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How the evolving epidemics of opioid misuse and HIV infection may be changing the risk of oral sexually transmitted infection risk through microbiome modulation

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Abstract

The epidemiology of sexually transmitted infections (STI) is constantly evolving, and the mechanisms of infection risk in the oral cavity are poorly characterized. Evidence indicates that microbial community (microbiota) compositions vary widely between the oral cavity, genitalia, and the intestinal and rectal mucosa, and microbiome-associated STI susceptibility may also similarly vary. The opioid misuse epidemic is at an epidemic scale, with >11 million US residents misusing in the past 30 days. Opioids can substantially influence HIV progression, microbiota composition, and immune function, and these three factors are all mutually influential via direct and indirect pathways. While many of these pathways have been explored independently, the supporting data is mostly derived from studies of gut and vaginal microbiotas and non-STI infectious agents. Our purpose is to describe what is known about the combination of these pathways, how they may influence microbiome composition, and how resultant oral STI susceptibility may change. A better understanding of how opioid misuse influences oral

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AUTHOR CONTRIBUTIONS

WDJ – manuscript conception, development, research, writing, and revision

LBB – manuscript development, research, figure design, and revision

CR – manuscript figure design, research, and revision

LC – manuscript research and revision

DECLARATIONS OF INTEREST

WDJ I have no conflicts of interest to report.

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microbiomes and STI risk may inform better mechanisms for oral STI screening and intervention. Further, the principles of interaction described may well be applied to other aspects of disease risk of other health conditions which may be impacted by the opioid epidemic.

Keywords

oral microbiome; sexually transmitted infection; opioid; HIV; immune function

INTRODUCTION

The United States is facing a perfect storm of sorts as it relates to the evolution of sexually transmitted infection (STI) epidemiology. Nuances relating to infection risk are becoming increasingly recognized, such as the impact of microbiomes (the circumstance of a microbiota in combination with its environment) on disease susceptibility and treatment. For example, recent work has shown that *Chlamydia trachomatis* (CT; an obligate intracellular pathogen) can survive up to 72 hours within a biofilm produced by *Candida* spp. and *Gardnerella vaginalis*.¹ While the cervicovaginal microbiota has a majority population of *Lactobacillus* spp. in healthy females, dysbiosis leading to increase in minority species may be caused by a number of factors (e.g. immunocompromised; existing STI). Separately, a longitudinal study found that perceived stress was associated with increased incident STI diagnosis.² Psychosocial stress is associated with vaginal microbial dysbiosis, mediated at least in part due to changes in immune function and inflammation dysregulation.^{3–5} Microbiota composition changes can have significant impact upon health and disease susceptibility, with a recent study finding that vaginal microbiome dysbiosis limits the efficacy of Tenofovir to prevent HIV infection.^{6,7}

In this work we explore how increasing recognition of oral STI may be related to changes in infection susceptibility. Of particular interest is the oral cavity and pharynx (OC) as a site of STI infection and the oral microbiome as a significant influencing factor. From a biological argument, these might be our dependent variables (microbiome status and subsequent oral STI risk). Independent variables of interest are those common to all people (immune function) and of increasing prevalence across the US (opioid misuse and HIV infection). In this review we describe: a) how opioid misuse, HIV status, and immune function are mutually influential; b) how these factors are known to influence microbiome constituency (generally); and c) by analogy argue how they then in turn may impact the oral microbiome and oral STI susceptibility.

The Dependent Variables

Oral STI Susceptibility—There is increasing recognition of the oral cavity as a site for STI, and this can have substantial impact on associated infections in other sites (e.g. genitals). A review article reports pharyngeal infection among women at 0–29.6% (median 2.1%) for *Neisseria gonorrhoeae* (GC) and 0.2–3.2% (median 1.7%) for *Chlamydia trachomatis* (CT); among men who have sex with men (MSM) at 0.5–16.5% (median 4.6%) for GC and 0–3.6% (median 1.7%) for CT, and among men who have sex with women (MSW) at 0.4–15.5% (median 2.2%) for GC and 0–22.0% (median 1.6%) for CT.⁸

Extragenital GC and CT rates of infection was highest among MSM but was also observed in WSM and MSW, representing a poorly characterized disease burden.⁹ Missed oral infections may result in ongoing transmission to other sexual partners and reinfection.¹⁰

