measured using Florida Probe® (Florida Probe Corporation, Gainesville, FL). Six sites were measured in all teeth considering a fixed reference point on the occlusal surface of teeth and cementoenamel junction, except third molars. A total number of natural teeth was recorded. BOP was calculated as the percentage of positive sites per subject. BOP was considered positive if bleeding was elicited within 30 seconds following periodontal probing. Plaque index was recorded (PI) [68]. No radiographs were taken. Periodontitis was defined by the presence of one site with PPD ≥4mm and CAL ≥3mm on at least 4 different teeth with or without BOP. HIV-related oral lesions were recorded according to classified criteria EC-Clearinghouse [69], and OHARA case definitions [48].

2.4 Samples and laboratory tests

Prior sampling all subjects were rapid tested for the presence of anti-HBc, HBsAg, and anti-HCV (Intec, Xiamen, China). In addition, non-fasted blood glucose levels (BGL) were determined (LifeScan, Inc., Milpitas, CA). Furthermore, oral fluid multiple drug screen test was used to determine drug abuse (Branan Medical Corp., Irvine, CA). All rapid tests were performed with appropriate counseling and referral.

2.4.1 GCF collection

Maxillary teeth including first molars, second premolars, and canines or central incisors (three teeth per subject) were selected. Sampled teeth were free of gingival inflammation, caries, prosthetic reconstruction and root canal therapy. After supragingival plaque had been removed, paper strips (PerioPaper Strips, OraFlow, Plainview, NY) were gently inserted into the crevice for 30 seconds. GCF volume was measured and converted to microliters using Periotron 8000 and MCCONVRT V2.52 (Oraflow Inc., Amityville, NY). Paper strips with traces of blood were discarded, and sampling was replicated from another non-sampled site of the tooth. Six paper strips of each patient were placed in 500µl of phosphate-buffered saline (PBS). Following 10s vortexing and 20min shaking, the strips were removed, and the eluates were centrifuged for 5min at 5800 x g to remove plaque and cellular elements. The supernatant was harvested and divided into aliquots and stored at -80°C until assayed.

2.4.2 Serum and plasma samples

Samples were taken following the standard operating procedures for serum and plasma collection for biomarker discovery and validation [70].

2.4.3 CD4+ T-cell counting

Blood samples were stained and analyzed by FACSCount (Becton Dickinson, San Jose, CA) within 2 hours and all measures were performed in triplicate according to manufacturer's instructions.

2.4.4 Cytokine assay

Selection and assessment of cytokines were based accordingly to their potential relevance as periodontal biomarkers of HIV pathology and infection immune response in which immunological correlates remain undefined. Levels of cytokines in serum and GCF samples from all subjects were determined using Bioplex ProTM Human Cytokine 17-plex Assay (Bio-Rad Lab., Inc., Hercules, CA) accordingly to manufacturer's protocol at the same time in duplicate. All proteins were determined using Bio-Plex array reader (Luminex, Austin, TX) at 405 nm wavelength. Samples with analyte concentrations beneath the detection limit were assigned an intermediate value between zero and the lowest detectable level in every assay plate before log transformation. Therefore all samples were preserved within the data set. Concentrations of cytokines were corrected for serum and GCF volume and were defined as pg/µl, for the GCF total amounts were expressed as pg/6 sites.

2.4.5 HIV-1 RNA assay

Plasma samples from HIV-infected individuals were analyzed using real-time PCR by Cobas Ampliprep/Cobas TaqMan HIV-1 test (Roche CAP/CTM-48 V2) on the TaqMan 48 analyzer (Roche Molecular Systems, Branchburg, NJ). This assay has a reportable range of 20 to 1.0E+7 HIV RNA copies/ml.

2.5 Statistical analysis

Data were tested for normal distribution using the Kolmogorov-Smirnov test [74] and Levene's test. Grubbs' test [75] was used to determine significant outliers from the data set. Outliers were winsorized from the analysis [76], and normality was reconfirmed with the above-mentioned normality test. Results based on normality and outlier tests were followed by repeated measures Multivariate Analysis of Variance (MANOVA) to test for group differences. Differences within groups are presented as means ± standard deviation (SD) for continuous variables and as proportions for categorical variables.

Additionally, all data were analyzed with a series of follow-up ANOVA, the homogeneity of variance assumption was tested on a series of Levene's *F*-test for all analyzed variables. Paired *"t"* test was used to compare the means of data

from two related samples. A series of post-hoc Scheffé's test were performed to examine individual mean difference comparisons (control of type I error) and determine the exact nature of group differences.

Pearson's correlation coefficient (PCC) and multivariate linear regression (MLR) analyses were used to compare means of immunological parameters among independent groups. The assumptions of independence and homoscedasticity for MLR was checked using Durbin-Watson test [77] and Breusch-Pagan test [78], respectively. Heteroscedasticity-consistent standard error estimators [79] were used to correct any presence of spatial non-stationarity (avoid type I errors) in the MLR models. All data were analyzed with SPSS® (version 22.0), and all test were performed considering $\alpha=0.05$ to indicate statistical significance.

3. Results

3.1 Demographic and clinical findings

Based on inclusion and exclusion criteria the study sample comprised 117 voluntary MSM. Descriptive statistics were used to analyze breakdown of subjects by the status of HIV test. 78 HIV-positive subjects (age range 22-54 years, median 35) as cases and 39 HIV-negative subjects (age range 18-49 years, median 32) as controls match in the race, sex, sexual orientation, and sexual behavior. All 39 HIV-negative subjects were retested 3 months after all study samples were taken and remained HIV negative.

HIV-positive subjects were grouped according to the Center for Disease Control (CDC) classification for HIV infection [71]. Included stage, and duration of HIV infection (calculated from HIV serodiagnosis date), use of ART, Anti-HIV drug classes, México's ART guideline (first, second or salvage) [72], duration of ART, CD4+ T-cell count, and HIV RNA viral load (table 14).

The cohort was then divided into subgroups, six HIV-infected subjects were not on antiretroviral therapy (Non-ART subgroup) at the time of the study, and seventy-two were receiving different combinations of ART, mainly one non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse

transcriptase inhibitors (NRTIs) n= 51, 71%. Those who had been on ART <1 year (n= 8, 11%) were classified as ART-naïve, those who had been taking ART ≥1<6 years (n= 41, 57%) were classified as short-term ART, and finally those who had been taking ART for ≥6 years (n= 23, 32%) were classified as long-term ART. Of those who had been on ART were sub-classified as first-line ART (n= 57, 79%), second-line ART (n= 13, 18%) and salvage ART subjects (n= 2, 3%), (table 14).

3.2 Data preprocessing and normalization

After data preprocessing and pretreatment was achieved, results for parameters based on normality and outlier tests were followed by MANOVA. Effect was obtained, Pillais' Trace= 2.58, F (192,000) = 2.57, p< 0.001. The multivariate effect size was estimated at 0.645, which implies that 64% of the variance in the canonically derived dependent variables were accounted for stages of HIV infection. There were significant differences (p< 0.05) among subgroups in Age, CD4+ count, HIV viral load and sites with PPD ≥4mm and CAL ≥3mm associated with the HIV/ART status. Nonetheless, Scheffé's post-hoc analysis did not reveal any reliable differences in sites with PPD ≥4mm and CAL ≥3mm among subgroups (table 15).

Besides, there were non-significant differences among subgroups in social factors such as educational attainment and monthly income, and none were there among personal behavior, and lifestyle factors like smoking habit and alcohol consumption, and nor did in systemic and oral clinical variables (table 15).

Prevalence of oral lesions among HIV-positive subjects with and without ART and HIV-negative subjects were rarely seen. Hyperpigmentation was the most common oral lesion in all subgroups, followed by only one case of linear gingival erythema in the Non-ART subgroup. Nevertheless, there were no significant differences.

3.3 GCF and serum cytokine levels

The values of GCF IL-6, IL-7, IL-10, IL-12, G-CSF, and MCP-1 were significantly higher in the Non-ART subgroup as compared to the control. However, IL-10 and IL-12 did not show a significant p-value in the post-hoc. On

the other hand, IL-1β, IL-2, and IL-6 were significantly higher in serum samples and again, only in the Non-ART subgroup (table 16).

The PCC was used to identify relationships with at least a medium effect size (r ≥0.30 or ≤ −0.30) [172] between GCF and serum equal cytokines in all subgroups (table 3). Furthermore, correlations were calculated between GCF and serum cytokines concentrations and all variables in all subgroups (table 17).

Finally, significant predictors were entered into an MLR model ($Y_n{}^x{}_p = X_n{}^x{}_{(k+1)}\ \beta_{(k+1)}{}^x{}_p + \varepsilon$) where the relationships between multiple dependent variables (i.e., *Y*s)—measures of outcomes—and multiple predictor variables (i.e., *X*s) were assessed to determine whether, and to what extent, GCF and serum cytokines remained significant HIV/ART status predictors. Separate models were created for each subgroup and assumptions of independence and homoscedasticity for MLR was checked using Durbin-Watson test and Breusch-Pagan test, respectively.

After removal of the non-significant explanatory variables via conducting a stepwise MLR, GCF and serum cytokines contributed to predict HIV/ART status (table 18) and combined explained 39% of the observed variance in the Non-ART group (R2= 0.394, *F*= 11.94, p< 0.01). The standardized coefficients showed that in this analysis, GCF IL-8 was the most important explanatory variable. Furthermore, GCF IL-8, IL-2, and serum MCP-1 showed a negative effect, which means that with decreasing concentrations decreased the probability to be classified in the Non-ART group. Per contra, any cytokine contributed to predict the ART-naïve subgroup. Moreover, the GCF G-CSF was the only explanatory variable (35% p< 0.01) and with a negative effect in the ART short-term subgroup. Serum GM-CSF and IL-8 were the ones that predicted the variance (11% p< 0.01) in the ART long-term subgroup.

No multicollinearity was present, and standardized residuals showed a normal distribution in all subgroups, meeting the important assumptions of normality and multicollinearity. However, the Breusch-Pagan post-hoc test exposed the presence of heteroscedasticity in some models (p≤ 0.05),

suggesting that the data was not being adequately explained by the statistical models of conditional means being estimated, invalidating the significance of the statistical tests (table 18). Thus, heteroscedasticity-consistent standard error estimators (HCSE) [79] were used to correct the presence of spatial non-stationarity in the Non-ART and Short-term ART subgroup MLR models. Under the null hypothesis that all regression coefficients for self-concept in the two MLR models were equal to zero, HCSE analysis was performed on each one. The null hypothesis was rejected only for GCF IL-8, G-CSF, and serum MCP-1 ($p< 0.05$) as predictors in the Non-ART model. Likewise, Ho was rejected for GCF G-CSF as a predictor in the ART short-term model (table 18).

4. Discussion

GCF is an exudate from blood vessels and periodontal tissues, it contains many proteins derived from the blood, and it is released into the gingival crevices or periodontal pockets [173]. In this study, we determined the concentrations of different cytokines from GCF and serum in an endemic population as part of an effort to identify a single biomarker or combination of cytokines which have a potential to detect differences in HIV stages of infection based on age-specific CD4+ count and ART compared to non-HIV-infected individuals. Up to our best knowledge, this is the first study to report the levels and correlation of 17 GCF and paired serum cytokines in HIV-infected and HIV-uninfected individuals.

We demonstrated that 16 of the 17 researched biomarkers in the GCF samples could be detected using the multiplex bead immunoassay, and the levels of 8 GCF biomarkers (IL-1β, IL-4, IL-6, IL-7, IL-8, IL-13, INF-γ, and MIP-1β) correlate with pair serum biomarkers in several HIV/ART stages. In addition, GCF biomarkers reflect systemic and oral clinical variables such as CD4+ count, ART guideline, BMI, BGL, BOP, PPD, CAL, the number of teeth and smoking habit. Moreover, in this study differences were observed in cytokine levels among subjects in a particular HIV/ART stage and those with non-HIV infection. Also, analyzed GCF and serum biomarkers discriminate between all studied groups, and through MLR we found that a combination of cytokines (GCF IL-8 and G-CSF, and serum IL-8, MCP-1, and GM-CSF) gave better discriminatory level in

different HIV/ART stages. These findings correlated with those reported by other researchers [174–176].

Oral innate immunity mostly maintains the oral cavity health through the innate defense mechanisms. Nevertheless, various oral infections and malignancies may evolve when it's impaired either by local or systemic causes [177,178]. Not to mention that it also appears to be modulated with the use of ART [178,179]. However, with the introduction of ART, HIV oral manifestations have become less widely seen in HIV-infected individuals [180,181]. In accordance, the prevalence of oral lesions was rarely seen in our study, to such a degree it was not possible to correlate GCF and serum cytokines with such manifestations. Of interest, no oral warts were diagnosed among subjects.

Nonetheless, ART provides an inadequate immune reestablishment of the oral epithelial cells of HIV-infected individuals, and the toxic side effects of ART and/or HIV chronicity silence the expression of multiple proteins that in healthy individuals, function to provide tough innate immune responses and battle cellular stress [182]. Our and others research findings [176], suggest that HIV infection and the use of ART may alter oral innate immunity and levels of circulating oral cytokines. However, no significant differences were noted in the expression of IL-4, IL-5, IL-8, IL-13, IL-17, GM-CSF, INF-γ, MIP-1β, and TNF-α according to their ART status.

HIV-infected subjects with or without ART are susceptible to comorbid fungal, bacterial, and viral infections in the oral cavity (e.g., periodontal disease). Oral microorganisms growth and the emergence of these or their byproducts accompanying chronic oral inflammatory diseases have the capability to reactivate HIV-1 from latently infected cells, showing a relationship of immature and mature dendritic cells, macrophages or T-cells, and could be risk modifiers for HIV-1 replication, systemic immune activation, and AIDS progression [43,168]. Numerous cytokines are released from the above mention cells, and the presence of a large number of cytokines, especially pro-inflammatory and inflammatory cytokines, in the GCF have been considered as potentially useful diagnostic or prognostic biomarkers of periodontal destruction [173]. In the

present study GCF IL-6, IL-10, IL-13, G-CSF, and serum IL-6 correlate with PPD ≥4mm and CAL ≥3mm in HIV-infected subjects and were also statistically significantly associated with ART status. Likewise serum IL-12, IL-17, MCP-1 correlate with PPD and CAL in HIV-uninfected subjects. Present results indicated that HIV-infected subjects who were not on ART had a greater risk of having periodontal pockets than those on ART.

Furthermore, medium to high positive PCC was found among GCF IL-1β, IL-4, IL-7, IL-10, IL-12, IL-13, GM-CSF, INF-γ, serum TNF-α and BOP in HIV-infected subjects who were in short and long-term ART. In like manner, there was significant association among GCF IL-8, IL-10 and the number of teeth of HIV-infected individuals in short-term ART, as well as GCF MIP-1β, serum IL-17 and G-CSF did the same but in the non-HIV-infected subjects. While smoking habit, was found to influence the expression of GCF IL-1β, IL-4, IL-6, IL-7, IL-10, IL-13, IL-17, MCP-1, MIP-1β, TNF-α and serum IL-8, IL-12, G-CSF MIP-1β in HIV-infected subjects. Notwithstanding HIV stage, ART, and age are not self-reliant risk factors for variations in the periodontal status of HIV-infected subjects, the degree of periodontitis risk seems to be higher in HIV-infected than in HIV-uninfected individuals; some studies correlate these findings with higher prevalence of smoking and poorer oral hygiene in HIV-infected individuals, as well as a possible effect of HIV-induced immunodeficiency [183,184].

Cytokines concentrations during acute HIV-1 infection are predictive of HIV disease progression [185]. In the present study GCF IL-8 and G-CSF as well as serum IL-8, MCP-1 and GM-CSF may be useful biomarkers for the detection of disease presence and/or its severity due to HIV infection and ART use. HIV-infected individuals have shown that IL-8 A/T genotype carriers are more susceptible to a diversity of diseases [186]. In our study, negative correlations were found between GCF IL-8 levels within the Non-ART subgroup and their corresponding CD4+ count. Additionally, as in other studies [187] IL-10, G-CSF and INF-γ were each found inversely associated with the CD4+ count. Moreover, our results have shown serum GM-CSF inversely associated with ART guideline in the long-term ART subgroup. Nevertheless, lower or unaffected levels of GM-CSF in serum profiles of HIV-suppressed subjects have been reported [188,189].

The impact of ART-induced HIV suppression on oral and systemic levels of serological molecular biomarkers of inflammation and immune activation still remains unclear. Therefore, data reported in this research should be interpreted with discretion based on the limitations of the study. As a transversal design, no causative inferences may be assumed, only association inferences. The modest sample size in some subgroups may be partially responsible for the lack of significance for some variables. It's also important to consider the preparation of biological sample since GCF and serum are not equivalent.

Despite these limitations, the current study may contribute to a better understanding of cytokine biomarkers. Omics analyses of GCF, measuring microbial and host interactions in association with the outbreak and progression of periodontal diseases, still show the potential to expand the landscape for the discovery of diagnostic, prognostic and therapeutic markers. Future large-scale studies need to be done to verify findings from this study and to discern into the molecular mechanisms of how HIV and ART modify the expression of cytokines and other systemic and oral innate immune factors in GCF and serum over time.

Tables

Table 14, Article 5. *Classification of HIV-infected Subjects on Infection Stage on age-specific CD4+ T-lymphocyte count and ART on date Base*

Parameters	*Infection stage based on age-specific CD4+ T-lymphocyte count (n = 78)*														
Years of infection	**<1 yr (mean 0.84 yr [SD 0.15] n = 14)**					**1–5 yrs (mean 2.43 yrs [SD 0.9] n = 41)**					**>5 yrs (mean 8.64 yrs [SD 3.27] n = 23)**				
HIV Stage	Cells/ µL	mean	n	n %		Cells/ µL	mean	n	n %		Cells/ µL	mean	n	n %	Total
1	≥1,500	/	/	/		≥1,000	1069.33 ± 113.23	3	3.8		≥500	773.07 ± 195.76 □	14	17.9	17
2	750–1,499	800	1	1.3		500–999	681.65 ± 127.98	17	21.8		200–499	340.86 ± 52.72	7	9	25
3	<750	365.31± 97.33	13	16.7		<500	362.19 ± 92.05	21	26.9		<200	161± 26.87	2	2.6	36
ART based on date, guideline and drug class (n = 72)															
Study Groups	Non-ART (n = 6)	Naïve ART (n = 8)					Short-term ART (n = 41)					Long-term ART (n = 23)					
Anti-HIV Drug Classes		**A**	**B**	**C**	**n**	**n %**	**A**	**B**	**C**	**n**	**n %**	**A**	**B**	**C**	**n**	**n %**	**Total**
First		7	1	/	8	10.3	31	7	/	38	48.7	7	4	/	11	14.1	57
Second		/	/	/	/	/	2	1	/	3	3.8	3	5	2	10	12.8	13
Salvage		/	/	/	/	/	/	/	/	/	/	1	/	1	2	2.6	2

Mean ± standard deviation, n %= distribution %, ART Guideline First, second and salvage (México's ART Guideline CENSIDA), **A**= 2 NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) + 1 NRTI (Nucleoside Reverse Transcriptase Inhibitors), **B**= 2 NNRTIs + Ritonavir-boosted PI (Protease Inhibitors), **C**= Other antiretrovirals with minimal cross-resistance risk.

Table 15, Article 5. *Demographic and Clinical Characteristics of the Study Subjects*

Study groups	Non-ART (n = 6)	ART Naïve (n = 8)	Short-term ART (n = 41)	Long-term ART (n = 23)	Non-HIV subjects (n = 39)	MANOVA p	Post hoc
Age	30.33 ± 6.56	28.38 ± 5.95	35.37 ± 8.07	40.65 ± 6.37	32.10 ± 6.98	0.0001	0.001
Educational attainment	14.33 ± 2.08	15.33 ± 3.26	13.97 ± 3.82	13.71 ± 4.05	15 ± 3.65	0.67	
Monthly income	1000.63 ± 308.35	1019.65 ± 497.99	1002.01 ± 551.45	1159.87 ± 708.89	1130.57 ± 708.57	0.50	
HIV Stage*	**HIV Stage 3**	**HIV Stage 3**	**HIV Stage 2**	**HIV Stage 1**			
CD4⁺ Range	251-491	220 - 800	136 - 1200	142 - 1200			
Mean	397.83 ± 95.94	395.25 ± 186.35	546.39 ± 239.85	588.30 ± 285.02		0.0001	0.0001
HIV viral copies Range	20 – 60500	20 – 39000	20 – 3250	20 – 3300			
Mean	28735 ± 20468	5131 ± 13702	81.22 ± 507.40	254.78 ± 843.43		0.0001	0.0001
Glucose	87.50 ± 8.40	90.25 ± 5.14	90.76 ± 11.40	95.22 ± 13.54	94.26 ± 12.70	0.37	
**BMI ** **	24.98 ± 6.17	24.35 ± 2.54	26.54 ± 3.22	25.34 ± 3.84	27.59 ± 4.1	0.07	
Number of teeth	29.33 ± 1.5	28.75 ± 0.88	28.05 ± 1.93	27.35 ± 2.18	1.94 ± 0.11	0.11	
Plaque Index	1.63 ± 0.46	1.61 ± 0.48	1.55 ± 0.49	1.58 ± 0.37	1.56 ± 0.39	0.58	
BOP	10.33 ± 14.37	6.38 ± 6.96	4.71 ± 5.46	7.13 ± 12.84	7.28 ± 13.26	0.70	
PPD Range	3.46 - 4.67	3.43 - 3.69	3.31 - 5.41	3.39 - 5.34	3.27 - 4.64		
Mean	3.96 ± 0.55	3.52 ± 0.08	3.67 ± 0.40	3.90 ± 0.56	3.73 ± 0.37	0.093	
CAL Range	2.66 -2.91	2.58 - 2.82	2.46 -3.01	2.55 - 2.94	2.45 - 3.11		
Mean	2.72 ± 0.09	2.65 ± 0.07	2.65 ± 0.09	2.70 ± 0.11	2.68 ± 0.12	0.36	
PPD /CAL	13.66 ± 8.28	8 ± 6.56	5.60 ± 4.45	6.78 ± 6.57	8.43 ± 7.77	0.046	0.095

	n	%	n	%	n	%	n	%	n	%	Total (n)	Total (%)
Homosexual	5	83.3	7	87.5	38	92.6	20	86.9	34	87.1	104	88.9
Bisexual	1	16.6	1	12.5	3	7.3	3	13	5	12.8	13	11.1
Non-smoker	3	50	6	75	22	53.7	10	43.5	19	48.7	60	51.2
Smoker	3	50	2	25	19	46.3	13	56.5	20	51.3	57	48.7
Alcohol Non-drinker	4	66.7	6	75	22	53.7	11	47.8	16	41	59	50.4

Alcohol Drinker	2	33.3	2	25	19	46.3	12	52.2	23	59	58	49.6

Mean ± standard deviation, Post hoc Scheffé, Age in years, Educational attainment = Years of school completed, Monthly income in USD, CD4 cell count (cell mm-3), HIV viral load (copies mm-3), Blood Glucose Level (mg/dL), BMI= Body Mass Index (kg/m2), Number of teeth, BOP=Bleeding On Probing, PPD= Probing Pocket Depth (mm),CAL= Clinical Attachment Level (mm), PPD /CAL = Sites with PPD ≥ 4 mm and CAL ≥ 3 mm, *Centers for Disease Control And Prevention Revised Surveillance Case Definition for HIV Infection, **World Health Organization International Classification of adult underweight, overweight and obesity according to BMI

Table 16, Article 5. *GCF and Serum Cytokine Levels, Comparison of paired, variance and differences of means, and Correlation Coefficients by Study Groups (pg/dl)*

Cytokine	Study groups	Non-ART (n = 6)	ART Naïve (n = 8)	Short-term ART (n = 41)	Long-term ART (n = 23)	Non-HIV subjects (n = 39)	ANOVA	Post hoc
IL-1β	GCF	61,56 ±44.95†	58.63 ± 90.63	47,56 ± 60.96 §	69,76 ± 62.02 § /**.470***	66,52 ± 119.45 §	.851	
	Serum	0,22 ± .53†	.00 ± .00	0 ± .00 §	0,03 ± .15 §	0 ± .00 §	.005	.009
IL-2	GCF	.00 ± .00	.00 ± .01	.01 ± .03	.01 ± .04	0,02 ± .05†	.437	
	Serum	1.63 ± 3.98	.00 ± .00	.00 ± .00	.08 ± .39	0 ± .01†	.001	.002
IL-4	GCF	0,01 ± .01†	0,1 ±.01 †	0,01 ± .01§	.01 ±.01/ **.442***	0,01 ± .01 §	.361	
	Serum	0 ± .00†	0 ± .00†	0 ± .00 §	.01 ± .03	0 ± .00 §	.418	
IL-5	GCF	.00 ± .00	.00 ± .00	.00 ± .00	.00 ±.00/ **.528***	.00 ± .00	.092	
	Serum	.00 ± .00	.00± .00	.00 ± .00	.00 ±.01	.00 ±.02	.612	
IL-6	GCF	.09 ± .12 /**.855***	.02 ± .03	0,02 ±.03 §	.02 ± .07	.01 ± .03	.017	.024
	Serum	1.25 ± 3.05	.00 ± .00	0 ± .00§	.25 ± 1.17	.01 ± .02	.012	.024
IL-7	GCF	.14 ± .18	.02 ± .03	.03 ± .04	0,06 ±.11† /**.443***	0,05 ±.07 §	.019	.031
	Serum	.00 ± .01	.01 ± .01	.02 ± .08	0,01 ± .01†	0,01 ±.02 §	.878	
IL-8	GCF	24,26 ±16.94†	9,15 ± 6.11 §	15,18 ± 19.36 § **/.327***	20,54 ± 19.31 §	15,01 ± 15.6§	.371	
	Serum	0,01 ± .01†	0,01± .01 §	0,01 ±.01 §	0,02 ± .02§	0,01 ±.01 §	.303	
IL-10	GCF	0,11 ±.07†	0,04 ± .02 §	0,05 ±.04§	0,06 ± .04§	0,06 .05± §	.040	.068
	Serum	0,01 ±0.02†	0 ± .00 §	0 ±.01 §	0 ±.01 §	0,01 ±.04 §	.348	
IL-12	GCF	.39 ± .44	0,08 ±.09†	.11 ± .18	.15 ± .32	.11 ± .16	.049	.087
	Serum	.14 ± .34	0 ± .00†	.04 ± .21	.03 ± .07	.08 ± .25	.589	
IL-13	GCF	.13 ± .20	0,03 ± .03†	0,05 ± .07§	0,06 ± .10§	0,04 ± .05 § **/.362***	.135	
	Serum	.00 ± .00	0 ± .00†	0 ± .00 §	0 ± .00 §	0 ± .01 §	.383	
IL-17	GCF	0,63 ±.29†	0,30 ± .26§	0,36 ± .30§	0,53 ± .39§	.45 ± .40	.187	
	Serum	0,09 ±.21†	0 ± .00 §	0 ± .02 §	0,08 ±.34 §	.19 ± .91	.661	
G-CSF	GCF	26.80 ±29.15	7,62 ± 5.63 §	6,87± 9.3§	11,68 ± 15.11 §	7,52 ± 9.94 §	.005	.010
	Serum	.01 ± .02	0,01 ± .01 §	0,03 ± .08§	0,24 ± 1.01 §	0,04 ± .14 §	.449	
GM-CSF	GCF	56,03 ± 25.06§	37,85 ± 19.17§	43,55 ± 18.84 §	48,52 ± 14.47 §	45,99 ± 18.8 §	.356	
	Serum	0 ±.00 §	0 ± .00 §	0±.00 §	0,67 ± 3.21 §	0 ±.00 §	.399	
INF-γ	GCF	3.88 ±2.07	1,91 ±1.74†	2,13 ±1.64 §	2.89 ± 1.86 /**.416***	2,70 ± 2.11 §	.144	
	Serum	12.91 ±31.61	0 ± .00†	0,02 ± .10 §	7.80 ± 37.38	0 ± .00§	.227	
MCP-1	GCF	1.10 ± 1.06	.39 ± .26	0,48 ± .42§	0,59± .61 †	0,43 ± §	.024	.042
	Serum	.12 ± .23	.14 ± .19	0,16 ± .17§	0,20 ± .38†	0,10 ± .09 §	.470	
MIP-1β	GCF	5.15 ± 7.62	0,82 ± .24§	2,34± 3.87† **/.352***	2.32 ± 3.36	1.39 ± 1.82	.094	

	Serum	2.55 ± 3.06	1,93 ± .67 §	2,59 ± 1.97†	2.14 ± .80	2.40 ± 1.35	.761	
TNF-α	GCF	.16 ± .10	0,08 ± .05 §	0,08 ± .07§	.10 ± .07	0,09 ± .09 §	.202	
	Serum	1.48 ± 3.59	0 ± .00 §	0 ± .01 §	.58 ± 2.78	0 ± .02 §	.102	

Mean ± standard deviation, ANOVA indicates p value, Post hoc Scheffé, In bold numbers Pearson´s correlation, (/XX), ART (Antiretroviral Therapy), GCF (Gingival Crevicular Fluid), IL (Interleukin), G-CSF (Granulocyte Colony-Stimulating Factor), GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), INF-γ (Interferon-gamma), MCP-1 (monocyte chemotactic protein-1), MIP-1β (macrophage inflammatory protein-1β), TNF-a (Tumor Necrosis Factor alpha), * significant at 0.05 level (p≤ 0.05), Correlations coefficient ≥0.30 were considered medium effect size, statistically significant (p ≤ 0.05), † Paired "t" test significant at 0.05 level (p≤ 0.05), § Paired "t" test significant at 0.01 level (p≤ 0.01).

