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Use of Nitrite Inhalants (Poppers) Among People with and At-Risk for HIV

A dissertation submitted in partial satisfaction of the
requirements for the degree of Doctor of Philosophy

in

Interdisciplinary Research on Substance Use

by

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This dissertation of Nicole Pepper is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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DEDICATION

For Mark and Max, always.

For my mom, my first teacher and a purposeful educator.

For those who live with addiction and those who support them.
Especially for Pete, Ray and Don. You are dearly missed.

EPIGRAPH

"It's like you just got dropped in the middle of the ocean I guess."

Study participant regarding poppers

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LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency syndrome
ANCOVA	Analysis of covariance
aOR/OR	Adjusted odds ratio/odds ratio
API	Asian or Pacific Islander
CAI	Condomless anal intercourse
DMT	N,N-dimethyltryptamine
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
G6PD	Glucose-6-phosphate dehydrogenase
GHB/GBL	Gamma-hydroxybutyrate/butyrolacton
HIV	Human immunodeficiency virus
HNRP	HIV Neurobehavioral Research Program
HRPP	Human Research Protections Program
IQR	Interquartile range
LSD	Lysergic acid diethylamide
MACS	Multicenter AIDS Cohort Study
MDMA	3,4-methylenedioxymethamphetamine
MeSH	Medical Subject Headings
MSM	Men who have sex with men
NHBS	National HIV Behavioral Surveillance
NIDA	National Institute on Drug Abuse
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NSDUH	National Survey on Drug Use and Health
PBMC	Peripheral blood mononuclear cell
PI	Protease inhibitor
PrEP	Pre-exposure prophylaxis
SD	Standard deviation
SEM	Social Ecological Model
SDSU	San Diego State University
STI	Sexually transmitted infection
UCSD	University of California San Diego
U.S.	United States
VPS	Vaccine Preparedness Study
YMSM	Young men who have sex with men

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PREFACE

This dissertation uses the term 'men who have sex with men' (MSM) throughout to broadly describe individuals of various identities (e.g., gay, bisexual, same gender loving, queer, pansexual, and others) who identify as male and have sex other men. It is important to recognize that MSM are a heterogeneous group of individuals with different identities, perspectives, experiences, strengths, and needs. The term MSM refers to *behavior* not *identity,* and originated during the first decade of the AIDS epidemic in response to the recognition that some men who have sex with men do not identify as gay or bisexual. Some researchers have pointed out that the widespread adoption of MSM as a label for this group by the health professions obscures the social and cultural dimensions of sexuality [1]. In response, some have called for the adoption of language that is more relevant and meaningful to members of sexual minority groups [1]. Because this dissertation contains a scoping review of existing literature, as well as a retrospective analysis of previously collected data, terminology (e.g., MSM) from source documents is used; whenever available, language used to describe identity is also provided.

This dissertation attempts to use person first non-stigmatizing language. Additional resources are available:

1. The Well Project: https://www.thewellproject.org/hiv-information/why-language-matters-facing-hiv-stigma-our-own-words
2. Canadian Centre on Substance Use and Addiction: https://www.ccsa.ca/sites/default/files/2019-09/CCSA-Language-and-Stigma-in-Substance-Use-Addiction-Guide-2019-en.pdf
3. National Institute on Drug Abuse: https://www.drugabuse.gov/nidamed-medical-health-professionals/health-professions-education/words-matter-terms-to-use-avoid-when-talking-about-addiction

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would ensue in its midst. Mark, thank you for embodying partnership in the truest sense of the word. You provided unconditional comfort and encouragement and believed I could do this when I doubted myself. You are unwavering in your support and this would truly not be possible without you. Thank you for many late nights sorting through Excel sheets, being my sounding board, pulling more than your fair share of childcare and housework, and for many meals and notes of encouragement. Max, you are my sunshine. Thank you for being my greatest teacher and inspiring me to work hard, play, be present, and continue reaching for the absolute best version of myself. The joy and wonder you infused into our home during a challenging and isolating year was the heartbeat of our family. You provide all the perspective on what truly matters I could ever need. I wish for you to stay curious, kind and authentic, love learning in all its forms, stand up for yourself and others, and find purpose.

Each chapter contained within is being prepared for publication. Chapter 1 co-authors include Dr. María Luisa Zúñiga and Nafisa Ferdous. Chapter 2 co-authors include Dr. Davey Smith, Donald Franklin, Dr. Mark Reed, Magali Porrachia, Brianna Scott, Dr. Tommi Gaines, and Dr. Sara Gianella. Chapter 3 co-authors include Dr. María Luisa Zúñiga and Dr. Heather Corliss.

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FIELDS OF STUDY

Major Field: Social Work

Studies in substance use, HIV, co-occurring disorders, trauma

ABSTRACT OF THE DISSERTATION

Use of Nitrite Inhalants (Poppers) Among People with and At-Risk for HIV

by

Nicole Pepper

Doctor of Philosophy in Interdisciplinary Research on Substance Use

University of California San Diego, 2021
San Diego State University, 2021

Dr. María Luisa Zúñiga, Chair

Statement of Problem: Alkyl nitrites (poppers) are potent short-acting inhalants commonly used by men who have sex with men (MSM). Despite their association with HIV risk, their causal association and mechanism for HIV transmission is not well understood. The aims of this dissertation are to describe available literature on popper use in the U.S. in the context of HIV, identify research gaps, contribute to a better understanding of biological impacts of popper use on MSM with HIV, qualitatively describe contextual factors of popper use among young MSM with HIV, and provide recommendations for clinical care and future research.

Methods: *Chapter 1* - A scoping review on the use of poppers as a risk factor for people living with and at-risk for HIV in the U.S. was conducted using the Social Ecological Model to contextualize findings. Studies were included (N=89) if they reported results on non-clinical use of alkyl nitrites, were related to HIV or HIV risk, were published between 2001 and 2021, and were conducted in the U.S. *Chapter 2* – Total HIV DNA from 90 stored peripheral blood mononuclear cells was measured. Non-parametric rank analysis of covariance (ANCOVA) was conducted on the dependent variable (HIV DNA), with group (popper use versus no popper use) as the independent variable and alcohol, tobacco, and cannabis use as covariates. *Chapter 3* – In-depth, semi-structured interviews with 15 young MSM (18-30 years old) living with HIV were conducted to explore individual, social and environmental contexts of popper use influencing HIV care outcomes.

Summary of Findings: Between 36% to 72% of MSM in the U.S. report lifetime popper use. Existing research supports the relationship between popper use and HIV risk, however the impact of popper use on the HIV care continuum remains unknown. Concurrent use of poppers and other drugs is common. Among MSM who use poppers, perceived risk of use is low and education is needed and desired. Clinicians caring for MSM and people with HIV are well situated to assess and address popper use. Implications for clinical care, public health, policy, and future research are discussed.

INTRODUCTION

This dissertation sought to better understand the use of nitrite inhalants (poppers), particularly among people with and at-risk for HIV. This dissertation makes the following contributions and additions to the body of knowledge about popper use among people with and at-risk for HIV to move science, care and treatment forward in order to promote the health of individuals with and at-risk for HIV who use poppers:

1. Provides an up-to-date and comprehensive scoping review on the use of poppers in the U.S. and associated risks to people with and at-risk for HIV to articulate what is known and guide the development of future research needed to fully understand implications of popper use and avenues for intervention in this population. No existing reviews on popper use in the U.S. were identified; this scoping review can serve as a reference guide for future research and clinical recommendations.
2. Explores the biological impact of popper use on men who have sex with men (MSM) with HIV. The effect of poppers on HIV DNA (i.e., the HIV reservoir) has not been measured. Given that MSM with HIV report higher rates of popper use than MSM without HIV [2, 3] and that the HIV reservoir plays an important role in potential avenues for a cure, this study offers an exploratory analysis of the impact of popper use on HIV DNA and recommendations for future research.
3. Elucidates the individual, interpersonal, community, and system-level context in which poppers are used among young MSM (YMSM) with HIV—a population experiencing significant disparities along the HIV care continuum [4]. The context in which poppers are used among YMSM and potential impacts on HIV care, treatment

and transmission has not been explored, representing a research gap limiting the ability to provide tailored interventions.

Collectively, this dissertation addresses research gaps regarding the impacts of popper use on individuals with and at-risk for HIV and the context in which poppers are used by mapping existing research, identifying gaps and making recommendations for future research, synthesizing clinical recommendations, exploring biological impacts of popper use on MSM with HIV, and gaining perspective on use among YMSM with HIV. Implications are explored in the context of the Social Ecological Model. Recommendations for individual, community and system level interventions, clinical care, and future research are discussed.

CHAPTER 1: U.S. Use of Nitrite Inhalants (Poppers) in the Context of HIV:

A Scoping Review Contextualized by the Social Ecological Model

Abstract

Purpose of Review

The aim of this study is to conduct a scoping review on use of nitrite inhalants (poppers) in the U.S. in the context of HIV in order to articulate research gaps and guide recommendations for future research. The Social Ecological Model was applied to thoroughly contextualize findings at the individual, interpersonal, community, and system level.

Recent Findings

No prior systematic reviews on this topic were identified. Over twenty years of research was reviewed (2000-2021), returning 89 results that met inclusion criteria. Less than a quarter of publications were from data collected in the past ten years and less than 10 publications were from research conducted in or after 2015. Recent publications focus on popper use among young men who have sex with men and the relationship between poppers and pre-exposure prophylaxis (PrEP).

Summary

Research published in the 2000s identified correlations between popper use among men who have sex with men (MSM), sexual risk behaviors and HIV acquisition. Almost all studies focused on MSM and most were cross-sectional, although several large cohort studies provide longitudinal data on popper use. While it is well established that poppers are associated with HIV among MSM, prevalence and context of use varies significantly in this non-homogenous group. Existing research focuses on individual behavior and provides clinical recommendations for assessing and addressing popper use, while community and structural findings are limited to

reporting differences in popper use based on environment and recommendations for health care. Future research should focus on developing and evaluating interventions and prevention strategies, including at the community and system level, aimed at reducing harms associated with popper use, such as HIV transmission.