Many of these infections occur in the presence of associated behaviors (e.g. oral sex), and the commonality of such activity contributes to their spread among partners and other infection sites.¹¹ This circumstance occurs within the context of the record rates of STI in the US (CT at 1,078,569 cases and a rate of 528.8/100,000; GC at 555,608 and 171.9; and syphilis at 30,664 and 9.5) being reported, with CT and GC the two most-reported bacterial infection in the US.^{12,13} While screening is effective to identify infection, this is generally underutilized, traditionally focused on genital infection, and there is often discordance between oral and genital infection.^{14–16} While generalized universal screening is likely simultaneously infeasible to implement and cost inefficient, means to identify those at increased infection risk should continue to be explored.

Oral Microbiota Composition—One factor possibly influencing oral infection is the oral microbiota (OM), the collection of over 700 prevalent taxa at the species level, with distinct subsets predominating at different habitats (e.g. teeth, tonsils, tongue).¹⁷ Understanding of the OM is just beginning, with initial characterizations of OM populations occurring within the past 10 years.¹⁸ There is a much greater knowledge concerning other microbiomes, including the gut, skin, and oral cavity, and their symbiotic relationship with the immune system. Generally speaking, the modulation of commensurate versus pathogenic organisms (symbiosis) in fact confers a degree of protection against the colonization of pathogenic organisms and reduction of inflammation.¹⁹ Symbiosis can, however, be disrupted by abnormal immune function resulting in dysbiosis and disease.²⁰ Further, microbiota constituency can change due to exogenous factors (e.g. diet) and the resultant different OM constituent proportions, perhaps now imbalanced, can adversely impact health and disease susceptibility.²¹

There is a substantial body of work showing how various microbiota populations may influence disease susceptibility. A recent review of *Mycobacterium tuberculosis* infection includes several examples of different ways that the microbiota relates to disease susceptibility: susceptibility and progression to active tuberculosis is altered by gut *Helicobacter* co-infection; the gut microbiota of those infected with *M. tuberculosis* is altered; oral anaerobes in the lung make metabolites that decrease pulmonary immunity; T-cell epitope depletion on commensal gut non-tuberculosis mycobacteria is associated with increased reinfection risk; and the prolonged tuberculosis antibiotic treatment may significantly alter the microbiota for extended periods.²² Other work has shown how human susceptibility to enterohemorrhagic *Escherichia coli* is modulated by the excess production of gut microbiota metabolites.²³ Here, the difference in pathogenicity between mice and human is the result of the production of four specific human gut microbiota metabolites which preferentially promote flagellin expression.

The Independent Variables

Opioid Misuse—Illicit opioid use and overdose have reached epidemic levels in the US, but the ramifications of such use are only partially understood. In 2017, an estimated 11.4 million Americans aged 12+ years misused opioids (including 7.3% of those aged 18–25 years) and 886,000 used heroin.²⁴ Approximately two thirds of the 63,632 drug overdose deaths in 2016 are attributed to opioids.²⁵ Much of this epidemic was fueled by increases in opioid prescribing in the 1990s, which in recent years has seen decline in response to control measures.^{26,27} Still, there remain millions of individuals misusing a product that has substantial impact upon individual health, including respiratory depression, hyperalgesia, muscle rigidity, myoclonus, and immunologic and hormonal dysfunction.²⁸ These last may have particular influence in disease susceptibility, especially as opioid addiction may last for decades and contribute to increased risk of multiple morbidities and mortality.²⁹ More specifically in relation to this review, individuals with opioid dependence have increased incidence of STIs such as chlamydia, and more frequently engage in high-risk sexual behaviors.^{30–35}

HIV Infection—The human immunodeficiency virus (HIV) epidemic has been subject to substantial research and intervention. In the US, there were 38,739 new HIV diagnoses and >1.1 million individuals living with HIV (though ~15% were unaware of their status; 2017 data).¹³ Fortunately, there now exist effective treatments for HIV which can lower virus levels to undetectable levels and prevent progression to acquired immunodeficiency syndrome (AIDS; also effective to prevent transmission).³⁶ Though HIV infection can now be adequately controlled, several key points bear consideration. First is that HIV is an infection primarily impacting immune function. Second is that the majority of those infected have at least one acute phase of infection before identification and treatment. Finally, those at greatest risk of new infection include MSM and injection drug users, who are also at increased risk of STI.^{13,37,38}