Table 17, Article 5. *Pearson's Correlation Coefficient test comparing the GCF and Serum Cytokines to Weighted Variables among the Study Groups*

Gingival Crevicular Fluid													
Cytokine	**Variables**	**1**	**2**	**3**	**4**	**5**	**Cytokine**	**Variables**	**1**	**2**	**3**	**4**	**5**
IL-1β	BOP			,336*			GM-CSF	ART				-,445*	
	Smoking	-,878*		-,341*				BOP				,442*	
	BMI					,403*	INF-γ	CD4+			-,345*		
IL-4	BOP			,380*	,441*	,317*		BOP				,419*	,326*
	Smoking			-,404**			MCP-1	Smoking	-,878*				
	BGL	,845*						BMI					,382*
	BMI					,354*	MIP-1β	CAL		-,747*			
IL-6	PPD/CAL			,367*				Teeth					,370*
	Smoking			-,456**				Smoking	-,878*				
	BMI				,430*	,345*	TNF-α	Smoking	-,878*				
IL-7	BOP				,466*			BMI				,449*	,530**
	Smoking	-,878*											
	BMI					,373*	**Serum**						
IL-8	CD4+	-,812*					IL-2	Smoking				,458*	
	CAL	,841*					IL-6	PPD/CAL				-,427	
	Teeth			,399**				CAL				-,437	
	BMI					,361*	IL-8	Smoking				-,440*	
IL-10	CD4+			-,438**			IL-12	PPD/CAL					,416**
	PPD				,468*			Smoking				-,438*	
	PPD/CAL			,324*			IL-13	ARV			,321*		
	BOP				,419*		IL-17	CD4+			,316*		
	Teeth			,376*				PPD/CAL					,343*
	Smoking	-,891*						Teeth					,392*
	BMI				,447*	,423**		BMI			,355*		
IL-12	BOP				,448*		G-CSF	Teeth					,390*
	BMI					,359*		Smoking				-,451*	
IL-13	PPD/CAL		,791*				MCP-1	PPD/CAL					-,334*
	BOP				,439*			PPD					-,358*
	Smoking	-,878*						BOP					-,329*
IL-17	BOP					,370*	MIP-1β	Smoking	,878*				
	Smoking			-,397*	,372*		TNF-α	BOP			,381*		
	BMI				,342*								

G-CSF	CD4+			-,373*		
	PPD/CAL		,737*	,433**		
	BMI					,414**

Correlations coefficient ≥0.30 were considered medium effect size, statistically significant *($p \leq 0.05$) and **($p \leq 0.01$), Study groups 1 (Non-ART), 2 (ART Naïve), 3 (Short-term ART), 4 (Long-term ART) and 5 (Non-HIV), ART (Antiretroviral Therapy), BOP (Bleeding On Probing), BGL (Blood Glucose Level), BMI= Body Mass Index (kg/m2), Teeth (Number of teeth), Bleeding On Probing, PPD= Probing Pocket Depth (mm),CAL= Clinical Attachment Level (mm), PPD /CAL = Sites with PPD ≥ 4 mm and CAL ≥ 3 mm

Table 18, Article 5. *Statistically Significant Independent Predictors of Multivariate Linear Regression Models by Study groups of HIV Infection and non-HIV subjects*

Regression Model Subgroup	Predictor Variable	R^2	Durbin-Watson test	*F*	ANOVA*	*B*	*SE*	Breusch-Pagan test	X^2 *	HCSE	p-value†*
Non-ART	Serum IL-2	.151				.115	.019			.075	0.12
	GCF G-CSF	.254				.008	.002			.003	0.03
	Serum MCP-1	.297				-.261	.082			.106	0.01
	GCF IL-2	.332				-1.07	.493			.621	0.08
	GCF MIP-1β	.366				.019	.006			.015	0.21
	GCF IL-8	.394				-.003	.001			.001	0.04
	Model Summary	.394	1.12	11.94	0.0001	.027	.024	96.08	0.0001	.023	0.25
ART Naïve	None	/	/	/	/	/	/	/	/	/	/
Short-term ART	GCF G-CSF	.351	.347	52.47	0.0001	-.007	.003	28.57	0.0001	.002	0.001
Long-term ART	Serum IL-8	.075				5.6	2.55				
	Serum GM-CSF	.112				.054	.025				
	Model Summary	.112	0	4.73	0.004	1.34	.513	7.04	0.07	/	/
Non-HIV	None	/	/	/	/	/	/	/	/	/	/

ART (Antiretroviral therapy), HIV (Human Immunodeficiency Virus), GCF (Gingival Crevicular Fluid), G-CSF (Granulocyte Colony-Stimulating Factor), GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), MCP-1 (monocyte chemotactic protein-1), MIP-1β (macrophage inflammatory protein-1β), R2 (Coefficient of multiple determination), F (Statistically expected level of heterozygosity), B (Unstandardized regression coefficient), SE (Standard Error), X2 (Pearson's chi-squared test), HCSE (Heteroscedasticity-consistent Standard Error estimator), †p-value from HCSE test, * Significant at 0.05 level ($p \leq 0.05$)

Chapter 5: Discussion

Chapter 5
Discussion

Molecular epidemiology and biopsychosocial unique approach systems are required to advance towards a better assessment and understanding of the complex interactions between HIV and its human host. This is the first research work that has evaluated in México the biopsychosocial risk factors of oral pathologies in HIV, determining the relationship between oral-systemic health status and antiretroviral treatment. Understanding the molecular interactions in the microbiome-virome and host's immune system using 'molecular profiling' and 'molecular perturbation' approaches through a combination of multiomics [92], is one of the main challenges towards discerning among the convoluted diverging and converging signaling pathways between human oral physiological and pathological states.

In the current study, most people living with HIV/AIDS attended a dental office one or more times a year for oral health care, as they recognize that oral diseases affect their overall state of health. The study of the current cohort indicate socioeconomic and education-related determinants related to social inequalities in HIV care [130]. This research has evaluated for the first time the biopsychosocial receptivity of a Mexican MSM group for the implementation of PR-HIV in the dental consultation in a voluntary, informed and consensual manner. Also, it is the first to develop and evaluate a psychometric scale of the perception of stigma and discrimination associated with sexual orientation and HIV/AIDS in the dental practice. As in other investigations [149–152,154,159], our results suggest that the dental consultation could be a potential location to perform PR-HIV and a favorable site for the early diagnosis of HIV-1/2 in one of the key populations most affected by the HIV pandemic [163].

MSM agreed that (i) dentists must be qualified to treat them; (ii) it is important to inform dental professionals about one's HIV-positive diagnosis; and (iii) that dentists must keep their patient's dental record information confidential.

In the end, patients decline to disclose their HIV-positive status to dental professionals. Stigma is a social process or personal experience which influences all aspects in one's life. Thus, the HIV/AIDS diagnosis is not divulged by people suffering from the condition to avoid being excluded socially. That is what Goffman calls "concealment" [93].

Similar to what was shown globally in other studies [131–133] with different population groups affected by HIV/AIDS pandemic, the main reasons why MSM do not disclose their HIV status to dentists are: (i) fear of being shunned, (ii) inconveniences that may arise in the dentist-patient relationship, and (iii) one's right not to disclose their diagnosis. Also, it is essential to consider that the majority of people diagnosed with HIV each year are MSM and that one-third of the new infections are attributed to those who were unaware they were infected [16–18,141].

Although our results have shown a low percentage of perceived stigma and discrimination in dental appointments, most MSM reported (through their answers to the questionnaire) not disclosing their HIV status to dental professionals, irrespective of whether previous experiences of stigma and discrimination in other situations or due to their collective social identity within a given context. Such omission may lead to workplace hazards for dentists and their staff, not only in the case of HIV transmission (and the provision of post-exposure prophylaxis) but also in the case of infection with other blood-borne pathogens, such as hepatitis B and C viruses [134,135,190]. Likewise, such practice and attitudes jeopardize the very health of MSM, as dental professionals will not be able to provide proper clinical care [136], and might prescribe a drug that could enhance or antagonize antiretroviral therapy [137–139].

Unlike the study by Blackstock et al. [158], who reported an undiagnosed HIV prevalence rate of 0.5% in the general public in a hospital-based dental clinic, our study had an undetected prevalence of 1.08% in a higher risk HIV key population in a private dental setting. Like Pollack et al. [163], we found that individuals with a high risk of HIV infection have been in recent contact with dental service provider. Therefore, the high HIV prevalence rate in MSM and their

frequent contact with dental providers may be indicative that the implementation of PR-HIV in the dental office would contribute to the achievement of UNAIDS public health goals 90-90-90 to help end the aids epidemic [18,141,143], by providing a timely detection service and a linkage to the "HIV care continuum" [161,162] with emphasis on key and vulnerable populations.

From a biologic perspective, in this study we determined the concentrations of different cytokines from GCF and serum in an endemic population as part of an effort to identify a single biomarker or combination of cytokines which may have a potential to detect differences in HIV stages of infection based on age-specific CD4+ T-cell count and ART compared to non-HIV-infected individuals. Up to our best knowledge, this is the first study to report the levels and correlation of 17 GCF and paired serum cytokines in HIV-infected and HIV-uninfected individuals.

We demonstrated that 16 of the 17 researched biomarkers in the GCF samples could be detected using the multiplex bead immunoassay, and the levels of 8 GCF biomarkers (IL-1β, IL-4, IL-6, IL-7, IL-8, IL-13, INF-γ, and MIP-1β) correlate with pair serum biomarkers in several HIV/ART stages. Also, GCF biomarkers reflect systemic and oral clinical variables such as CD4+ count, ART guideline, BMI, BGL, BOP, PPD, CAL, the number of teeth and smoking habit. Moreover, in this study differences were observed in cytokine levels among subjects in a particular HIV/ART stage and those with non-HIV infection. Also, analyzed GCF and serum biomarkers discriminate between all studied groups, and through MLR we found that a combination of cytokines (GCF IL-8 and G-CSF, and serum IL-8, MCP-1, and GM-CSF) gave better discriminatory level in different HIV/ART stages. These findings correlated with those reported by other researchers [174–176].

Oral innate immunity helps maintain oral health through a multitude of innate defense mechanisms. Nevertheless, various oral infections and malignancies may evolve when it is impaired either by local or systemic causes [177,178]. Not to mention that it also appears to be modulated with the use of ART [178,179]. However, with the introduction of ART, HIV oral manifestations

have become less widely seen in HIV-infected individuals [180,181]. In accordance, the prevalence of oral lesions was rarely seen in our study, to such a degree it was not possible to correlate GCF and serum cytokines with such manifestations. Of interest, no oral warts were diagnosed among subjects.

Nonetheless, ART provides an inadequate immune reestablishment of the oral epithelial cells of HIV-infected individuals, and the toxic side effects of ART and HIV chronicity silence the expression of multiple proteins that in healthy individuals, function to provide tough innate immune responses and battle cellular stress [182]. Our together with previous research findings [176], suggest that HIV infection and the use of ART may alter oral innate immunity and levels of circulating oral cytokines. However, no significant differences were noted in the expression of IL-4, IL-5, IL-8, IL-13, IL-17, GM-CSF, INF-γ, MIP-1β, and TNF-α according to their ART status.

HIV-infected subjects with or without ART are susceptible to comorbid fungal, bacterial, and viral infections in the oral cavity (e.g., periodontal disease). Oral microbial growth and the emergence of these or their byproducts accompanying chronic oral inflammatory diseases have the capability to reactivate HIV-1 from latently infected cells, showing a relationship of immature and mature dendritic cells, macrophages or T-cells, and could be risk modifiers for HIV-1 replication, systemic immune activation, and AIDS progression [43,168]. Numerous cytokines are released from the above mentioned cells, and the presence of a large number of cytokines, especially pro-inflammatory and inflammatory cytokines, in the GCF have been considered as potentially useful diagnostic or prognostic biomarkers of periodontal destruction [173]. In the present study GCF IL-6, IL-10, IL-13, G-CSF, and serum IL-6 correlate with PPD ≥4mm and CAL ≥3mm in HIV-infected subjects and were also statistically significantly associated with ART status. Likewise, serum IL-12, IL-17, MCP-1 correlate with PPD and CAL in HIV-uninfected subjects. Present results indicated that HIV-infected subjects who were not on ART had a greater risk of having periodontal pockets than those on ART.

Furthermore, medium to high positive PCC was found among GCF IL-1β, IL-4, IL-7, IL-10, IL-12, IL-13, GM-CSF, INF-γ, serum TNF-α and BOP in HIV-infected subjects who were in short and long-term ART. In like manner, there was significant association among GCF IL-8, IL-10 and the number of teeth of HIV-infected individuals in short-term ART, as well as GCF MIP-1β, serum IL-17 and G-CSF did the same but in the non-HIV-infected subjects. While smoking habit, was found to influence the expression of GCF IL-1β, IL-4, IL-6, IL-7, IL-10, IL-13, IL-17, MCP-1, MIP-1β, TNF-α and serum IL-8, IL-12, G-CSF MIP-1β in HIV-infected subjects. Notwithstanding HIV stage, ART, and age are not self-reliant risk factors for variations in the periodontal status of HIV-infected subjects, the degree of periodontitis risk seems to be higher in HIV-infected than in HIV-uninfected individuals; some studies correlate these findings with higher prevalence of smoking and poorer oral hygiene in HIV-infected individuals, as well as a possible effect of HIV-induced immunodeficiency [183,184].

Cytokines concentrations during acute HIV-1 infection are predictive of HIV disease progression [185]. In the present study GCF IL-8 and G-CSF as well as serum IL-8, MCP-1 and GM-CSF were found to be useful biomarkers for the detection of disease presence and its severity due to HIV infection and ART use. HIV-infected individuals have shown that IL-8 A/T genotype carriers are more susceptible to a diversity of diseases [186]. In our study, negative correlations were found between GCF IL-8 levels within the Non-ART subgroup and their corresponding CD4+ count. Additionally, as in other studies [187] IL-10, G-CSF and INF-γ were each found inversely associated with the CD4+ T-cell count. Moreover, our results have shown serum GM-CSF inversely associated with ART guideline in the long-term ART subgroup. Nevertheless, lower or unaffected levels of GM-CSF in serum profiles of HIV-suppressed subjects have been reported [188,189].

Chapter 6: Conclusion

Chapter 6
Conclusion

The contact hypothesis suggests that facilitating social interaction between people living with HIV/AIDS and others (e.g., healthcare providers, friends, family, co-workers, etc.) may help to reduce prejudice, stereotypes, and discrimination among others via the mechanisms of increased knowledge of HIV, reduced social anxiety regarding PLWH, and increased empathy towards PLWH [123]. As stigma and discrimination place people at a substantial social disadvantage, it increases their exposure to risks and limits access to protective factors, potentially adding to their burden of disease or disability. Stigma not only predisposes PLWH to greater HIV- and AIDS-related stigma and discrimination, but also critically reinforces stereotyping and status loss of all them, regardless of how they may have acquired the infection. In such manner, underestimating the insidious power of stigma jeopardizes the success of public health programs aimed to prevent, timely detect, and treat HIV and AIDS.

Accordingly, to the Global Report 2013 of the Joint United Nations Program on HIV/AIDS, mostly all countries reported the existence of laws against discrimination that protect PLWHA. In México – based on the provisions of the first article of its federal constitution and on the first article, second paragraph, section II of the federal law for preventing and eliminating discrimination – it is illegal to stigmatize and deny rights that are afforded to all other citizens. Consequently, denying oral health care to PLWHA and other patients with infectious diseases is discrimination, as it violates the Universal Declaration of Human Rights, such as the right to adequate health. Nonetheless, the lack of accessible legal services leads to the frequent neglect of many HIV-related discrimination cases.

Both realities (individuals who chose not to disclose their HIV status and dental professionals who deny care to people with infectious diseases) do not ensure that dental professionals or their patients avoid being exposed to HIV and

other pathogens, as individuals living with HIV or other infectious diseases may not be aware of being infected. For that reason, dentists and all health care professionals are responsible for and ethically bound to seek training concerning the treatment of HIV and other diseases in its category. They also must keep up-to-date regarding gender studies, diversity, and human rights, to keep high professional standards and to ensure all patients are provided dignified and egalitarian care. From our perspective, it is essential to generate public health programs that include the participation of dental care professionals beyond the fight against caries or gum disease, but also actively collaborating in the international response to the HIV/AIDS epidemic.

The current study may contribute to a better biopsychosocial understanding of HIV/AIDS in México. Omics analyses of GCF, measuring microbial and host interactions in association with the outbreak and progression of periodontal diseases, still show the potential to expand the landscape for the discovery of diagnostic, prognostic and therapeutic markers. Future large-scale studies need to be done to verify findings from this study and to discern into the molecular mechanisms of how HIV and ART modify the expression of cytokines and other systemic and oral innate immune factors in GCF and serum over time. Multiomics milieu will be transformed by the evolution of high-throughput techniques and bioinformatics resources, facilitating novel approaches, rapid analysis, and interpretation of large datasets. Thus, providing health care professionals with new insights into oral health and disease, potentiating multiomics clinical application and advancing towards the implementation of a 'precise medicine and dentistry' within the next decade. In the interim further and better designed large-scale longitudinal studies in various populations, with the application of nouveau multiomics sciences and technologies. The use of biopsychosocial determinants for assessing potential targets for HIV/AIDS may ultimately provide the means to modify epidemic and thus reduce the impact of HIV/AIDS on human health.

Thesis' final research highlights

1. Stigma and discrimination place people at a substantial social disadvantage.
2. Involvement of dental care professionals is essential in the international response to the HIV/AIDS epidemic.
3. Proposed oral biomarkers correlated with systemic and oral clinical variables in HIV.
4. Cytokines expression vary among subjects in a particular HIV/ART stage.
5. HIV stage, ART, and age are not self-reliant risk factors for periodontal breakdown.
6. IL-8, MCP-1, and GM-CSF may be useful biomarkers in HIV infection and ART use.
7. G-CSF and INF-γ were found inversely associated with the CD4+ T-cell count.

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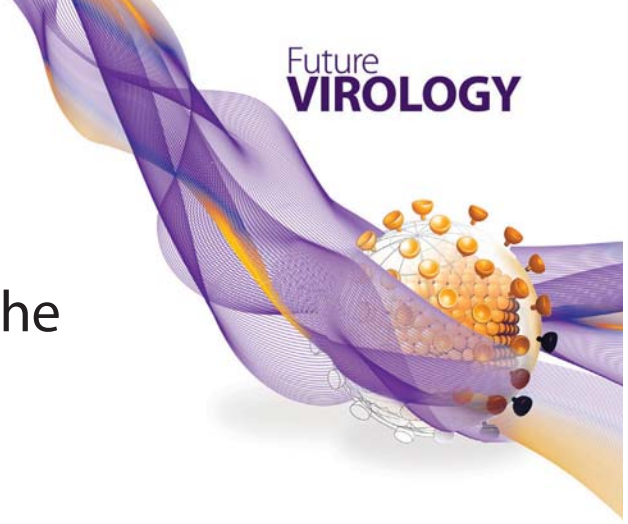
Appendix A

Appendix A

Original published versions of the articles as they appear in their respective journals (Please note article #1 and #4 are still in print you will see in their place editors' proof of acceptance. Also, notice that article #3 was published in English and Spanish language, and article #4 only in Spanish).

EDITORIAL



Contribution of multi '-OMICS' to the future of oral health

"-OMICS' technologies including epigenomics, genomics, exomics, transcriptomics, proteomics, metabolomics … generate and process massive biological data."

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The scientific '-OMICS' turmoil began at the end of the last century, leading to a new and deeper level of complex biological insights that completely change the way scientist understands the molecular mechanisms of the diseases. Health professionals in the post -omics era will use thousands of disease-associated biomarkers provided by high-throughput technology. Thus, clinical practice will grant the adaptation of multiomics data to personal healthcare.

Multiomics biomedical approach resides on wide profiling methods that haul considerable amount of -omics data. '-OMICS' technologies including epigenomics, genomics, exomics, transcriptomics, proteomics, metabolomics and nascent fields such as viromics – the study of virus in our body and how they might cause certain conditions – coupled with bioinformatics and biostatistics to generate and process massive biological data. Nevertheless, multiomics gained results and knowledge are assessed individually rather than conjointly. In this manner, interactomics deals with studying both the interactions and the consequences of those interactions. Recent studies of metagenomes have opened the door to characterize the size and diversity of the human 'virobiota' and to identify its associated genes (the 'virome'), promoting the emerging field of host–virobiota interactions.

Viruses prevail on or in just about every species and every ecological niche [1], although viral structure differ considerably among different types of viruses, many of them can colonize the human oral cavity as well as other microbes such as oral bacteria [2,3]. The mouth offers a

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splendid portal to a new host. Viruses in the oral cavity are most commonly acquired in early childhood, from mother to infant via infected saliva, or in adulthood transmitted by the oral–oral, oral–genital or oral–anal route, but other factors such as environmental, developmental, social, behavioral or others may also play a major role ('exposomics'). Novel findings had highlighted the role of the immune system in shaping the composition of the oral virobiota and consider how resident viruses may impact host immunity [4]. Many viruses have 'high' mutation rates and constantly shift as means of eluding the host's immune system. Evidence suggests a bidirectional association with a range of oral and systemic diseases [5,6].

"Evidence suggests a bidirectional association with a range of oral and systemic diseases."

Leading-edge scientific research has revealed the possible role that latent and active viral infections have in the etiopathogenesis, progression and severity of periodontal diseases (PDs) [2]. After dental caries, PDs are the second most prevalent oral diseases affecting up to 90% of the worldwide population, contributing to the global burden of chronic disease and meeting criteria as a public health problem [7,8]. Essentially PDs are poly-periodontopathogenic and multifactorial infectious diseases which trigger chronic inflammatory and immune responses that lead to tissue destruction of the supporting structures of the teeth, also known as periodontium gingiva, periodontal ligament and alveolar bone. PD is a chronic oral infection associated with numerous oral microbial species organized in planktonic or biofilms communities.

Specific microorganisms are believed to play an essential role in PDs, so far their relative numbers and significant contribution to the initiation and progress of the disease is still unclear [9,10]. The collection of microorganisms found in the oral cavity has been referred to as the oral microflora, the oral microbiota or currently as the oral microbiome. The ultimate diversity of the oral microbiome was estimated to be around 19,000 phylotypes. Notwithstanding, viruses surpass microbial cells 10:1 in most environments, as far as viruses inhabit oral tissues, saliva, gingival crevicular fluid and the subgingival and supragingival biofilms, little is still known about how oral viruses are spread throughout the oral cavity and their role as constituents of the human microbiome. However, viral sequence databases have considerably expanded since the beginning of the viromics era and particular species are detected now and then in the oral cavity [11].

Human viruses may occur in periodontal lesions with relatively high prevalence; common conditions are the different herpes viruses, human papillomaviruses, hepatitis-causing viruses and HIV [12]. Viruses that replicate or not in the oral tissue but that are capable of infecting and impairing immune-mediated response, resulting in proinflammatory signaling events or bacteriophages that predate upon cellular oral microbiota rather than the human host may contribute in shifting oral microbiome diversity and constitution, causing an increased pathogenicity of the periodontal microbiota [2,3]. Viral infection of certain cell types, upregulate cellular surface receptors enhancing polymicrobial adhesion. Therefore, viral coinfection with other polymicrobial pathogens may lead to immunomodulatory effects that repress more than one microorganism clearance mechanisms and therefore increasing colonization, being a key issue in host–symbiont evolutionary dynamics where hosts and their symbionts speciate in parallel, by cospeciation or through host shifts.

Periodontal viral–polymicrobial interactions initiate various and distinct mechanisms. For example, virus-induced alteration in epithelial cells, reduced cellular functions, cell death/decreased junctional epithelium or epithelial barrier function, virus-upregulated cellular surface receptors for polymicrobial adhesion, virus-enhanced polymicrobial colonization, virus-mediated inhibition of innate immune cells, suppressed phagocytosis, impaired polymicrobial killing, depressed leukocyte migration, antiviral immune molecules, suppressed innate immunity, inhibited IL-17 responses, dysregulated inflammation, enhanced periodontal tissue injury from increased inflammation (e.g., chemokines) and increased susceptibility from induction of anti-inflammatory cytokines. Therefore, viral–polymicrobial interactions may explain in part the etiopathogenesis and progression of PD [2].

Progression of PDs in the presence of virus-induced infection is dependent on the immune competency of the host and the local inflammatory response to typical and atypical subgingival microorganisms [13]. PDs may participate in the wound healing process and tissue destruction via the inflammatory process and various dental plaque biofilm periodontopathogens induce different cytokine response profiles in gingival epithelial cells that may reflect their particular virulence or commensal status. The aforementioned suggests that the inflammatory and

infectious components of PD as an oral infection might have the capacity to prompt viral reactivation and recrudescence. Nowadays it has become evident that cytokines have a major relevance in immune responses to persistent viral infections and that the functional impact of a specific cytokine can be strikingly distinct or even opposite in chronic versus acute contexts of infection [13,14].

Some theories about common susceptibility, systemic inflammation with increased circulating cytokines and mediators, direct infection and cross-reactivity or molecular mimicry between oral microbiome–virome antigens and self-antigens try to explain periodontal etiopathogenesis and disease progression. Thus, understanding the molecular interactions in the microbiome–virome and host's immune system using 'molecular profiling' and 'molecular perturbation' approaches through a combination of multiomics [15], is one of the main challenges toward discerning among the convoluted diverging and converging signaling pathways between human oral physiological and pathological states.

Oral multiomics milieu will be transformed by the evolution of high-throughput techniques and bioinformatics resources, facilitating novel approaches, rapid analysis and interpretation of large datasets. Thus, providing healthcare professionals with new insights into oral health and disease, potentiating multiomics clinical application and advancing toward the implementation of a 'precise medicine and dentistry' within the next decade. In the interim further and better designed large-scale longitudinal studies in various populations, with the application of nouveau multiomics sciences and technologies; the use of molecular determinants for assessing potential targets for the inhibition of co-adhesion, biofilm development and regulation of the ecological balance in the oral cavity; may ultimately provide the means to modify microbiome–virome colonization and thus reduce the impact of oral diseases on human health. In the following years, oral treatment based upon multiomics – genetic and nongenetic – criteria will contribute to a more 'precise medicine and dentistry' accentuated upon individualized periodontal prevention, diagnosis and treatment strategies, along with a professional practice focused on specific biological, psychological, social and environmental contexts.

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Perceived HIV-associated stigma among HIV-seropositive men: psychometric study of HIV stigma scale

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Objectives: To assess the internal consistency and factor structure of the abridged Spanish version of the Berger HIV Stigma Scale (HSS-21), to provide evidence for its convergent and discriminant validity, and to describe perceived stigma in an urban population from northeast Mexico.

Methods: Seventy-five HIV-positive men who have sex with men (MSM) were recruited. Participants answered the Spanish versions of three Likert-type scales: HSS-21, Rosenberg's self-esteem scale, and the abbreviated version of the Zung's Depression Scale.

Results: HSS-21 showed high reliability and validity; its factor structure included four components: concern with public attitudes; negative self-image; disclosure concerns; and enacted stigma. The level of stigma was high in 27 out of 75 (36%) participants; nevertheless, the score found in the component related to disclosure concerns indicated high level of stigma in 68% of participants. The score of HSS-21 was positively correlated with the score of depression and negatively correlated with the score of self-esteem.

Conclusion: Results demonstrated high reliability for the HSS-21; correlations with other scales supported its validity. This scale demonstrated to be a practical tool for assessing stigma among Mexican HIV-positive MSM. High level of stigma was found only in the factor related to disclosure concerns.

Policy implications: Identifying HIV-associated stigma through a short, reliable, and validated instrument will allow the development of interventions that cope and manage stigma in HIV-positive MSM. HSS-21 distinguishes between different dimensions of stigma and will contribute to a better understanding of this phenomenon.

Keywords: HIV, AIDS, social stigma, men who have sex with men, public health, validation studies, psychometrics, Mexico

Introduction

As the human immunodeficiency virus (HIV) epidemic enters in its fourth decade, it is still regarded as an important public health issue worldwide. In turn, the social perception toward those individuals who live with HIV and AIDS (PLWH) continues to be a negative one. HIV's ways of transmission, its implications regarding the more traditional gender roles, and its association in the social imaginary to socially marginalized groups are the cause of stigma and discrimination in various circles (1). Stigma can be conceptualized as a "mark" (attribute) linking an individual with a set of undesirable characteristics (stereotypes) (2, 3). Three main sub-types of stigma have been described: *acted stigma* refers to the actual experience of acts of discrimination. *Perceived stigma* refers to the fear experienced by an individual in the presence of negative attitudes of a society toward a given attribute considered as undesirable, for example, an ethnic group, a disease, some personal behaviors, etc. A third sub-type is *internalized stigma* (*self-stigma)*, a term which includes the negative beliefs, opinions, and feelings that an individual holds toward a given attribute and toward himself/herself as a result of an internalization process of the societies' opinions and beliefs toward such attribute (4).

The term HIV- and AIDS-related stigma (HARS) makes reference to the negative appraisal that society as a whole give to any person who lives, or is believed to live with HIV and AIDS. In the psychosocial model developed by Berger et al. (5), the term "*perceived stigma*" is conceptualized as the perception of PLWH of social disqualification (incomplete social acceptance or even rejection), denial or limitation of opportunities (e.g., housing and employment offers, access to medical services, etc.), as well as negative changes to their social identity as a result of their HIV serostatus. This stigmatization process is also associated to other factors involved in judgment formation, such as sexual orientation, diversity of sexual partners, and use of illegal substances. This "blame the victim" attitude increases the isolation sensation and the interiorized sense of shame by the HIV infected individual (1).

From a public health perspective, HARS is an important factor that hinders voluntary testing for a timely diagnosis and treatment of HIV infection (1, 6, 7). HARS is also an obstacle for individual's serodiagnosis disclosure to their sexual partners, thus prolonging sexual risk behaviors and contributing to HIV transmission (6, 8); particularly in socially stigmatized and discriminated groups such as gay men and men who have sex with men (MSM), where social conditions generated by HARS lead MSM to participate in sexual risk behaviors with a higher risk of acquisition and propagation of HIV (9, 10). Thus, it is not a surprise that worldwide gay men and other MSM are 19 times more likely to be living with HIV than the general population (11). The incidence of HIV among MSM is rising in several parts of the world and Mexico is not the exception (11–13).