Introduction

Alkyl nitrites (poppers) are potent short-acting inhalants that are legal to purchase in the United States (U.S.) under the guise of commercial use (e.g., cleaners and liquid incense). In the National Survey on Drug Use and Health (NSDUH), a nationally representative survey of non-institutionalized U.S. adults, 3.3% of adult respondents (2015-2017) endorsed lifetime popper use, however use was much higher among men identifying as gay (35.1%) or bisexual (11.3%) [5]. Unlike other inhalants, poppers are used primarily in the context of sexual encounters to enhance and facilitate anal intercourse due to their ability to relax smooth muscle tissue [6].

While poppers have been linked to HIV, the correlation is not well understood. Research has concentrated on men who have sex with men (MSM) and has been conducted mostly early in the HIV epidemic (i.e., 1980s and 1990s). A lack of systematic reviews on popper use pose challenges to a comprehensive understanding of popper use in the context of HIV—especially given changes in HIV treatment and prevention in recent years, such as well-tolerated single pill medication regimens and pre-exposure prophylaxis (PrEP). A review of existing literature is needed to establish clinical recommendations and guide future research.

Historical Context of Popper Use

Amyl nitrite was first used clinically in 1867 for the treatment of angina [7]. Small, mesh-lined capsules were crushed between the fingers to release vapors that were inhaled, earning the nickname “poppers.” In 1960 the Food and Drug Administration (FDA) waived the

prescription requirement for amyl nitrite, however it was reinstated in 1969 [8]. Manufacturers instead produced butyl and isobutyl nitrites [8]. In 1988, butyl nitrites were banned under the Anti-Drug Abuse Act, but other alkyl nitrite compounds (e.g., isopropyl) remained legal until 1990 when they too were banned by the Crime Control Act [9]. However, production and sale of alkyl nitrites has continued outside the purview of the law and FDA regulation by marketing them for commercial use as cleaners and odorizers.

Association with Kaposi Sarcoma, AIDS and Immune Function

Previous summaries on research from the 1980s and 1990s related to the possible link between poppers and HIV, AIDS and Kaposi sarcoma have been published [9-11]. Beginning in 1982, published case-control studies identified a possible connection between poppers and Kaposi sarcoma [12-14]. Larger cohort studies failed to support the association between the use of poppers and Kaposi sarcoma or the development of AIDS [15-17].

A National Institute on Drug Abuse (NIDA) monograph published in 1988 described the health hazards of nitrite inhalants, including impacts on the immune system. Poppers were found to be associated with a cycle of immunosuppression and stimulation [8] and immunosuppressive effects were particularly noted in Natural Killer cell activity [18]. By the 1990s, research began to focus on the association between popper use and sexual risk behaviors, such as condomless anal intercourse (CAI) [19, 20].

Adverse Effects

Adverse effects can range from mild to life threatening and include: headache, contact dermatitis, sinusitis and dyspnea [11], vision problems [21], liver disease [22], elevated risk of virus-associated cancers [23-25], hypotension [26], and methemoglobinemia [27]. Oral ingestion can be life-threatening and lead to respiratory failure [28]. Individuals with glucose-6-phosphate

dehydrogenase (G6PD) deficiency may experience more serious side effects of popper use [11, 29, 30]. Huffing solvents or propellant inhalants (e.g., the brand name aerosol solvent "Maximum Impact") is more dangerous due to mode of administration (huffing) and formulation, but is sometimes perceived as equivalent to inhaling poppers [31]. Popper use has been associated with fatal drug overdose among individuals who inject drugs [32] and with suicide among young MSM (YMSM) [33].

Study Aim

The aim of this study is to conduct a scoping review of contemporary use of nitrite inhalants (poppers) in the U.S. in the context of HIV to identify research gaps and guide recommendations for future research.

Methods

Theoretical Framework

The Social Ecological Model (SEM) [34, 35] was applied to thoroughly contextualize findings at the individual, interpersonal, community, and system level (Figure 1). SEM has been used effectively in HIV-related scoping reviews to structure and interpret findings [36, 37]. Social ecological frameworks do not supersede other behavioral models, rather they incorporate them at various levels of influence. SEM allows for embedded and interacting levels of influence impacting individual substance use behaviors, providing a rich context for understanding and mitigating associated harms. This flexible model can be adapted and allows for the exploration of both risk and protective factors related to the use of poppers. SEM was applied as a topical guide to organize this review.

Design and Analysis

A scoping review [38, 39] on the use of poppers as a risk factor for people living with and at-risk for HIV was conducted. Scoping reviews use an iterative approach to map existing literature on a specific topic, summarize and disseminate findings, identify research gaps, and make recommendations for future research [38]. They have been used in HIV [37, 40] and substance use [41-43] research. Stages of the scoping review are described below [38, 44].

Identifying overarching research questions. This scoping review sought to answer the following questions: 1) What are individual, interpersonal, community, and system factors influencing popper use in the U.S. among individuals with and at-risk for HIV?; 2) What are the clinical implications of popper use, including recommendations for clinical practice?; and 3) What is known about the use of poppers in relation to HIV risk and what research gaps remain?

Identifying relevant studies. The initial search strategy was designed to be intentionally inclusive and comprehensive in order to establish the breadth of existing literature. Using established best practices for review searches [45], this search included: two primary biomedical and life sciences databases (PubMed, which includes Medline, and Embase), an interdisciplinary database (Web of Science, which utilizes citation indexing) and several subject-specific databases (PsycINFO and Social Services and Sociology Abstracts via ProQuest). Searches used Boolean terms and Medical Subject Headings (MeSH).

Search strategies for this topic presented several challenges and were developed in consultation with a Health Sciences Librarian. First, terminology for poppers varies greatly in the literature and ‘nitrites’ comprise an entire chemical family with numerous variations, some of which are used as inhalants (e.g., butyl, isopropyl, isobutyl, amyl) and others which are not (e.g., sodium nitrite). Second, amyl nitrites have clinical uses outside the aim of this research. Third, a significant number of returned results, typically case studies, focused exclusively on adverse

effects of popper use (primarily vision problems and methemoglobinemia); these also fell outside the scope of this study to address poppers in the context of HIV. Finally, a prominent philosopher named Karl Popper, a pathologist named Hans Popper and a perovskite (mineral) structure called Ruddlesden-Popper also inflated search results. Title, abstract and keyword search terms included: *poppers*, *amyl nitrite/s*, *alkyl nitrite/s*, *inhaled nitrite/s*, *nitrite inhalant/s*, *volatile nitrite/s,* and *volatile inhalant/s*. Search terms excluded were: Popper (author), Karl (title, abstract), Popperian and Ruddlesden (title, abstract, keyword), and Philosophy (journal).

Selection of studies. Studies were included if they: reported results on the non-clinical use of inhaled alkyl nitrites, were related to HIV or HIV risk and were published in or after 2000. Studies were excluded if they were: published prior to 2000 or not conducted in the United States. Animal studies were included if they drew conclusions with relevance for use in humans (e.g., impact on immune function). Publication year (rather than data collection timeframe) was used for inclusion criteria, thus some included publications report findings based on research conducted prior to 2000. Rationale for inclusion/exclusion was based on the study aim to understand what is known about the impact of popper use on people with or at-risk for HIV in the context of the SEM. Significant changes have occurred since the identification of HIV, including stigma, treatment and prevention, morbidity and mortality, and the introduction of the internet and social media. The year 2000 was therefore chosen as a conservative search cutoff for exclusion criteria in an effort to present relevant data that can move the science forward and identify current research gaps. Since structural factors (e.g., marriage equality, legal status of poppers) vary across cultures and countries, only research focused on U.S. populations was included. An initial title and abstract screen was conducted to eliminate articles that did not meet

inclusion criteria. Full text reviews and consultation among authors were used as needed to determine inclusion.

Charting the data. Charting recommendations [44, 46] were adapted to the study aim. The following elements were abstracted from each included study: *terms used for poppers, study design, publication year, data collection period, study population and sample size, key findings, and SEM level(s).*

Collating, summarizing and reporting results. This scoping review was organized according to levels of the SEM. Based on the uniformly abstracted elements described above, results were summarized using a narrative approach to broadly present and contextualize main study findings related to the aim of this review [38]. Implications for future research, practice and policy are discussed [39].

Commonly Cited Studies

Multiple results originated from several prospective longitudinal cohort studies, which are briefly described below.

Multicenter AIDS Cohort Study (MACS). MACS is a longitudinal study spanning over three decades and including over 7,300 MSM with and without HIV across three distinct cohorts (1984-1985, 1987-1990 and 2001-2003) from Baltimore, Chicago, Pittsburgh, and Los Angeles. Biological and behavioral data were collected every six months. Additional information can be accessed at http://mwccs.org/.

VAX004 (AIDSVAX) Trial. The VAX004 trial was a 36-month randomized, double-blind, placebo-controlled efficacy trial of an HIV vaccine, which began in 1998 and was conducted at 61 sites in the U.S. (57 sites), Canada (three sites) and the Netherlands (one site). The study included 5,100 MSM and 300 women. HIV counseling and testing, as well as vaccine

trial information, were provided at baseline and every six months. Additional information can be accessed at http://gsid.org.

HIVNet Vaccine Preparedness Study (VPS). VPS was a prospective cohort study (1995-1997) which included 4,892 individuals at high-risk for HIV in nine U.S. cities. Participants completed questionnaires and HIV testing every six months for 18 months [19].

Project EXPLORE. Project EXPLORE was a 48-month multi-site randomized controlled behavioral intervention study conducted 1999-2005 among 4,295 MSM at-risk for HIV in six cities (Boston, Chicago, Denver, New York, San Francisco, and Seattle) which included 10 behavioral risk reduction sessions and twice yearly study follow-up [47].

National HIV Behavioral Surveillance (NHBS). NHBS is an ongoing surveillance project developed by the Centers for Disease Control and Prevention (CDC) in 2003 to conduct behavioral surveillance among individuals at high-risk for HIV in three populations (MSM, people who inject drugs and heterosexually active individuals at increased risk for HIV). Cycles repeat in rounds so that data from each risk group is collected every three years. Venue-based time-space sampling is used to recruit MSM. A minimum of 500 individuals participate in each cycle. Participants complete an anonymous survey on HIV risk behaviors, testing and use of prevention services. Additional information can be accessed at https://www.cdc.gov/hiv/statistics/systems/nhbs/index.html.