HIV infection progresses through three broad phases.³⁹ The *acute* phase occurs approximately 2–4 weeks after infection and is characterized by flu-like symptoms (some individuals), a large increase in HIV viral load, and significant reduction in the number of CD4+ T lymphocytes which are primary targets of HIV virions. Knowledge regarding the actual mechanisms cell death (among both activated CD4+ cells and those resting in lymphatic tissues) is still evolving, with recent evidence suggesting host response to DNA produced during abortive cell infection is more important versus active destruction via virion replication and release.⁴⁰ The *chronic* phase begins approximately 10 weeks post-infection, is characterized by very low counts of HIV virions, and may last 10+ years. Progression to *acquired immunodeficiency syndrome* (AIDS) is the final phase, and is characterized by consistently low CD4+ counts and the emergence of opportunistic infections (e.g. candidiasis of the esophagus, bronchi, trachea, or lungs; cervical cancer; some cytomegalovirus disease; histoplasmosis; Burkitt's lymphoma, or wasting syndrome).⁴¹

Immune Function—Moreover, both HIV and opioid use (external factors) and microbiota composition (internal factors) can disrupt and modulate host innate and adaptive immune responses. An increasing amount of research shows that even when people living with HIV

(PLWH) are treated immediately upon infection, HIV has lasting effects on both systemic inflammation levels⁴² as well as gut microbiota composition and mucosal immunity.⁴³ These heightened pro-inflammatory responses in turn result in increased susceptibility to other infectious and non-communicable chronic health conditions.^{44,45} Moreover, these additional conditions themselves (e.g., hepatitis C infection, diabetes, heart diseases) also contribute to higher levels of inflammation.^{46,47} Opioid use has also been shown to modulate innate and adaptive immune processes.⁴⁸ Traditionally, opioid use has been considered to have an immunosuppressive effect, but more recent research has shown that opioids can also have immunostimulatory effects through a variety of complex mechanisms.⁴⁸ These biological mechanisms are further complicated by the presence of psychosocial and environmental factors which may themselves modulate immune responses. Populations at high risk for HIV infection, such as people who inject drugs, often experience heightened chronic stress levels. Higher stress is also independently associated with increased inflammation.⁴⁹ Interestingly, one recent study found equally high levels of C-reactive protein among men who have sex with men (MSM) living with HIV and those who were not infected.⁵⁰ High stress levels are also associated with substance misuse and changes to the microbiota composition. Taken together, these findings describe an association between biological and psychosocial stressors and changes in the immune response that are associated with heightened chronic disease risk and disease progression. These pro-inflammatory changes in the immune response may be further exacerbated by opioid use and changes to the microbiome.

The data regarding how opioid misuse may lead to increased infection susceptibility are few and somewhat contradictory.⁵¹ There are inadequate trial data at this time, due in part to both few studies of varying design and varying influence of specific opioids. Our purpose here is to propose, from existing studies and by analogy, that the impact of opioid misuse on oral STI susceptibility via compositional changes to the oral microbiome is deserving of further specific examination.

RATIONAL FOR HOW THESE VARIABLES MAY INTERACT

A PubMed search for research examining opioid misuse, HIV status, and immune function in relation to the oral microbiome returns few studies, and none on oral STI risk. Therefore, much of the proceeding argument is based upon analogy on studies of these independent variables and how they influence each other and the rectal, intestinal and vaginal, microbiomes. This is illustrated in the figure.

The Influence of Opioids on HIV, Immune Function, and Microbiota Composition

Path #1: Opioid misuse → HIV status—Opioid use may plausibly influence the progression of HIV to AIDS. A 1998 review of basic and epidemiological studies finds that while there is a theoretical basis for postulating that opioid use can up-regulate HIV-1 progression, the data are inconsistent and may conditionally vary (e.g. by consistency of opioid use, other associated behaviors).⁵² Many studies of HIV-1 replication in human CD4+ leucocytes, monocytes, and macrophages have demonstrated that these cells all contain the μ opioid receptor, morphine's major receptor. A review in 2005 by Kapadia et al

describes work showing multiple impacts of opioids (including heroin) on immune function, including T and B lymphocyte function, antibody production, and HIV expression via μ receptor activation.⁵³ Specifically, morphine has been shown to activate latent HIV in neuroblastoma cell cultures; tissue susceptible to damage by opioid use.⁵⁴ Opioids are also known to potentially modulate immune function via transmembrane G protein-coupled receptors, though longitudinal epidemiologic studies are needed to support the evidence of *in vitro* and animal models.⁵⁵