Likewise, HARS can also lead PLWH to postpone the use of medical public health services (6, 14), to a suboptimal adherence to antiretroviral therapy (15–17), and to a poor overall health (7, 18). Furthermore, HARS is associated with stress, anxiety, depressive symptomatology, and a decreased quality of life (19, 20). Aforementioned, HARS and its multiple consequences have a deep impact on the HIV epidemic development by reinforcing existing social inequalities with serious implications in public health policies.

Several instruments have been developed and validated to evaluate HARS in PLWH (5, 21–23). One of the best known is the HIV Stigma Scale (HSS-40) developed by Berger et al. (5). This scale has been used to assess perceived stigma among adult PLWH (24–27), likewise it has been adapted for PLWH children (28), and as well to assess perceived stigma of other diseases (29).

The HSS-40 scale assesses how PLWH feel in regards to four dimensions of stigma: (a) personalized stigma (or acted stigma), (b) individuals' concerns related to disclose his/her own HIV serostatus, (c) negative self-image (self-stigma), and (d) individuals' concerns related to public attitudes toward PLWH. The instrument has shown evidence of construct validity and high internal consistency for a set of 40 items ($\alpha = 0.96$), as well as for its factors ($\alpha = 0.90$–0.93) (20). The HSS-40 Spanish language translation, adaptation, and validation were done by Franke et al. (30), who also developed a shorter version (HSS-21). Likewise, as the complete scale version, the HHS-21 also showed evidence of construct validity ($\alpha = 0.84$ as a total score), and an adequate-to-high internal consistency ($\alpha = 0.68$–0.80) in assessing the four dimensions of stigma.

Since HARS not only represents one of the greatest obstacles in preventing new HIV infections but also deeply and negatively affects multiple aspects of HIV treatment, as well as the physical, mental, and emotional well-being of the PLWH (31), it becomes important to assess perceived stigma among PLWH. Considering the lack of adapted and validated instruments for HARS assessment that could improve current HIV and AIDS public health policies in México (e.g., Healthy Border 2010/2010 initiative), this study aims to evaluate the internal consistency, factorial structure, convergent, and discriminant validity of the HSS-21, as well as to describe HARS in a sample of HIV-positive MSM in Nuevo León (Mexican border state with U.S. Texas state).

Materials and Methods

Participants

Research involved 185 MSM and who collaborated with non-governmental and community-based organizations members of Nuevo Leon's Multisectoral STI/HIV/AIDS Response Board (MEMUREVIH). Inclusion criteria involved only male subjects who had had sexual experiences with other men, HIV-positive, aged 18 years or more, and who resided in Nuevo León, Mexican state. Taken into account that most HIV-positive MSM do not disclose their serological HIV status, this study adopted a non-probability sampling and a respondent-driven sampling. The sample consisted of 75 MSM who voluntarily declared to have an HIV-positive serodiagnosis, and who responded to a written or an online survey.

Recruitment

The data collection process lasted 60 days. Prior to the data collection process, collaboration was requested to the different non-governmental and community-based organizations members of MEMUREVIH to implement the survey in their office location and to their MSM affiliates. Four properly qualified surveyors

visited all sites and applied the written or online surveys on the previously agreed dates and time with the aforementioned organizations.

Procedure

In order to guarantee information input reliability, a digital survey database was created and submitted to a double-quality control check. All subjects were given both verbal and written information about the nature of the study, prior to responding to either the written or online questionnaire. The study procedures were undertaken according to ethical principles with the understanding and written consent of each subject. The study protocol was reviewed and approved by the ethics and research committee at the Tecnologico de Monterrey. Anonymity was guaranteed throughout the process, as well as confidentiality of both physical and electronic data. To access the *online* questionnaire, respondents accessed the survey via the website – (www.encuestas.no-ip.org), and none of the log-in data (IP address, etc.) was stored in the electronic access. Completion of either the written or online survey took an average of 25 min.

Instrument

The study used an analytical-type structured questionnaire (closed-ended questions and multiple response alternatives) in either written or online formats. The questionnaire explored socio-demographic characteristics, perception of HARS, self-esteem, and depression by means of the following Likert-type scales:

HIV Stigma Scale (HSS-21)

The abridged and Spanish-adapted version of the HIV stigma scale (HSS-21) used in this study was developed by Franke et al. (29); it is composed of 21 positively keyed items that are evaluated along a 4-point Likert-type scale (from 1 = strongly disagree to 7 = strongly agree), and was shown to be internally consistent. The sum of these items yields a total score, with higher scores representing a greater degree of perception of stigma.

Rosenberg Self-Esteem Scale (RSS-10)

It is composed of 10 items rated on a 4-point Likert-type scale. Possible scores range from 10 to 40, with higher ones indicating greater self-esteem. Among men, scores lower than 28 indicate low self-esteem (32).

Zung Depression Scale (ZDS-10)

Zung depression scale constituted of 20 items that involve affective, psychological, and somatic symptoms. Respondents indicate the frequency with which any symptom is experienced: the higher the score, the greater the degree of depressive symptoms. Diaz et al. (33) developed and validated a short, Spanish-adapted version of this scale (ZDS-10); the cut-off point to distinguish the presence of clinically significant depressive symptoms is 22 (sensitivity = 92.3%, specificity = 71.4%).

Statistical Analysis

Two psychometric properties of the items in HSS-21 were estimated: discrimination and internal consistency. Discrimination was estimated by the ability to differentiate in a statistically significant manner the high score group (percentile equal or >73) and the low score group (percentile equal or <27) in the sum score of the 21 items. A mean difference higher than two was considered to be significant, as well as a reliable discriminant property for each one of the assessed items. The internal consistency of the items was estimated by means of: corrected correlation, estimation of Cronbach's alpha excluding the item, and communalities. It was sought that the corrected correlation values were >0.30, that a non-decrease value of Cronbach's coefficient alpha after eliminating the item could demonstrated a reliable internal consistency, and that the communalities values were >0.20. Consistency was interpreted as high when it expressed a value equal or >0.70. The distribution fitting to a normal curve was contrasted using Kolmogorov–Smirnov test or Shapiro–Wilk test (34). All data were analyzed with SPSS® software (version 20.0).

The dimensional structure was studied by means of exploratory factor analysis; considering appropriate factoring characteristics: (a) that the determinant of the correlation matrix would tend to 0 ($|R| < 0.01$), (b) $KMO > 0.6$, and (c) that the null hypothesis of equivalence of the correlation matrix to an identity matrix by Bartlett's sphericity test would be rejected (34). The extraction was executed by generalized least squares (GLS) and the Promax rotation method of the factor matrix, adjusting the solution to four factors in agreement with the structure found in other studies (5, 30).

The correlations between factors were calculated by Pearson's correlation coefficient. The correlations between the HSS-21 scores and the EDZ-10 and RSS-10 scores were established by Spearman's *rho*. The significance of the score difference in the scales ZDS-10 and RSS-10 among the respondents who expressed or did not expressed HARS was carried out by the Mann–Whitney *U* test. The effect size was calculated by Cohen's d (34).

Results

Respondents

The 75 HIV-positive MSM respondents had an average age of 35 (SD = 7.38) years old. Median time since HIV infection diagnosis was 18 months. Average years in school was 13.93 (SD = 3.73) years. At the time of the survey 81.9% of men were working full time, while 10.6% worked part time, and 7.4% were unemployed. Moreover, despite of employment status, 69.2% indicated that they received a monthly income of ≤15,000 MXN ($ 1.146/867.45 €). Regarding sexual orientation, 88% of participants defined themselves as homosexual, 9.23% as bisexual, and 2.67% as heterosexual.

HSS-21 Descriptive Statistics

The HSS-21 mean total score was 76.28 (SD = 21.522) and its distribution was fitted to a normal curve (ZK-S = 0.67, $p = 0.20$). Considering the whole scale items, its mean can be transformed into a continued value between 1 and 7 or equal to 3.63. Using the same procedure, most items means scores were also between 2.5 and 4. However, eight items (V2, V6, V11, V12, V14, V15, and V17) had a mean value ≥4 (**Table 1**).

TABLE 1 | HSS-21 items' descriptive statistics, interpretation, homoscedasticity, discrimination, and internal consistency.

Item	Descriptive statistics						K–S		I	Homoscedasticity		Discrimination				Consistency		
	M	Mdn	Mo	SD	Sk	*K*	Z	*p*		*F*	*p*	MD	*t*	df	*p*	$r_{i,\,t-i}$	α_{t-i}	hi
V1	2.95	3	1	2.18	0.63	−1.03	0.29	0.00	2	1.67	0.20	2.7	−4.75	38	0.00	0.48	0.88	0.62
V2	4.73	5	5	1.84	−0.69	−0.17	0.30	0.00	3	18.10	0.00	2.5	−4.54	26.66	0.00	0.52	0.87	0.70
V3	3.85	3	3	2.23	0.16	−1.33	0.21	0.00	2	0.79	0.38	2.6	−3.86	38.00	0.00	0.38	0.88	0.70
V4	2.73	3	1	1.95	0.81	−0.47	0.28	0.00	2	2.10	0.15	2.2	−4.41	38.00	0.00	0.36	0.88	0.44
V5	3.21	3	1[a]	1.96	0.14	−1.36	0.25	0.00	2	0.05	0.82	2.4	−4.22	38.00	0.00	0.43	0.88	0.56
V6	4.07	5	5	1.65	−0.55	−0.39	0.33	0.00	3	3.63	0.06	2.6	−5.81	38.00	0.00	0.55	0.87	0.74
V7	2.52	1	1	1.83	0.83	−0.50	0.32	0.00	2	9.62	0.00	2.6	−5.64	30.76	0.00	0.56	0.87	0.71
V8	2.20	1	1	1.68	1.16	0.28	0.36	0.00	1	12.10	0.00	2.5	−5.54	29.67	0.00	0.55	0.87	0.62
V9	3.53	3	5	1.72	−0.16	−9.98	0.26	0.00	2	0.21	0.65	2.3	−5.04	38.00	0.00	0.40	0.88	0.64
V10	1.99	1	1	1.48	1.35	0.97	0.39	0.00	1	20.14	0.00	2.3	−5.68	23.89	0.00	0.56	0.87	0.68
V11	4.44	5	5	1.70	−0.52	−0.16	0.31	0.00	3	8.37	0.00	2.5	−5.15	32.44	0.00	0.55	0.87	0.73
V12	6.31	7	7	1.21	−1.94	4.45	0.42	0.00	4	3.35	0.07	0.5	−1.12	38.00	0.27	0.06	0.88	0.65
V13	3.00	3	1	2.00	0.67	−0.23	0.23	0.00	2	15.31	0.00	2.5	−4.86	26.32	0.00	0.41	0.88	0.60
V14	4.44	5	5	1.56	−0.50	0.55	0.32	0.00	3	0.02	0.90	2.7	−6.76	38.00	0.00	0.58	0.87	0.59
V15	4.23	5	7	2.39	−0.28	−1.48	0.21	0.00	3	9.30	0.00	4.4	−8.63	25.59	0.00	0.68	0.87	0.76
V16	2.16	5	5[a]	2.16	0.33	−1.12	0.21	0.00	1	6.81	0.01	2.7	−4.34	32.67	0.00	0.44	0.88	0.64
V17	4.84	5	7	2.13	−0.53	−0.99	0.23	0.00	3	6.73	0.01	3.3	−5.96	28.57	0.00	0.63	0.87	0.67
V18	3.87	3	3	2.07	0.44	−0.95	0.23	0.00	2	8.25	0.00	2.2	−3.47	31.76	0.00	0.32	0.88	0.77
V19	2.97	3	3	1.72	0.55	−0.36	0.24	0.00	2	2.25	0.14	2.1	−4.58	38.00	0.00	0.38	0.88	0.74
V20	3.37	3	1	2.02	0.26	−1.10	0.20	0.00	2	6.75	0.01	2.9	−5.22	29.50	0.00	0.53	0.87	0.62
V21	3.03	3	3	1.82	0.64	−0.30	0.25	0.00	2	9.76	0.00	3.1	−6.94	27.84	0.00	0.64	0.87	0.73

M, mean; Mdn, median; Mo, mode; SD, standard deviation; Sk, skewness; K, kurtosis; K–S, Kolmogorov–Smirnov test; p, probability; I, interpretation; 1, totally in disagreement; 2, in disagreement; 3, in agreement; 4, totally in agreement; MD, mean difference between the group with high scores and the group with low scores in the scale; df, degrees of freedom; $r_{i,t\text{-}i}$, correlation between the item and the scale; α_{t-i}, Cronbach's alpha coefficient after removing the item; hi, communality.

[a] *α_{t-i}, Cronbach's alpha coefficient after removing the item (significance $\alpha \geq 0.70$).*

Discrimination, Internal Consistency, and Validity of HSS-21 Items

HSS-21 presented a high internal consistency ($\alpha = 0.88$). Items expressed reliable internal consistency values, since deletion of none of them increased Cronbach's alpha coefficient. Items' corrected correlations ranged from 0.32 to 0.68 (except item V12, whose corrected correlation was 0.06). Initial communalities varied between 0.44 and 0.77, except for item V12 (MD = 0.05). Thus, with the exception of item V12, the remaining 20 items had reliable psychometric properties (**Table 1**).

HSS-21 Dimensional Structure

The correlation matrix of the 21 items of the HSS-21 scale showed adequate properties for factor extraction. Its determinant tended to 0 ($|R| < 0.01$), the *KMO* index was >0.6 ($KMO = 0.777$), and the null hypothesis of equivalence of the correlation matrix to an identity matrix by Bartlett's sphericity test was rejected [χ^2 (210, $N = 75$) = 752.413, $p < 0.001$]. Four components were extracted, which accounted for 60.51% of the total variance.

After rotating the factor component matrix by the Promax method and performing the extraction by GLS, four factors were found with a high internal consistency; they were constituted by positive indicators and factor loadings >0.32 (**Table 2**). The first factor (self-stigma, VNS) integrated by six items (V1, V4, V7, V8, V10, and V16) related to feelings of not being as good as others and emotion of guilt or shame ($\alpha = 0.81$). The second factor (acted stigma, VES) integrated by five items (items V13, V18, V19, V20, and V21) related to the consequences of others finding out the individuals' serodiagnosis and personal experiences of rejection ($\alpha = 0.83$). The third factor (concern about public attitude toward HIV and AIDS, VPA) integrated by five items (V5, V6, V9, V11, and V14) related to what PLWH believe that other people could think of them if they knew their serostatus ($\alpha = 0.83$). The fourth factor (PLWH concern about HIV serodiagnosis disclosure, VDC) integrated by five items (V2, V3, V12, V15, and V17) related to the perceived need of controlling HIV serodiagnosis information ($\alpha = 0.76$). Item 21 had a high factor loading in two factors. Nevertheless, including it in the second factor increased its internal consistency from 0.80 to 0.83, due to its content item 21 is highly related to acted stigma. The correlations between factors were medium ($r = 0.32$–0.46), with the exception of the correlation between factors 3 and 4, which was small ($r = 0.21$).

HSS-21 Factors' Descriptive Statistics

The score range for all items is from 1 to 7 and the higher score results are correlated to a high stigma. Considering the number of items in each of the four factors, their mean can be transformed into a continuous value within 1 and 7. Such value can be interpreted as the answer label for each item, dividing the answer range value by four intervals of constant amplitude. **Table 3** exposes factor descriptive statistics.

The mean of VNS can be interpreted as a non-definitive disagreement with HARS dimension. Means comparison among the 36 (48%) respondents who expressed stigma [$M = 5.04$, SD = 0.59; 95% IC = (4.85, 5.24)] and the 39 (52%) respondents who did not express stigma [$M = 3.02$, SD = 0.74; 95% IC = (2.78, 3.26)] were statistically significant ($p < 0.01$).

Also, VES mean can be interpreted as a non-definitive disagreement with HARS dimension. The comparison of means among

TABLE 2 | HSS-21 factors' loadings from exploratory factor analysis.

	Item	Factor			
		1	2	3	4
V6	Most people believe a person who has HIV is dirty	0.88			
V11	Most with HIV are rejected when others learn I have HIV	0.77			
V9	Most people think a person with HIV is disgusting	0.73			
V5	People with HIV are treated like despicable persons	0.71			
V14	Most people are uncomfortable around someone with HIV	0.59			
V21	People seem afraid of me because I have HIV	0.53			0.44
V7	Having HIV makes me feel unclean		0.93		
V8	I feel set apart, isolated from the rest of the world		0.71		
V10	Having HIV makes me feel I am a bad person		0.68		
V1	I feel guilty because I have HIV		0.67		
V4	I feel I am not as good as others because I have HIV		0.36		
V16	Having HIV in my body is disgusting to me		0.32		
V2	Telling someone I have HIV is risky			0.77	
V15	I worry that people may judge me when they learn I have HIV			0.76	
V17	I worry people who know I have HIV will tell others			0.69	
V3	I work hard to keep my HIV a secret			0.65	
V12	I am very careful whom I tell that I have HIV		−0.39	0.50	
V18	I regret having told some people that I have HIV				0.93
V19	As a rule, telling others has been a mistake				0.92
V20	Some people act as though it is my fault I have HIV				0.51
V13	Some people who know have grown more distant	0.37			0.48

Extraction method: GSL. Rotation method: Promax with Kaiser normalization.

the 23 (30.7%) respondents who expressed stigma [$M = 4.96$, DE = 0.69; 95% IC = (4.66, 5.26)] and the 52 (69.3%) respondents who did not express stigma [$M = 2.34$, SD = 0.91; 95% IC = (2.09, 2.60)] was statistically significant ($p < 0.01$).

The VPA mean can be interpreted as a non-definitive disagreement with HARS dimension. The comparison of means among the 40 (53.3%) respondents who expressed stigma [$M = 4.99$, DE = 0.65; 95% IC = (4.78, 5.20)] and the 35 (36.7%) respondents who did not express stigma [$M = 2.74$, SD = 0.75; 95% IC = (2.48, 3.00)] was statistically significant ($p < 0.01$).

Likewise, VDC mean can be interpreted as a non-definitive disagreement with HARS dimension. Means comparison among the 51 (68%) respondents who expressed stigma [$M = 5.59$, DE = 0.94; 95% IC = (5.32, 5.85)] and the 24 (32%) respondents who did not express stigma [$M = 3.10$, SD = 0.74; 95% IC = (2.79, 3.41)] were statistically significant ($p < 0.01$).

ZDS-10 Descriptive Statistics

ZDS-10 scale had an average score of 20.48 (SD = 4.82) with a non-normal distribution curve (ZK-S = 0.11, $p = 0.02$). Likewise, scores among the 48 respondents who did not express stigma showed a non-normal distribution curve (ZS-W = 0.93, $p = 0.01$). Whereas, distribution among the 27 respondents who expressed stigma was adjusted to a normal curve (ZS-W = 0.95, $p = 0.17$).

After running the Mann–Whitney *U* test, it was found that the respondents with HARS had significantly higher scores in ZDS-10 [$M = 22.41$, SD = 4.40, $n = 27$; 95% IC (20.67, 24.15)] than the scores of the respondents without HARS [$M = 19.40$, SD = 4.74, $n = 48$; 95% IC (18.02, 20.77)], with a medium size effect of stigma on the total ZDS-10 score; $Z = -2.37$, $p < 0.02$, $d = 0.65$, 95% IC (0.16, 1.13).

Of the 48 HIV-positive MSM respondents who did not express HARS, 14 (29.17%) presented clinically significant symptoms of depression, while 34 (70.83%) did not show such symptoms. Of the 27 respondents who expressed HARS, 16 (59.26%) showed clinically significant symptoms of depression, while 11 (40.74%) did not showed such symptoms.

RSS-10 Descriptive Statistics

The mean in the total score of the RSS-10 was 34.43 (SD = 4.78) with a non-normal distribution curve (ZK-S = 0.20, $p < 0.0.001$). Similarly, the distribution of the scores between the respondents who did not express stigma (ZS-W = 0.87, $p = 0.001$) and those who did express stigma (ZS-W = 0.88, $p = 0.007$) presented a non-normal distribution curve.

After running the Mann–Whitney *U* test, it was found that the HIV-positive MSM respondents who did not express HARS had significantly higher RSS-10 scores [$M = 35.53$, SD = 3.62, 95% IC (34.50, 36.60)] than those of the respondents who did express HARS [$M = 32.48$, SD = 5.93, 95% IC (30.14, 34.83)], with a medium size effect of stigma on the total RSS-10 score; $Z = -2.26$, $p < 0.03$, $d = -0$–67, 95% IC (−1.14, −0.18).

Of the 48 respondents who did not express HARS, one (2%) respondent presented a low self-esteem and 47 (98%) presented a high self-esteem. Of the 27 respondents who expresses HARS, six (22.2%) respondents presented a low self-esteem and 16 (77.8%) presented a high self-esteem.

Validity Evidences

The total HSS-21 score expressed convergent validity with a significant and direct correlation to the ZDS-10 total score. The factors that expressed a high correlation were VNS ($\rho = 0.336$, $p < 0.001$) and VES ($\rho = 0.252$, $p < 0.01$). Also, the total HSS-21 score demonstrated discriminant validity with significant and reverse correlation to RSS-10 total score. HSS-21 factors showed correlations from small (VNS, VDC, and VES) to trivial (VPA) with the RSS-10, but did not reached a statistical significance.

TABLE 3 | HSS-21 factors' descriptive statistics.

Factor	Descriptive statistics						K–S		Interpretation
	M	Mdn	Mo	SD	Sk	*K*	*Z*	*p*	
VNS	3.99	3.83	3.83	1.22	−0.17	−0.66	0.10	0.07	In disagreement
VES	3.15	3	1	1.48	0.56	−0.40	0.10	0.07	In disagreement
VPA	3.94	4.2	5	1.33	−0.22	−0.71	0.18	0.01	In disagreement
VDC	4.79	4.6	4.6	1.46	0.81	−0.47	0.10	0.07	In agreement

M, mean; Mdn, median; Mo, Mode; SD, standard deviation; Sk, skewness; K, kurtosis; K–S, Kolmogorov–Smirnov test; p, probability; VNS, negative self-image; VES, enacted stigma; VPA, public attitude; VDC, disclosure concerns.

Discussion

Stigma can be conceptualized as a deeply degrading attribute that binds an individual with one or more undesirable characteristics and finally diminish socially his/her self-image. Concern about stigma is widely extended among PLWH, although this is not universal (35). The results of the study determined that the Spanish-adapted version of the HSS-21 scale developed by Franke et al. (30) has good overall internal consistency, reliability, and psychometric characteristics among the sub-population studied (HIV-positive MSM).

From the HSS-21 total scores, more than half (64%) of the HIV-positive MSM respondents did not express HARS. However, VDC factor scores showed that 68% of the respondents perceived HARS. The HSS-21 score had a significant and direct correlation with the ZDS-10 total score, showing evidence of convergent validity. Likewise, it also presented a significant and reverse correlation with the RSS-10 total score, demonstrating evidence of discriminant validity. The respondents who perceive HARS had significantly higher scores ($p < 0.02$) in ZDS-10 and significantly lower scores ($p < 0.03$) in RSS-10 than the respondents who do no perceive HARS.

There are only a small number of published studies on interventions and programs designed to reduce HARS. Given the difficulties in defining and measuring stigma, few such interventions and programs described in the literature have been rigorously evaluated in developing countries (10, 21). One of the limitations of this study – typically found in other HIV-related studies – is the fact that it was conducted with a small and convenience sample. For this reason, the study does not offer sufficient data to assess the true meaning of the stigma scores of the scale, and herein reported results and derived conclusions should be considered as hypothetical for similar social groups, which limits the ability to apply it to the general PLWH population, or to draw conclusions about the impact of perceptions of HARS in Mexico. Moreover, HARS data were obtained through a self-reported evaluation and therefore they can be different from those obtained through an interview, projective tests, or psychophysiological tests, etc. Also, sexual orientation, gender identity, social, economic, and cultural differences need to be assessed. Nevertheless, the findings can serve as the basis for HARS measurement research with Spanish-speaking populations in Mexico and other countries.

To improve our understanding of HARS, it is necessary to focus on a series of distinguishable variables across different societies. Implementing HARS evaluation in PLWH is important, as it can lead to identify clinically significant symptoms of depression which could have a negative influence in treatment adherence (15–17), it could also limit the use of public health services (36, 37) and limit social support seeking due to fear of rejection (38, 39). Identifying perceived stigma among PLWH through a short, reliable, and validated instrument provides data that will help governments make efficient and effective use of resources spent on stigma and discrimination reduction as well as the opportunity to develop public health interventions that help PLWH to cope and manage stigma. The implementation and evaluation of these strategies will benefit from the availability of a widely validated and user-friendly psychometric instruments to assess the HARS.

This study was the first to use the Spanish-adapted version of the HSS-21 scale in HIV-positive MSM in Mexico, and the findings help move from evaluating HARS to implementing reduction interventions to mitigate the impact of HARS and promote empowerment among HIV-positive men and to enhance the sexual health of gay and bisexual men through a community-based process involving the MEMUREVIH (program developed by a consortium of members who represent four sectors: academia, government, key population, non-governmental and community-based organizations in Nuevo León state). Through study results, the MEMUREVIH intervention aimed to diminish HARS, create greater support for HIV-positive men, make disclosure safer and easier, discourage reliance on disclosure to prevent HIV transmission and encourage testing. The contact hypothesis suggests that facilitating social interaction between PLWH and others (e.g., healthcare providers, friends, family, co-workers, etc.) may help to reduce prejudice, stereotypes, and discrimination among others via the mechanisms of increased knowledge of HIV, reduced social anxiety regarding PLWH, and increased empathy toward PLWH (40). The corresponding author is currently working on MEMUREVIH intervention data.

As HARS places people at a substantial social disadvantage, it increases their exposure to risks and limits access to protective factors, potentially adding to their burden of disease or disability. Stigma not only predisposes PLWH to greater HARS and discrimination but also critically reinforces stereotyping and status loss of all them, regardless of how they may have acquired the infection. In such manner, underestimating the insidious power of stigma jeopardizes the success of public health programs aimed to prevent, timely detect, and treat HIV and AIDS. HSS-21 scale distinguishes different dimensions of stigma and contributes to better understand HARS impact in public health-related issues. Furthermore, the intention is also to encourage researchers to

consider additional ways to reduce stigma and discrimination, acknowledging and addressing HARS challenges with research methodology; thereby, creating a sense of timeliness and urgency for the development and testing of HARS, and thus, contributing with discrimination reduction efforts. It is only with stronger, more nuanced understandings of HARS that we will be able to break the associations between HIV stigma and indicators of poor affective, behavioral, and physical health and well-being among PLWH within interventions.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Dentistry and HIV/AIDS related stigma

ABSTRACT

OBJECTIVE: To analyze HIV/AIDS positive individual's perception and attitudes regarding dental services.

METHODS: One hundred and thirty-four subjects (30.0% of women and 70.0% of men) from Nuevo León, Mexico, took part in the study (2014). They filled out structured, analytical, self-administered, anonymous questionnaires. Besides the sociodemographic variables, the perception regarding public and private dental services and related professionals was evaluated, as well as the perceived stigma associated with HIV/AIDS, through a Likert-type scale. The statistical evaluation included a factorial and a non-hierarchical cluster analysis.

RESULTS: Social inequalities were found regarding the search for public and private dental professionals and services. Most subjects reported omitting their HIV serodiagnosis and agreed that dentists must be trained and qualified to treat patients with HIV/AIDS. The factorial analysis revealed two elements: experiences of stigma and discrimination in dental appointments and feelings of concern regarding the attitudes of professionals or their teams concerning patients' HIV serodiagnosis. The cluster analysis identified three groups: users who have not experienced stigma or discrimination (85.0%); the ones who have not had those experiences, but feel somewhat concerned (12.7%); and the ones who underwent stigma and discrimination and feel concerned (2.3%).

CONCLUSIONS: We observed a low percentage of stigma and discrimination in dental appointments; however, most HIV/AIDS patients do not reveal their serodiagnosis to dentists out of fear of being rejected. Such fact implies a workplace hazard to dental professionals, but especially to the very own health of HIV/AIDS patients, as dentists will not be able to provide them a proper clinical and pharmaceutical treatment.

DESCRIPTORS: HIV Long-Term Survivors. Dental Health Services. Health Knowledge, Attitudes, Practice. Prejudice. Social Discrimination. Health Inequalities. Psychometrics. Mexico.

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INTRODUCTION

HIV epidemic is about to reach its fourth decade. It is considered a relevant public health care problem worldwide, regardless of antiretroviral therapy advances, which has made of this infection a chronic illness. Life quality and expectancy rates of people living with HIV/AIDS (PLWHA) may be compared to those of the general population.[18,23] Nevertheless, social perception towards PLWHA remains a negative one.[2,12] Its transmission routes, its implications regarding the most traditional gender roles, and its association in the social imaginary to socially marginalized groups are the cause of stigma and discrimination at different levels.[2,12]

Stigma is a degrading social evaluation or label that is attached to people that exhibits socially undesirable characteristics.[9] Stigmatization is the social process by which such evaluations or labels and the consequent negative emotional and behavioral responses are generated and sustained. Therefore, originating and shaping social exclusion.[4]

Stigma is sustained by a complex set of factors difficult to address. An existing duality is observed between the social rejection and approval of attitudes and behaviors of people with certain characteristics. In addition, factors such as beliefs and the environment in which stigma is developed, impose the intensity of the rejection or the acceptance of individuals in a certain context.[20]

HIV/AIDS related stigma and discrimination have multiple consequences that affect HIV epidemic development and reinforce existing social inequalities, especially those related to gender roles, sexuality, and ethnicity. The stigma PLWHA go by is an obstacle in their access to health care services and their engagement into the "HIV continuum of care".[6,12,19]

Evidence-based scientific research shows PLWHA's needs in oral health care, due to the high incidence of HIV-related oral problems that diminish their quality of life.[1,25] This study intends to analyze HIV/AIDS positive individual's perception and attitudes towards the received oral health care.