National Survey on Drug Use and Health (NSDUH). NSDUH (directed by the Substance Abuse and Mental Health Services Administration in the U.S. Department of Health and Human Services) began in 1971 and is conducted annually in all 50 states and the District of Columbia. Approximately 70,000 individuals participate annually through random household selection. Additional information can be accessed at https://nsduhweb.rti.org.

Results

Scoping Review Search Results

The initial search returned 872 results, of which 88 met inclusion criteria (66 from PubMed, 10 from Embase, eight from Web of Science and four from PsycInfo) (Figure 2). One additional study meeting inclusion criteria was identified through searching reference lists of included studies [48]. Of eligible results, only 10 included poppers or an associated term in the keyword and 10 in the title (five overlapped). Keywords included *amyl nitrite/s, poppers, inhaled nitrite/s* and title terms included *amyl nitrite, nitrite inhalant/s, popper/s, amyl nitrite inhalant, inhalant nitrites, inhaled nitrite, isobutyl nitrite, abused inhalant*. Over half of the results that met inclusion criteria (N=50) were from studies or research groups cited more than once. The highest represented studies or groups were: MACS (N=10), Seattle and King County Public Health (N=5), NHBS (N=4), VPS (N=4), VAX004 (N=4), and Project EXPLORE (N=4). Two-thirds of the studies (N=59) were cross-sectional, 27% (N=24) were longitudinal (of which nine were from MACS), three were animal studies, one was a review of sildenafil use by gay and bisexual men, one was a summary on epidemiology and clinical management of inhaled nitrite abuse, and one was a case-control study. Figure 3 shows the distribution of data collection and publication years of included studies. Less than a quarter of results came from data collected after 2010 and less than 10 results reflect data collected in or after 2015. Findings are organized below in the context of the SEM.

Individual

Results included in this review point to poppers being used predominantly by older [49] urban non-Hispanic white [2, 50] MSM [5] with higher educational attainment and income [5, 50-53]. Results related to prevalence of popper use are summarized below and shown in Table 1.

Gender and sexual orientation. Prevalence of popper use varied considerably across studies and populations, however popper use is significantly more common among MSM compared to women or men who do not have sex with men [5, 52, 54, 55]. Poppers were the most commonly used drug by MACS participants (excluding alcohol; tobacco use was not reported) [56, 57]. Two recently published reports using representative U.S. NSDUH data 2015-2017 [5] and 2015-2018 [52] presented prevalence of popper use by gender and sexual orientation. Overall, 2.9% of respondents (N=168,560) endorsed lifetime popper use; among men who identified as gay, 36.5% reported lifetime popper use (compared to 12.6% and 3.2% of men who identified as bisexual or heterosexual respectively) and 7.1% of women who identified as lesbian reported lifetime popper use (compared to 4.7% and 1.5% of women who identified as bisexual or heterosexual respectively) [52]. Men who identified as gay reported significantly increased odds of lifetime popper use compared to men who identified as heterosexual in a multivariate model (aOR=24.64, CI 95% 18.02, 33.68, $p<0.001$) [5]. Population level data from 2011 NHBS, found that 21.6% of urban MSM surveyed reported past year popper use (N=379) [58]. Only one study reported on popper use among individuals identifying as transgender; in a cross-sectional survey of individuals identifying as transgender women in Houston (N=67), 31% reported lifetime popper use [59].

Available data on the prevalence of popper use comes predominantly from data collected in the 1990s and 2000s among MSM. Studies reporting popper use prevalence among MSM included in this review are summarized as follows: 35.5% to 71.8% lifetime use [52, 60], 13% to 21.6% past 12 month use [50, 58], 29.1% to 50% past six month use [56, 61, 62], and 21.4% past three month use [60]. Past six-month popper use prevalence ranged from 39% to 50% among MSM participating in four longitudinal HIV prevention studies (1992-2003): VPS (42%), Project

EXPLORE (50%), VAX004 (45%), and CDC Jumpstart (39%) [62]. In 2008, 13% of NHBS participants (N=8,175) reported past year popper use [50]. Results from MACS (N=3,366, 1996-2007), showed that poppers were the most used drug in the past six months (53%) and usage was similar among participants with and without HIV [56].

Analysis comparing 1995 data between VPS respondents (N=3,212) to NSDUH respondents who identified as heterosexual men found that 29.1% of VPS respondents used poppers in the past six months (compared to 1.35% of NSDUH respondents who used poppers in the past year) [61]. The comparison revealed that relative risk for use of any substance (excluding alcohol) was higher for VPS participants than NSDUH participants and was the highest for popper use (RR=21.6, CI 95% 15.2, 30.8). The NSDUH used a past 12-month report of substance use and VPS used a past six-month report (likely underestimating the differences between groups) and VPS reported on poppers specifically while the NSDUH reported on inhalants generally.

Age. Available literature points to popper use being associated with older age, however longitudinal substance use patterns were assessed among San Francisco participants in Project EXPLORE (N=736, enrolled 1999-2000) and found that although popper use declined overall, use increased among younger participants (≤25 years) compared to older participants (≥45 years) [63]. Among 446 urban adolescent (16-18 years old) NBHS participants (2014-2015), 6% reported using poppers in the past year [64]. Among YMSM (defined in the study as 18-29 years) without HIV (N=1,113) recruited from three cities between 2013-2015 to participate in a randomized controlled trial of an HIV prevention program, poppers were the most frequently used drug after cannabis; 20.7% of participants used poppers in the past three months and popper use was associated with older age [51]. YMSM (≤30 years) VAX004 participants (N=4,684)

were less likely than older men (31-60 years) to report use of poppers in the past six months [49]. Among people with HIV over 50 years old (N=914), 7.4% endorsed past three-month popper use; however rates were significantly higher among gay and bisexual men (21.4%) compared to men who identified as heterosexual (1.7%) [54]. Another study among people with HIV aged 50 years and older (N=557) found overall past-month prevalence of popper use was 9.5% [65]. MSM aged 50 to 59.5 years from the MACS Pittsburg site (N=237) were assessed for number of sexual partners in the past six months and grouped into low (low to no sex partners), medium (two median partners) or high (30 or more sexual partners) categories; past six month popper use ranged from 6.5% to 55.6%, and was significantly correlated with having more sexual partners [66].

Race/ethnicity. Overall, popper use appears to be more prevalent among people who are non-Hispanic white compared to other racial/ethnic groups [2]. Latino Project EXPLORE participants were significantly less likely than non-Hispanic white participants to use poppers [63, 67]; however, popper use was a predictor of both serodiscordant CAI and HIV seroconversion among Latino participants [67]. In a 2011 cross-sectional study of Latinos with HIV (N=121) in the U.S.-Mexico border region (San Diego, U.S. and Tijuana, Mexico), 25.6% of participants reported lifetime popper use and individuals recruited in the U.S. were significantly more likely to report popper use than those recruited in Mexico [55]. In a cross-sectional study of Latino MSM of mixed HIV status recruited online (N=171), 31.6% reported popper use in the past six months; among individuals who used poppers, 55.6% used less than monthly, 29.7% used a few times a month, 11.1% used a few times a week, and 3.7% used daily [68].

Non-Hispanic white 2008 NHBS participants (N=8,175) were significantly more likely to report popper use than participants who were black [50]. Three studies reported popper use specifically among black MSM. Among black MSM without HIV (N=226), 18% reported popper use in the past three months [69]. Among black MSM of mixed HIV status, 7.7% reported past month popper use (N=210) [70] and 14% reported popper use during sex in the past year (N=197) [71]. Among MACS participants (N=1940, 2003-2009), black race/ethnicity was associated with less popper use than non-Hispanic white race/ethnicity [2].

In a cross-sectional study of Asian or Pacific Islander (API) YMSM (18-29 years old) in San Francisco (N=496), 16% reported past six-month popper use [72]. In a cross-sectional study of MSM in New York City and Los Angeles (N=2,335), men identifying as API were the least likely to report lifetime use of poppers [73].

Popper use among people with HIV. MACS participants with HIV reported higher rates of popper use than participants without HIV [2]. In a cross-sectional study of urban MSM (N=1,976), participants with HIV were more likely to use poppers than participants without HIV and poppers were the most frequently used drug among MSM with HIV (36.6% reported past-year use and 7.4% reported weekly or daily use) [3].

Biological impact. In MSM without HIV, acquisition of Kaposi sarcoma-associated herpes virus was independently correlated with popper use, however the biological mechanism remained unclear [74]. In animal studies, while single exposure to isobutyl nitrite impacted T cell proliferation and macrophage tumorcidal activity, cumulative effects from multiple exposures were necessary to impair immune function—likely through inhibition of nitric oxide production [75, 76]. Animal studies also found that poppers accelerated tumor growth—explaining a potential mechanism for the link between popper use and Kaposi sarcoma [77]. Several

longitudinal analyses of MACS participants identified biological findings: no association was identified between popper use and T cell count, percentage or rate of change in MSM with or without HIV [78]; heavy use of poppers was associated with increased frequency of cardiovascular, renal and malignant comorbidities for participants both with and without HIV [56]; long-term heavy popper use was associated with elevated risk of some virus-associated cancers among older MSM without HIV [23].

Polysubstance Use. Poppers are very commonly used in the context of polysubstance use, especially with cannabis, methamphetamine and erectile dysfunction medications. Data from the NSDUH (2015-2018) found that lifetime use of alcohol, cannabis, other illegal drugs, and non-medical use of psychotherapeutic medications, were associated with lifetime popper use [5, 52]. A latent class analysis of sexually active MSM (N=8,717) recruited from gay-affiliated websites identified polysubstance use groupings for drugs associated with sex; overall past year popper use was 34.2%, but use varied considerably (6% to 82.4%) depending on latent class polysubstance group [79]. In a cross-sectional study assessing polysubstance use (defined as use of three or more drugs associated with sex) and sexual risk among MSM (N=214), 21% reported use of poppers during sex in the past 12 months; however among polysubstance users, 71% reported popper use [80].