Path #2: Opioid misuse → immune function—Opioids are known to adversely impact immune function. Opioid use can affect both innate and adaptive immunity, in part by decreasing the proliferative capacity of macrophage progenitor cells and lymphocytes (directly or via centrally mediated pathways).⁵⁶ This may be in part situationally dependent, as morphine use in the absence of pain is immunosuppressant, and continued such use is associated with increased risk of infectious disease.⁵⁷ This influence in immunosuppression and recovery were demonstrated in an animal model of lymphocyte recovery following morphine challenge, where lymphocyte proliferation differed between challenged and control mice.⁵⁸ Lastly, a 2016 review finds that the evidence is variable, based in part on different immune profiles of different opioids and their direct and centrally mediated impacts. Still, data indicate that relatively long term and high dose regimens have negative immune impact.⁴⁸

Path #3: Opioid misuse → microbiota composition—Opioid use can influence microbiota composition.⁵⁹ For example, morphine treatment has been shown to induce significant gut bacterial translocation to the liver and mesenteric lymph node by Toll-like receptor (2 and 4) signaling.⁶⁰ This in turn can influence ileum tight junction protein organization and lead to increased infection risk. In a similar murine model, Wang et al demonstrated gut microbiome (and metabolome) dysbiosis after a single day of morphine treatment.⁶¹ More specifically, there were observed decreases in microbial alpha diversity, increases in pathogenic bacteria, and significant expansion of *Enterococcus faecalis* species. Kang et al also demonstrated in mice that broad-spectrum antibiotic treatment before chronic morphine exposure decreased gut permeability (as observed by Meng et al) as well as mucosal destruction and IL-1 β expression.⁶² These studies demonstrate specific mechanisms whereby opioid use can increase infection risk via microbiome changes.

Interactions Between HIV, Immune Function, and Microbiota Constituents

Paths #4 and #5: HIV infection ↔ immune function—Most individuals infected with HIV experience an acute infection, comprised in turn of eclipse, expansion, and containment phases.⁶³ A tremendous amount of work has explored the impact of HIV infection on immune function, such as the review of innate immunity function by Persephone Borrow in 2011.⁶⁴ Conversely, there exist a tremendous number of articles describing how the immune system keeps HIV in check (initially) and ultimately fails in the absence of ART (for example the 2010 review by McMichael et al).⁶⁵ Furthermore, HIV infection is associated with increased progression of HPV cervical disease and cancer mortality, indicating immune dysfunction.^{66,67}

Key for our discussion are two specific aspects of HIV epidemiology. First is the occurrence of acute illness experienced by essentially all of those infected. Recent work by Fonseca et al describes how acute infections in animal models may permanently impact immune function, even after clinical ‘recovery’ from the illness.⁶⁸ In this model, mice infected with *Yersinia pseudotuberculosis* experienced sustained inflammation and associated lymphatic leakage in mesenteric adipose. Post-infection, there remain persistent changes in mucosal immune function and tissue homeostasis. This suggests the possibility for HIV infection-related immune function changes, even with the use of ART. This has been demonstrated by Chung et al. who found that HIV infection, even though controlled with ART, is associated with increased colonic permeability due to reduced tight junction production, leading to increased inflammation and microbial translocation.⁶⁹ Such changes, and persistent innate and adaptive immune activation, are also associated with other cardiovascular, neurological, and liver diseases among PLWH.⁷⁰

At the population level, this potential is additive to the nearly 15% of HIV infected individuals who are unaware of their status (and therefore do not take ART) and are subject to the more direct impacts of active HIV infection and viral replication upon immune function and disease susceptibility.³⁷

Paths #6 and #7: HIV infection ↔ microbiota composition—There is evidence to suggest that HIV infection can impact microbiota composition.⁷¹ A longitudinal examination of rectal microbiota between 76 HIV+/- MSM found that those with uncontrolled HIV experienced reduced alpha microbial diversity and changed composition (fewer *Firmicutes* and increased *Fusobacteria*).⁷² This change over 1–5 years follow up was only partially attributed to antibiotic use. An increase in *Fusobacteria* may be significant as members contain virulence factors which may disrupt local immunity.^{73,74} A similar cross-sectional study of 130 MSM found no difference in alpha diversity between HIV- and HIV+ regardless of treatment. However, those treated for HIV had species diminishment within the *Bacteroidetes* phylum, and changes in genera (e.g. increase in *Peptoniphilius* and *Fingoldia* and decrease in *Prevotella*).⁷⁵ This change in diversity may be attributed to antibiotic use associated with ART, though other studies have indicated association with ART itself.^{76–78} Other data indicate that ‘elite controllers’ who spontaneously control HIV viral load in the absence of ART have a microbiota constituency similar to HIV- individuals.⁷⁹