METHODS

One hundred and thirty-four subjects (30.0% of women and 70.0% of men) from Nuevo León, Mexico, took part in the study (2014). They filled out a written or online format questionnaire at the non-governmental and community-based organizations members of Nuevo Leon's Multisector Response Board to HIV, AIDS, and other sexually-transmitted infections (MEMUREIVH). A non-probabilistic and convenience sample including HIV-positive men and women was adopted.

The data collection process lasted 60 days. Prior to the data collection, collaboration was requested to the different non-governmental and community-based organizations members of the MEMUREIVH, to implement the survey in their office location and to their HIV/AIDS positive affiliates. Four properly qualified surveyors visited all sites and applied the written or on-line surveys on the previously agreed dates and time with the aforementioned organizations. There were no cancellations.

An analytical-type structured questionnaire was used (closed-ended questions and multiple response alternatives) in either written or online formats. Self-administered questionnaires have been shown to be proper methods to collect several data, since they are fully anonymous and, unlike interviews, do not involve a face-to-face confrontation, which could possibly lead to false answers.[3] The following topics were covered: sociodemographic characteristics, perception regarding public and private dental professionals and services, and that regarding the received HIV-related oral health care. Perception of HIV-AIDS-related stigma in the dental office was analyzed through a Likert-type scale.[15] Following the procedure recommended by Lynn,[17] a group of reviewers assessed how well the 11 items evaluated the concepts of stigma and discrimination in terms of their accuracy and relevance for both concepts. Such scale consisted of five alternatives that ranged from "never" to "very often".

A digital survey database was created and submitted to a double-quality control to assure reliability of information. The subjects accessed the survey website (www.encuestas.no-ip.org) to answer the online questionnaire. No log-in data (e.g., internet protocols) were stored in the electronic access. After survey was completed (average of 25 minutes), and as a benefit to all participants, voluntarily, informed, and consented oral examination and oral prophylaxis were offered free by qualified, certified and sensitized dentists.

An exploratory factor analysis was performed to empirically synthesize the variables concerning the perception of HIV/AIDS-related stigma and discrimination. In this analysis, the inclusion of variables was conditioned by a matrix that validates the presence of marked correlations among all of them and ensures that their application is fitting. Items with no statistical significance were disregarded. The analytical criterion to determine the number of covered factors included the ones whose values were shown to have proper internal consistency index through Cronbach's alpha.[24] Principal components

analysis was used to extract core factors. Prior to the extraction Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity were used to assess the suitability of the respondent data for factor analysis. A Varimax rotation method with Kaiser Normalization were performed to facilitate the interpretation of the factor loadings. A k-means clustering procedure was performed after the factor analysis. Once those clusters had been outlined, each of the factors that were used in their differentiation was proven to be statistically significant by an analysis of variance (ANOVA).

All data were analyzed using SPSS software, version 20.0.

The study protocol was approved by the Ethics Committee at the Tecnologico de Monterrey (BIO-ELB-2012-01). Participants signed informed consent forms. The anonymity and confidentiality of written or electronic data were guaranteed.

RESULTS

The sample consisted of 134 PLWHA (30.0% of women and 70.0% of men). The mean age of women was 41.7 years (standard deviation [SD] = 10.9; range: 22 to 57 years). Median time of HIV diagnosis was five years.. The average education level was 8.4 (SD = 4.1) and all female subjects reported being heterosexual. The mean age of male participants was 34.9 years (SD = 9; range: 22 to 57), and their median time of HIV diagnosis was two years. In regards to men's education levels, the average was 14 years (SD = 3.5), and most of them (88.4%) reported being homosexual (Table 1).

Forty percent of the women included reported working full time, and the remaining ones were unemployed. However, regardless of their job statuses, their monthly incomes exceeded the minimum wage in northeastern Mexico (≤ 15,000 MXN or 1,146 USD) In the case of men, 81.9% of them reported working full time, whereas 10.6% reported working part-time and the remaining 7.4% were unemployed. Out of the total, 69.2% men earned a monthly income of ≤ 15,000 MXN (1,146 USD).

Out of all women, 44.7% reported having had dental appointments at least once a year. On the other hand, half of the men reported having them once a year and the remaining half reported having them two times or more a year. (Table 2).

In regards to the modalities of services, 39.5% of women used public dental services and 74.5% of men reported using private ones. Whilst 37.1% of women reported not knowing whether they received a general or specialist oral health care service, 40.4% of the men reported having the general one and 33.0%, the specialist oral health service.

The main reasons the women pointed out for choosing a certain dentist were their professional knowledge (32.4%) and good chairside manner (18.9%).

Table 1. Sociodemographic characteristics of the subjects. Nuevo León, Mexico, 2014.

Variable	Women			Men			p[a]
	Mean	SD	Median	Mean	SD	Median	
Age (years)	41.7	10.9	41[b]	34.9	8	34[b]	< 0.0001
HIV (years of diagnose)	6.10	5.51	5[d]	3.19	4.18	2[d]	< 0.001
Education level (years of schooling)	8.4	4.1	9[b]	14	3.5	15[b]	< 0.0001
Sexual orientation	n		%	n		%	
Homosexual	0		0	83		88.3[b,c]	< 0.0001
Bisexual	0		0	9		9.6	
Heterosexual	40		100[b,c]	2		2.2	
Workload							
Full-time	16		40.0	77		81.9[b,c]	< 0.0001
Part-time	0			10		10.6	
Does not work	24		60.0[b,c]	7		7.4	
Monthly income							
≤ 15,000 MXN (1,146 USD)	40		100[c]	65		69.2[b,c]	< 0.0001
≤ 30,000 MXN (2,292 USD)	0		0	22		23.4	
> 30,000 MXN (2,292 USD)	0		0	7		7.5	

[a] Through ANOVA.
[b] ($p < 0.001$) intergroups.
[c] ($p < 0.001$) intragroups.
[d] ($p < 0.001$) intergroups.

Conversely, most men (29.8%) based their choices on the professionals' length of experience, followed by their knowledge (26.6%).

Regarding the women, 72.5% of them reported they considered the dental offices they went to as being neither safe, clean, nor complying with infection control rules required by health care authorities. The perception from most men (91.5%) regarding their elected offices was another one entirely. Besides that, 84.6% of the women and 91.5% of the men considered that dentist have to be specifically trained to deal with PLWHA (Table 3).

In 58.3% of the cases involving women and in 68.1% of cases involving men, dentists were said to be reliable concerning the confidentiality of the information in their dental records. However, only 48.7% of the women and 30.9% of the men reported disclosing their HIV serodiagnosis to dental professionals. Despite PLWHA (61.5% of the women and 78.7% of the men) considered it was important that their dentists were aware of their HIV-positive condition, they did not disclose it, since they (63.5% of women and 68.1% of men) were concerned they would be denied oral health care or that inconveniences would arise during dental appointment (in this last case, 62.5% of women and 43.6% of men). In turn, 65.0% of the women and 70.3% of the men believed they were entitled to keep from disclosing their HIV/AIDS serodiagnosis to their dentists (Table 3).

Most women (54.1%) considered that their dentists do not take professional ethics into account, and that is why they thought they would not receive the same care a non-HIV patient would receive. Such perception regarding the dental professionals ran contrary to the women's by most men (80.9%).

Most PLWHA (66.7% of women and 54.3% of men) do not believe HIV can be transmitted in dental office environments; 85.0% of the women and 83.0% of the men do not believe the dental professionals can transmit the virus to their patients, or

Table 2. Perception regarding private and public oral health care professionals and services. Nuevo León, Mexico, 2014.

Variable	Women		Men		p[a]
	n	%	n	%	
How many times a year do you have dental appointments?					
None	11	28.9	0	0	
Once a year	17	44.7[c]	47	50.0	< 0.001
Twice or more a year	10	26.3	47	50.0	
Do you have appointments in a public or in a private dental office?					
None	11	28.9	0	0	
Public	15	39.5[b]	24	25.5	
Private	12	31.6	70	74.5[b,c]	< 0.001
Do you have appointments with a general or with a specialty dentist?					
None	2	5.7	0	0	
I do not know	13	37.1[b]	25	26.6	
General	11	31.4	38	40.4[b,c]	< 0.001
Specialty	9	25.7	31	33.0	
Among the following options, which is the most similar to the main reason why you select a certain dentist?					
Knowledge	12	32.4[b,c]	25	26.6	
Experience	5	13.5	28	29.8[b,c]	< 0.001
Formality	3	8.1	6	6.4	
Price	5	13.5	11	11.7	
Good chairside manner	7	18.9	7	7.4	
Office appearance	1	2.7	6	6.4	
Office hygiene	2	5.4	8	8.5	
Dentist's personal appearance	2	5.4	3	3.2	

[a] Through ANOVA.
[b] ($p < 0.001$) intergroups.
[c] ($p < 0.001$) intragroups.

Table 3. Perception regarding HIV care in dental appointments. Nuevo León, Mexico, 2014.

Variable	Women		Men		p[a]
	n	%	n	%	
Is the dental office you have appointments in safe, clean, and complying with infection-control regulations?					
Yes	11	27.5	86	91.5[b,c]	< 0.001
No	29	72.5[b,c]	8	8.5	
Do you trust your dentist to keep the confidentiality of the information in your dental record?					
Yes	21	58.3[c]	64	68.1[c]	< 0.001
No	15	41.7	29	30.9	
Do you believe it is important that your dentist be qualified to treat HIV patients?					
Yes	33	84.6[c]	86	91.5[c]	< 0.001
No	6	15.4	8	8.5	
Have you informed your dentist of your HIV status?					
Yes	19	48.7	29	30.9	
No	20	51.3	65	69.2[c]	< 0.001
Do you think it is important that you tell your dentist you live with HIV?					
Yes	24	61.5[c]	74	78.7[c]	< 0.001
No	15	38.5	20	21.3	
I have a right not to disclose my HIV status, and that is why I do not tell it to my dentist:					
Yes	26	65.0[b]	66	70.3[c]	< 0.001
No	14	35.0	28	29.8	
I am afraid to be denied dental care, and that is why I do not tell my dentist I live with HIV:					
Yes	25	62.5[c]	64	68.1[c]	< 0.001
No	15	37.5	30	31.9	
I am afraid of the inconveniences that may arise in dental care, and that is why I do not tell my dentist I have HIV:					
Yes	25	62.5[b,c]	41	43.6	< 0.001
No	15	37.5	53	56.4[b,c]	
Do you think dentists in general are health care professionals who follow ethical principles, and because of that, they treat you like any other patient, regardless of whether you are HIV positive or not?					
Yes	16	43.2	76	80.9[b,c]	< 0.001
No	20	54.1[b]	18	19.1	
I do not know	1	2.7	0	0	
Do you believe HIV/AIDS can be transmitted in dental offices?					
Yes	13	33.3	42	44.7	
No	26	66.7[b]	51	54.3[c]	< 0.001
I do not know	0	0	0	0	
Do you believe your dentist may transmit HIV?					
Yes	5	12.5	16	17.0	
No	34	85.0[c]	78	83.0[c]	< 0.001
I do not know	1	2.5	0	0	
Do you believe you can transmit HIV to your dentist?					
Yes	10	25.6	31	33.0	
No	29	74.4[c]	50	53.2[c]	< 0.001
I do not know	0	0	13	13.8	

Continue

Continuation

Do you believe you can transmit HIV to other people going to the same dental office or clinic?					
Yes	9	22.5	18	19.1	
No	31	77.5[c]	75	79.7[c]	< 0.001
I do not know	0	0	0	0	
Do you believe you can catch a secondary infection during or after being treated in a dental office or clinic because you have HIV?					
Yes	13	33.3	37	39.4	
No	24	61.5[c]	57	60.7[c]	< 0.001
I do not know	2	5.1	0	0	
Do you believe people living with HIV must only seek care in dental offices or clinics which are exclusive to HIV patients?					
Yes	15	38.5	21	23.3	
No	24	61.5[c]	73	77.7[c]	< 0.001
I do not know	0	0	0	0	
Do you believe oral illnesses affect your general state of health?					
Yes	35	87.5[c]	63	67.0[c]	< 0.001
No	5	12.5	31	33.0	
I do not know	0	0	0	0	
How do you appraise your overall oral health?					
Excellent	8	20.5	6	6.4	
Good	28	71.8[c]	40	42.6[c]	< 0.001
Fair	1	2.6	36	38.3	
Poor	2	5.1	12	12.8	
I do not know	0	0	0	0	

HIV: human immunodeficiency virus
[a] Through ANOVA.
[b] ($p < 0.001$) intergroups.
[c] ($p < 0.001$) intragroups.

vice versa (74.4% of women and 53.2% of men) during appointments. Most PLWHA (77.5% of the women and 79.7% of the men) does not believe they can transmit HIV to other people going to the same office or clinic. The same way, 61.5% of the women and 77.7% of the men do not find it necessary for them to go to specific dental offices or clinics due to their HIV-positive status.

In spite of most PLWHA (71.8% of the women and 42.6% of the men) considering they have good oral and dental health, they do not believed (61.5% of the women and 60.7% of the men) they can come down with a secondary infection during or after dental care, due to the fact they are infected with HIV. Nonetheless, they stated (87.5% of the women and 67.0% of the men) that their general state of health could be affected by the lack of dental care if they will suffer from any HIV-related oral manifestations.

Most PLWHA (69.4% of the women and 84.0% of the men) reported never had experienced any discrimination from dentists, nor that dental professionals had denied them care due to their HIV-positive status (79.5% of the women and 90.4% of the men). Most subjects (76.9% of the women and 83.0% of the men) were never given excuses to denied their oral health care service, nor did most of them (69.2% of the women and 86.2% of the men) had their oral care purposefully delayed due to their PLWHA condition, as compared to the other patients (Table 4).

Most subjects (81.6% of the women and 83.0% of the men) never felt being the target of whispers, glances, or laughter during their dental appointments. The majority of them (81.6% of the women and 88.2% of the men) have never received negative opinions about their lifestyles or sexual behaviors either, nor have they been belittled by their dentists or by their staff (74.4% of the women and 87.2% of the men).

Among the subjects, 78.4% of the women and 89.4% of the men reported that never had noticed that dentists

Table 4. Perception of the HIV/AIDS-related stigma and discrimination Nuevo León, Mexico, 2014.

Items	Never		Rarely		Occasionally		Often		Very often	
	n (%)		n (%)		n (%)		n (%)		n (%)	
	W	M	W	M	W	M	W	M	W	M
Have you ever been discriminated by a dentist because you live with HIV?	25 (69.4)	79 (84.0)	4 (11.1)	8 (8.5)	4 (11.1)	5 (5.3)	2 (5.6)	1 (1.1)	1 (2.8)	1 (1.1)
Over the last 12 months, how often were you denied dental care for being HIV positive?	31 (79.5)	85 (90.4)	3 (7.7)	7 (7.4)	5 (12.8)	1 (1.1)	0	1 (1.1)	0	1 (1.1)
When you go to a dental office or clinic, has any one given you a reason for denying you dental care services cos you are HIV positive?	30 (76.9)	78 (83.0)	2 (5.1)	10 (10.6)	4 (10.3)	3 (3.2)	3 (7.7)	2 (2.1)	0	1 (1.1)
When you go to a dental office or clinic, does it take you longer to be treated than other patients?	27 (69.2)	81 (86.2)	3 (7.7)	5 (5.3)	6 (15.4)	5 (5.3)	2 (5.1)	2 (2.1)	1 (2.6)	1 (1.1)
When you go to a dental office or clinic, do you notice whispers, glances, or laughter towards you?	31 (81.6)	78 (83)	0	9 (9.6)	4 (10.5)	5 (5.3)	3 (7.9)	2 (2.1)	0	0
Have you ever been made to fell blamed, undermined, or belittled for having HIV whilst being treated in a dental office or clinic?	31 (81.6)	83 (88.2)	1 (2.6)	4 (4.3)	3 (7.9)	5 (5.3)	1 (2.6)	0	2 (5.3)	2 (2.1)
Have you ever been given negative opinions about your lifestyle or sexual behaviors whilst being treated in a dental office or clinic?	30 (78.9)	82 (87.2)	0	6 (6.4)	5 (13.2)	5 (5.3)	2 (5.3)	1 (1.1)	1 (2.6)	0
Have you ever been treated with disdain, indifference, or criticism whilst being treated in a dental office or clinic?	29 (74.4)	82 (87.2)	3 (7.7)	6 (6.4)	4 (10.3)	6 (6.4)	1 (2.6)	0	2 (5.1)	0
Has anyone ever avoided getting in contact with your skin whilst being treated in a dental office or clinic?	29 (78.4)	84 (89.4)	1 (2.7)	7 (7.4)	3 (8.1)	2 (2.1)	2 (5.4)	1 (1.1)	2 (5.4)	0
Has anybody ever behaved in a way to display fear or insecurity at the time they had to dress wounds, apply sutures, injections, or other dental procedures during treatment in a dental office or clinic?	29 (74.4)	82 (87.2)	0	7 (7.4)	7 (17.9)	2 (2.1)	1 (2.6)	2 (2.1)	2 (5.1)	1 (1.1)
Whilst being treated in a dental office or clinic, has anybody ever requested that the materials used in your treatment be discarded, based on the argument that your HIV-positive status offered a higher risk?	29 (76.3)	83 (88.3)	1 (2.6)	7 (7.4)	2 (5.3)	0	2 (5.3)	1 (1.1)	4 (10.5)	3 (3.2)

HIV: human immunodeficiency virus; W: women; M: men

or their staff avoided direct contact with them, neither have most of them (74.4% of the women and 87.2% of the men) noticed fear or insecurity by dental professionals during their appointments. Finally, 76.3% of the women and 88.3% of the men reported never had heard any request to discard materials used in their appointments under the argument that they are highly risky patients due to HIV.

The 11 items have shown evidence of proper internal consistency,[24] as none of them were discarded. A Cronbach's alpha of 0.942 was obtained. The first factor consisted of variables related to stigma and discrimination experiences perceived by participants during dental appointments; the second one, for variables related to participants' concern towards dentists or their staff attitudes regarding their HIV serodiagnosis. After factor analysis, a non-hierarchical clustering analysis was conducted. The first group included subjects identified as "users who have not experienced HIV-related stigma and discrimination in dental appointments" (85.0%). The second group was characterized by a group of subjects referred to as "users who have not experienced stigma and discrimination, but feel slightly concerned about dentists or their staffs' reaction if they knew about their HIV-positive status" (12.7%). The third group comprised "users who had experienced stigma and discrimination, and feel concerned about dentists or their staffs' reaction if they knew about their HIV-positive status" (2.3%) (Table 5).

DISCUSSION

Most PLWHA went to a dental office once or more times a year in search of oral health care, as they recognize that oral diseases affect their overall state of health. The socioeconomic and education-related determinants revealed social inequalities in HIV care.[16] The women who took part in this study tended to seek general and public dental health care services, whereas male participants in this study, as they were observed to have a higher income, tended to seek for dental private and specialized services.

Even though, men and women agreed that (i) dentists must be qualified to treat PLWHA; (ii) it is important to inform dental professionals about one's HIV-positive diagnose; and (iii) that dentists are believed to keep their patient's dental record information confidential. At the end, both men and women decline to disclose their HIV-positive status to dental professionals. Stigma is a social process or personal experience which influences all aspects in one's life. Thus, the HIV/AIDS diagnose is omitted by people suffering from it, in order to avoid being excluded socially. That is what Goffman calls "concealment".[9] Similar to what was shown globally in other studies[14,21,22] with different population groups affected by HIV/AIDS pandemic, among the main reasons why PLWHA do not disclose their HIV status to dentists are fear of being shunned, inconveniences that may arise in the dentist-patient relationship, and one's right not to disclose their diagnose.

One of the limitations of this study – typically found in other HIV-related studies – is the fact that it was conducted with a small sample, as most patients do not disclose their HIV-positive status.[14] Nonetheless, the obtained results provide an overview of opinions and problems that PLWHA have undergone concerning their dentists.

Although the results from this study have shown a low percentage of perceived stigma and discrimination in dental appointments, most PLWHA reported (through their answers to the questionnaire) not disclosing their HIV status to dental professionals, whether because of previous experiences of stigma and discrimination these people were submitted to in other situations or due to their social collective identity within a given context. Such omission may lead to workplace hazards for dentists and their staff, not only in the case of HIV transmission (and the provision of post-exposure prophylaxis), but also in the case of infection with other blood-borne pathogens, such as hepatitis B and C viruses.[7,8] Likewise, such fact jeopardizes the very health of PLWHA, as dental professionals will not be able to provide proper clinical care,[13] and might prescribe a drug that could enhance or antagonize with antiretroviral therapy.[5,10,11]

According to the Global Report 2013 of the Joint United Nations Programme on HIV/AIDS, 61.0% of the countries reported the existence of laws against discrimination that protect PLWHA. In Mexico – based on the provisions in the first article of its federal constitution and on the first article, second paragraph, section II of the federal law for preventing and eliminating discrimination – it is illegal to stigmatize and deny rights that are afforded to all other citizens. Consequently, denying oral health care to PLWHA and other patients with infectious diseases is considered to be discrimination, as it violates the Universal Declaration of Human Rights, such as the right to adequate health. Nonetheless, the lack of accessible legal services leads to the frequent neglect of many HIV-related discrimination cases.

Both realities (individuals who chose not to disclose their HIV status and dental professionals who denies care to people with infectious diseases) do not ensure that dental professionals or their patients avoid being exposed to HIV and other pathogens, as individuals living with HIV or other infectious diseases may not

Table 5. Factorial analysis of the perception of the HIV and AIDS- related stigma and discrimination in dental appointments. Nuevo León, Mexico, 2014.

Items	Means and correlation matrix										
	Mean	1	2	3	4	5	6	7	8	9	10
a	0.338										
b	0.185	0.583									
c	0.308	0.661	0.589								
d	0.346	0.514	0.305	0.579							
e	0.323	0.574	0.462	0.658	0.663						
f	0.431	0.522	0.523	0.567	0.545	0.758					
g	0.285	0.540	0.484	0.541	0.596	0.822	0.713				
h	0.262	0.456	0.431	0.537	0.525	0.776	0.676	0.790			
i	0.238	0.516	0.432	0.554	0.541	0.803	0.741	0.802	0.880		
j	0.308	0.539	0.506	0.543	0.555	0.804	0.747	0.771	0.823	0.819	
k	0.308	0.529	0.405	0.469	0.491	0.470	0.613	0.472	0.495	0.472	0.636

Items	Rotated component matrix		
	Factor 1. Non personal disparagement experiences from dentists or their staff	Factor 2. Non concern with dentists or their staffs' attitudes	Commonalities
a	0.286	0.821	0.756
b	0.207	0.785	0.659
c	0.368	0.768	0.725
d	0.552	0.458	0.514
e	0.822	0.402	0.838
f	0.719	0.456	0.726
g	0.834	0.337	0.809
h	0.890	0.239	0.849
i	0.891	0.271	0.868
j	0.831	0.378	0.833
k	0.422	0.569	0.502
Eigenvalues	7.049	1.030	
Percentage of explained variance	64.079	9.361	

Cluster	Distances between final cluster centers		
	1. Users who have not experienced HIV-related stigma and discrimination in dental appointments.	2. Users who have not experienced stigma and discrimination, but feel slightly concerned about dentists or their staffs' reaction regarding their HIV+ serodiagnosis.	3. Users who have experienced HIV-related stigma and discrimination, and feel concerned about dentists and their staffs' reaction regarding their HIV+ serodiagnosis.
	85.0% (n = 114)	12.7% (n = 17)	2.3% (n = 3)
1		9.434	5.292*
2	9.434		4.394*
3	5.292	4.394	

Rotation method: Varimax with Kaiser Normalization. Kaiser-Meyer-Olkin measure of sampling adequacy: 0.904. Bartlett's sphericity test $p < 0.0001$; it converges to three iterations. Non-hierarchical clustering analysis (K-means Cluster)
* $p < 0.001$ through ANOVA.

be aware of being infected. For that reason, dentists and all health care professionals are responsible for and ethically bound to seek training concerning the treatment of HIV and other diseases in its category. They also have to keep up-to-date regarding gender studies, diversity, and human rights, to keep high professional standards and to ensure all patients are provided dignified and egalitarian care.

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CONTRIBUTIONS FROM THE AUTHORS

Elizondo JE and Treviño AC conceived, planned, and executed (conducted) the fieldwork. Elizondo JE statistically analyzed the data, interpreted the results, and wrote the article. Violant D facilitated, supervised, gave technical advice, offered ideas to interpret results, revised, edited, and approved the final version of the manuscript.

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La odontología y el estigma asociado al VIH

RESUMEN

OBJETIVO: Analizar la percepción y las actitudes de las personas que viven con VIH/sida hacia los servicios odontológicos.

MÉTODOS: Participaron 134 voluntarios (30.0% mujeres y 70.0% hombres) de Nuevo León, México (2014), que contestaron un cuestionario estructurado de tipo analítico, auto-administrado y anónimo. Además de las variables sociodemográficas, fueron analizadas la percepción sobre los servicios y los prestadores de servicios odontológicos públicos y privados; igualmente se exploró mediante escala tipo Likert la percepción del estigma asociado al VIH/sida. El análisis estadístico incluyó análisis factorial y de *clusters* no jerárquico.

RESULTADOS: Se presentaron desigualdades sociales en la búsqueda de atención de prestadores y servicios odontológicos públicos y privados. La mayoría ocultó su serodiagnóstico y concordó en que el odontólogo debe capacitarse en la atención del VIH. El análisis factorial reveló dos factores: experiencias de estigma y discriminación en la consulta odontológica y sentimientos de preocupación por la actitud del odontólogo o su personal hacia el serodiagnóstico del paciente. El análisis de *clusters* identificó tres grupos: usuarios que no han experimentado estigma ni discriminación (85.0%); los que no han experimentado estigma ni discriminación, pero sienten una ligera preocupación (12.7%); y finalmente, los que han experimentado estigma y discriminación, y sienten preocupación (2.3%).

CONCLUSIONES: Se presentó un bajo porcentaje de estigma y discriminación en la consulta odontológica; sin embargo, la mayoría de las personas que viven con VIH/sida no revelan al odontólogo su serodiagnóstico por temor al rechazo. Estos hechos plantean un riesgo laboral para el odontólogo, pero especialmente para la propia salud de las personas que viven con VIH/sida, dado que el odontólogo no podrá proporcionar un tratamiento clínico y farmacológico adecuado.

DESCRIPTORES: Sobrevivientes de VIH a Largo Plazo. Servicios de Salud Dental. Conocimientos, Actitudes y Práctica en Salud. Prejuicio. Discriminación Social. Desigualdades en la Salud. Psicometría. México.

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INTRODUCCIÓN

La epidemia de VIH entra en su cuarta década. Es considerado un importante problema de salud pública en todo el mundo, independientemente de los avances en la terapia antirretroviral que ha hecho de esta infección una enfermedad crónica. La calidad y la esperanza de vida de las personas que viven con VIH/sida (PVVS) podrían equipararse a la del resto de la población.[18,23] A pesar de esto, la percepción social hacia quienes viven con VIH continua negativa.[2,12] Sus vías de transmisión, sus implicaciones respecto a los mandatos de género más tradicionales y su asociación con el imaginario social a grupos socialmente excluidos causan estigma y discriminación en distintos ámbitos.[2,12]

El estigma es una evaluación o etiqueta social degradante que se adjunta a quienes exhiben características socialmente indeseables.[9] La estigmatización es el proceso social por el cual las evaluaciones o etiquetas degradantes y las consecuentes respuestas emocionales y conductuales negativas se generan y se mantienen, dando origen y forma a la exclusión social.[4]

El estigma se sustenta en un complejo conjunto de factores que no son fáciles de resolver. Hay dualidad entre el rechazo y la aprobación social de las actitudes y los comportamientos de las personas con determinadas características. Además, factores como las creencias y el medio ambiente en donde se desarrolla el estigma precisan la magnitud del rechazo o la aprobación de los individuos en determinado contexto social.[20]

El estigma y la discriminación relacionados con el VIH/sida tienen múltiples consecuencias que afectan al desarrollo de la epidemia y refuerzan las desigualdades sociales existentes, en especial las relacionadas con el género, la sexualidad y la etnia. El estigma que sufren las PVVS es un obstáculo para el acceso a los servicios de salud y al modelo del "Continuo del tratamiento del VIH".[6,12,19]

La investigación científica basada en evidencia muestra la necesidad de las PVVS en recibir atención buco-dental, debido a la alta incidencia de padecimientos orales asociados al VIH que afectan su calidad de vida.[1,25] El objetivo del presente estudio fue analizar la percepción y las actitudes de las personas que viven con VIH/sida hacia la asistencia odontológica recibida.

MÉTODOS

En este estudio transversal, participaron 134 PVVS (30.0% mujeres e 70.0% hombres) de Nuevo León, México (2014), los cuales contestaron una encuesta impresa u *on-line*, en las organizaciones no gubernamentales y de base comunitaria, pertenecientes a la Mesa Multisectorial de Respuesta al VIH, el sida y otras Infecciones de Transmisión Sexual (ITS) en Nuevo León, México (MEMUREVIH). Se realizó un muestreo no probabilístico, incidental y la muestra estudio la conformaron mujeres y hombres con serodiagnóstico positivo para VIH.

La recogida de datos ocurrió durante 60 días. Para contactar con las PVVS que frecuentaron alguna de las organizaciones no gubernamentales y de base comunitaria pertenecientes a la MEMUREVIH, se solicitó autorización a los directivos así como su colaboración para aplicar las encuestas en sus oficinas. Cuatro encuestadores debidamente capacitados visitaron todas las organizaciones en día y hora previamente pactados con los directivos de las organizaciones para la aplicación de las encuestas. No hubo pérdidas o rechazos.