Among MSM with HIV who used methamphetamine, concurrent use of cannabis and poppers was very common [81, 82]. Motivations for co-use included “taking the edge of the methamphetamine,” “getting a better high,” and enhancing sexual pleasure [81]. Poppers were typically used prior to methamphetamine, while with other polysubstance use combinations, methamphetamine was typically used first [82]. Further, individuals reporting co-use of poppers

endorsed significantly more sexual risk behaviors (e.g., CAI, greater number of sex partners, anonymous and paid sex partners) compared to MSM with methamphetamine use alone [82].

In addition to being used concurrently with other illicit drugs, poppers are also commonly used with prescription medications. A cross-sectional convenience sample of undergraduate students aged 18-25 years (N=435) who were predominantly non-Hispanic white and female found that individuals who endorsed non-medical use of prescription drugs were more likely to have used poppers in the past three months compared to those who did not (6% versus 0.7%) and also had higher rates of sexual risk behaviors (e.g., more sex partners, sex after alcohol and/or drugs and condomless sex) [83].

In a cross-sectional survey of MSM attending a gay pride festival (N=350), 38% reported lifetime non-medical use of prescription drugs and participants reporting non-medical use of prescription drugs were significantly more likely to report past three-month popper use [84]. In a cross-sectional study of MSM with HIV in San Francisco and New York City (N=1,168) examining correlates of prescription drug use (testosterone, Viagra and antidepressants) and sexual risk behaviors, poppers were the only drug measured that was significantly associated with all three prescription drug groups; of participants who reported use of Viagra, 38.9% also used poppers in the past three months [85].

Among MSM with past year Viagra use seeking services for sexually transmitted infections (STI) (N=352), 15% reported co-use of poppers, over half (56%) received Viagra from a friend and individuals with HIV were slightly more likely to use Viagra than individuals without HIV [48]. In latent class analysis, two groups were identified with high co-use of poppers and erectile dysfunction medications (participants in these groups were more likely to be white, have higher incomes, have HIV, and endorse casual sex partners and group sex than other

groups) [79]. In a cross-sectional study of predominantly white MSM with and without HIV attending a sex resort (N=143), 50% reported past three-month use of poppers (of which 21.1% also used Viagra) [86]. A 2004 review on the use of Viagra among MSM describes risks (including life-threatening hypotension and cardiac complications) and recommendations regarding the co-use of Viagra and poppers [87].

HIV Acquisition. The strongest evidence that popper use increases risk for HIV acquisition comes from longitudinal cohort studies. A study that pooled data from several longitudinal studies of MSM (Project EXPLORE, VAX004, VPS, CDC Jumpstart) analyzed per-contact risk of HIV seroconversion and found that popper use increased likelihood of HIV acquisition [62]. In longitudinal multivariate analysis of VPS participants in six cities (N=3,257) using time-dependent covariates, past six-month popper use was independently associated with more than doubled risk of HIV seroconversion; there were no significant interactions between use of poppers and sexual practices, incidence of STI or number of sex partners [88].

A hazard regression analysis of MACS participants without HIV (N=1,667) was conducted to determine risk for HIV seroconversion associated with drugs commonly used during sexual encounters: poppers, stimulants (methamphetamine and crack/cocaine) and erectile dysfunction medications [89]. Analysis adjusted for other risk factors (e.g., sexual behavior, alcohol and other drug use and depression). Poppers were associated with an increased risk of HIV seroconversion and risk increased with concurrent use of stimulants and erectile dysfunction medications. The largest adjusted attributable risk was popper use (alone or combined with other substances). Sixteen percent of the overall sample reported popper use compared with 26% of individuals who acquired HIV. Hazard ratios were 4.98 for popper use, 12.36 for stimulant and popper use and 20.15 for popper, stimulant and erectile dysfunction medication use.

Another analysis of MACS participants without HIV (N=4,003) assessed time to HIV-seroconversion associated with recent popper use [90]. After adjusting for covariates (race/ethnicity, cohort, study site, educational level, number of CAI partners, insertive rimming, other substance use, and depression), there was a twofold increased risk for HIV seroconversion with popper use and a threefold increased risk for popper use with methamphetamine. Lifetime use of poppers was reported by 93% of individuals who seroconverted with recent methamphetamine use [90].

Longitudinal analysis of participants with mixed HIV status (with HIV, seroconverters and without HIV) across three cohorts (N=1,044) examined temporal patterns of substance use over four year periods centered around HIV seroconversion [91]. Individuals who seroconverted had the highest odds of stimulant/nitrite use (aOR 10.3, CI 95% 4.8, 22.0) compared to MSM with and without HIV. The overall rate of popper use in this sample was 58.1%. Individuals who seroconverted had the most pronounced declines in stimulant/nitrite use following diagnosis, yet remained the group with the highest rates of use. Most reported findings in this study combined stimulant (cocaine, methamphetamine and ecstasy/MDMA) and popper use.

There is also evidence from large cross-sectional studies that poppers are associated with HIV risk. Cross-sectional analysis of VAX004 participants (N=5,095) identified eight demographic and behavioral contextual HIV risk groups [92]. Groups with highest rates of HIV seroincidence (‘extreme number of partners,’ ‘young party drug users’ and ‘older popper users’), were also the groups that reported the highest rates of popper use (59%, 56% and 100% respectively). Among both MSM with and without HIV participating in a phone survey (N=311), popper use was correlated with potential HIV transmission [93]. Potential risk for acquisition or transmission was defined as having CAI in the past year with a partner with HIV or unknown

status (for MSM without HIV) or with a partner without HIV or unknown status (for MSM with HIV). Among MSM without HIV, 52% with a potential exposure to HIV used poppers in the past six months, compared to 15% without potential exposure to HIV (OR 6.2, CI 95% 2.6, 14.8). Among MSM with HIV, 43% with a potential transmission reported use of poppers in the past six months compared with 19% without a potential transmission (OR 3.3, CI 95% 0.78, 12.5) [93].

A case control study comparing MSM with recent HIV acquisition (N=111) to MSM without HIV (N=333) found that poppers were associated with HIV seroconversion (recent acquisition was defined as having a verified HIV test with a negative result followed by a verified HIV test with a positive result in the past 12 months) [94].

Interpersonal

Poppers are used by MSM primarily during sexual encounters and results of this review indicate that use is associated with behaviors that place an individual at risk for HIV acquisition, such as condomless anal sex (including with serodiscordant partners), group sex participation and increased number of sexual partners. Poppers were the most frequently used drug during sex, after cannabis [95, 96]. In one sample, 40% of MSM surveyed (N=189) used poppers during sex in the past year [95]. Among MSM recruited from gay-affiliated websites (N=8,717) 24% reported using poppers during their last sexual encounter [79].

Condomless Sex. With the exception of two studies [97, 98], results reporting the association between popper use and condomless sex come from data collected prior to 2010. Many studies pertaining to poppers and condom use are out of San Francisco and the majority are cross-sectional; however, two longitudinal studies on the association between poppers and CAI were identified [63, 99, 100].

Among Project EXPLORE participants across all sites (N=4,295), the influence of episode-level predictors of serodiscordant CAI was assessed [99]. Over a third (37%) of the sample used poppers in the past six months and popper use during sex was independently associated with serodiscordant CAI in univariate and multivariate modeling at both the participant- and episode-level [99]. In a sub-study of San Francisco Project EXPLORE participants (N=736), periods of popper use were associated with high-risk sexual behavior (e.g., serodiscordant CAI) and even intermittent use was associated with high-risk sexual behaviors [63]. Another longitudinal study among San Francisco MSM with and without HIV (N=937) also found that popper use was associated with more episodes of serodiscordant CAI [100].

Several cross-sectional studies with sample sizes ranging from 657 to 3,173 also identified an association between popper use and CAI among MSM [53, 98, 101, 102]. The largest was a study of San Francisco MSM without HIV who used substances (N=3,173), which also found that episodic popper use was more prevalent than at least weekly use (27% and 8%) and poppers were used by 15% of the sample before or during CAI [98]. Another study that supported the correlation between popper use and CAI found that among MSM without HIV, popper use was significantly correlated with selecting sexual partners based on HIV status (i.e., serosorting) [101]. In a study of MSM with HIV across six cities (N=675), while other drugs were individually associated with serodiscordant CAI, only alcohol and popper use during sex in the past three months remained significantly associated with CAI in multivariate modeling [53]. After adjusting for sociodemographic and psychosexual variables, poppers were the substance most associated with CAI with a partner who was HIV-negative and a dose response was identified—more frequent use of poppers during sex was associated with more instances of serodiscordant CAI [53].

A large phone survey conducted among San Francisco MSM (N=1,976) in 1996 determined popper use was independently associated with receptive CAI with a partner with HIV among MSM without HIV [3]. Two online surveys among MSM [103, 104] identified a correlation between popper use and CAI. Popper use was compared among individuals who reported no CAI (32%), insertive CAI (12.2%), receptive CAI (17.8%), and both insertive and receptive CAI (38.1%) [104].

Two studies identified a correlation between use of poppers and CAI at circuit parties [105-107]. A study which recruited MSM attending circuit parties in three cities 1998-1999 (N=1,169) [105, 106] reported that 39% of respondents had used poppers at circuit parties in the past year and poppers were the 'club drug' (defined as alcohol, Ecstasy, Special K, cocaine, crystal meth, GHB, marijuana) most associated with CAI [106]. Researchers used factor analysis to identify two constructs of motivation for club drug use in the context of circuit parties (social motivators and sensation-seeking motivators); popper use was associated with the sensation-seeking construct, which was significantly associated with CAI [105].

A convenience sample of men utilizing mobile van STI and vaccination services (N=241) found that popper use during sex was associated with CAI in the past year [80]. Studies identified the association between popper use and CAI among MSM identifying as black [70, 71] and YMSM (18-29 years) identifying as API [72]. A case-control study of MSM with recent HIV acquisition (N=111) and MSM without HIV (N=333) similarly found that popper use was significantly associated with CAI and that cases with recent HIV acquisition reported more frequent use of poppers compared with controls [94]. Partner-level data between MSM (N=23) and their sexual partners (N=52) assessed the relationship between partner-level substance use during the most recent sexual encounter and CAI; the odds of engaging in CAI (including

serodiscordant CAI) were significantly higher when poppers were used during the encounter [97].