There exist some data to suggest that the gut microbiome influences HIV infection. To begin, a series of studies with transplanted fecal material (mouse model) and infection susceptibility (cell model) found that: MSM have gut microbial composition distinct from MSW; that this profile is associated with increased immune activation (measured in part by CD38+ HLADR+ and CD103+ levels in blood); and that this in turn is associated with increased frequency of HIV-infected cells during challenge.⁸⁰ Thus, microbiota composition might directly influence HIV infection susceptibility. Further, a clinical study by Serrano-Villar et al. found that a specific active fraction of the gut microbiota was partially associated with reduced inflammation and immune recovery.⁸¹ The implication is that microbiota composition, especially in regards of more active genus/species, can influence HIV suppression and immune system function.

Paths #8 and #9: Immune function ↔ microbiota composition—Alterations in immune responses are known to affect microbiota composition. In the presence of chronic stressors – whether biological or psychosocial – the innate immune system may become chronically activated.^{82–84} Under conditions of chronic innate immune activation, immune responses shift toward a pro-inflammatory state.⁸⁵ Inflammatory cytokines, such as IL-1beta and TNF-alpha become upregulated, while anti-inflammatory cytokines are downregulated.⁸⁶ Inflammation, furthermore, is known to contribute to changes in microbiota composition.⁷⁰ Under certain conditions (e.g., HIV infection), these shifts in microbiota composition have been shown to contribute to further increases in inflammation.⁸⁷ In this way, heightened chronic stress can lead to a cascade of mechanisms associated with heightened persistent systemic and mucosal inflammation.

The previous paragraphs described, in a binary sense, how the independent variables possibly influence each other. This of course leads to the argument that they are not a series of independent events, but different aspects of an entire system (of which we have only superficially described). A recent review of how the three variables combine is presented by Bandera et al, where they show how HIV infection (and ART) leads to microbial dysbiosis, and that to chronic inflammation and immune dysfunction.⁸⁸

The Influence of the Microbiome on Site-specific Infection Susceptibility

Path #10: Microbiome composition → site-specific infection susceptibility—Microbiome composition is known to affect site-specific infection susceptibility to HIV.^{89,90} Prior work has shown that vaginal candidiasis and STI are associated with increased HIV susceptibility.^{90–92} HIV infection itself has also been associated with increased presence of candida within the oral cavity.^{93,94} Notably, oral candidiasis is a common oral manifestation of HIV infection and many people living with HIV are colonized by *Candida albicans*.^{95–98} One investigation reported this increased susceptibility may be associated with changes in E-cadherin production and IFN gamma response.⁹⁴ As previously noted, HIV infection has dramatic and lasting effects on the composition of the gut microbiome. HIV infection is associated with decreases in the integrity of tight junctions within the colonic epithelium.⁶⁹ These shifts have been shown to be associated with microbial translocation or “leaky gut syndrome,” that is further thought to increase systemic inflammation levels in PLWH.⁶⁹ Changes within the oral microbiome may also lead to increased susceptibility to other STI and may also contribute to increased persistent systemic inflammation.

BUILDING A CASE FOR SPECIFIC ASSOCIATIONS WITH THE ORAL MICROBIOME AND ORAL DISEASE SUSCEPTIBILITY

To this point the data and studies are both limited in scope and the great majority limited to non-oral microbiome sites. Still, there are some data and/or logical reasoning to support analogous interactions between our three independent variables (opioid exposure, HIV status, and immune function) with our primary and secondary outcomes (oral microbiome composition and oral infectious disease susceptibility).