Se utilizó un cuestionario estructurado analítico (de pregunta cerrada y alternativas múltiples) con formato impreso u *on-line*. El cuestionario auto-administrado ha demostrado ser un medio adecuado para recopilar información diversa, dado que es totalmente anónimo y a diferencia de las entrevistas, no implica una confrontación cara a cara, lo que eventualmente podría conducir a respuestas falsas.[3] Los temas explorados fueron: características sociodemográficas, percepción hacia los prestadores y servicios odontológicos públicos y privados, y hacia recibir atención y tratamiento odontológico integral del VIH. Se exploraron la percepción del estigma y discriminación asociados al VIH/sida en la consulta odontológica mediante una escala tipo Likert.[15] Siguiendo el procedimiento recomendado por Lynn,[17] un grupo de revisores valoró qué tan bien los 11 ítems evaluaban el concepto de estigma y discriminación en términos de la claridad del ítem y de su relevancia para ambos conceptos. Esta escala constaba de cinco alternativas en gradiente desde "nunca" hasta "muy a menudo".

Se creó una base de datos digital de la encuesta, que fue sometida a un doble control de calidad para asegurar la fiabilidad en el ingreso de la información. Los participantes accedían a la página web de la encuesta (www.encuestas.no-ip.org) para responder el cuestionario *on-line*. No se almacenó ningún registro de datos (dirección y protocolo de internet, entre otros) en el caso del acceso electrónico. Después de la encuesta (duración media de 25 min), se les ofreció como beneficio a las PVVS participantes la realización de una exploración y profilaxis oral de forma voluntaria, informada, consentida y gratuita, realizado por odontólogos capacitados, sensibilizados y certificados.

Se realizó análisis factorial exploratorio para sintetizar empíricamente las variables relacionadas con la percepción del estigma y discriminación asociados al VIH/sida. En este análisis, la inclusión de las

variables fue condicionada por una matriz que convalida la presencia de una notable correlación entre todas las variables y garantiza la idoneidad de la aplicación de un análisis factorial. Ítems sin significación estadística no se incluyeron en el análisis factorial. El criterio analítico para determinar el número de los factores conservados en el análisis fueron aquellos cuyos valores mostraran índices adecuados de consistencia interna mediante la estimación del coeficiente alfa de Cronbach.[24] El método de extracción de los factores fue el de los componentes principales. Se calculó la medida de adecuación muestral de Kaiser, Meyer y Olkin (KMO) y se realizó la prueba de esfericidad de Barlett para comprobar la conveniencia de este análisis. Se realizó una rotación por el método Varimax con Kaiser para facilitar la interpretación de los resultados. Después del análisis factorial, se realizó un análisis de *clusters* no jerárquico (K-Means Cluster). Una vez delimitados estos grupos o *clusters*, se comprobó que cada uno de los factores utilizados en la diferenciación de los grupos fuera estadísticamente significativo mediante el análisis de la varianza (ANOVA).

Se analizaron los datos del programa de análisis estadístico SPSS® versión 20.0.

El estudio fue aprobado por el Comité de Ética del Tecnológico de Monterrey (BIO-ELB-2012-01). Los participantes firmaron consentimiento informado. Se garantizó el anonimato y la confidencialidad de los datos escritos o electrónicos.

RESULTADOS

La muestra estudio la conformaron 134 PVVS (30.0% mujeres y 70.0% hombres). La edad media de las mujeres encuestadas fue de 41.7 años (desviación estándar [DE]: 10.9; rango: 22 a 57 años). La mediana de tiempo del diagnóstico del VIH fue cinco años. La edad media de escolarización fue 8.4 años (DE = 4.1) y todas se definieron como heterosexuales. Los hombres encuestados presentaron edad media de 34.9 años (DE = 8; rango: 22 a 57), mediana de tiempo del diagnóstico del VIH, dos años. La edad media de escolarización fue 14 (DE = 3.5) y la mayoría (88.3%) se definió como homosexual (Tabla 1).

El 40.0% de las mujeres contaba con empleo a tiempo completo y el 60.0% no trabajaba. Sin embargo, independientemente de su situación laboral, recibían un ingreso económico mensual superior al salario mínimo, en el noreste de México, de ≤ 15,000 MXN (1,146 USD). El 81.9% de los hombres trabajaba a tiempo completo, mientras el 10.6% lo hacía a tiempo parcial y el 7.4% no trabajaba. El 69.2% de los hombres recibía un ingreso económico mensual de ≤ 15,000 MXN (1,146 USD).

El 44.7% de las mujeres acudió a la consulta odontológica al menos una vez al año. Por otro lado, el 50.0% de los hombres declaró asistir al menos una vez al año y el 50.0% restante asistió dos o más veces al año (Tabla 2).

El 39.5% de las mujeres acudió a los servicios odontológicos públicos y el 74.5% de los hombres a los

Tabla 1. Características sociodemográficas de los participantes. Nuevo León, México, 2014.

Variable	Mujeres			Hombres			p[a]
	Media	DE	Mediana	Media	DE	Mediana	
Edad (años)	41.7	10.9	41[b]	34.9	8	34[b]	< 0.0001
VIH (años del diagnóstico)	6.10	5.51	5[d]	3.19	4.18	2[d]	< 0.001
Escolarización (años cursados)	8.4	4.1	9[b]	14	3.5	15[b]	< 0.0001
Orientación sexual	n		%	n		%	
Homosexual	0		0	83		88.3[b,c]	< 0.0001
Bisexual	0		0	9		9.6	
Heterosexual	40		100[b,c]	2		2.2	
Trabajo							
Tiempo completo	16		40.0	77		81.9[b,c]	< 0.0001
Medio tiempo	0			10		10.6	
No trabaja	24		60.0[b,c]	7		7.4	
Ingresos mensuales							
≤ 15,000 MXN (1,146 USD)	40		100[c]	65		69.2[b,c]	< 0.0001
≤ 30,000 MXN (2,292 USD)	0		0	22		23.4	
> 30,000 MXN (2,292 USD)	0		0	7		7.5	

[a] Mediante ANOVA.
[b] ($p < 0.001$) inter-grupos.
[c] ($p < 0.001$) intra-grupos.
[d] ($p < 0.001$) inter-grupos.

servicios privados. El 37.1% de las mujeres desconocía si la atención odontológica que recibía era general o de especialidad. El 40.4% de los hombres recibía atención odontológica general y el 33.0%, especialidad.

Las razones principales por la que las mujeres elegían un determinado odontólogo fueron los conocimientos del profesional (32.4%) y el trato amable (18.9%). Por el contrario, la mayoría de los hombres (29.8%) basaba su elección en la experiencia del odontólogo, seguido por los conocimientos de éste (26.6%).

El 72.5% de las mujeres consideraba que el consultorio al que acudían no era seguro ni limpio y no contaba con las normas de control de infección requeridas por las instancias de salud pública. La percepción del consultorio o clínica dental al que acudían la mayoría de los hombres (91.5%) era totalmente opuesta. Además, el 84.6% de las mujeres y el 91.5% de los hombres creían que era necesario que el odontólogo estuviese capacitado para brindar atención a las PVVS (Tabla 3).

El 58.3% de las mujeres y el 68.1% de los hombres creían en la confidencialidad del expediente odontológico, sin embargo, solo el 48.7% de las mujeres y el 30.9% de los hombres le informaban al odontólogo su serodiagnóstico al VIH. A pesar de que las PVVS (61.5% de las mujeres y 78.7% de los hombres) consideraban importante que el profesional estuviese enterado de que viven con VIH, no lo referían, dado que (62.5% de las mujeres y 68.1% de los hombres) les preocupaba que se les negase la atención o que surgieran inconvenientes durante la consulta odontológica (62.5% de las mujeres y 43.6% de los hombres). A su vez, el 65.0% de las mujeres y el 70.3% de los hombres creían estar en su derecho de no revelar su condición de PVVS al odontólogo (Tabla 3).

La mayoría de las mujeres (54.1%) consideraba que los odontólogos no se rigen por la ética profesional y, por consiguiente, no serían atendidas como cualquier otra usuaria que no viva con VIH. La percepción hacia los odontólogos, por la mayoría de los hombres (80.9%) fue contraria a la de las mujeres.

La mayor parte de las PVVS (66.7% de las mujeres y 54.3% de los hombres) no creían que el VIH se pudiese transmitir en el consultorio odontológico. El 85.0% de

Tabla 2. Percepción hacia los prestadores y servicios de salud oral públicos y privados. Nuevo León, México, 2014.

Variable	Mujeres		Hombres		p[a]
	n	%	n	%	
¿Cuántas veces al año acudes a consulta odontológica?					
Ninguna	11	28.9	0	0	
Una vez al año	17	44.7[c]	47	50.0	< 0.001
Dos o más veces al año	10	26.3	47	50.0	
¿Acudes con un odontólogo del sector público o privado?					
Ninguno	11	28.9	0	0	
Público	15	39.5[b]	24	25.5	
Privado	12	31.6	70	74.5[b,c]	< 0.001
¿Acudes con un odontólogo de práctica general o de especialidad?					
Ninguno	2	5.7	0	0	
No sé	13	37.1[b]	25	26.6	
General	11	31.4	38	40.4[b,c]	< 0.001
Especialidad	9	25.7	31	33.0	
¿De las siguientes opciones marca la que más se asemeje a la razón principal por la que elijes a un odontólogo?					
Conocimientos	12	32.4[b,c]	25	26.6	
Experiencia	5	13.5	28	29.8[b,c]	< 0.001
Formalidad	3	8.1	6	6.4	
Precio	5	13.5	11	11.7	
Trato amable	7	18.9	7	7.4	
Aspecto del consultorio	1	2.7	6	6.4	
Higiene del consultorio	2	5.4	8	8.5	
Aspecto personal del odontólogo	2	5.4	3	3.2	

[a] Mediante ANOVA.
[b] ($p < 0.001$) inter-grupos.
[c] ($p < 0.001$) intra-grupos.

Tabla 3. Percepción hacia la atención y tratamiento del VIH en la consulta odontológica. Nuevo León, México, 2014.

Variable	Mujeres		Hombres		p[a]
	n	%	n	%	
¿El consultorio o clínica dental al que acudes es seguro, limpio y cuenta con las normas de control de infección?					
Si	11	27.5	86	91.5[b,c]	< 0.001
No	29	72.5[b,c]	8	8.5	
¿Crees en la confidencialidad de los expedientes odontológicos?					
Si	21	58.3[c]	64	68.1[c]	< 0.001
No	15	41.7	29	30.9	
¿Crees que sea importante que tu odontólogo esté capacitado para brindar atención a personas que viven con VIH?					
Si	33	84.6[c]	86	91.5[c]	< 0.001
No	6	15.4	8	8.5	
¿Le informaste al odontólogo que vives con VIH?					
Si	19	48.7	29	30.9	
No	20	51.3	65	69.2[c]	< 0.001
¿Consideras que sea importante decirle a tu odontólogo que vives con VIH?					
Si	24	61.5[c]	74	78.7[c]	< 0.001
No	15	38.5	20	21.3	
Estoy en mi derecho de no revelar mi condición de persona que vive con VIH razón por la que no le informo al odontólogo:					
Si	26	65.0[b]	66	70.3[c]	< 0.001
No	14	35.0	28	29.8	
Me preocupa se me niegue la atención odontológica razón por la que no le informo al odontólogo que vivo con VIH:					
Si	25	62.5[c]	64	68.1[c]	< 0.001
No	15	37.5	30	31.9	
Me preocupan los inconvenientes que puedan surgir en el servicio odontológico razón por la que no le informo al odontólogo que vivo con VIH:					
Si	25	62.5[b,c]	41	43.6	< 0.001
No	15	37.5	53	56.4[b,c]	
¿En general los odontólogos(as) son profesionales de la salud que se rigen por la ética profesional y por consiguiente te atienden como a cualquier otro usuario independientemente de que vivas con VIH?					
Si	16	43.2	76	80.9[b,c]	< 0.001
No	20	54.1[b]	18	19.1	
No sé	1	2.7	0	0	
¿Crees que el VIH/sida se pueda trasmitir en el consultorio odontológico?					
Si	13	33.3	42	44.7	
No	26	66.7[b]	51	54.3[c]	< 0.001
No sé	0	0	0	0	
¿Crees que tu odontólogo te puede transmitir el VIH?					
Si	5	12.5	16	17.0	
No	34	85.0[c]	78	83.0[c]	< 0.001
No sé	1	2.5	0	0	
¿Crees que puedas tú trasmitirle el VIH al odontólogo?					
Si	10	25.6	31	33.0	
No	29	74.4[c]	50	53.2[c]	< 0.001
No sé	0	0	13	13.8	

Continúa

Continuación

¿Crees que puedas tú trasmitirles el VIH a otras personas que acudan al mismo consultorio o clínica odontológica en el que recibes atención?					
Si	9	22.5	18	19.1	
No	31	77.5[c]	75	79.7[c]	< 0.001
No sé	0	0	0	0	
¿Crees que tú puedas adquirir una infección secundaria, durante o después de la atención en el consultorio o clínica odontológica por vivir con VIH?					
Si	13	33.3	37	39.4	
No	24	61.5[c]	57	60.7[c]	< 0.001
No sé	2	5.1	0	0	
¿Crees que las personas que viven con VIH deban atenderse en consultorios o clínicas odontológicas en donde SOLO se atiendan a personas con VIH?					
Si	15	38.5	21	23.3	
No	24	61.5[c]	73	77.7[c]	< 0.001
No sé	0	0	0	0	
¿Crees que las enfermedades buco-dentales afectan tu estado de salud general?					
Si	35	87.5[c]	63	67.0[c]	< 0.001
No	5	12.5	31	33.0	
No sé	0	0	0	0	
¿Cómo consideras tu estado de salud buco-dental?					
Excelente	8	20.5	6	6.4	
Bueno	28	71.8[c]	40	42.6[c]	< 0.001
Regular	1	2.6	36	38.3	
Malo	2	5.1	12	12.8	
No sé	0	0	0	0	

VIH: virus de inmunodeficiencia humana
[a] Mediante ANOVA.
[b] ($p < 0.001$) inter-grupos.
[c] ($p < 0.001$) intra-grupos.

las mujeres y el 83.0% de los hombres no creía que los odontólogos pudiesen trasmitirles a sus usuarios el VIH, o viceversa (74.4% de las mujeres y 53.2% de los hombres), durante la atención odontológica. La mayoría de las PVVS (77.5% de las mujeres y 79.7% de los hombres) no creían que pudiesen transmitirles el VIH a terceras personas que acudieran al mismo consultorio o clínica odontológica. De la misma forma, el 61.5% de las mujeres y el 77.7% de los hombres no creían que por vivir con VIH debieran atenderse en consultorios o clínicas odontológicas donde únicamente se atiendan a las PVVS.

A pesar que la mayoría de las PVVS (71.8% de las mujeres y 42.6% de los hombres) considera tener un buen estado de salud buco-dental, no creían (61.5% de las mujeres y 60.7% de los hombres) que por vivir con VIH pudiesen adquirir una infección secundaria durante o después de la atención en el consultorio o clínica odontológica. Sin embargo, dijeron (87.5% de las mujeres y 67.0% de los hombres) que su estado de salud general resultaría afectado de no recibir atención o tratamiento odontológico al presentarse alguna comorbilidad buco-dental asociada al VIH.

La mayoría de las PVVS (69.4% de las mujeres y 84.0% de los hombres) señalaron que nunca han experimentado alguna situación de discriminación por parte de algún odontólogo. Tampoco el odontólogo les ha negado la atención odontológica debido a que viven con VIH (79.5% de las mujeres y 90.4% de los hombres). A la mayoría de los participantes (76.9% de las mujeres y 83.0% de los hombres) nunca le han dado excusas para negarles la atención, ni tampoco a la mayor parte (69,2% de las mujeres y 86.2% de los hombres) nunca le han demorado el servicio odontológico por vivir con VIH, con relación al resto de los usuarios (Tabla 4).

La mayoría (81.6% de las mujeres y 83.0% de los hombres) nunca ha experimentado murmullos, miradas o risas hacia su persona, igualmente a la mayoría (81.6% de las mujeres y 88.2% de los hombres), en la consulta odontológica, nunca se les ha culpabilizado o descalificado por vivir con VIH. La mayor parte (78.9% de las mujeres y 87.2% de los hombres) nunca ha recibido

Tabla 4. Percepción del estigma y discriminación asociados al VIH y el sida. Nuevo León, México, 2014.

Ítems	Nunca		Casi nunca		De vez en cuando		A menudo		Muy a menudo	
	n (%)		n (%)		n (%)		n (%)		n (%)	
	M	H	M	H	M	H	M	H	M	H
¿Has experimentado alguna situación de discriminación por parte de algún odontólogo por vivir con VIH?	25 (69.4)	79 (84.0)	4 (11.1)	8 (8.5)	4 (11.1)	5 (5.3)	2 (5.6)	1 (1.1)	1 (2.8)	1 (1.1)
¿En los últimos 12 meses ¿Con qué frecuencia se te ha negado la atención odontológica debido a que vives con VIH?	31 (79.5)	85 (90.4)	3 (7.7)	7 (7.4)	5 (12.8)	1 (1.1)	0	1 (1.1)	0	1 (1.1)
¿Cuándo has asistido a un consultorio o clínica odontológica dan o te dieron excusas para negarte el servicio debido a que vives con VIH?	30 (76.9)	78 (83.0)	2 (5.1)	10 (10.6)	4 (10.3)	3 (3.2)	3 (7.7)	2 (2.1)	0	1 (1.1)
¿Cuándo has asistido a un consultorio o clínica odontológica se demoran o han demorado más en atenderte que al resto de los usuarios?	27 (69.2)	81 (86.2)	3 (7.7)	5 (5.3)	6 (15.4)	5 (5.3)	2 (5.1)	2 (2.1)	1 (2.6)	1 (1.1)
¿Cuándo has asistido a un consultorio o clínica odontológica realizan o han realizado murmullos, miradas o risas sobre tu persona?	31 (81.6)	78 (83)	0	9 (9.6)	4 (10.5)	5 (5.3)	3 (7.9)	2 (2.1)	0	0
¿Cuándo has asistido a un consultorio o clínica odontológica se te culpabilizó, deslegitimó, o calificó por vivir con VIH?	31 (81.6)	83 (88.2)	1 (2.6)	4 (4.3)	3 (7.9)	5 (5.3)	1 (2.6)	0	2 (5.3)	2 (2.1)
¿Cuándo has asistido a un consultorio o clínica odontológica opinaron negativamente sobre tu vida y comportamientos sexuales?	30 (78.9)	82 (87.2)	0	6 (6.4)	5 (13.2)	5 (5.3)	2 (5.3)	1 (1.1)	1 (2.6)	0
¿Cuándo has asistido a un consultorio o clínica odontológica te atendieron con disgusto, indiferencia o de manera despectiva?	29 (74.4)	82 (87.2)	3 (7.7)	6 (6.4)	4 (10.3)	6 (6.4)	1 (2.6)	0	2 (5.1)	0
¿Cuándo has asistido a un consultorio o clínica odontológica evitaron el contacto con tu sudor o con tu piel?	29 (78.4)	84 (89.4)	1 (2.7)	7 (7.4)	3 (8.1)	2 (2.1)	2 (5.4)	1 (1.1)	2 (5.4)	0
¿Cuándo has asistido a un consultorio o clínica odontológica mostraron temor o inseguridad al momento de realizarte curaciones, suturas, aplicarte inyecciones y/u otros procedimientos odontológicos?	29 (74.4)	82 (87.2)	0	7 (7.4)	7 (17.9)	2 (2.1)	1 (2.6)	2 (2.1)	2 (5.1)	1 (1.1)
¿Cuándo has asistido a un consultorio o clínica odontológica solicitaron que se desechen los materiales que utilizaron contigo, argumentando el alto riesgo que se tiene debido a que vives con VIH?	29 (76.3)	83 (88.3)	1 (2.6)	7 (7.4)	2 (5.3)	0	2 (5.3)	1 (1.1)	4 (10.5)	3 (3.2)

VIH: virus de inmunodeficiencia humana; M: mujeres; H: hombres

opiniones negativas sobre su vida y comportamientos sexuales ni han recibido un trato despectivo por parte del odontólogo o su personal (74.4% de las mujeres y 87.2% de los hombres).

El 78.4% de las mujeres y el 89.4% de los hombres nunca han percibido que el odontólogo o su personal evita el contacto directo, o la mayoría (74.4% de las mujeres y 87.2% de los hombres), nunca ha percibido temor o inseguridad al momento de brindárseles la atención odontológica. El 76.3% de las mujeres y el 88.3% de los hombres nunca han escuchado que se hubiese solicitado desechar el material empleado durante su atención bajo el argumento de alto riesgo debido al VIH.

Los 11 ítems mostraron índices adecuados de consistencia interna;[24] por lo que ninguno fue eliminado, obteniéndose el valor del coeficiente alfa de Cronbach de 0.942. El primer factor estuvo compuesto por aquellas variables relacionadas con las experiencias de estigma y discriminación percibidas por los usuarios en la consulta odontológica; y el segundo, por aquellas relacionadas con la preocupación de los usuarios por la actitud del odontólogo o su personal hacia su serodiagnóstico. Tras el análisis factorial, se realizó un análisis de *clusters* no jerárquico. En el primer grupo, se identificó a los individuos como "usuarios que no han experimentado estigma ni discriminación asociados al VIH en la consulta odontológica" (85.0%). El segundo grupo se caracterizó por el conglomerado de individuos denominados "usuarios que no han experimentado estigma ni discriminación, pero sienten una ligera preocupación hacia la reacción del odontólogo o su personal al enterarse de su serodiagnóstico de VIH" (12.7%). El tercer grupo se caracterizó como "usuarios que han experimentado algún tipo de estigma y discriminación, y sienten preocupación por la reacción del odontólogo o su personal al enterarse de su serodiagnóstico de VIH" (2.3%) (Tabla 5).

DISCUSIÓN

La mayor parte de las PVVS visitan una o más veces al año al odontólogo en busca de atención odontológica, pues tienen claro que las enfermedades buco-dentales afectan el estado de su salud general. Los determinantes socioeconómicos y educativos denotaron desigualdades sociales en la atención y tratamiento del VIH.[16] Las mujeres que participaron en el presente estudio se inclinaron hacia los servicios dentales públicos y la atención odontológica de práctica general, mientras que los hombres que viven con VIH, y con mayor ingreso mensual que las mujeres, en este estudio, se inclinaron por los servicios dentales privados y de especialización.

Pese a que, las mujeres y los hombres concordaron (i) que el odontólogo debe capacitarse en la atención de las PVVS, (ii) que es importante notificar al odontólogo de su serodiagnóstico al VIH y (iii) que existe la confianza en la confidencialidad del expediente odontológico; finalmente, ambos desistieron en notificar al odontólogo su serodiagnóstico al VIH. El estigma es un proceso social o una experiencia personal conexa que influye sobre todos los aspectos sociales del afectado. De esta forma, el diagnostico de VIH/sida es ocultado por la persona que lo padece para tratar de evitar el rechazo social que este le pueda generar; es lo que Goffman llama "encubrimiento".[9]

Al igual que en otras investigaciones[14,21,22] alrededor del globo y con distintos grupos poblaciones afectados por la pandemia del VIH/sida, entre las razones principales por las cuales las PVVS no le informan al odontólogo la infección por el VIH, perpetúan, el temor al rechazo, inconvenientes que puedan surgir en la relación odontólogo-paciente y el derecho a no revelar el serodiagnóstico.

Una de las limitaciones de este estudio, común con otros relacionados con el VIH, es el empleo de una muestra relativamente pequeña, debido a que la mayoría no revela su estado serológico.[14] Sin embargo, los resultados obtenidos ofrecen un panorama de las opiniones y los problemas que las PVVS han experimentado con los odontólogos.

Aun cuando los resultados del presente estudio revelaron bajo porcentaje de estigma y discriminación percibidos en la consulta odontológica, no debemos olvidar que la mayoría de las PVVS encuestadas no comunican al odontólogo que viven con VIH, ya sea por las experiencias de estigma y discriminación vividas por las PVVS participantes o por la identidad social colectiva de éstas en su contexto. Lo anterior plantea un riesgo laboral para el odontólogo y el resto del personal que colabora en la clínica o consultorio odontológico, no sólo para el VIH (y la provisión de la profilaxis post-exposición), sino igualmente para otros patógenos transmitidos por vía sanguínea, como los virus de la hepatitis B y C.[7,8] De igual forma, este hecho plantea un riesgo para la propia salud de las PVVS, dado que el odontólogo no podrá proporcionar un tratamiento clínico adecuado[13] y pudiere prescribir algún fármaco que potencie o antagonice con la terapia antirretroviral.[5,10,11]

De acuerdo con el Informe Global 2013 del Programa Conjunto de las Naciones Unidas sobre el VIH/sida, 61.0% de los países informaron de la existencia de leyes contra la discriminación que protegen a las PVVS. En México, con base en lo establecido en el artículo primero constitucional federal y el artículo 1, párrafo segundo, fracción III de la ley federal para prevenir y eliminar la discriminación, se considera un acto contrario a derecho estigmatizar y negar derechos a las PVVS. Por consiguiente, se considera discriminatorio y antiético negar la atención odontológica a las PVVS y a otros usuarios con enfermedades infectocontagiosas puesto que ello vulnera garantías primordiales de los seres humanos

Tabla 5. Análisis factorial de la percepción del estigma y discriminación asociados al VIH y el sida en la consulta odontológica. Nuevo León, México, 2014.

Ítems	Medias y matriz de correlaciones										
	Medias	1	2	3	4	5	6	7	8	9	10
a	0.338										
b	0.185	0.583									
c	0.308	0.661	0.589								
d	0.346	0.514	0.305	0.579							
e	0.323	0.574	0.462	0.658	0.663						
f	0.431	0.522	0.523	0.567	0.545	0.758					
g	0.285	0.540	0.484	0.541	0.596	0.822	0.713				
h	0.262	0.456	0.431	0.537	0.525	0.776	0.676	0.790			
i	0.238	0.516	0.432	0.554	0.541	0.803	0.741	0.802	0.880		
j	0.308	0.539	0.506	0.543	0.555	0.804	0.747	0.771	0.823	0.819	
k	0.308	0.529	0.405	0.469	0.491	0.470	0.613	0.472	0.495	0.472	0.636

Ítems	Matriz de componentes rotados		
	Factor 1. Sin experiencias personales de rechazo por parte del odontólogo o su personal	Factor 2. Sin preocupación por la actitud del odontólogo o su personal	Comunalidades
a	0.286	0.821	0.756
b	0.207	0.785	0.659
c	0.368	0.768	0.725
d	0.552	0.458	0.514
e	0.822	0.402	0.838
f	0.719	0.456	0.726
g	0.834	0.337	0.809
h	0.890	0.239	0.849
i	0.891	0.271	0.868
j	0.831	0.378	0.833
k	0.422	0.569	0.502
Autovalores	7.049	1.030	
Porcentaje de la varianza explicada	64.079	9.361	

Conglomerado	Distancias entre los centros de los conglomerados finales		
	1. Usuarios que no han experimentado estigma ni discriminación asociados al VIH en la consulta odontológica	2. Usuarios que no han experimentado estigma ni discriminación pero sienten una ligera preocupación por la reacción del odontólogo o su personal al enterarse de su serodiagnóstico al VIH	3. Usuarios que han experimentado estigma, discriminación y sienten preocupación por la reacción del odontólogo o su personal al enterarse de su serodiagnóstico al VIH
	85.0% (n = 114)	12.7% (n = 17)	2.3% (n = 3)
1		9.434	5.292*
2	9.434		4.394*
3	5.292	4.394	

Método de rotación: normalización Varimax con Kaiser. Medida de adecuación muestral Kaiser-Meyer-Olkin: 0,904. Prueba de esfericidad de Bartlett $p < 0.0001$; converge en tres iteraciones. Análisis de *cluster* no jerárquico (K-means Cluster)
* $p < 0.001$ mediante ANOVA.

como lo es la atención médica eficiente. Sin embargo, con frecuencia, la falta de servicios legales accesibles resulta en que muchos casos de discriminación, relacionados con el VIH, nunca se aborden.

Ambas realidades (el usuario no notifica su serodiagnóstico y el odontólogo niega la atención al usuario infectocontagioso) no garantizan que los odontólogos o sus usuarios eviten la exposición al VIH y a otros

patógenos, ya que los individuos que viven con VIH o con alguna otra enfermedad infectocontagiosa pueden no ser conscientes de estar infectados. Por tal motivo, los odontólogos y todos los profesionales de la salud tienen la responsabilidad profesional y ética de capacitarse, sensibilizarse y certificarse en el manejo del VIH y otras enfermedades infectocontagiosas, así como en estudios de género, diversidad y derechos humanos, para mantener altos estándares profesionales y asegurar que todos los usuarios reciban un trato digno y equitativo.

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Elizondo JE y Treviño AC, concibieron, diseñaron y ejecutaron (realizaron el trabajo de campo). Elizondo JE realizó el análisis estadístico de los resultados, su interpretación, redactó y es responsable del artículo. Violant D facilitó, supervisó, asesoró técnicamente, aportó ideas para la interpretación de los resultados, revisó, editó y aprobó la versión final del manuscrito.