Number of sexual partners. Use of poppers was associated in cross-sectional studies among MSM with group sex participation [58] and a greater number of sexual partners compared with MSM who did not use poppers [72].

Community

Results of this review point to several community-level influences on popper use among MSM with and at-risk for HIV, including: frequenting gay-identified venues (e.g., bars, clubs, circuit parties, bathhouses, and public cruising sites), the internet and geosocial networking applications, geographic location, peer norms, and social networks.

Social-sexual environments. Among MSM in four cities (N=2,2881), public environments where sexual encounters occurred (e.g., bathhouses and public cruising areas) impacted risk behaviors; individuals frequenting bathhouses (38.2%) and individuals frequenting both bathhouses and public cruising areas (43.3%) used more poppers than individuals who only frequented public cruising areas (17.8%) [108]. Among urban API YMSM, individuals with more frequent attendance at gay bars or clubs, or who had ever attended a circuit party, were more likely to report using poppers during sex than those who did not frequent these settings [72]. Among MSM who had attended a circuit party in the past year, popper use was higher during party weekends compared to non-party weekends and 12% of individuals reported use of poppers during their most recently attended party [107]. Over a third (39%) of MSM in a large sample (N=1,169) of individuals attending circuit parties in three cities reported popper use in the past year [106].

The internet and geosocial networking applications (e.g., Grindr) were identified as virtual environments potentially influencing popper use and sexual risk behaviors. A study compared Hispanic MSM (N=262) recruited from public venues (e.g., bars, bathhouses, gyms, parks, street) to Hispanic MSM (N=171) recruited online; popper use was higher in the internet sample (31.6% in the past six months) compared to the community sample (9.2% in the past 3 months) and the internet sample also had higher rates of HIV (50%) compared to the community sample (29%) [109]. Among YMSM using geosocial networking applications, 25.6% reported using poppers in the past six months; this sample also reported high rates of engagement in behaviors associated with HIV risk (e.g., CAI and serodiscordant partners) [110].

Geographic location. Several studies revealed differences in popper use by city. An online cross-sectional survey of MSM with and without HIV recruited from six U.S. regions (N=2,741) found that 19% of the overall sample reported popper use, however significant regional differences existed with use ranging from 7% (Mountain region) to 22% (South Central region) [103]. MSM in Los Angeles were significantly more likely to report lifetime use of poppers than MSM in New York City [73]. Among YMSM (18-29 years), use of poppers was higher in New York City (27%) than in Chicago (21%) or Atlanta (11%) [51]. Among MSM with HIV across six cities (N=675), popper use varied by city with participants in Boston reporting the highest use of poppers with sex in the past three months (39%) compared to participants in other cities [53].

Social norms and networks. Poppers have been identified as part of gay culture and the 'party scene' [53]. Community norms around drug use and sex, potentially influenced by fear and anxiety around HIV acquisition and non-affirming environments, may undermine accurate

risk perceptions and promote risk behaviors [111]. Community-level interventions that address risk norms should be developed and evaluated [93].

MSM attending weekend dance events (N=489) assumed that about half of other party goers would use poppers and 17.8% intended to use poppers themselves; however only 12.5% of participants reported having used poppers during the event at follow-up [112]. Partygoers with HIV were significantly more likely to use poppers and to have insertive and receptive CAI than partygoers without HIV (24.3% versus 10.7%) [113]. Poppers were also associated with lower scores on a peer condom norm scale among MSM with HIV (N=675) [53]. MSM surveyed in bars (N=609) were asked how many people they knew who had used poppers at least twice in the last year; 42.2% of respondents did not know anyone who used poppers, 44.2% knew one to five people, and 13.6% knew six or more people [96]. Older participants reported knowing more individuals who used poppers. In this study, past 12-month popper use was associated with HIV infection and participants with HIV knew more people who had used poppers in the last year compared to participants without HIV [96].

System

System level influences on popper use included systems of care (e.g., health care, HIV care and substance use treatment) and HIV prevention efforts, including PrEP.

Health Care System. Several studies identified clinical care recommendations to address popper use and associated risks:

1. Health care providers, especially those caring for gay and bisexual men and individuals with or at risk for HIV, should be informed about populations most at-risk for popper use (e.g., MSM) and the effects and management of acute popper intoxication [11].

2. Health care providers may contribute to low perception of risk related to popper use due to lack of awareness or screening [111]. Health care providers are essential in screening for popper use and educating about potential risks [114] and should provide referral to substance use treatment when indicated [11]. In addition to medical providers, a multidisciplinary approach to popper screening, counseling and referral is warranted; social workers in particular are well trained to conduct comprehensive assessments which recognize the need for individualized interventions that contextualize person in environment and culturally responsive approaches [109].
3. Prescribers of medications found to be commonly used with poppers (e.g., testosterone, erectile dysfunction medications and antidepressants) [60, 85] should screen for popper use and provide education aimed at reducing harms. Medical providers should be aware that Viagra is abused and often used concurrently with poppers, which is contraindicated, and should counsel patients to seek medical attention if they experience symptoms of hypotension (e.g., dizziness, lightheadedness, blurred vision, confusion, nausea, syncope, tremors) in the context of concurrent use [87]. HIV clinicians should also be aware that protease inhibitors interact with Viagra and concurrent use of protease inhibitors, Viagra and poppers could be especially dangerous [87].

Substance Use Treatment. Results and recommendations from this review emphasize that MSM with substance use disorder are not a homogenous group. Effective treatment should be substance-specific, acknowledge the treatment needs associated with polysubstance use, address the reason and context for use (e.g., sexual encounters), and consider longer treatment episodes and post-treatment care [57]. Interventions should be culturally responsive and tailored to age and developmental stage given the variance in popper use by race/ethnicity and age [63].

Assessments and interventions should include intermittent popper use since it is also associated with high-risk sexual behaviors [63].

Substance use treatment that addresses popper use could play an important role in reducing HIV transmission [91, 93]. Individuals who are diagnosed with HIV appear to decrease popper use following diagnosis (perhaps demonstrating motivations to promote their own health and reduce risk of transmission to partners); however, despite decreases in use upon diagnosis, sex and drug risk behaviors (e.g., popper use and CAI with multiple partners) persist among individuals with recent HIV diagnosis [91]. Findings indicate that tailored interventions are needed, including substance use assessment and treatment upon HIV diagnosis [91].

HIV Prevention. Past year popper use was associated with more frequent HIV testing [115, 116], representing a need and opportunity to develop HIV prevention programs focused on popper use [72, 85]. Based on medical record review (N=1,903) researchers developed a simple validated predictive model for HIV acquisition among MSM which determined the strongest predictors in the model were past six-month methamphetamine or popper use [117]. Popper use should be included in criteria developed to define MSM at high-risk for HIV acquisition, for whom enhanced prevention services are recommended [115].

Behavioral interventions focusing on popper use could be especially effective in reducing HIV risk since individuals who use poppers are amongst those at the highest risk for HIV [93]. Popper use, especially when coupled with other HIV risk factors (e.g. serodiscordant receptive CAI) should be a focus for HIV prevention strategies; there is a need to develop HIV prevention strategies which aim to decrease popper use and/or support the adoption of harm reduction strategies [88]. The heterogeneity among MSM, in terms of risk behaviors, is clear: while 33% of overall VAX004 participants reported popper use, use ranged within identified contextual risk

groups from none to 100% [92]. The development of assessments and interventions that consider individual-contextual dynamics is needed and should include tailored community-level interventions that are relevant to sub-populations with similar profiles and risk behaviors [92].

Given findings that indicate MSM with HIV engage in high rates of substance use and sexual risk behaviors, focused prevention efforts geared toward MSM with HIV are needed [102, 113]. HIV prevention programs should integrate and emphasize the relationship between popper (and polysubstance) use and sexual risk behaviors [99, 103]. Among MSM with HIV, interventions supporting self-efficacy and access to substance use treatment may play an important role in reducing HIV transmission [53]. Other potential opportunities for HIV prevention which address popper use could include STI testing sites and partner notification services; popper use was associated with higher likelihood of syphilis testing [118] and greater odds of partner notification [95]. The internet is also recommended as an important arena for HIV prevention efforts focused on those most at-risk for substance use and HIV transmission [79]. Researchers call for future research aimed at better understanding the motivations and needs of MSM with HIV who continue to engage in high-risk drug and sex behaviors in an effort to better tailor interventions [91].

Pre-exposure prophylaxis (PrEP). Although the CDC recommends that clinicians briefly screen for alcohol and drug abuse (including poppers), the most current PrEP guidelines and screening tool [119] do not include popper use [110]. However, some state and local health departments have included poppers in PrEP implementation guidelines to define high-risk priority populations for PrEP referral [120, 121]. From results of two large cohort studies (VAX004 and Project EXPLORE), researchers were able to predict HIV acquisition and develop a seven-item screening index (which included past six month popper use) that was predictive of

HIV seroconversion in order to prioritize patients in need of intensive HIV prevention efforts [122].

Popper use was significantly associated with being on PrEP [120], including among YMSM [110] and MSM identifying as black or Latino [123]. Among MSM initiating PrEP (N=172), past three month popper use was reported by 26% of participants and poppers were the most commonly used substance after cannabis [124]. In one study of MSM participating in a PrEP trial (N=400), over a quarter (27%) reported using poppers in the past three months [125]. Another study of YMSM who used geosocial networking applications (N=761) reported higher rates of popper use among individuals on PrEP (63.5%) [110]. Popper use did not appear to decrease PrEP initiation or adherence among black MSM [69].

In a longitudinal cohort study of MSM requesting PrEP, 16% of respondents who identified themselves as low-risk for HIV endorsed having used poppers; these behaviors were disclosed in self-assessments, but not discussed with their provider during their clinical visit [111]. Providers of PrEP may be uniquely positioned to talk to patients about popper use, as safer sex behaviors may be influenced by counseling during PrEP follow-up visits [111].