Path #11: Opioid misuse → oral microbiome composition

We could not locate any studies in PubMed explicitly examining how opioid misuse (opioid, morphine, heroin) might influence oral microbiome composition. However, the data suggest similar mechanisms of microbiome change exist between oral and gut. For example, disruption of epithelial integrity via myosin light-chain kinase in a Toll-like receptor-manner as described by Meng et al. is not inherently limited to the gut environment.⁶⁰ Further, Toll-like receptor activated immune response is likewise not limited to the gut environment, and plays a direct role in combatting oral infection.⁹⁹ Oral bacteria (periodontopathic) bacteria are subject to possible translocation via lymphatic drainage.¹⁰⁰ Thus, many of the mechanisms by which opioid compounds impact microbiome composition are not inherently limited to the physiological environments in which they have been expressly examined.

Path #12: HIV infection → oral microbiota composition

There are a few studies examining how HIV may influence oral microbiota composition. Dang et al. reported greater proportion of pathogenic bacteria in lingual surfaces among untreated HIV+ individuals; Kistler et al. reported 'minor but significant' difference in salivary microbiota depending on HIV status (HIV+ individuals were receiving ART); and Noguera et al. found differences in OM composition by HIV status in the context of periodontal disease, with an increase in *Neisseria* genus among those HIV+ (39/40 receiving ART).^{101–103} Preliminary data from a clinical trial of microbiota between HIV- and HIV+ (but ART naïve) individuals finds the infected persons presenting with greater microbial diversity in the OM, and subsequent resampling after ART initiation found further differences now across all three groups (HIV-; HIV+ no ART; and HIV+ with ART).¹⁰⁴ This is similar to a study conducted by Beck et al within the Lung HIV Microbiome Project where analysis of oral washes found mutually significantly different microbial communities between those HIV-, those HIV+ and receiving ART, and those HIV+ but ART naïve.¹⁰⁵ Presti et al. also describe OM differences as a result of ART, and speculate that the salivary OM composition may influence T-cell recovery after ART initiation.⁹³ These direct observations support the thought that the mechanisms of HIV ↔ microbiome interaction described earlier may well be present in the oral cavity.

Path #13: Immune function → oral microbiome composition

There are multiple studies examining how immune function may influence oral microbiome composition. For example, individuals with Kostmann syndrome-associated neutropenia had lower OM diversity and a different bacterial profile than healthy controls.¹⁰⁶ Studies show that the OM can be impacted by other conditions impacting immune function, such as leukemia and lymphomas, inflammatory bowel disease, and rheumatoid arthritis.^{107–109} Conversely, OM constituency may influence immune function in manner similar to the gut and other microbiomes.^{110–112} Still, the OM may be distinctly dissimilar to other human microbiomes, with speculation that the OM enjoys a special tolergenic state (and thereby immune-privileged).^{111,113}

Path #14: oral microbiome → oral sexually transmitted infection susceptibility

We could not locate any studies in PubMed explicitly examining how oral microbiome composition might influence oral STI susceptibility. However, many of the mechanisms associated with increased susceptibility derived from other microbiomes (e.g. loosed cell junctions; increased inflammation) are not necessarily tissue-specific and there is no *a priori* reason why they should not be a factor in the oral environment as well.

GAPS IN KNOWLEDGE AND NEEDED FUTURE RESEARCH

The purpose of this work is to illustrate how new and existing risks to health may be coalescing to create specific circumstances for increased disease susceptibility. While the work is rational in nature, it is limited by an absence of empirical work to expressly examine how the identified variables may/may not influence individual susceptibility to oral sexually transmitted infection. We propose that this be done, and may be incorporated into existing programs of opioid and HIV research sponsored by the National Institute on Drug Abuse, such as the cohorts exploring HIV infection and impact, and the large-scale, population-level opioid programs in the Rural Opioid Initiative.^{114,115}

There are also multiple associated gaps in understanding and the literature which may generate hypotheses and future research. For example, we could not find any published study examining either *Path #11: Opioid misuse → oral microbiome composition* or *Path #14: Oral microbiome composition → oral infection susceptibility* (figure). An obvious early area of further research might explicitly examine these pathways. Other gaps in knowledge include the following:

- Data indicate that microbiome composition might significantly vary by gender.^{116–118} As there exist significant differences in sexual behaviors and exposures between genders, possible disease risk dynamics differences should be explored, and expanded to include the transgender community as well.
- Much of the research cited here has been done with morphine, which may significantly differ from more commonly abused substances such as heroin and fentanyl. Synthetic and processed versions of opioids have a wide range of analgesic effects (less/more potent than morphine). While opioids all interact with μ receptors, the route of administration and amount of exposure can significantly vary.¹¹⁵
- How do different microbiomes interact with the discussed variables? The human body is comprised of distinct microbial populations, and their metabolism, signaling, and influence on human health and disease are in many ways mutually distinct.¹¹⁹ In a similar sense, the ‘oral’ microbiome is not necessarily a homogeneous environment, and there are distinct microbial habitats (e.g. teeth, gingival sulcus, tongue, cheek, soft palate) influenced by tissue-specific levels of acidity and oxygen.^{18,112,118} These different habitats might be expected to react differently to opioids and immune function, and also have differential susceptibility to infection.

CONCLUSION

The United States is experiencing the emergence of a new circumstance of health and disease risk at a population-level scale not before seen. There are in excess of 1 million individuals living with HIV, nearly 2.3 million new STIs in 2017, approximately 12 million have misused opioids at some point during the preceding year (3.7% prevalence), and an estimated 2.6% of adults inject drugs.^{13,24,120,121} The risk of incident and chronic HIV infection, combined with widespread opioid misuse, have the potential to change the infection risk for millions of individuals. While the inspiration for this review is the potential for increased oral STI risk, the mechanisms and arguments are perhaps equally valid for other human microbiomes and diseases. There remains much work to be performed to adequately explore the nature and level of risk associated with our evolving profile of exposure, health, and systemic interactions.

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As corresponding author, I (Wiley D. Jenkins) confirm that I have had access to all data associated with this study.

AUTHORS BIO NOTES

WD Jenkins

Dr. Jenkins is Research Associate Professor and Chief of Epidemiology and Biostatistics at Southern Illinois University School of Medicine (Springfield, IL). He graduated with a double major in chemistry and biology in 1991 and performed laboratory work for Washington University and the Illinois Department of Public Health. He subsequently earned his MPH and PhD in public health and entered academia in 2007. His early research work focused on STI epidemiology and interventions, and more recent work has involved in exploring methods to interrupt infectious disease transmission among injection drug users. Dr. Jenkins is currently co-PI of a NIH/NIDA Rural Opioid Initiative UH3 grant.

LB Beach

Dr. Beach is a Research Assistant Professor in the Department of Medical Social Sciences and the Associate Director of the Evaluation, Data Integration, and Technical Assistance (EDIT) program within the Institute for Sexual and Gender Minority Research and Wellbeing (ISGMH) at Northwestern University. Scientifically, Dr. Beach investigates the epidemiology of chronic physical health conditions over the life course among diverse sexual and gender minority populations and people living with HIV. She also studies how multilevel health and identity related stigmas affect healthcare quality, chronic condition management, and health outcomes of marginalized populations. Dr. Beach holds a K12

award from the Third Coast Center for AIDS Research to investigate social and biological mechanisms contributing to heart failure with preserved ejection fraction among PLWH.

C Rodriguez

After serving in the Navy as a pharmacy technician for nine years, Mr. Rodriguez separated from the service to complete both a BS in Healthcare Administration and Masters in Public Health. His research interests include LGBT sexual and mental health, infectious diseases (specifically HIV and other STIs), opioids, and mental health disparities among disadvantaged populations. He is also the co-chair to the SIU School of Medicine's Administrative Professional Council and serves on the Illinois HIV Integrated Planning Council. He is currently working with Dr. Jenkins on the rural opioid project, and another project implementing pre-exposure prophylaxis in rural areas via telehealth.

L Choat

Ms. Choat has 25+ years with the Illinois Department of Public Health. She has received training in medical technology and been certified by the American Society for Clinical Pathology (MT [ASCP]). Her first years at IDPH were in the laboratory performing (in part) clinical specimen analysis for sexually transmitted infections. She has since move to the IDPH Division of STD Prevention where she is a STD Counseling and Testing Coordinator and guides the implementation of multiple STD prevention activities across the state, including screening guidelines, PrEP expansion and analysis, and aspects of the state's Getting to Zero HIV initiative.

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Figure 1.

Concept map of factors contributing to sexually transmitted infection susceptibility in context of the microbiome. Pathways 1–10 are those more thoroughly described in the literature and generalized across microbiomes and interactions (4–9 are bidirectional and 1–3 and 10 are unidirectional) and pathways 11–14 are those specific to the oral microbiome and oral STI risk and of which generally less is known.