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Original

Hombres que tienen sexo con hombres y detección del virus de la inmunodeficiencia humana en odontología

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Psicometría
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R E S U M E N

Objetivo: Determinar la percepción de hombres que tienen sexo con hombres (HSH) sobre la aplicación de la prueba rápida del virus de la inmunodeficiencia humana (VIH) 1/2 en el consultorio odontológico, y evaluar el estigma y la discriminación asociados a la orientación sexual percibidos en la consulta odontológica.
Método: Estudio transversal mediante cuestionario autoadministrado y estructurado de tipo analítico contestado anónimamente por 185 HSH en México. Además de las variables sociodemográficas, la percepción sobre los servicios y los prestadores de servicios odontológicos, y sobre la aplicación de la prueba rápida anti VIH-1/2, se diseñó y exploró mediante una escala psicométrica tipo Likert la percepción del estigma y la discriminación asociados a la orientación sexual. El análisis estadístico incluyó análisis factorial y análisis de *clusters* no jerárquico.
Resultados: El 86,5% se mostró a favor de la aplicación de la prueba del VIH-1/2 en la consulta odontológica. El 91,9% considera importante que el odontólogo esté capacitado y sensibilizado para realizar la prueba. El análisis factorial reveló dos factores: experiencias de estigma y discriminación en la consulta odontológica, y sentimientos de preocupación por la actitud del odontólogo o su personal hacia su orientación sexual. El análisis de *clusters* identificó tres grupos: usuarios que no han experimentado estigma ni discriminación (90,3%); usuarios que no han experimentado estigma ni discriminación, pero que sienten una ligera preocupación (8,1%); y usuarios que han experimentado algún tipo de estigma y discriminación, y sienten preocupación (1,6%).
Conclusión: La consulta odontológica podría representar una ubicación para realizar la prueba rápida del VIH-1/2, contribuyendo en el diagnóstico temprano de la infección.

Men who have sex with men and human immunodeficiency virus testing in dental practice

Keywords:
AIDS serodiagnosis
HIV/AIDS prevention
Public health dentistry
Dental staff
Men who have sex with men
Cross-sectional studies
Psychometrics
Mexico

A B S T R A C T

Objective: To explore the attitudes of men who have sex with men (MSM) towards the implementation of rapid HIV-1/2 testing in the dental practice, and to evaluate MSM's perceptions of stigma and discrimination related to sexual orientation by dental care professionals.
Methods: Cross-sectional study using a self-administered, anonymous, structured analytical questionnaire answered by 185 MSM in Mexico. The survey included sociodemographic variables, MSM's perceptions towards public and private dental providers, and dental services, as well as their perception towards rapid HIV-1/2 testing in the dental practice. In addition, the perception of stigma and discrimination associated with their sexual orientation was explored by designing a psychometric Likert-type scale. The statistical analysis included factor analysis and non-hierarchical cluster analysis.

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Results: 86.5% of the respondents expressed their willingness to take a rapid HIV-1/2 screening test during their dental visit. Nevertheless, 91.9% of them considered it important that dental professionals must be well-trained before administering any rapid HIV-1/2 tests. Factor analysis revealed two factors: experiences of sexual orientation stigma and discrimination in dental settings, and feelings of concern about the attitude of the dentist and dental staff towards their sexual orientation. Based on these factors and cluster analysis, three user profiles were identified: users who have not experienced stigma and discrimination (90.3%); users who have not experienced stigma and discrimination, but feel a slight concern (8.1%), and users who have experienced some form of discrimination and feel concern (1.6%).
Conclusion: The dental practice may represent a potential location for rapid HIV-1/2 testing contributing to early HIV infection diagnosis.

Introducción

El virus de la inmunodeficiencia humana (VIH) sigue siendo uno de los más graves problemas de salud pública en Latinoamérica y el Caribe[1]. El Centro Nacional para la Prevención y el Control del VIH y el Sida en México (CENSIDA) reportó que una de cada tres personas con VIH desconoce su estado serológico frente a la infección[2,3]. El índice de transmisión de las personas con VIH, pero que aún no han sido diagnosticadas, es de 6,6 transmisiones por 100 personas-año[4].

Con el fin de lograr las metas de salud pública 90-90-90 del Programa Conjunto de las Naciones Unidas sobre el VIH y el Sida (ONUSIDA)[5], México y muchos países consideran prioritario que la prueba rápida para la detección de anticuerpos VIH-1/2 (PR-VIH) se ofrezca y realice en los centros de servicios médicos y en las instalaciones de las organizaciones comunitarias de la sociedad civil, a los adolescentes y adultos de 13 a 64 años de edad al menos una vez a lo largo de sus vidas, a los que tienen factores de riesgo (p. ej., usuarios de drogas inyectables, hombres que tienen sexo con hombres [HSH], entre otros) cada 3 a 6 meses, y a las mujeres embarazadas, incluyendo las que se presentan en labor de parto y cuyo serodiagnóstico del VIH se desconozca[6–9].

Por su parte, la declaración de Phucket promueve la integración de los odontólogos en la prevención, la detección y la atención del VIH[10]. Sin embargo, a pesar de que el VIH puede ser detectado mediante métodos no invasivos en suero, plasma, sangre total o líquido crevicular-saliva[7], los odontólogos aún hoy debaten, no solo en México sino también en el resto del mundo, si deberían o no ofrecer la PR-VIH en la consulta privada y las escuelas de odontología[11–16].

Por contraste, se han realizado algunos estudios concernientes a la opinión de la población general para la realización de la PR-VIH durante la consulta odontológica[14,17–21]. No obstante, nada en cuanto a conocer la opinión de los grupos considerados como de alto riesgo en la adquisición y transmisión del VIH; tal es el caso de los HSH, en quienes las condiciones sociales generadas por el estigma y la discriminación asociados a la orientación sexual (EDAOS) favorecen que incurran en conductas sexuales de riesgo, fomentando así una mayor incidencia en la adquisición y la propagación del virus[2,3,22,23].

Desde una perspectiva de salud pública, el EDAOS es un factor importante que obstaculiza a los HSH la divulgación de su orientación sexual y prácticas sexuales a los trabajadores de la salud[24]; por ende, obstruye el acceso a los servicios de salud y al modelo del «continuo del diagnóstico-atención del VIH»[25,26]. La investigación científica demuestra que más del 70% de los individuos que reportan comportamientos sexuales de alto riesgo y que nunca se han realizado un análisis de detección del VIH han estado en contacto reciente con un proveedor de servicios odontológicos[27]. Por consiguiente, el objetivo principal del presente estudio fue analizar la percepción y las actitudes de los HSH hacia la implementación de la PR-VIH y el EDAOS en la consulta odontológica.

Tabla 1
Características sociodemográficas de los participantes

Variable	Mediana	RI
Edad (años)	34	11
Escolarización (años cursados)	15	4
	n	%
Orientación sexual		
Homosexual	159	86
Bisexual	23	12,4
HSH que no se definen como homosexual o bisexual	3	1,6
Trabajo		
Tiempo completo	142	76,8
Medio tiempo	26	14
No trabaja	17	9,2
Ingresos mensuales		
≤15.000 MXN (US$ 1.146)	124	67
≤30.000 MXN (US$ 2.292)	43	23,3
≥30.000 MXN (US$ 2.292)	18	9,7

HSH: hombres que tienen sexo con hombres; RI: rango intercuartílico.

Método

Participantes y reclutamiento

En este estudio transversal participaron 185 HSH. Como criterios de inclusión se tuvo en cuenta que los participantes fueran hombres mayores de 18 años que hubieran tenido relaciones sexuales (anales u orales) con otro hombre. Las características sociodemográficas de los participantes se muestran en la tabla 1.

Los participantes fueron reclutados mediante la técnica de muestreo por cadena de referencia para el estudio de poblaciones de difícil acceso[28], con la colaboración de las organizaciones no gubernamentales y de base comunitaria de HSH en Monterrey, México. La recogida de datos se realizó durante 10 semanas, de marzo a mayo de 2015, en un consultorio odontológico privado de fácil acceso en el centro de la ciudad. Después de la encuesta (duración media de 25 minutos) a los HSH participantes se les ofreció como beneficio la realización de la PR-VIH en saliva (OraSure Technologies, Inc., Bethlehem, PA), así como una exploración y profilaxis oral de forma voluntaria, informada, consentida y gratuita, por dos odontólogos capacitados, sensibilizados y certificados. No hubo pérdidas ni rechazos.

Ética

El protocolo del estudio fue revisado y aprobado por los comités de ética e investigación del Tecnológico de Monterrey y de la Universitat Internacional de Catalunya. Los procedimientos del estudio se realizaron con el consentimiento por escrito de cada sujeto y de acuerdo con la Declaración de Helsinki[29].

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Tabla 2
Percepción hacia los prestadores y los servicios de salud oral públicos y privados

Variable	n	%
¿Cuántas veces al año acude a consulta odontológica?		
Ninguna	0	
Una vez al año	94	50,8
Dos o más veces al año	91	49,2
¿Acude con un/a odontólogo/a del sector público o privado?		
Ninguno	0	
Público	47	25,4
Privado	138	74,6
¿Acude con un/a odontólogo/a de práctica general o de especialidad?		
Ninguno	0	
No sé	51	27,6
General	75	40,5
Especialidad	59	31.9
De las siguientes opciones, marque la que más se asemeje a la razón principal por la que elige a un/a odontólogo/a		
Conocimientos	46	24,9
Experiencia	57	30,8
Formalidad	10	5,4
Precio	27	14,6
Trato amable	15	8,1
Aspecto del consultorio	10	5,4
Higiene del consultorio	15	8,1
Aspecto personal del/de la odontólogo/a	5	2,7

Tabla 3
Percepción sobre realizar la detección de anticuerpos del VIH-1/2 en la consulta odontológica

Variable	n	%
¿El consultorio o clínica dental al que acude es seguro, limpio y cuenta con las normas de control de infección?		
Sí	170	91,9
No	15	8,1
No sé	0	0
¿Se ha realizado en alguna ocasión la prueba del VIH?		
Sí	96	51,9
No	87	47,0
No sé	2	1,1
¿Le gustaría que en el consultorio o clínica dental al que acude le ofrecieran la prueba rápida de detección del VIH de manera voluntaria, bajo consentimiento informado y firmado?		
Sí	160	86,5
No	25	13,5
No sé	0	0
¿Cree que es importante que el/la odontólogo/a esté capacitado/a para hacer la prueba del VIH?		
Sí	170	91,9
No	15	8,1
No sé	0	0
¿Cree en la confidencialidad de los expedientes odontológicos?		
Sí	128	69,2
No	55	29,7
No sé	2	1,1
¿En general, los/las odontólogos/as son profesionistas de la salud que se rigen por la ética profesional y por consiguiente le atenderán como a cualquier otro/a usuario/a independientemente del resultado de la prueba del VIH?		
Sí	152	82,2
No	33	17,8
No sé	0	0
¿Algún familiar cercano, amigo o pareja falleció por causa de alguna enfermedad asociada al VIH?		
Sí	86	46,5
No	99	53,5

VIH: virus de la inmunodeficiencia humana.

Instrumento

Se utilizó un cuestionario autoadministrado de tipo estructurado analítico (de pregunta cerrada y alternativas múltiples) mediante la recopilación de datos asistida por ordenador[30]. Los temas explorados fueron las características sociodemográficas, la percepción hacia los prestadores y los servicios odontológicos públicos y privados, y hacia realizar el diagnóstico del VIH-1/2 en la consulta odontológica. En las tablas 2 y 3 se encuentran las preguntas de la encuesta. Además, se exploró mediante el desarrollo de una escala psicométrica tipo Likert[31], siguiendo el procedimiento recomendado por Lynn,[32] la percepción del EDAOS en la consulta odontológica. Esta escala constó de cinco alternativas en gradiente, desde «nunca» hasta «muy a menudo». En la tabla 4 se muestran los ítems de la escala.

Tabla 4
Percepción del estigma y la discriminación asociados a la orientación sexual en la consulta odontológica

Ítems	Nunca n (%)	Casi nunca n (%)	De vez en cuando n (%)	A menudo n (%)	Muy a menudo n (%)
¿Ha experimentado alguna situación de discriminación por parte de algún/alguna odontólogo/a por su orientación sexual?	167 (90,3)	11 (6)	5 (2,7)	1 (0,5)	1 (0,5)
¿Con qué frecuencia se le ha negado la atención odontológica debido a su orientación sexual?	173 (93,5)	8 (4,3)	0	2 (1,1)	2 (1,1)
Cuando ha asistido a un consultorio o clínica odontológica, ¿dan o le dieron excusas para negarle el servicio debido a su orientación sexual?	160 (86,9)	15 (8,1)	6 (3,2)	2 (1,1)	2 (1,1)
Cuando ha asistido a un consultorio o clínica odontológica, ¿se demoran o han demorado más en atenderle que al resto de los/las usuarios/as?	154 (83,2)	18 (9,7)	6 (3,3)	4 (2,2)	3 (1,6)
Cuando ha asistido a un consultorio o clínica odontológica, ¿realizan o han realizado murmullos, miradas o risas sobre su persona?	160 (86,4)	15 (8,1)	6 (3,3)	4 (2,2)	0
Cuando ha asistido a un consultorio o clínica odontológica, ¿opinaron negativamente sobre su vida y comportamientos sexuales?	169 (91,3)	8 (4,3)	6 (3,3)	2 (1,1)	0
Cuando ha asistido a un consultorio o clínica odontológica, ¿le atendieron con disgusto, indiferencia o de manera despectiva?	168 (90,8)	9 (4,9)	8 (4,3)	0	0
Cuando ha asistido a un consultorio o clínica odontológica, ¿evitaron el contacto con su sudor o con su piel?	172 (92,9)	9 (4,9)	2 (1,1)	2 (1,1)	0
Cuando ha asistido a un consultorio o clínica odontológica, ¿mostraron temor o inseguridad al realizarle curaciones, suturas, o aplicarle inyecciones u otros procedimientos odontológicos?	171 (92,4)	8 (4,3)	2 (1,1)	2 (1,1)	2 (1,1)
Cuando ha asistido a un consultorio o clínica odontológica, ¿solicitaron que se desecharan los materiales que utilizaron argumentando un alto riesgo debido a su orientación sexual?	172 (92,9)	6 (3,3)	0	4 (2,2)	3 (1,6)
¿Se ha sentido discriminado por la forma en la que expresa su orientación sexual?	138 (74,7)	27 (14,6)	18 (9,7)	1 (0,5)	1 (0,5)

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En todo momento se garantizaron el anonimato y la confidencialidad. No se almacenó ningún registro de datos (dirección y protocolo de Internet, entre otros) en el acceso electrónico.

Análisis estadístico

Se analizaron los datos en el programa de análisis estadístico SPSS® versión 20.0. Se realizó análisis factorial exploratorio para sintetizar empíricamente las variables relacionadas con el EDAOS. La inclusión de las variables fue condicionada por la matriz de correlaciones que convalida la presencia de una notable correlación entre ellas y garantiza la idoneidad de la aplicación de un análisis factorial. Los ítems sin significación estadística no se incluyeron en el análisis factorial. Se conservaron los factores cuyos valores mostraran índices adecuados de consistencia interna mediante la estimación del coeficiente alfa de Cronbach[33]. El método de extracción de los factores fue el de los componentes principales. Se calculó la medida de adecuación muestral de Kaiser, Meyer y Olkin (KMO), y se realizó la prueba de esfericidad de Barlett para comprobar la conveniencia de este análisis. Se realizó una rotación por el método Varimax con Kaiser para facilitar la interpretación de los resultados. Después del análisis factorial se hizo un análisis de *clusters* no jerárquico *(K-Means Cluster)* para detectar el número óptimo de grupos y su composición a partir de la similitud existente entre los casos. Una vez delimitados estos grupos o *clusters*, se comprobó que cada uno de los factores utilizados en la diferenciación de los grupos fuera estadísticamente significativo mediante el análisis de la varianza (ANOVA).

Resultados

La muestra de estudio la conformaron 185 HSH. La mediana de edad de los encuestados fue de 34 años (rango intercuartílico: 11). La mediana de escolarización fue de 15 años (rango intercuartílico: 4). En relación a la orientación sexual, la mayoría (86%) se definió como homosexual. No obstante, el 85,4% prefiere no expresar de manera abierta su orientación sexual. Por otra parte, solo el 76,8% de los participantes trabajan a tiempo completo. Sin embargo, independientemente de su situación laboral, recibían un ingreso económico mensual ≤15.000 MXN (US$ 1146) (tabla 1).

Percepción de los servicios odontológicos

El 50,8% acudió a la consulta odontológica al menos una vez al año y el 49,2% restante asistió dos o más veces en un año. La mayoría (74,6%) asistía a los servicios odontológicos del sector privado. El 40,5% recibía atención odontológica general, mientras el 31,9% de especialidad. Entre las razones principales por las que los encuestados elegían un determinado odontólogo se encontraron la experiencia (30,8%) y los conocimientos (24,9%) de este (tabla 2).

Percepción de la PR-VIH en la consulta odontológica

La mayor parte (91,9%) consideraba que el consultorio al que acudía era seguro, limpio y contaba con las normas de control de infección requeridas por las instancias de salud pública. El 69,2% creía en la confidencialidad del expediente odontológico y el 82,2% consideró que el odontólogo se rige por la ética profesional y, por ende, no discriminaría a sus usuarios independientemente del resultado de la PR-VIH. Además, el 86,5% desearía que en el consultorio o la clínica odontológica a la que acude se le ofreciera la PR-VIH de manera voluntaria, mediante consejería, consentimiento informado y firmado. Sin embargo, el 91,9% creía que era necesario que el odontólogo estuviese capacitado y sensibilizado para realizar dicha prueba.

Entre los participantes, el 48,1% indicó que no se había realizado una PR-VIH (tabla 3). Dos participantes resultaron reactivos (tasa de prevalencia de VIH sin detectar del 1,08%). Por otra parte, el 62,2% (n = 115) de los HSH encuestados tenía un familiar, amigo o pareja con VIH, y el 46,5% (n = 86) comentó que esa persona falleció a causa de alguna enfermedad o padecimiento asociado al virus. La asociación entre ambas variables de riesgo relativo (RR) e intervalo de confianza del 95% (IC95%) de muerte por el VIH fue RR 3,9 e IC95% 2,17-7,01.

Precepción del estigma y la discriminación asociados a la orientación sexual en la consulta odontológica

El 90,3% señaló que nunca ha experimentado una situación de discriminación por parte de ningún odontólogo. Tampoco el odontólogo le ha negado la atención odontológica debido a su orientación sexual (93,5%). A la mayoría (86,9%) nunca les han dado excusas para negarles la atención, ni tampoco a la mayoría (83,2%) les han demorado el servicio odontológico por su orientación sexual, con relación al resto de los usuarios. Finalmente, el 74,6% de los HSH encuestados nunca se han sentido discriminados por la forma en que expresan su orientación sexual (tabla 4).

En relación a la evaluación estadística de la escala psicométrica del EDAOS en la consulta odontológica, los 11 ítems mostraron índices adecuados de consistencia interna (alfa de Cronbach de 0,938)[33], por lo que ninguno fue eliminado. El determinante de la matriz de correlaciones tendió a cero ($|R < 0,01|$), el índice KMO fue 0,885 y se rechazó la hipótesis nula de equivalencia de la matriz de correlaciones a una matriz identidad por la prueba de esfericidad de Bartlett (p <0,001). Tras rotar la matriz de componentes factoriales por el método Varimax con Kaiser se extrajeron dos componentes, los cuales explicaron el 73,24% de la varianza total. El primer factor estuvo compuesto por aquellas variables relacionadas con las experiencias de estigma y discriminación percibidas por los usuarios en la consulta odontológica, y el segundo por aquellas relacionadas con la preocupación de los usuarios por la actitud del odontólogo o su personal hacia su orientación sexual (tabla 5).

Tras el análisis factorial se realizó un análisis de *clusters* no jerárquico. En el primer grupo se identificaron los individuos como «usuarios que no han experimentado estigma ni discriminación en la consulta odontológica» (90,3%). El segundo grupo se caracterizó por el conglomerado de individuos denominados «usuarios que no han experimentado estigma ni discriminación, pero sienten una ligera preocupación hacia la reacción del odontólogo o su personal al enterarse de su orientación sexual» (8,1%). El tercer grupo se caracterizó como «usuarios que han experimentado algún tipo de estigma y discriminación, y sienten preocupación por la reacción del odontólogo o su personal al enterarse de su orientación sexual» (1,6%) (tabla 5).

Discusión

Esta investigación es la primera que ha evaluado en México la receptividad del colectivo HSH para la implementación de la PR-VIH en la consulta odontológica de manera voluntaria, informada y consentida. Además, es la primera en desarrollar y evaluar una escala psicométrica de la percepción del EDAOS en la consulta odontológica. Al igual que en otras investigaciones[11–14,16,21], nuestros resultados sugieren que la consulta odontológica podría ser una posible ubicación para hacer la PR-VIH y un sitio favorable para realizar el diagnóstico temprano del VIH-1/2 en una de las poblaciones clave más afectadas por la pandemia del VIH[27].

Aunque la composición sociodemográfica de nuestra población difiere de las de estudios anteriores, la alta tasa global (n = 160, 86,5%) de aceptación de la PR-VIH en la consulta odontológica es

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Tabla 5
Análisis factorial de la percepción del estigma y la discriminación asociados a la orientación sexual en la consulta odontológica

	Medias y matriz de correlaciones										
Ítems	Medias	1	2	3	4	5	6	7	8	9	10
a	0,266										
b	0,149	0,652									
c	0,277	0,759	0,579								
d	0,266	0,636	0,411	0,694							
e	0,266	0,748	0,468	0,655	0,704						
f	0,202	0,709	0,562	0,558	0,593	0,760					
g	0,191	0,747	0,544	0,584	0,569	0,801	0,847				
h	0,149	0,856	0,622	0,646	0,746	0,850	0,848	0,842			
i	0,223	0,804	0,656	0,542	0,611	0,790	0,801	0,787	0,894		
j	0,234	0,635	0,518	0,446	0,435	0,496	0,550	0,501	0,633	0,746	
k	0,309	0,192	0,164	0,203	0,137	0,206	0,287	0,228	0,192	0,202	0,190
Ítems	Matriz de componentes rotados										
	Factor 1. Sin experiencias personales de rechazo por parte del/de la odontólogo/a o su personal	Factor 2. Sin preocupación por la actitud del/de la odontólogo/a o su personal				Comunalidades					
a	0,902	0,082				0,820					
b	0,701	0,105				0,503					
c	0,767	0,066				0,592					
d	0,777	−0,026				0,605					
e	0,873	0,097				0,772					
f	0,846	0,240				0,773					
g	0,856	0,168				0,762					
h	0,952	0,087				0,915					
i	0,906	0,130				0,839					
j	0,689	0,154				0,499					
k	0,111	0,982				0,977					
Autovalores	7,101				0,954						
Porcentaje de la varianza explicada	64,553				8,677						

Distancias entre los centros de los conglomerados finales			
Conglomerado	1. Usuarios que no han experimentado estigma y discriminación en la consulta odontológica	2. Usuarios que no han experimentado, pero sienten una ligera preocupación por lo que el/la odontólogo/a o su personal opinen sobre su orientación sexual	3. Usuarios que han experimentado algún tipo de discriminación y sienten preocupación por lo que el/la odontólogo/a o su personal opinen sobre su orientación sexual
	90,3% (n = 167)	8,1% (n = 15)	1,6% (n = 3)
1		7,104	11,061[a]
2	7,104		4,401[a]
3	11,061	4,401	

Método de rotación: normalización Varimax con Kaiser. Medida de adecuación muestral Kaiser-Meyer-Olkin: 0,885.
Prueba de esfericidad de Bartlett, p <0,001; converge en tres iteraciones. Análisis de *cluster* no jerárquico *(K-means Cluster)*.
[a] p <0,001 mediante ANOVA.

coherente con los resultados obtenidos por Durall et al.[17] (71%), Dietz et al.[21] (73%), VanDevanter et al.[18] (74%), Greenberg et al.[19] (80%), Nassry et al.[14] (88%) y Blackstock et al.[20] (97%). Sin embargo, a diferencia del presente estudio (n = 185, 100%), solo algunas de estas investigaciones encuestaron a los HSH sobre la PR-VIH: Durall et al.[17] (n = 19, 5%), Blackstock et al.[20] (n = 93, 2,6%) y Dietz et al.[21] (n = 3, 12,5%).

Es indispensable considerar que la mayoría de las personas diagnosticadas con VIH cada año son HSH, y que una tercera parte de las nuevas infecciones se atribuyen a quienes desconocían que estaban infectados[2,3,22,23]. El 48,1% de los HSH encuestados en el presente estudio respondió que no se había realizado la PR-VIH, lo que significa que desconocían su diagnóstico serológico frente al VIH. Aunado a lo anterior, el riesgo relativo percibido (RR: 3,9; IC95%: 2,17-7,01) por los encuestados en torno a la muerte por un padecimiento asociado al VIH podría ser el factor por el cual la mayoría de los HSH aceptaron la implementación de la PR-VIH en la consulta odontológica.

A diferencia del estudio de Blackstock et al.[20], quienes reportaron una tasa de prevalencia del VIH no diagnosticada del 0,5% en la población general, nuestro estudio obtuvo una prevalencia del virus sin detectar en HSH del 1,08%. Relacionado con lo anterior, al igual que Pollack et al.[27] encontramos que los individuos con alto riesgo de infección por VIH han estado en contacto reciente con un proveedor de servicios odontológicos (51% y 70%, respectivamente). Por tanto, la alta tasa de prevalencia en los HSH y su contacto frecuente con los proveedores de servicios odontológicos podrían ser indicativos de que la implementación de la PR-VIH en la consulta odontológica contribuiría al alcance de las metas de salud pública 90-90-90[2,3,5], al brindar un servicio de detección oportuna y de vinculación al «continuo del diagnóstico-atención del VIH»[25,26] con énfasis en las poblaciones clave y vulnerables.

No obstante, el EDAOS es un factor importante que obstaculiza a los HSH la divulgación de su orientación sexual y sus prácticas sexuales a los trabajadores de la salud[24], pero nuestros resultados mostraron una baja percepción del mismo en la consulta odontológica. Lo anterior puede deberse a que medir el EDAOS resulta complicado porque las personas son más propensas a reconocer la discriminación contra los colectivos sociales que a reconocer la discriminación contra ellos mismos como individuos[34]. Asimismo, puede existir un subregistro del EDAOS debido a la «homonegatividad internalizada», en la cual el individuo se autovigila para no realizar ninguna acción que pueda evidenciar su orientación sexual[35].

Orientaciones futuras: implicaciones y retos de la intervención

Antes de la implementación de la PR-VIH en el ámbito odontológico deben resolverse importantes cuestiones éticas, legales y económicas. Igualmente, debe realizarse un énfasis educativo dentro del plan de estudios de las escuelas de odontología con el fin de ampliar la cobertura y promover e incorporar la aplicación de la PR-VIH en la consulta odontológica. A su vez, deben fomentarse programas de capacitación, sensibilización y certificación en los conocimientos científicos relacionados con el VIH, la consejería y la implementación de la PR-VIH, así como en estudios de género, diversidad sexual y derechos humanos, para asegurar que todos/as los/las usuarios/as reciban un trato digno y equitativo en la consulta odontológica.

De igual forma, existe una serie de cuestiones logísticas relacionadas con la implementación de la detección rápida del VIH: la obtención de resultados reactivos de la prueba; la necesidad de consejería profesional y los protocolos de confirmación, vinculación y retención de los casos reactivos a los servicios de salud en coordinación con las autoridades locales; el suministro de insumos de prevención e información focalizada del VIH; y la confidencialidad de los resultados de la PR-VIH y del expediente odontológico.

Fortalezas y debilidades

En el presente estudio deben considerarse las limitaciones de haberse implementado con un modesto tamaño de muestra, lo que imposibilita realizar cualquier tipo de subanálisis y afirmaciones generales con peso estadístico sobre la población. Al diseñar estudios de intervención en poblaciones ocultas, y específicamente en HSH, hay que considerar que por ser un grupo estigmatizado se desconoce su tamaño real, que no todos se reconocen como homosexuales o bisexuales, y que no pueden ser alcanzados por las metodologías de muestreo tradicionales. Por ende, los estudios realizados hasta el momento no permiten un conocimiento certero de la realidad epidemiológica de esta población ni la estandarización de los resultados. Los resultados y las conclusiones obtenidos deben ser considerados como hipotéticos para otros grupos sociales, lo que limita la capacidad de la utilización de la escala en la población general o sacar conclusiones sobre el impacto del EDAOS percibido en la consulta odontológica. Sin embargo, el presente estudio proporciona un panorama sobre las actitudes y percepciones de una de las poblaciones con mayor riego de adquirir el VIH en México.

Conclusión

Desde nuestro particular punto de vista, es indispensable generar programas que incluyan la participación del odontólogo en los esfuerzos de salud pública, más allá de la lucha contra la caries o los padecimientos de las encías, sino también en otras enfermedades crónico-degenerativas como la infección por el VIH. Sumar al odontólogo a esta respuesta coadyuvaría a concienciar a sus usuarios de la infección por VIH a través de la PR-VIH, y a la vez ofrecería una ubicación más para la detección oportuna como un primer paso esencial para vincular a las personas al «continuo del diagnóstico-atención del VIH», lo que contribuiría a la reducción de la incidencia de nuevos casos de VIH y a un avance importante en salud pública. No obstante, es poco probable que dentro de la consulta odontológica se ofrezca la PR-VIH a todos los usuarios. Un enfoque específico parecería más adecuado, pero la logística de cómo sería ofrecida requiere un poco de pensamiento crítico para evitar prácticas discriminatorias. Se requiere realizar investigación futura a mayor escala para verificar los hallazgos del presente estudio y para conocer los principales obstáculos que se anteponen a la aplicación de la PR-VIH en la consulta odontológica.

¿Qué se sabe sobre el tema?

A través de la evidencia científica conocemos algunas de las opiniones del odontólogo sobre incluir la prueba rápida anti-VIH 1/2 en la consulta odontológica. Sin embargo, poco se sabe de la percepción de los hombres que tienen sexo con hombres en relación a la detección del virus y la percepción del estigma y la discriminación asociados a la orientación sexual en la consulta odontológica.

¿Qué añade el estudio a la literatura?

La validación de un instrumento psicométrico para la medición de la percepción del EDAOS en la consulta odontológica, y brinda un panorama de la receptividad del colectivo de hombres que tienen sexo con hombres para realizarse la prueba del VIH 1/2 en la consulta odontológica.

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Declaración de transparencia

El autor principal (garante responsable del manuscrito) afirma que este manuscrito es un reporte honesto, preciso y transparente del estudio que se remite a Gaceta Sanitaria, que no se han omitido aspectos importantes del estudio, y que las discrepancias del estudio según lo previsto (y, si son relevantes, registradas) se han explicado.