Discussion

The Social Ecological Model allowed for contextualized understanding of findings, including individual, interpersonal, community, and system level influences on risks associated with popper use. Overall, individual and interpersonal factors were overrepresented in results of this review. Identified individual factors influencing popper use included sociodemographic characteristics (e.g., age, race, geographic location, HIV status, and polysubstance use) and biological impacts. Although nationally representative data indicates that popper use is more common among MSM, most available research on poppers focuses exclusively on MSM.

Research is needed to better understand popper use in other groups. Further, existing studies have not evaluated the association between popper use and mental health and experiences of trauma—which are known to impact other substance use behaviors [126].

Results of this review provide significant insight for clinical care. Providers in various systems of care (e.g., primary care, HIV care and substance use treatment) are well situated to assess and address popper use. However, in order to provide accurately tailored education and risk reduction counseling, providers need to assess gender identity and sexual orientation, sexual practices, use of erectile dysfunction medications (prescribed and unprescribed), use of substances (including poppers, cannabis and alcohol), and how individuals meet sexual partners. Given the high rates of popper use among people with HIV, HIV providers especially should assess use and develop partnerships for referrals to substance use services. Integrated or co-located HIV and substance use services may be especially effective. When such services are not possible within the same system of care, partnerships which enable facilitated referrals (or "warm handoffs") can support effective linkage to needed treatment.

Individualized substance use treatment should be tailored to the needs of individuals at high-risk for popper use (e.g., MSM and people with HIV), adopt harm reduction approaches and address popper use specifically and in context (e.g., polysubstance use, sexual encounters). Suggestions for harm reduction-based counseling include providing information about adverse effects and risks associated with ingestion, counseling about concurrent use of poppers with erectile dysfunction medications, strategies to reduce risk of relapse on other substances (e.g., methamphetamine), and empowering clients to engage in conversations with their sexual partners about substance and condom use [127].

Although other substances (e.g., methamphetamine) are commonly used during sexual encounters, poppers appear to be unique in their almost *exclusive* use in the context of sex. While other drugs are also associated with HIV risk, this review supports that poppers seem to have the strongest association with CAI and HIV acquisition, however the mechanism of risk is likely multifaceted and not well established. Potential factors associated with popper use warranting additional research include: use based on sexual positioning (e.g., receptive versus insertive), dissociative effects, localized blood flow and tissue damage, duration of sexual encounters, and ability to reduce pain during anal sex.

This review did not identify any studies that assessed the impact of popper use on the HIV care continuum (e.g., diagnosis and linkage to care, engagement and retention in care and viral suppression). Given developments in biological prevention strategies, such as treatment as prevention and PrEP, future research should focus on the impact of popper use (and popper use in the context of polysubstance use) on the HIV care continuum—especially since influencing community viral load is an effective way to eliminate new HIV transmissions. As antiretroviral treatment and PrEP present the biological opportunity to eliminate HIV transmission, interventions and services that address the comprehensive wellness (e.g., mental health, substance use, trauma informed care, interpersonal relationships, support systems, integrated services, etc.) of people with and at-risk for HIV are the next frontier in eliminating HIV transmission.

Given that popper use was associated with gay bars and clubs, circuit parties, bathhouses and public cruising areas, and use of the internet and geosocial networking applications, physical and virtual venues for meeting sexual partners associated with popper use present an opportunity for education and intervention aimed at reducing HIV transmission. Gay culture, peer norms and

social networks influenced popper use, indicating that community interventions and effective education campaigns are needed and could influence individual risk behaviors. The emphasis on individual behavioral interventions may represent missed opportunities for reducing HIV transmission at community and system levels.

System level influences on popper use were not well addressed in findings from this review. Poppers have a unique legal status, discussion of which was largely absent in studies included in this review. Further, many validated substance use screening tools do not include poppers (or capture them broadly as inhalants) and biological screening for popper use is not widely available. Researchers should broadly consider adopting screening for popper use when assessing substance use. Although this review focuses on popper use among MSM, the majority of MSM do not use poppers. Future research should include studies seeking to establish factors related to resilience and behaviors associated with health promotion.

Limitations

Primary limitations include the temporality and design of studies included in this review. Much of the data presented was collected in the 1990s and 2000s and comes from cross-sectional studies, many of which used convenience sampling. Thus, the majority of findings presented are not causal and may not be representative of all MSM populations at-risk for HIV. It is outside the purview of scoping reviews to thoroughly assess methodological design and limitations of included studies. This review did not identify any qualitative studies, which could perhaps provide a deeper understanding of findings—especially where discrepancies exist between studies and in underrepresented populations. The majority of studies present data on urban MSM over 30 years of age. Several populations are underrepresented, including youth, individuals residing in suburban or rural areas, racial and ethnic minorities, and non-MSM populations

(including individuals who identify as transgender). Popper use is assessed via self-report, leading to potential reporting and recall bias. Use of the term MSM is used throughout to reflect the way in which most research was reported; however it should be acknowledged that grouping all men who have sex based on behavior regardless of identity minimizes the unique research and health needs of a non-homogenous group.

Conclusions

Poppers are widely used by MSM, although use varies significantly in this heterogeneous group. The literature overwhelmingly supports the relationship between poppers and HIV risk. Poppers are used predominantly during sex and often concurrently with other substances. There is a need for individuals who use poppers, and their clinicians, to be better informed about the risks of poppers and strategies for harm reduction. The impact of popper use on the HIV care continuum is not well established. Future research, intervention and prevention efforts should focus on enhanced screening for popper use, education on related risks, and substance use referral and treatment that addresses polysubstance use. Community level interventions are needed that provide tailored information to specific groups.

Acknowledgements

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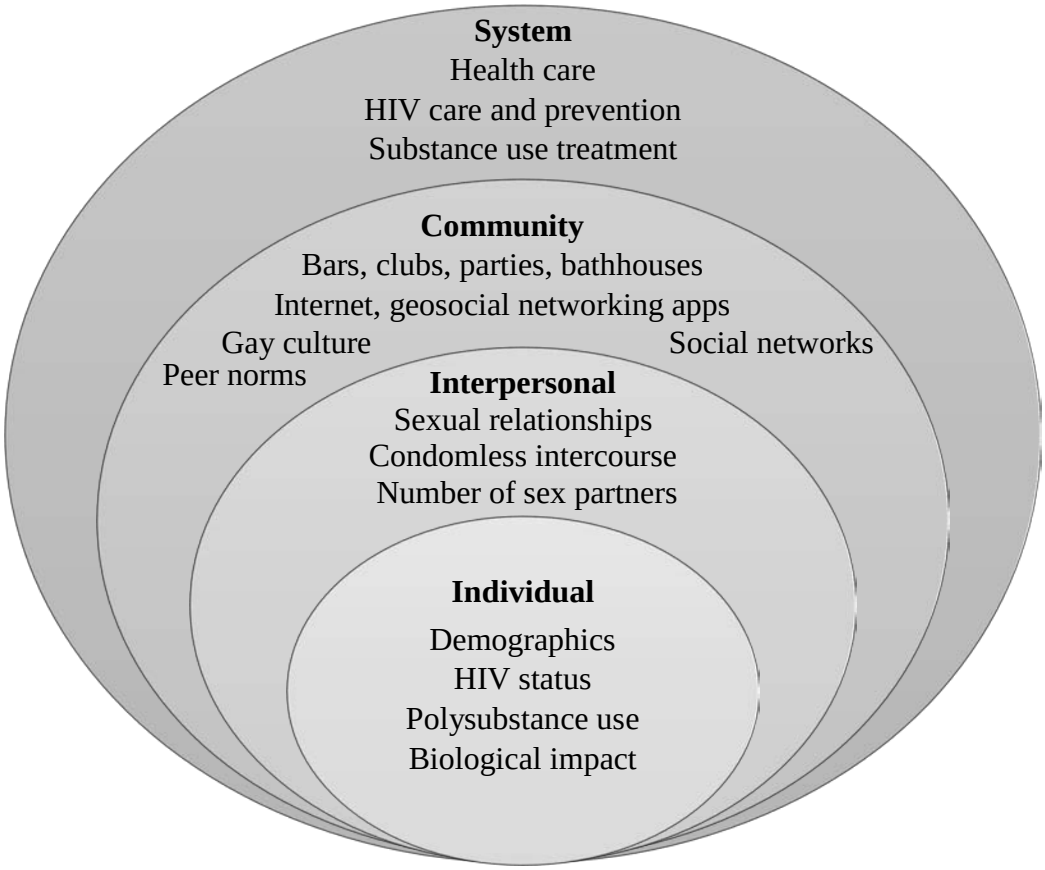


Figure 1. Identified themes of a scoping review on U.S. use of poppers and HIV risk (2000-2021) contextualized in the Social Ecological Model

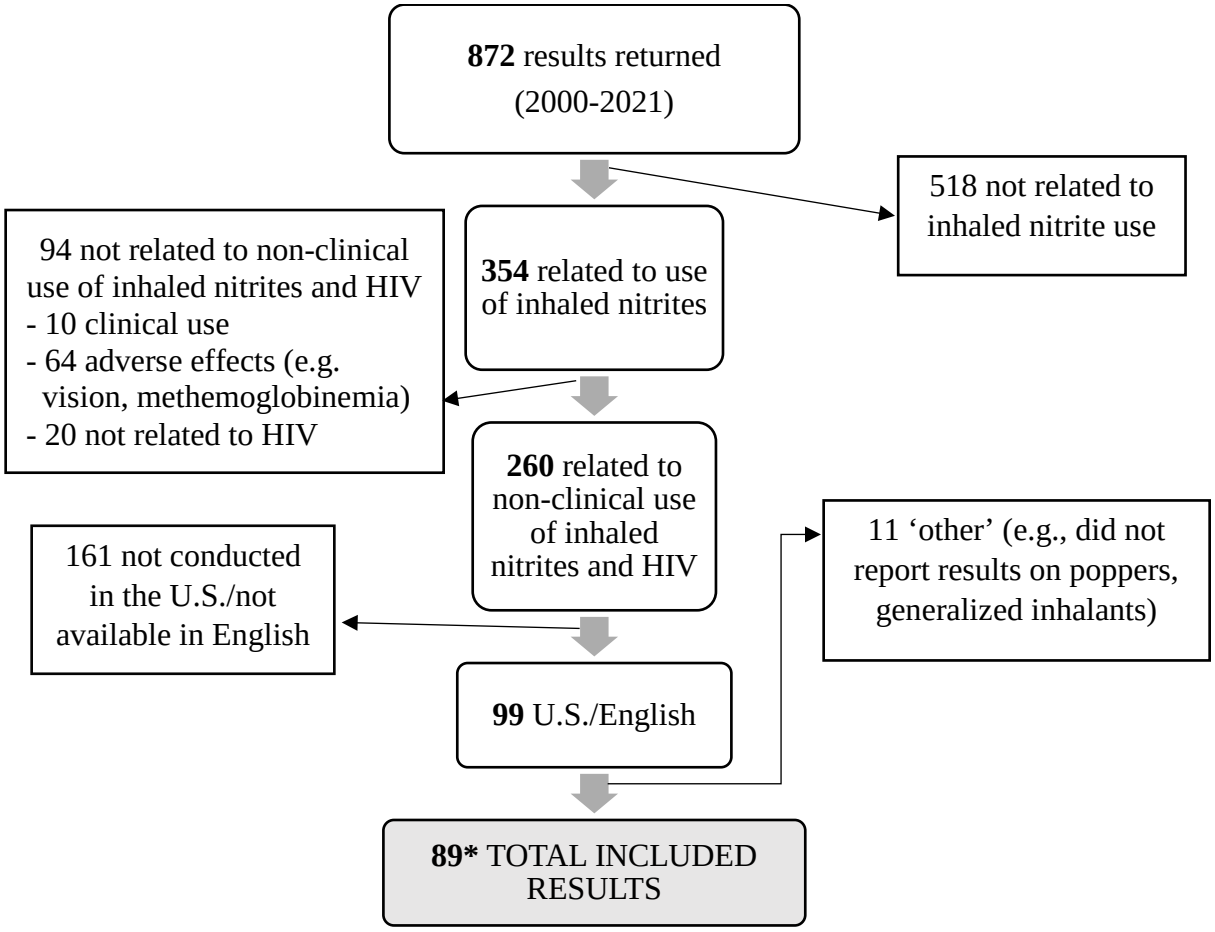
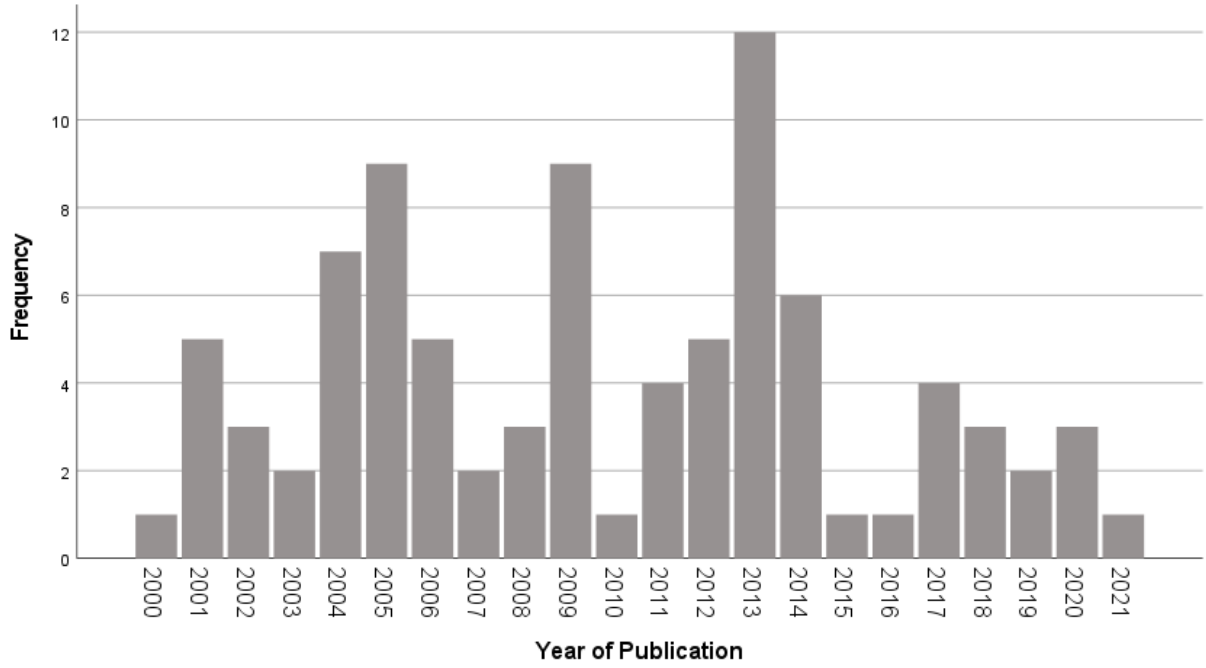


Figure 2. Studies included in a scoping review of popper use and HIV risk in the U.S. (2000-2021)

*** 1 study meeting inclusion criteria was identified via reference list search that was not in the search results**



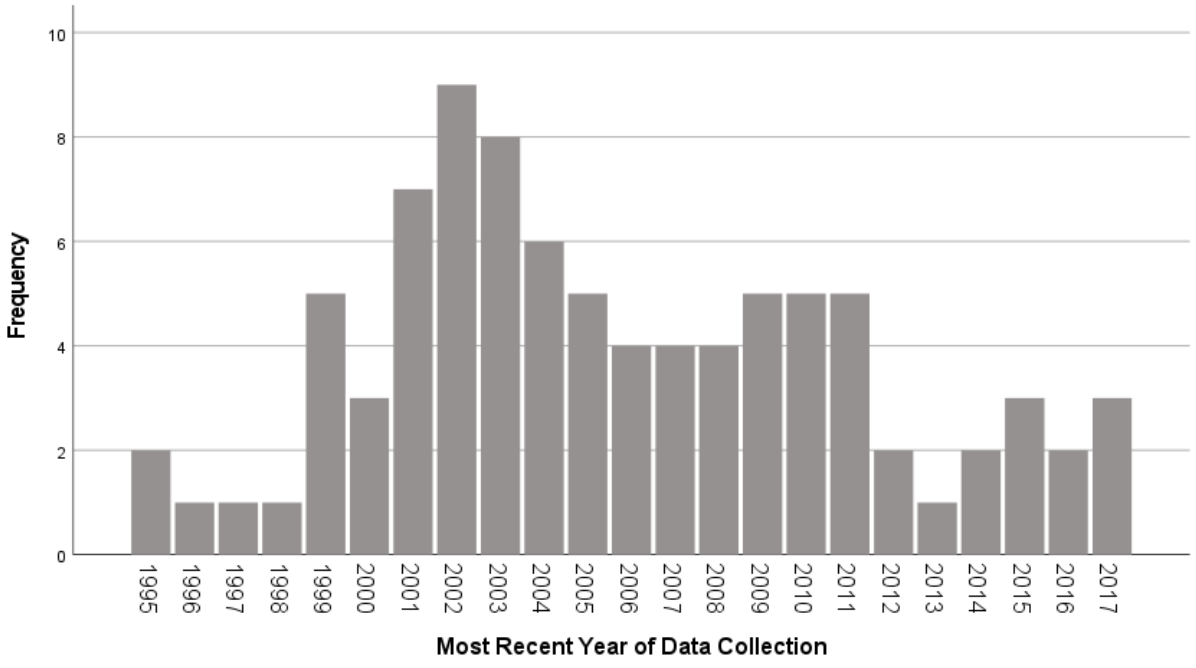


Figure 3. Year of publication versus year of data collection* from studies included in a scoping review of popper use and HIV risk in the U.S. (2000-2021)

*** For studies that collected data over a range of years, the most recent year of data collection is shown; 1 study did not report data collection period.**

Table 1. Selected studies reporting prevalence of popper use included in a scoping review

Population*	Data Collection	N	Timeframe	Design	Reference
NSDUH	2015-2018	168,560	Lifetime	Cross-sectional	[52]
Men and women with HIV ≥50 years	2011-2013	557	1 month	Cross-sectional	[65]
Men and women with HIV ≥50 years	2005-2006	914	3 months	Cross-sectional	[54]
Transgender women	2002	67	Lifetime	Cross-sectional	[59]
MSM					
Without HIV					
MSM at a public STI clinic	2014-2017	3,238	12 month	Cross-sectional	[120]
18-29 year olds	2013-2015	1,113	3 months	Cross-sectional	[51]
Black MSM	2013-2014	226	3 months	Longitudinal	[69]
MSM surveyed at bars	2007-2009	490	12 months	Cross-sectional	[96]
MSM at public STI clinic	2001-2008	1,802	6 months	Cross-sectional	[117]
NHBS	2003-2005	4,322	12 months	Cross-sectional	[128]
Project EXPLORE	1999-2003	3,913	6 months	Longitudinal	[62]
Project EXPLORE (baseline data)	1999-2000	4,295	6 months	Cross-sectional	[99]
Project EXPLORE (control baseline data)	1999-2003	1,937	6 months	Cross-sectional	[117]
VAX004	1998-2002	4,581	6 months	Longitudinal	[62]
VAX004	1998-2002	4,684	6 months	Longitudinal	[49]
VAX004 (baseline data)	1998-2002	5,095	6 months	Cross-sectional	[92]
VPS	1995-1999	2,266	6 months	Longitudinal	[62]
VPS (baseline data)	1995	3,212	6 months	Cross-sectional	[61]
CDC Jumpstart	1992-1995	1,813	6 months	Longitudinal	[62]
MSM in San Francisco	1996	1,476	12 months	Cross-sectional	[3]
With and Without HIV					
NHBS (16-18 year olds)	2014-2015	446	12 months	Cross-sectional	[64]
NHBS (Washington, D.C. only)	2011	379	12 months	Cross-sectional	[58]

(Table 1 continued)