Contribuciones de autoría

J.E. Elizondo desarrolló la propuesta, dirigió el proyecto, ejecutó el análisis estadístico de los datos, interpretó los resultados y redactó y es responsable del artículo. J.E. Elizondo, A.C. Treviño, A. Rivas-Estilla y M.M. Álvarez solicitaron los fondos para la investigación. J.E Elizondo y A.C. Treviño realizaron el trabajo de campo y revisaron y editaron el manuscrito. D. Violant, A. Rivas-Estilla y M.M. Álvarez facilitaron, supervisaron, asesoraron técnicamente, aportaron ideas para la interpretación de los resultados, revisaron, editaron y aprobaron la versión final del manuscrito.

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Conflictos de intereses

Ninguno.

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Potential gingival crevicular fluid and serum biomarkers by stage of HIV infection

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ABSTRACT

Objective: This study evaluates the potential of gingival crevicular fluid and serum cytokines as HIV stage biomarkers.
Methods: Gingival crevicular fluid (GCF) and serum samples from 78 HIV-positive adult male subjects (cases) and 39 HIV-negative male subjects (controls) from Mexico were examined for 17 cytokines using multiplex ELISA. Participants were divided into five subgroups by HIV stage of infection on age-specific CD4+ T-lymphocyte count and antiretroviral therapy (ART), and further correlated to the cytokine levels.
Results: GCF concentrations of IL-6, IL-7, IL-10, IL-12, G-CSF and MCP-1, as well as serum concentrations of IL-1β, IL-2 and IL-6 showed a statistically significant difference among subgroups. We found a significant effect size correlation on cytokines expression levels. Subjects who were not in ART showed significantly higher levels of some of the analyzed cytokines compared to the rest. We found that GCF IL-8 was a significant predictor for the Non-ART HIV status ($p < 0.05$). We observed the same result for GCF G-CSF in the ART Short-term group and serum GM-CSF in the ART Long-term subgroup.
Conclusion: Results indicate a high variability of GCF and serum cytokines concentrations and low frequency of their detection in different HIV/ART stages. However, within the limits of the present study, some GCF and serum cytokine concentrations correlate positively. Oral and periodontal innate immunity is affected by HIV viremia and ART. GCF IL-8, G-CSF, as well as serum IL-8, MCP-1 and GM-CSF may be useful biomarkers for the detection of disease presence and/or its severity due to HIV infection and ART use.

1. Introduction

Viruses and other periodontopathogens are risk factors in many oral and systemic diseases and human immunodeficiency virus (HIV) is not the exception. Co-pathogenesis is characterized by numerous complex interactions between the co-infecting pathogens and their host, inducing disruption of physical barriers, dysregulation of immune responses and arrears to achieve immune homeostasis. HIV targets and infects CD4+ T-cells by binding to cell surface glycoprotein CD4 and then to chemokine coreceptors CCR5 or CXCR4. Infected HIV cells releases newly formed virions in a semi-synchronous wave pattern and are also thought to spread them through direct contact with their neighbors via virological synapses and by pools of free virions [1]. The oral cavity seems to be a potential reservoir of HIV, as its RNA and DNA can be detected and quantified in the subgingival biofilm, gingival crevicular fluid (GCF) and saliva of HIV-infected individuals [2–4]. There-

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fore, the oral epithelial cells are susceptible to either cell-free or cell-associated HIV infection.

The biological and clinical basis of the probable relationship among oral chronic inflammatory disorders, such as periodontal disease and the exacerbation of HIV viremia have received limited attention [5]. Nevertheless, controversial data regarding the association among immunosuppression and prevalence/severity of oral and periodontal diseases in HIV-infected individuals had been reported [6,7].

The cytokines, chemokines, and their receptors have been receiving notable consideration afterward the discoveries that some of them could specifically block HIV infection and that some specific chemokine receptors were the long-sought co-receptors which, along with CD4+ T-cell, are required for the productive entry of HIV [8]. The intricate and complex balance of factors that regulate the HIV-1 pathogenic process is highlighted by both the inhibition and enhancement that cytokines, chemokines and their receptor signaling events elicit on the HIV entry and replication processes.

Extending our prior work, where we examined whether the levels of interleukin (IL)-2, IL-4, IL-6, IL-8, IL-10, granulocyte–macrophage-colony-stimulating factor (GM-CSF), interferon-gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) in GCF were altered in HIV-infected individuals with non-periodontal disease, and whether CD4+ T-cell count, HIV viral load and antiretroviral therapy (ART), affected those levels [9]. We decided to explore the possible association between GCF and serum levels of IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, GM-CSF, IFN-γ, granulocyte colony-stimulating factor (G-CSF), monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein-1β (MIP-1β), tumor necrosis factor alpha (TNF-α), with CD4+ T-cell count, HIV viral load and ART, as well as their association with HIV/ART status, in an effort to identify and quantify periodontal and systemic risk biomarkers by objective methods and measures.

2. Material and methods

2.1. Recruitment and participants

Participants were recruited from HIV/AIDS healthcare providers, non-governmental and community-based organizations in Monterrey, Mexico and adopted a non-probability and snowball sampling [10]. The research involved 202 consenting adult men who have sex with men (MSM). Eligible participants in the cross-sectional study were those 18 years or older and who had engaged in sex - anal or oral - with another male.

HIV-infected subjects were diagnosed in advance of the study as HIV-positive by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western Blot [11]. All self-declared non-HIV subjects were provided with an opportunity to undergo voluntary counseling and testing for HIV (at screening and if enrolled, 3 months after all study samples were taken), detected by rapid HIV-1/2 test (OraSure Technologies, Inc., Bethlehem, PA).

2.2. Ethics

The study protocol was reviewed and approved by the ethics, research and biosafety committees at Tecnologico de Monterrey and Universitat Internacional de Catalunya. The study procedures were undertaken with the written consent of each subject and according to the Declaration of Helsinki [12].

2.3. Clinical examination

2.3.1. Anamnesis

All participating patients were offered a general health survey and baseline electronic medical/dental records were collected. Exclusion criteria included history or current manifestation of any systemic, autoimmune, and infectious diseases, or other than HIV/AIDS. Likewise, diabetes, concurrent psychiatric or psychological treatment, illicit drug use, current alcohol abuse, chronic or intermittent usage of anti-inflammatory or antidepressant drugs, antibiotics, chlorhexidine digluconate, previous vaccination (⩽4 weeks), previous periodontal treatment (⩽6 months) and current use of prosthetic or orthodontic appliances (fixed or removable), that could affect periodontal or systemic cytokine expression. Smoking habit was recorded and not excluded due to its prevalence among MSM with that among other men [13,14]. In like manner, obesity could not be avoided and body mass index (BMI) was taken into account due to obesity prevalence among Mexican adult population [15].

2.3.2. Oral examination

All participants underwent a standardized baseline oral examination. Gingival recession (REC), probing pocket depth (PPD), clinical attachment level (CAL) and bleeding on probing (BOP) were measured using Florida Probe® (Florida Probe Corporation, Gainesville, FL). Six sites were measured in all teeth considering a fixed reference point on the occlusal surface of teeth and cementoenamel junction, except third molars. A total number of natural teeth was recorded. BOP was calculated as the percentage of positive sites per subject. BOP was considered positive if bleeding was elicited within 30 s following periodontal probing. Plaque index was recorded (PI) [16]. No radiographs were taken. Periodontitis was defined by the presence of one site with PPD ⩾ 4 mm and CAL ⩾ 3 mm on at least 4 different teeth with or without BOP. HIV-related oral lesions were recorded according to classified criteria EC-Clearinghouse [17], and OHARA case definitions [18].

2.4. Samples and laboratory tests

Prior sampling all subjects were rapid tested for the presence of anti-HBc, HBsAg and anti-HCV (Intec, Xiamen, China). In addition, non-fasted blood glucose levels (BGL) were determined (LifeScan, Inc., Milpitas, CA). Furthermore, oral fluid multiple drug screen test was used to determine drug abuse (Branan Medical Corp., Irvine, CA). All rapid tests were performed with appropriate counseling and referral.

2.4.1. GCF collection

Maxillary teeth including first molars, second premolars, and canines or central incisors (three teeth per subject) were selected. Sampled teeth were free of gingival inflammation, caries, prosthetic reconstruction and root canal therapy. After supragingival plaque was removed, paper strips (PerioPaper Strips, OraFlow, PlainView, NY) were gently inserted into the crevice for 30 s. GCF volume was measured and converted to microliters using Periotron 8000 and MCCONVRT V2.52 (Oraflow Inc., Amityville, NY). Paper strips with traces of blood were discarded and sampling was replicated from another non-sampled site of the tooth. Six paper strips of each patient were placed in 500 μl of phosphate-buffered saline (PBS). Following 10 s vortexing and 20 min shaking, the strips were removed and the eluates were centrifuged for 5 min at 5800 x *g* to remove plaque and cellular elements. The supernatant was harvested and divided into aliquots and stored at −80 °C until assayed.

2.4.2. Serum and plasma samples

Samples were taken following the standard operating procedures for serum and plasma collection for biomarker discovery and validation [19].

2.4.3. CD4+ T-cell counting

Blood samples were stained and analyzed by FACSCount (Becton Dickinson, San Jose, CA) within 2 h and all measures were performed in triplicate according to manufacturer's instructions.

2.4.4. Cytokine assay

Selection and assessment of cytokines was based accordingly to their potential relevance as periodontal biomarkers of HIV pathology and infection immune response in which immunological correlates remain undefined. Levels of cytokines in serum and GCF samples from all subjects were determined using Bioplex ProTM Human Cytokine 17-plex Assay (Bio-Rad Lab., Inc., Hercules, CA) accordingly to manufacturer's protocol at the same time in duplicate. All proteins were determined using Bio-Plex array reader (Luminex, Austin, TX) at 405 nm wavelength. Samples with analyte concentrations beneath the detection limit were assigned an intermediate value between zero and the lowest detectable level in every assay plate before log transformation, therefore all samples were preserved within the data set. Concentrations of cytokines were corrected for serum and GCF volume, and were defined as pg/μl, for the GCF total amounts were expressed as pg/6 sites.

2.4.5. HIV-1 RNA assay

Plasma samples from HIV-infected individuals were analyzed using real-time PCR by Cobas Ampliprep/Cobas TaqMan HIV-1 test (Roche CAP/CTM-48 V2) on the TaqMan 48 analyzer (Roche Molecular Systems, Branchburg, NJ). This assay has a reportable range of 20 to 1.0E+7 HIV RNA copies/ml.

2.5. Statistical analysis

Data were tested for normal distribution using the Kolmogorov-Smirnov test [20] and Levene's test. Grubbs' test [21] was used to determine significant outliers from the data set. Outliers were winsorized from the analysis [22], and normality was reconfirmed with the above-mentioned normality test. Results based on normality and outlier tests were followed by repeated measures Multivariate Analysis of Variance (MANOVA) to test for group differences. Differences within groups are presented as means ± standard deviation (SD) for continuous variables and as proportions for categorical variables.

Additionally, all data were analyzed with a series of follow-up ANOVA, the homogeneity of variance assumption was tested on a series of Levene's *F*-test for all analyzed variables. Paired "*t*" test was used to compare the means of data from two related samples. A series of post hoc Scheffé's test were performed to examine individual mean difference comparisons (control of type I error) and determine the exact nature of group differences.

Pearson's correlation coefficient (PCC) and multivariate linear regression (MLR) analyses were used to compare means of immunological parameters among independent groups. The assumptions of independence and homoscedasticity for MLR was checked using Durbin-Watson test [23] and Breusch-Pagan test [24], respectively. Heteroscedasticity-consistent standard error estimators [25] were used to correct any presence of spatial nonstationarity (avoid type I errors) in the MLR models. All data were analyzed with SPSS® (version 22.0) and all test were performed considering $\alpha = 0.05$ to indicate statistical significance.

3. Results

3.1. Demographic and clinical findings

Based on inclusion and exclusion criteria the study sample comprises 117 voluntary MSM. Descriptive statistics were used to analyze breakdown of subjects by the status of HIV test. 78 HIV-positive subjects (age range 22–54 years, median 35) as cases and 39 HIV-negative subjects (age range 18–49 years, median 32) as controls match in race, sex, sexual orientation, and sexual behavior. All 39 HIV-negative subjects were retested 3 months after all study samples were taken and remained HIV negative.

HIV-positive subjects were grouped according to the Center for Disease Control (CDC) classification for HIV infection [26]. Included stage, and duration of HIV infection (calculated from HIV serodiagnosis date), use of ART, anti-HIV drug classes, Mexico's ART guideline (first, second or salvage) [27], duration of ART, CD4+ T-cell count, and HIV RNA viral load (Table 1).

The cohort was then divided into subgroups, six HIV-infected subjects were not on antiretroviral therapy (Non-ART subgroup) at the time of the study and seventy-two were receiving different combinations of ART, mainly one non-nucleoside reverse transcriptase inhibitor (NNRTI) and two nucleoside reverse transcriptase inhibitors (NRTIs) n = 51, 71%. Those who had been on ART < 1 year (n = 8, 11%) were classified as ART-naïve, those who had been taking ART $\geqslant$ 1 < 6 years (n = 41, 57%) were classified as short-term ART, and finally those who had been taking ART for $\geqslant$ 6 years (n = 23, 32%) were classified as long-term ART. Of those who had been on ART were sub-classified as first-line ART (n = 57, 79%), second-line ART (n = 13, 18%) and salvage ART subjects (n = 2, 3%), (Table 1).

3.2. Data preprocessing and normalization

After data preprocessing and pretreatment was achieved, results for parameters based on normality and outlier tests were followed by MANOVA. Effect was obtained, Pillais' Trace = 2.58, $F(192{,}000) = 2.57$, $p < 0.001$. The multivariate effect size was estimated at 0.645, which implies that 64% of the variance in the canonically derived dependent variables were accounted for stages of HIV infection. There were significant differences ($p < 0.05$) among subgroups in Age, CD4+ count, HIV viral load and sites with PPD $\geqslant$ 4 mm and CAL $\geqslant$3 mm associated with the HIV/ART status. Nonetheless, Scheffé's post hoc analysis did not reveal any reliable differences in sites with PPD $\geqslant$4 mm and CAL $\geqslant$3 mm among subgroups (Table 2).

Besides, there were non-significant differences among subgroups in social factors such as educational attainment and monthly income, and none were there among personal behavior and lifestyle factors like smoking habit and alcohol consumption, and nor did in systemic and oral clinical variables (Table 2).

Prevalence of oral lesions among HIV-positive subjects with and without ART and HIV-negative subjects were rarely seen. Hyperpigmentation was the most common oral lesion in all subgroups, followed by only one case of linear gingival erythema in the Non-ART subgroup. Nevertheless, there were no significant differences.

3.3. GCF and serum cytokine levels

The values of GCF IL-6, IL-7, IL-10, IL-12, G-CSF, and MCP-1 were significantly higher in the Non-ART subgroup as compared to the control. However, IL-10 and IL-12 did not show a significant p-value in the post hoc. On the other hand, IL-1β, IL-2, and IL-6 were

Table 1
Classification of HIV-infected subjects on infection stage on age-specific CD4+ T-lymphocyte count and ART on date base.

Parameters	*Infection stage based on age-specific CD4+ T-lymphocyte count (n = 78)*												
Years of infection	<1 yr (mean 0.84 yr [SD 0.15] n = 14)				1–5 yrs (mean 2.43 yrs [SD 0.9] n = 41)				>5 yrs (mean 8.64 yrs [SD 3.27] n = 23)				
HIV Stage	Cells/μL	Mean	n	n%	Cells/μL	Mean	n	n%	Cells/μL	Mean	n	n%	Total
1	⩾1500	/	/	/	⩾1000	1069.33 ± 113.23	3	3.8	⩾500	773.07 ± 195.76	14	17.9	17
2	750–1499	800	1	1.3	500–999	681.65 ± 127.98	17	21.8	200–499	340.86 ± 52.72	7	9	25
3	<750	365.31 ± 97.33	13	16.7	<500	362.19 ± 92.05	21	26.9	<200	161 ± 26.87	2	2.6	36

ART based on date, guideline and drug class (n = 72)

Study Groups	Non-ART (n = 6)	Naïve ART (n = 8)					Short-term ART (n = 41)					Long-term ART (n = 23)					
Anti-HIV Drug Classes		A	B	C	n	n%	A	B	C	n	n%	A	B	C	n	n%	Total
First		7	1	/	8	10.3	31	7	/	38	48.7	7	4	/	11	14.1	57
Second		/	/	/	/	/	2	1	/	3	3.8	3	5	2	10	12.8	13
Salvage		/	/	/	/	/	/	/	/	/	/	1	/	1	2	2.6	2

Mean ± standard deviation, n% = distribution %, ART Guideline First, second and salvage (Mexico's ART Guideline CENSIDA), **A** = 2 NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors) + 1 NRTI (Nucleoside Reverse Transcriptase Inhibitors), **B** = 2 NNRTIs + Ritonavir boosted PI (Protease Inhibitors), **C** = Other antiretrovirals with minimal cross-resistance risk.

Table 2
Demographic and clinical characteristics of the study subjects.

Study groups	Non-ART (n = 6)	ART Naïve (n = 8)	Short-term ART (n = 41)	Long-term ART (n = 23)	Non-HIV subjects (n = 39)	MANOVA p	Post hoc
Age	30.33 ± 6.56	28.38 ± 5.95	35.37 ± 8.07	40.65 ± 6.37	32.10 ± 6.98	0.0001	0.001
Educational attainment	14.33 ± 2.08	15.33 ± 3.26	13.97 ± 3.82	13.71 ± 4.05	15 ± 3.65	0.67	
Monthly income	1000.63 ± 308.35	1019.65 ± 497.99	1002.01 ± 551.45	1159.87 ± 708.89	1130.57 ± 708.57	0.50	
HIV Stage[a]	HIV Stage 3	HIV Stage 3	HIV Stage 2	HIV Stage 1			
$CD4^+$ Range	251–491	220–800	136–1200	142–1200			
Mean	397.83 ± 95.94	395.25 ± 186.35	546.39 ± 239.85	588.30 ± 285.02		0.0001	0.0001
HIV viral copies Range	20–60,500	20–39,000	20–3250	20–3300			
Mean	28,735 ± 20,468	5131 ± 13,702	81.22 ± 507.40	254.78 ± 843.43		0.0001	0.0001
Glucose	87.50 ± 8.40	90.25 ± 5.14	90.76 ± 11.40	95.22 ± 13.54	94.26 ± 12.70	0.37	
BMI[b]	24.98 ± 6.17	24.35 ± 2.54	26.54 ± 3.22	25.34 ± 3.84	27.59 ± 4.1	0.07	
Number of teeth	29.33 ± 1.5	28.75 ± 0.88	28.05 ± 1.93	27.35 ± 2.18	1.94 ± 0.11	0.11	
Plaque Index	1.63 ± 0.46	1.61 ± 0.48	1.55 ± 0.49	1.58 ± 0.37	1.56 ± 0.39	0.58	
BOP	10.33 ± 14.37	6.38 ± 6.96	4.71 ± 5.46	7.13 ± 12.84	7.28 ± 13.26	0.70	
PPD Range	3.46–4.67	3.43–3.69	3.31–5.41	3.39–5.34	3.27–4.64		
Mean	3.96 ± 0.55	3.52 ± 0.08	3.67 ± 0.40	3.90 ± 0.56	3.73 ± 0.37	0.093	
CAL Range	2.66–2.91	2.58–2.82	2.46–3.01	2.55–2.94	2.45–3.11		
Mean	2.72 ± 0.09	2.65 ± 0.07	2.65 ± 0.09	2.70 ± 0.11	2.68 ± 0.12	0.36	
PPD/CAL	13.66 ± 8.28	8 ± 6.56	5.60 ± 4.45	6.78 ± 6.57	8.43 ± 7.77	0.046	0.095

	n	%	n	%	n	%	n	%	n	%	Total (n)	Total (%)
Homosexual	5	83.3	7	87.5	38	92.6	20	86.9	34	87.1	104	88.9
Bisexual	1	16.6	1	12.5	3	7.3	3	13	5	12.8	13	11.1
Non-smoker	3	50	6	75	22	53.7	10	43.5	19	48.7	60	51.2
Smoker	3	50	2	25	19	46.3	13	56.5	20	51.3	57	48.7
Alcohol Non-drinker	4	66.7	6	75	22	53.7	11	47.8	16	41	59	50.4
Alcohol Drinker	2	33.3	2	25	19	46.3	12	52.2	23	59	58	49.6

Mean ± standard deviation, Post hoc Scheffé, Age in years, Educational attainment = Years of school completed, Monthly income in USD, CD4 cell count (cell mm^{-3}), HIV viral load (copies mm^{-3}), Blood Glucose Level (mg/dL), BMI = Body Mass Index (kg/m^2), Number of teeth, BOP = Bleeding On Probing, PPD = Probing Pocket Depth (mm), CAL = Clinical Attachment Level (mm), PPD/CAL = Sites with PPD ⩾4 mm and CAL ⩾3 mm.

[a] Centers for disease control and prevention revised surveillance case definition for HIV infection.

[b] World Health Organization International Classification of adult underweight, overweight and obesity according to BMI.

significantly higher in serum samples and again, only in the Non-ART subgroup (Table 3).

The PCC was used to identify relationships with at least a medium effect size ($r \geqslant 0.30$ or $\leqslant -0.30$) [28] between GCF and serum equal cytokines in all subgroups (Table 3). Furthermore, correlations were calculated between GCF and serum cytokines concentrations and all variables in all subgroups (Table 4).

Finally, significant predictors were entered into an MLR model ($Y^x_{\mathbf{p}} = X^x_{(k+1)}\ \beta^x_{(k+1)} + \varepsilon$) where the relationships between multiple dependent variables (i.e., *Y*s)—measures of outcomes—and multiple predictor variables (i.e., *X*s) were assessed to determine whether, and to what extent, GCF and serum cytokines remained significant HIV/ART status predictors. Separate models were created for each subgroup and assumptions of independence and homoscedasticity for MLR was checked using Durbin-Watson test and Breusch-Pagan test, respectively.

After removal of the non-significant explanatory variables via conducting a stepwise MLR, GCF and serum cytokines contributed to predict HIV/ART status (Table 5) and combined explained 39% of the observed variance in the Non-ART group ($R2 = 0.394$, $F = 11.94$, $p < 0.01$). The standardized coefficients showed that in this analysis, GCF IL-8 was the most important explanatory variable. Furthermore, GCF IL-8, IL-2, and serum MCP-1 showed a negative effect, which means that with decreasing concentrations decreased the probability to be classified in the Non-ART group. Per contra, any cytokine contributed to predict the ART-naïve subgroup. Moreover, the GCF G-CSF was the only explanatory variable (35% $p < 0.01$) and with a negative effect in the ART short-term subgroup. Serum

Table 3
GCF and serum cytokine levels, comparison of paired, variance and differences of means, and correlation coefficients by study groups (pg/dl).

Cytokine	Study groups	Non-ART (n = 6)	ART Naïve (n = 8)	Short-term ART (n = 41)	Long-term ART (n = 23)	Non-HIV subjects (n = 39)	ANOVA	Post hoc
IL-1β	GCF	61.56 ± 44.95†	58.63 ± 90.63	47.56 ± 60.96§	69.76 ± 62.02§/**0.470***	66.52 ± 119.45§	0.851	
	Serum	0.22 ± 0.53†	0.00 ± 0.00	0 ± 0.00§	0.03 ± 0.15§	0 ± 0.00§	0.005	0.009
IL-2	GCF	0.00 ± 0.00	0.00 ± 0.01	0.01 ± 0.03	0.01 ± 0.04	0.02 ± 0.05†	0.437	
	Serum	1.63 ± 3.98	0.00 ± 0.00	0.00 ± 0.00	0.08 ± 0.39	0 ± 0.01†	0.001	0.002
IL-4	GCF	0.01 ± 0.01†	0.1 ± 0.01†	0.01 ± 0.01§	0.01 ± 0.01/**0.442***	0.01 ± 0.01§	0.361	
	Serum	0 ± 0.00†	0 ± .00†	0 ± 0.00§	0.01 ± 0.03	0 ± 0.00§	0.418	
IL-5	GCF	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00/**0.528***	0.00 ± 0.00	0.092	
	Serum	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.01	0.00 ± 0.02	0.612	
IL-6	GCF	0.09 ± 0.12/ **0.855***	0.02 ± 0.03	0.02 ± 0.03§	0.02 ± 0.07	0.01 ± 0.03	0.017	0.024
	Serum	1.25 ± 3.05	0.00 ± 0.00	0 ± 0.00§	0.25 ± 1.17	0.01 ± 0.02	0.012	0.024
IL-7	GCF	0.14 ± 0.18	0.02 ± 0.03	0.03 ± 0.04	0.06 ± 0.11†/**0.443***	0.05 ± 0.07§	0.019	0.031
	Serum	0.00 ± 0.01	0.01 ± 0.01	0.02 ± 0.08	0.01 ± 0.01†	0.01 ± 0.02§	0.878	
IL-8	GCF	24.26 ± 16.94†	9.15 ± 6.11§	15.18 ± 19.36§/**0.327***	20.54 ± 19.31§	15.01 ± 15.6§	0.371	
	Serum	0.01 ± 0.01†	0.01 ± 0.01§	0.01 ± 0.01§	0.02 ± 0.02§	0.01 ± 0.01§	0.303	
IL-10	GCF	0.11 ± 0.07†	0.04 ± 0.02§	0.05 ± 0.04§	0.06 ± 0.04§	0.06 ± 0.05§	0.040	0.068
	Serum	0.01 ± 0.02†	0 ± 0.00§	0 ± 0.01§	0 ± 0.01§	0.01 ± 0.04§	0.348	
IL-12	GCF	0.39 ± 0.44	0.08 ± .009†	0.11 ± 0.18	0.15 ± 0.32	0.11 ± 0.16	0.049	0.087
	Serum	0.14 ± 0.34	0 ± 0.00†	0.04 ± 0.21	0.03 ± 0.07	0.08 ± 0.25	0.589	
IL-13	GCF	0.13 ± 0.20	0.03 ± 0.03†	0.05 ± 0.07§	0.06 ± 0.10§	0.04 ± 0.05§/**0.362***	0.135	
	Serum	0.00 ± 0.00	0 ± 0.00†	0 ± 0.00§	0 ± 0.00§	0 ± 0.01§	0.383	
IL-17	GCF	0.63 ± 0.29†	0.30 ± 0.26§	0.36 ± 0.30§	0.53 ± 0.39§	0.45 ± 0.40	0.187	
	Serum	0.09 ± 0.21†	0 ± 0.00§	0 ± 0.02§	0.08 ± 0.34§	0.19 ± 0.91	0.661	
G-CSF	GCF	26.80 ± 29.15	7.62 ± 5.63§	6.87 ± 9.3§	11.68 ± 15.11§	7.52 ± 9.94§	0.005	0.010
	Serum	0.01 ± 0.02	0.01 ± 0.01§	0.03 ± 0.08§	0.24 ± 1.01§	0.04 ± 0.14§	0.449	
GM-CSF	GCF	56.03 ± 25.06§	37.85 ± 19.17§	43.55 ± 18.84§	48.52 ± 14.47§	45.99 ± 18.8§	0.356	
	Serum	0 ± 0.00§	0 ± 0.00§	0 ± 0.00§	0.67 ± 3.21§	0 ± 0.00§	0.399	
INF-γ	GCF	3.88 ± 2.07	1.91 ± 1.74†	2.13 ± 1.64§	2.89 ± 1.86/**0.416***	2.70 ± 2.11§	0.144	
	Serum	12.91 ± 31.61	0 ± 0.00†	0.02 ± 0.10§	7.80 ± 37.38	0 ± 0.00§	0.227	
MCP-1	GCF	1.10 ± 1.06	0.39 ± 0.26	0.48 ± 0.42§	0.59 ± 0.61†	0.43 ±§	0.024	0.042
	Serum	0.12 ± 0.23	0.14 ± 0.19	0.16 ± 0.17§	0.20 ± 0.38†	0.10 ± 0.09§	0.470	
MIP-1β	GCF	5.15 ± 7.62	0.82 ± 0.24§	2.34 ± 3.87†/**0.352***	2.32 ± 3.36	1.39 ± 1.82	0.094	
	Serum	2.55 ± 3.06	1.93 ± 0.67§	2.59 ± 1.97†	2.14 ± 0.80	2.40 ± 1.35	0.761	
TNF-α	GCF	0.16 ± 0.10	0.08 ± 0.05§	0.08 ± 0.07§	0.10 ± 0.07	0.09 ± 0.09§	0.202	
	Serum	1.48 ± 3.59	0 ± 0.00§	0 ± 0.01§	0.58 ± 2.78	0 ± 0.02§	0.102	

Mean ± standard deviation, ANOVA indicates p value, Post hoc Scheffé, In bold numbers Pearson's correlation, (/XX), ART (Antiretroviral Therapy), GCF (Gingival Crevicular Fluid), IL (Interleukin), G-CSF (Granulocyte Colony-Stimulating Factor), GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), INF-γ (Interferon-gamma), MCP-1 (monocyte chemotactic protein-1), MIP-1β (macrophage inflammatory protein-1β), TNF-a (Tumor Necrosis Factor alpha).
Correlations coefficient ⩾ 0.30 were considered medium effect size, statistically significant ($p \leqslant 0.05$).
* significant at 0.05 level ($p \leqslant 0.05$).
† Paired "t" test significant at 0.05 level ($p \leqslant 0.05$).
§ Paired "t" test significant at 0.01 level ($p \leqslant 0.01$).

GM-CSF and IL-8 were the ones that predicted the variance (11% $p < 0.01$) in the ART long-term subgroup.

No multicollinearity was present and standardized residuals showed a normal distribution in all subgroups, meeting the important assumptions of normality and multicollinearity. However, the Breusch-Pagan post hoc test exposed the presence of heteroscedasticity in some models ($p \leqslant 0.05$), suggesting that the data was not being adequately explained by the statistical models of conditional means being estimated, invalidating the significance of the statistical tests (Table 5). Thus, heteroscedasticity-consistent standard error estimators (HCSE) [25] were used to correct the presence of spatial non-stationarity in the Non-ART and Short-term ART subgroup MLR models. Under the null hypothesis that all regression coefficients for self-concept in the two MLR models were equal to zero, HCSE analysis was performed on each one. The null hypothesis was rejected only for GCF IL-8, G-CSF, and serum MCP-1 ($p < 0.05$) as predictors in the Non-ART model. Likewise, Ho was rejected for GCF G-CSF as a predictor in the ART short-term model (Table 5).

4. Discussion

GCF is an exudate from blood vessels and periodontal tissues, it contains many proteins derived from the blood, and it is released into the gingival crevices or periodontal pockets [29]. In this study, we determined the concentrations of different cytokines from GCF and serum in an endemic population as part of an effort to identify a single biomarker or combination of cytokines which have a potential to detect differences in HIV stages of infection based on age-specific CD4+ count and ART compared to non-HIV-infected individuals. Up to our best knowledge, this is the first study to report the levels and correlation of 17 GCF and paired serum cytokines in HIV-infected and HIV-uninfected individuals.

We demonstrated that 16 of the 17 researched biomarkers in the GCF samples could be detected using the multiplex bead immunoassay, and the levels of 8 GCF biomarkers (IL-1β, IL-4, IL-6, IL-7, IL-8, IL-13, INF-γ, and MIP-1β) correlate with pair serum biomarkers in several HIV/ART stages. In addition, GCF biomarkers reflect systemic and oral clinical variables such as CD4+ count, ART

Table 4
Pearson's correlation coefficient test comparing the gingival crevicular fluid and serum cytokines to weighted variables among the study groups.

Gingival crevicular fluid												
Cytokine	Variables	1	2	3	4	5	Cytokine	Variables	1	2	3	4	5
IL-1β	BOP			,336*			GM-CSF	ART				-,445*	
	Smoking	-,878*		-,341*				BOP				,442*	
	BMI					,403*	INF-γ	CD4+			-,345*		
IL-4	BOP			,380*	,441*	,317*		BOP				,419*	,326*
	Smoking			-,404**			MCP-1	Smoking	-,878*				
	BGL	,845*						BMI					,382*
	BMI					,354*	MIP-1β	CAL		-,747*			
IL-6	PPD/CAL			,367*				Teeth					,370*
	Smoking			-,456**				Smoking	-,878*				
	BMI				,430*	,345*	TNF-α	Smoking	-,878*				
IL-7	BOP				,466*			BMI				,449*	,530**
	Smoking	-,878*											
	BMI					,373*	Serum						
IL-8	CD4+	-,812*					IL-2	Smoking				,458*	
	CAL	,841*					IL-6	PPD/CAL				-,427	
	Teeth			,399**				CAL				-,437	
	BMI					,361*	IL-8	Smoking				-,440*	
IL-10	CD4+			-,438**			IL-12	PPD/CAL					,416**
	PPD				,468*			Smoking				-,438*	
	PPD/CAL			,324*			IL-13	ARV			,321*		
	BOP				,419*		IL-17	CD4+			,316*		
	Teeth			,376*				PPD/CAL					,343*
	Smoking	-,891*						Teeth					,392*
	BMI				,447*	,423**		BMI			,355*		
IL-12	BOP				,448*		G-CSF	Teeth					,390*
	BMI					,359*		Smoking				-,451*	
IL-13	PPD/CAL		,791*				MCP-1	PPD/CAL					-,334*
	BOP				,439*			PPD					-,358*
	Smoking	-,878*						BOP					-,329*
IL-17	BOP					,370*	MIP-1β	Smoking	,878*				
	Smoking			-,397*	,372*		TNF-α	BOP			,381*		
	BMI				,342*								
G-CSF	CD4+			-,373*									
	PPD/CAL		,737*	,433**									
	BMI					,414**							

Correlations coefficient ⩾0.30 were considered medium effect size, statistically significant *($p \leqslant 0.05$) and **($p \leqslant 0.01$), Study groups 1 (Non-ART), 2 (ART Naïve), 3 (Short-term ART), 4 (Long-term ART) and 5 (Non-HIV), ART (Antiretroviral Therapy), BOP (Bleeding On Probing), BGL (Blood Glucose Level), BMI = Body Mass Index (kg/m^2), Teeth (Number of teeth), Bleeding On Probing, PPD = Probing Pocket Depth (mm),CAL = Clinical Attachment Level (mm), PPD/CAL = Sites with PPD ⩾4 mm and CAL ⩾3 mm.

Table 5
Statistically significant independent predictors of multivariate linear regression models by study groups of HIV infection and non-HIV subjects.

Regression model subgroup	Predictor variable	R^2	Durbin-Watson test	*F*	ANOVA*	*B*	*SE*	Breusch-Pagan test	X^{2*}	HCSE	p-value†,*
Non-ART	Serum IL-2	0.151				0.115	0.019			0.075	0.12
	GCF G-CSF	0.254				0.008	0.002			0.003	0.03
	Serum MCP-1	0.297				-0.261	0.082			0.106	0.01
	GCF IL-2	0.332				-1.07	0.493			0.621	0.08
	GCF MIP-1β	0.366				0.019	0.006			0.015	0.21
	GCF IL-8	0.394				-0.003	0.001			0.001	0.04
	Model Summary	0.394	1.12	11.94	0.0001	0.027	0.024	96.08	0.0001	0.023	0.25
ART Naïve	None	/	/	/	/	/	/	/	/	/	/
Short-term ART	GCF G-CSF	0.351	.347	52.47	0.0001	-0.007	0.003	28.57	0.0001	0.002	0.001
Long-term ART	Serum IL-8	0.075				5.6	20.55				
	Serum GM-CSF	0.112				0.054	0.025				
	Model Summary	0.112	0	4.73	0.004	1.34	0.513	7.04	0.07	/	/
Non-HIV	None	/	/	/	/	/	/	/	/	/	/

ART (Antiretroviral therapy), HIV (Human Immunodeficiency Virus), GCF (Gingival Crevicular Fluid), G-CSF (Granulocyte Colony-Stimulating Factor), GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor), MCP-1 (monocyte chemotactic protein-1), MIP-1β (macrophage inflammatory protein-1β), R2 (Coefficient of multiple determination), F (Statistically expected level of heterozygosity), B (Unstandardized regression coefficient), SE (Standard Error), X2 (Pearson's chi-squared test), HCSE (Heteroscedasticity-consistent Standard Error estimator).

† p-value from HCSE test.

* Significant at 0.05 level ($p \leqslant 0.05$).

guideline, BMI, BGL, BOP, PPD, CAL, the number of teeth and smoking habit. Moreover, in this study differences were observed in cytokine levels among subjects in a particular HIV/ART stage and those with non-HIV infection. Also, analyzed GCF and serum biomarkers discriminate between all studied groups, and through MLR we found that a combination of cytokines (GCF IL-8 and G-

CSF, and serum IL-8, MCP-1, and GM-CSF) gave better discriminatory level in different HIV/ART stages. These findings correlated with those reported by other researchers [30–32].

Oral innate immunity mostly maintains the oral cavity health through the innate defense mechanisms. Nevertheless, various oral infections and malignancies may evolve when it's impaired either by local or systemic causes [33,34]. Not to mention that it also appears to be modulated with the use of ART [34,35]. However, with the introduction of ART, HIV oral manifestations have become less widely seen in HIV-infected individuals [36,37]. In accordance, the prevalence of oral lesions was rarely seen in our study, to such a degree it was not possible to correlate GCF and serum cytokines with such manifestations. Of interest, no oral warts were diagnosed among subjects.

Nonetheless, ART provides an inadequate immune reestablishment of the oral epithelial cells of HIV-infected individuals, and the toxic side effects of ART and/or HIV chronicity silence the expression of multiple proteins that in healthy individuals, function to provide tough innate immune responses and battle cellular stress [38]. Our and others research findings [32], suggest that HIV infection and the use of ART may alter oral innate immunity and levels of circulating oral cytokines. However, no significant differences were noted in the expression of IL-4, IL-5, IL-8, IL-13, IL-17, GM-CSF, INF-γ, MIP-1β, and TNF-α according to their ART status.

HIV-infected subjects with or without ART are susceptible to comorbid fungal, bacterial, and viral infections in the oral cavity (e.g., periodontal disease). Oral microorganisms growth and the emergence of these or their byproducts accompanying chronic oral inflammatory diseases have the capability to reactivate HIV-1 from latently infected cells, showing a relationship of immature and mature dendritic cells, macrophages or T-cells, and could be risk modifiers for HIV-1 replication, systemic immune activation, and AIDS progression [2,3]. Numerous cytokines are released from the above mention cells and presence of a large number of cytokines, especially pro-inflammatory and inflammatory cytokines, in the GCF have been considered as potentially useful diagnostic or prognostic biomarkers of periodontal destruction [29]. In the present study GCF IL-6, IL-10, IL-13, G-CSF, and serum IL-6 correlate with PPD $\geqslant$4 mm and CAL $\geqslant$3 mm in HIV-infected subjects and were also statistically significantly associated with ART status, likewise serum IL-12, IL-17, MCP-1 correlate with PPD and CAL in HIV-uninfected subjects. Present results indicated that HIV-infected subjects who were not on ART had a greater risk of having periodontal pockets than those on ART.

Furthermore, medium to high positive PCC were found among GCF IL-1β, IL-4, IL-7, IL-10, IL-12, IL-13, GM-CSF, INF-γ, serum TNF-α and BOP in HIV-infected subjects who were in short and long-term ART. In like manner, there was significant association among GCF IL-8, IL-10 and the number of teeth of HIV-infected individuals in short-term ART, as well as GCF MIP-1β, serum IL-17 and G-CSF did the same but in the non-HIV-infected subjects. While smoking habit, was found to influence the expression of GCF IL-1β, IL-4, IL-6, IL-7, IL-10, IL-13, IL-17, MCP-1, MIP-1β, TNF-α and serum IL-8, IL-12, G-CSF MIP-1β in HIV-infected subjects. Notwithstanding HIV stage, ART, and age are not self-reliant risk factors for variations in the periodontal status of HIV-infected subjects, the degree of periodontitis risk seems to be higher in HIV-infected than in HIV-uninfected individuals; some studies correlate these findings with higher prevalence of smoking and poorer oral hygiene in HIV-infected individuals, as well as a possible effect of HIV-induced immunodeficiency [39,40].

Cytokines concentrations during acute HIV-1 infection are predictive of HIV disease progression [41]. In the present study GCF IL-8 and G-CSF as well as serum IL-8, MCP-1 and GM-CSF may be useful biomarkers for the detection of disease presence and/or its severity due to HIV infection and ART use. HIV-infected individuals have shown that IL-8 A/T genotype carriers are more susceptible to a diversity of diseases [42]. In our study negative correlations were found between GCF IL-8 levels within the Non-ART subgroup and their corresponding CD4+ count. Additionally, as in other studies [43] IL-10, G-CSF and INF-γ were each found inversely associated with CD4+ count. Moreover, our results have shown serum GM-CSF inversely associated with ART guideline in the long-term ART subgroup. Nevertheless, lower or unaffected levels of GM-CSF in serum profiles of HIV-suppressed subjects have been reported [44,45].

The impact of ART-induced HIV suppression on oral and systemic levels of serological molecular biomarkers of inflammation and immune activation still remains unclear. Therefore, data reported in this research should be interpreted with discretion based on the limitations of the study. As a transversal design, no causative inferences may be assumed, only association inferences. The modest sample size in some subgroups may be partially responsible for the lack of significance for some variables. It's also important to consider the preparation of biological sample since GCF and serum are not equivalent.

Despite these limitations, the current study may contribute to a better understanding of cytokine biomarkers. Omics analyses of GCF, measuring microbial and host interactions in association with the outbreak and progression of periodontal diseases, still show the potential to expand the landscape for the discovery of diagnostic, prognostic and therapeutic markers. Future large-scale studies need to be done to verify findings from this study and to discern into the molecular mechanisms of how HIV and ART modify the expression of cytokines and other systemic and oral innate immune factors in GCF and serum over time.

Conflicts of interest and Source of funding

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Contributions from the authors

Elizondo JE developed the proposal, directed the project, executed data statistical analysis, interpreted the results, wrote, drafted and is responsible for the article. Elizondo JE and Rocha-Pizaña MR performed the lab work, prepare and revised the manuscript. Elizondo JE and Treviño AC applied for the research grant, carried out the clinical work and gathered samples. Violant D, Alvarez MM and Rivas-Estilla AM facilitated, supervised, gave technical advice, offered ideas to interpret results, revised, edited, and approved the final draft of the manuscript.

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Appendix B

1. Approval of the PhD Thesis project by the Ethics, Research, and Biosafety Committees at Tecnológico de Monterrey, México. Document in Spanish language.
2. Approval of the PhD Thesis project by the Ethics in Research Committee (Comité d'Ética de Recerca, CER) at the Universitat Internacional de Catalunya, Spain. Document in Spanish language.
3. Informed Consent Form (Information Sheet). Document in Spanish language.
4. Informed Consent Form (Certificate of Consent). Document in Spanish language.

TECNOLÓGICO DE MONTERREY
Escuela de Medicina

Monterrey, N.L. a 25 de Enero del 2012

Dr. Jesús Eduardo Elizondo

Investigador Principal
Presente:

Estimado Dr. Elizondo:

Notificamos a usted, que el día 24 de Agosto de 2011 fue **REVISADO Y APROBADO** por las Comisiones de Ética, Investigación y de Bioseguridad de la Escuela de Medicina del Tecnológico de Monterrey, el estudio clínico titulado:

Protocolo de Investigación Titulado:

"ANALISIS DE EXPRESIÓN DE CITOCINAS EN LÍQUIDO CREVICULAR GINGIVAL DE PORTADORES DE VIH/SIDA"

Documentos Aprobados:

- Protocolo: **"ANALISIS DE EXPRESIÓN DE CITOCINAS EN LÍQUIDO CREVICULAR GINGIVAL DE PORTADORES DE VIH/SIDA"** relacionado con el área de Biotecnología, Biomedicina Oral, Salud y VIH, (Versión 2. 0), en la ciudad de Monterrey, Nuevo León, México, Junio 2011.

Sin más por el momento.

Atentamente,

Dr. Federico Ramos Ruiz
Director Ejecutivo
Comisión de Ética

Dr. Carlos Cuello García
Director Ejecutivo
Comisión de Investigación

TECNOLÓGICO DE MONTERREY
ESCUELA DE MEDICINA
Comisión de Investigación

Dr. Jorge Eugenio Moreno Cuevas
Director Ejecutivo
Comisión de Bioseguridad

TECNOLÓGICO DE MONTERREY
ESCUELA DE MEDICINA
Comisión de Etica

APROBADO
24 AGO 2011

Edificio CITES 3er. piso lado poniente
Ave. Morones Prieto 3000 Pte. Col. Los Doctores
64710, Monterrey, N.L., México
Tel: 52/81 8888 2223
Fax: 52/81 8888 2052

CER Comitè d'Ètica de Recerca | Universitat Internacional de Catalunya

CARTA APROVACIÓ PROJECTE PEL CER

Codi de l'estudi: BIO-ELB-2014-02
Versió del protocol: 1.0
Data de la versió: 10.04.14
Títol: Citocinas Orales: progresión del VIH/SIDA

Sant Cugat del Vallès, 19 de maig de 2014

Investigador: Jesús Eduardo Elizondo

Títol de l'estudi: Citocinas Orales: progresión VIH/SIDA

Benvolgut(da),

Valorat el projecte presentat, el CER de la Universitat Internacional de Catalunya, considera que, des del punt de vista ètic, reuneix els criteris exigits per aquesta institució i, per tant, ha

RESOLT FAVORABLEMENT

emetre aquest CERTIFICAT D'APROVACIÓ per part del Comitè d'Ètica de la Recerca, per que pugui ser presentat a les instàncies que així ho requereixin.

Em permeto recordar-li que si en el procés d'execució es produís algun canvi significatiu en els seus plantejaments, hauria de ser sotmès novament a la revisió i aprovació del CER.

Atentament,

Dr. Josep Argemí
President CER-UIC

Folio / Lugar / Fecha

CONSENTIMIENTO INFORMADO

PARA PARTICIPAR EN UN ESTUDIO DE INVESTIGACIÓN TRANSDISCIPLINARIO (MÉDICO, ODONTOLÓGICO, NUTRICIONAL, PSICOLÓGICO Y SOCIAL) EN HOMBRES QUE TIENEN SEXO CON OTROS HOMBRES QUE VIVEN CON Y SIN VIH/SIDA

ITESM-UANL-UIC-SSNL-OSC

Investigadores responsables:

Jesús Eduardo Elizondo Ochoa (Maestría en Ciencias Odontológicas con Especialidad en Periodoncia. Doctorando Biotecnología, Escuela Nacional de Posgrado en Ciencias e Ingeniería, ITESM, México. Doctorando Odontología, Escuela de Doctorado UIC-Barcelona, España))
Ana Cecilia Treviño Flores (Maestría en Ciencias Odontológicas con Especialidad en Periodoncia, Doctorando Psicología, Facultad de Psicología, UANL. México)
Adrián Valle de la O (Maestría en Ciencias con Especialidad en Medicina Interna. Doctorando Psicología, Facultad de Psicología, UANL. México)
Karla Elizabeth Urriola González (Maestría en Sexología con Especialidad en Psicología. Doctorando Psicología, Facultad de Psicología, UANL)
Farith Zambrano Medina (Lic. en Psicología. Doctorando en Ciencias Sociales, Escuela de Humanidades y Ciencias Sociales, ITESM. México)
Sede donde se realizará el estudio: Centro Académico de Atención Odontológica (CAAD) del Programa Médico Cirujano Odontólogo del Instituto Tecnológico y de Estudios Superiores de Monterrey. Av. Morones Prieto # 3000 Pte. Col. Doctores. Monterrey, Nuevo León, México.

Nombre del participante: _____

A usted se le está invitando a participar en este estudio de investigación multidisciplinaria dentro del campo de la salud. Antes de decidir si participa o no, debe conocer y comprender cada uno de los siguientes apartados. Este proceso se conoce como consentimiento informado. Siéntase con absoluta libertad para preguntar sobre cualquier aspecto que le ayude a aclarar sus dudas al respecto. Una vez que haya comprendido el estudio y si usted desea participar, entonces se le pedirá que firme esta forma de consentimiento, de la cual se le entregará una copia firmada y fechada.

JUSTIFICACIÓN DEL ESTUDIO.

Se estima que en México existen 220 mil personas que viven con VIH/SIDA. Se estima que cada año, 10 mil personas son infectadas, de las cuales 90% son por transmisión sexual. La epidemia del VIH/SIDA, considerada como la peor crisis de alcance mundial en materia de salud pública debido a las características de su transmisión, alcance e intensidad de su impacto, requiere una respuesta eficaz abordándolo como un problema de emergencia nacional y como un problema de desarrollo a largo plazo.

Por ello es importante generar equipos transdisciplinares entorno a la atención integral del VIH/SIDA, que apoye no solo a las personas que viven con VIH/SIDA sino también a los miembros de su familia y la comunidad en general. Este tipo de estrategia pretende asegurar atención continua de accesibilidad, equidad, alta calidad, costo-efectiva, libre de estigma, discriminación y al mismo tiempo proveer de guía con una secuencia lógica de eventos, que debe ser útil para priorizar acciones y establecer objetivos de intervenciones posteriores de creciente complejidad.

OBJETIVO DEL ESTUDIO

A usted se le está invitando a participar en un estudio de investigación que tiene como objetivo: Fortalecer las capacidades institucionales, formación en el manejo y atención integral del VIH/SIDA en la población de hombres que tienen sexo con otros hombres (HSH) para potenciar el mejoramiento de su calidad de vida mediante el diagnóstico temprano de infecciones oportunistas, incluyendo exámenes, tratamiento racional y seguimiento.

BENEFICIOS DEL ESTUDIO

Mejorar la oportunidad en el diagnóstico en los grupos con mayor vulnerabilidad, fortalecer la prevención y control del VIH/SIDA, aumentando la efectividad del acceso al tratamiento integral, y con ello evitar nuevas infecciones.

Con este estudio conocerá de manera clara si usted presenta algún problema que requiera de tratamiento y a su vez este estudio permitirá que en un futuro otros individuos puedan beneficiarse del conocimiento obtenido por el equipo transdisciplinario en el diagnóstico, prevención y tratamiento de las enfermedades y problemáticas multifactoriales relacionadas al VIH/SIDA.

PROCEDIMIENTOS DEL ESTUDIO

En caso de aceptar participar en el estudio se le realizarán algunas preguntas sobre usted, su entorno, sus hábitos, sus antecedentes médicos, odontológicos, nutricionales, psicológicos y se le realizara un examen clínico minucioso de su boca, procedimiento indoloro y que no requiere de uso de anestesia.

RIESGOS ASOCIADOS CON EL ESTUDIO

Este estudio consta de las siguientes fases:

- La primera implica contestar una sencilla encuesta.
- La segunda fase es realizarle posterior a consejería y educación, una prueba voluntaria para la detección de: glucosa, VIH, VHB, VHC y de uso de drogas, mediante una pequeña muestra de sangre por una punción en la punta de un dedo y muestra de fluido oral mediante una paleta. Todas bajo la Norma Oficial Mexicana NOM-010-SSA2-1993 y los principios de consentimiento informado y confidencialidad del resultado. Igualmente muestras de tejido conectivo periodontal, liquido crevicular, placa dentobacteriana y plasma sanguíneo para fines diagnósticos y de investigación. El plasma muestra a utilizarse para fines diagnósticos y de investigación será utilizado de conformidad a lo que establece la norma Oficial Mexicana NOM-253-SSA1-2012 apartado 16.3.
- La tercera fase es realizarle un examen clínico y radiográfico de su boca
- En caso de que usted desarrolle algún efecto adverso secundario o requiera otro tipo de atención, ésta se le brindará en los términos que siempre se le ha ofrecido.

ACLARACIONES

- Su decisión de participar en el estudio es completamente voluntaria.
- No habrá ninguna consecuencia desfavorable para usted, en caso de no aceptar la invitación.
- Si decide participar en el estudio puede retirarse en el momento que lo desee, aun cuando los investigadores responsables no se lo soliciten, informando las razones de su decisión, la cual será respetada en su integridad.
- No tendrá que hacer gasto alguno durante el estudio.
- No recibirá pago por su participación.
- En el transcurso del estudio usted podrá solicitar información actualizada sobre el mismo, al o los investigadores responsables.
- La información obtenida en este estudio, utilizada para la identificación de cada paciente, será mantenida con estricta confidencialidad por el grupo de investigadores, solo serán utilizados para los fines del proyecto conforme a lo establecido en la Ley Federal De Protección De Datos Personales En Posesión De Los Particulares
- En caso de que usted desarrolle algún efecto adverso secundario no previsto, tiene derecho a una indemnización, siempre que estos efectos sean consecuencia de su participación en el estudio.
  Este proyecto de investigación esta conducido de acuerdo a la DECLARACION DE HELSINKI DE LA ASOCIACION MEDICA MUNDIAL Principios éticos para las investigaciones médicas en seres humanos revisada en 59ª Asamblea General, Seúl, Corea, octubre 2008. (http://www.wma.net/es/30publications/10policies/b3/17c_es.pdf)
- Usted también tiene acceso a las Comisiones de Investigación y Ética del programa Médico Cirujano Odontólogo de la Escuela de Medicina del Instituto Tecnológico de Monterrey y de la Facultad de Medicina y de la Facultad de Psicología de la Universidad Autónoma de Nuevo León.
  En caso de que tenga dudas sobre sus derechos como participante del estudio a través de:
  Dr. Federico Ramos Ruiz, Presidente de la Comisión de Ética
  Dr. Carlos Cuello García, Presidente de la Comisión de Investigación
  Escuela de Medicina del Instituto Tecnológico y de Estudios Superiores de Monterrey
  Teléfono: (01-81) 83.33.11.21
- Si considera que no hay dudas ni preguntas acerca de su participación, puede, si así lo desea, firmar la Carta de Consentimiento Informado anexa a este documento.

Folio / Lugar / Fecha

CARTA DE CONSENTIMIENTO INFORMADO

PARA PARTICIPAR EN UN ESTUDIO DE INVESTIGACIÓN MULTIDISCIPLINARIO (MÉDICO, ODONTOLÓGICO, NUTRICIONAL, PSICOLÓGICO Y SOCIAL) EN HOMBRES QUE TIENEN SEXO CON OTROS HOMBRES QUE VIVEN CON Y SIN VIH/SIDA

UANL-ITESM-UIC-SSNL-OSC

Yo, _____he leído y comprendido la información anterior y mis preguntas han sido respondidas de manera satisfactoria. Por este conducto expreso que me ha sido explicado qué es la infección por el virus de inmunodeficiencia humana (VIH), el virus de la hepatitis B (VHB) y el virus de la hepatitis C (VHC), las consecuencias que puede tener para mi salud y la importancia de realizarme una prueba para saber si tengo o no estos virus, así como el procedimiento de estas pruebas rápidas de detección, a las cuales accedo de manera voluntaria. De igual manera, confirmo que he recibido la información sobre las formas de transmisión y cómo prevenirla; así como consejería relativa a las implicaciones de un resultado reactivo en estas pruebas rápidas, en cuyo caso se me enviará al lugar apropiado para que se realicen las pruebas confirmatorias y se me brinde la atención médica requerida.

Manifiesto estar informado claramente de los fines de este documento, del procedimiento de diagnóstico médico, odontológico, nutricional, psicológico y social, que he entendido las explicaciones brindadas, que se me proporciono la oportunidad de hacer preguntas y que estas fueron contestadas satisfactoriamente, por lo cual declaro mi conformidad con la presente autorización. Autorizo la toma de registros médicos auxiliares (radiografías, pruebas rápidas y fotografías), para el determino del diagnóstico. Así como la utilización de dichos registros a los investigadores responsables. Reconozco que todos los registros médicos escritos y auxiliares del diagnóstico (radiografías, fotografías y resultados de pruebas rápidas) son propiedad los investigadores responsables y que copias de estos estarán a mi disposición de así solicitarlo a través de una forma escrita y acepto liquidar los cargos que generara el realizar un duplicado de estos registros.

He sido informado, entiendo y autorizo que los datos obtenidos en el estudio pueden ser publicados o difundidos con fines científicos por cualquier medio y propósito de ilustración, publicación ya sea internet, revistas médicas o cualquier tipo de medio de difusión, con pleno consentimiento que los investigadores responsables serán propietarios del derecho de autor. Entiendo que, aunque las pruebas rápidas son voluntarias, confidenciales y el resultado me será entregado personalmente, un consejero y personal de salud capacitado debe saber mi resultado para poder orientarme, pero bajo ninguna circunstancia, divulgará el resultado de mi prueba o dato alguno que permita la identificación de mi persona a terceros. Accedo de manera voluntaria y convengo en participar en este estudio de investigación transdisciplinario. Recibiré una copia firmada y fechada de esta forma de consentimiento.

_____	_____
Nombre y Firma del participante	**Lugar y fecha**
_____	_____
Testigo	**Lugar y fecha**
_____	_____
Testigo	**Lugar y fecha**

Esta parte debe ser completada por el Investigador (o su representante):

He explicado al Sr. _____la naturaleza y los propósitos de la investigación; le he explicado acerca de los riesgos y beneficios que implica su participación. He contestado a las preguntas en la medida de lo posible y he preguntado si tiene alguna duda. Acepto que he leído y conozco la normatividad correspondiente para realizar investigación con seres humanos y me apego a ella. Una vez concluida la sesión de preguntas y respuestas, se procedió a firmar el presente documento.

Appendix C

Jesus Eduardo Elizondo,

Jesus E Elizondo earned his Doctor of Dental Surgery (DDS) degree in 1991, a Periodontics specialty in 1997, and a Master of Science in Dentistry in 1999 from Universidad Autonoma de Nuevo Leon. Certificate of Completion in HIV/AIDS prevention, management, treatment, care, and support in 2009 from Universidad de Monterrey. Doctor of Science (D.Sc.) in Biotechnology degree in 2015 from Tecnologico de Monterrey, and Master of Science in Laser Dentistry degree in 2017 from Instituto de Tecnologia Avanzada.

Dr. Elizondo is a Doctoral candidate in Dentistry at Universitat Internacional de Catalunya, Spain. He has been working in transdisciplinary research on HIV, infectious and immune diseases since 2010 and has published several articles in this field.

Dr. Elizondo is Executive Director of the NGO Gremio Vita Novus which he co-founded in 2008. An NGO specializing in STDs, HIV/AIDS, human rights, development, and life skills training that have provided quality training for education, research, and other community-based projects. He is also member and co-founder of Northeast Mexico Association of HIV/AIDS Treating Physicians. Elizondo's work enhances government-NGO-University-PLWH collaboration in HIV/AIDS policy and services. He currently serves as Academic Member of the National Council for the Prevention and Control of Acquired Immunodeficiency Syndrome in Mexico (CONASIDA).

Likewise, Dr. Elizondo participates as an associate professor in the Department of Basic Sciences at the National School of Medicine at Tecnologico de Monterrey. He has presented many lectures and posters at national and international conference meetings. He also has been the recipient of numerous honors and awards, being one of the most outstanding, the first place at the National Research Competition of the Mexican Association of Periodontology, within the XXII National Meeting, 21st International Congress of Periodontology in 2011.

Furthermore, Dr. Elizondo collaborates since 2012 as an editorial advisor for Grupo Reforma Newspaper “El Norte” and as a medical/dental technical reviewer for McGraw- Hill Publishing Co. in México and Journal Odontology from Elsevier B.V.

Open Researcher and Contributor ID: http://orcid.org/0000-0003-1763-9399