Population*	Data Collection	N	Prevalence	Timeframe	Design	Reference
NHBS	2008	8,175	13.00%	12 months	Cross-sectional	[50]
Black MSM	2011	210	7.70%	1 month	Cross-sectional	[70]
Black MSM	2008	197	14.00%	12 months	Cross-sectional	[71]
MACS	1996-2007	3,366	53.00%	12 months	Longitudinal	[56]
MSM in NYC	2003	1,654	46.70% 24.24	Lifetime 3 months	Cross-sectional	[73]
MSM in Los Angeles	2003	681	53.50% 24.20%	Lifetime 3 months	Cross-sectional	[73]
Hispanic/Latino MSM	2003	171	31.60%	6 months	Cross-sectional	[68, 109, 129]
MSM attending sex resort	2002	143	50.00%	3 months	Cross-sectional	[86]
MSM in 6 U.S. regions	2001-2002	2,741	19.00%	6 months	Cross-sectional	[103]
Seroconverted (public health clinic)	2001-2008	101	17%	6 months	Longitudinal	[117]
Seroconverted (Project EXPLORE)	1999-2003	144	38%	6 months	Longitudinal	[117]
With HIV						
Age ≥ 50 years	2005-2006	239	71.80% 21.40%	Lifetime 3 months	Cross-sectional	[54]
MSM in San Francisco	1996	500	36.50%	12 months	Cross-sectional	[3]
MSM with HIV (overall)	2005-2006	669	32.00%	3 months	Cross-sectional	[53]
African American/Black	2005-2006	300	22.00%	3 months	Cross-sectional	
Caucasian	2005-2006	168	46.00%	3 months	Cross-sectional	
Hispanic/Latino	2005-2006	157	34.00%	3 months	Cross-sectional	
Other/multi-racial	2005-2006	44	34.00%	3 months	Cross-sectional	
Latinos in the border region	2011	121	25.60%	Lifetime	Cross-sectional	[55]

***Race/ethnicity descriptors from reference articles are presented**

CHAPTER 2: The Impact of Nitrite Inhalants (Poppers) on the HIV Reservoir and Recommendations for Future Research

Abstract

Background: Use of nitrite inhalants ("poppers") is common among men who have sex with men (MSM) and associated with HIV acquisition. Information is lacking on the impact of popper use on the health of individuals with HIV and its consequences on the immune system and HIV persistence. This study investigated associations between popper use and the HIV reservoir (i.e., HIV DNA levels) in MSM with HIV. Setting: Ninety stored peripheral blood mononuclear cell (PBMC) samples (45 with past 30-day popper use and 45 matched comparisons with no popper use in the past 30 days) from MSM with HIV who were virologically suppressed were selected for this study from a larger database of stored blood samples. Methods: We measured total HIV DNA from PBMCs. Non-parametric rank analysis of covariance (ANCOVA) was conducted on the dependent variable (HIV DNA), with group (recent popper use versus no recent popper use) as the independent variable and alcohol, tobacco and cannabis use as covariates. Results: No difference in HIV DNA was found between samples from MSM with recent popper use and those without. Conclusions: Lifetime popper was high (42%) in the overall sample of MSM with HIV (N=823). A deeper understanding of the impact of poppers on the health of people with HIV, including on the HIV reservoir, is needed. As the HIV reservoir harbors latent virus (even among individuals virally suppressed on antiretroviral therapy), it remains key to unlocking a cure; future research exploring the impact of popper use on HIV DNA should focus on prospective longitudinal studies with larger sample sizes and improved screening for popper use in research involving MSM.

Introduction

Men who have sex with men (MSM), especially black and Latino MSM, are disproportionally impacted by HIV in the United States. In 2018, gay and bisexual men comprised 69% of new HIV diagnoses [128]. Use of nitrite inhalants (poppers) is common among MSM [5], is associated with behaviors that can place one at risk for HIV acquisition (such as condomless sex) and with HIV transmission [89]. Poppers are rapid-onset, short-acting vasodilators which produce a head rush and are often used during sexual encounters to enhance pleasure and facilitate intercourse by relaxing smooth muscle tissue. Poppers are widely available and legal to purchase under the guise of room odorizers and cleaners [11].

Early in the HIV epidemic, there was speculation that use of poppers was linked to the development of AIDS-related Kaposi sarcoma [129]. While that theory has been debunked [17], little is known about the impact of popper use on the health of individuals with HIV and its consequences on the immune system and on HIV persistence. There is some evidence that poppers are associated with a cycle of immunosuppression and stimulation [18, 75]. Immunosuppressive effects are noted particularly in Natural Killer cell activity [18], which plays a critical role in host defense against viral infection [130].

These effects on immune function might impact the size of the HIV reservoir (i.e., HIV DNA). On one side, the immune-stimulatory effects could cause cell clonal expansion and thus cause an increase in the circulating HIV reservoir [131]. On the other side, immune dysfunction might be associated with residual HIV replication and expansion of the HIV reservoir, even in the setting of effective HIV therapy [132]. Achieving and maintaining HIV viral suppression through continued adherence to antiretroviral therapy, promotes the health of individuals with HIV [133] and eliminates the risk of transmission to their sexual partners [134]. Yet despite viral

suppression, HIV persists in the body in latent and active reservoirs (measured as HIV DNA), presenting barriers to HIV cure [135].

In this exploratory study, we were interested in determining how recent popper use might impact the size of the HIV reservoir in the blood of MSM, as compared to individuals who did not report recent popper use. Given poppers' impact on immune function, which in turn may increase the size of the HIV reservoir, our hypothesis was that we would observe an increase in HIV DNA in blood associated with recent popper use in individuals with HIV.

Methods

Ethics Statement

This secondary analysis of de-identified data was reviewed by the University of California San Diego (UCSD) Human Research Protections Program (HRPP) and certified as not qualifying as human subjects research. The parent study was approved by the UCSD HRPP; all participants provided written informed consent.

Participants

Data for this analysis was collected between 2003 and 2017 from the UCSD HIV Neurobehavioral Research Program (HNRP). HNRP's database of 4,074 participants across 13,757 visits was queried; 823 participants across 2,488 visits were identified who were MSM with available specimens. Overall lifetime prevalence of popper use among MSM in the sample was 42%. Forty-five stored peripheral blood mononuclear cell (PBMC) samples were identified for this study based on reported popper usage. Eligible individuals were MSM who were virologically suppressed (plasma HIV RNA levels <50 copies/ml) and reported use of poppers in the 30 days prior to the visit and blood draw. Individuals who reported use of illicit substances in the past 30 days were excluded.

Substance Use Assessment

Participants self-reported substance use via interviewer-administered Timeline Followback method [136], a widely used retrospective calendar approach to measure substance use. Substance use variables included age of first use and days since last use. Lifetime substance use is reported in Table 1. Since poppers are often used in combination with other drugs, past 30-day use of alcohol, cannabis and tobacco were included as covariates in the poppers group in order to identify an adequate sample size.

A comparison group of 45 MSM who reported no substance use in the 30 days prior to visit and blood draw was identified and matched to the poppers group on age, education, gender, ethnicity, AIDS status, nadir CD4, and lifetime substance use. Given that the HIV reservoir is established soon after infection, it is possible that more distal popper use (i.e., lifetime use) in the comparison group could have affected HIV DNA. A sensitivity analysis was conducted comparing the poppers group to 28 samples from individuals who reported either a) no lifetime popper use or b) last popper use prior to HIV diagnosis.

Biological Method

Total DNA was extracted from PBMCs as previously described using the QIAamp DNA Blood Midi Kit from QIAGEN. Total HIV DNA (polymerase) was quantified by HIV-1 DNA Quantitative Detection Kit from Ultrabio Technologies, Inc. [137]. Additional details on biological analysis method are described elsewhere [138].

Statistical Analysis

Descriptive statistics, chi square and Mann-Whitney U tests were used to analyze participant demographics and group differences. Cell sizes less than five (e.g., race/ethnicity) were collapsed. A non-parametric rank analysis of covariance (ANCOVA) [139] was conducted

using IBM SPSS Version 27 on the dependent variable (HIV DNA), with group (recent popper use versus no recent popper use) as the independent variable and alcohol use, tobacco use and cannabis use as covariates. A non-parametric test was used due to the data not meeting assumptions of normality. An α level of .05 was used for statistical significance. Additionally, a Bayesian rank ANCOVA was conducted to calculate a Bayes factor (BF_{01}) for this analysis. BFs are advantageous over *p* values as they provide a quantitative estimate of the likelihood of one hypothesis over another, which *p* values cannot do [140]. This also applies to the null hypothesis: if a *p* value is greater than α (typically .05), this implies that either there is no effect or that the study is underpowered to detect the effect, but there is no way to distinguish between the two. However, a BF indicates the degree to which the null hypothesis is more or less likely than the alternative hypothesis. BFs of 1-3 are considered to be insufficient evidence in favor of either hypothesis, 3-10 is considered to be moderate evidence of one hypothesis over the other, and a BF greater than 10 is considered to be strong evidence for one hypothesis over the other [141]. JASP 0.14 was used to conduct the Bayesian rank ANCOVA. The default prior distributions for ANCOVA in JASP were used for analyses (fixed effects and covariates both use *r* scales with values of 0.5 and 0.354, respectively).

Results

There were no significant differences between group characteristics (Table 2). Median age was 47 years and most participants were non-Hispanic white (68%) and had completed high school education or above (69%). Most participants had been diagnosed with HIV for over a decade and about half the sample had an AIDS diagnosis. Among participants who used poppers in the past 30 days, mean age of first popper use was 23 (SD 7.2) and past 30-day use of alcohol, cannabis and tobacco was 64%, 38% and 22% respectively. Twenty-seven individuals in the

comparison group reported lifetime popper use; median time since last use was 5.1 years (minimum 60 days and maximum 42.0 years). Median total lifetime use of poppers in the comparison group was 120 days versus 323 days in the popper group.

There were no significant differences in HIV DNA levels between the poppers group and the comparison group ($F[1,88]=0.025$, $p=0.874$); sensitivity analysis similarly did not reveal a significant difference ($F[1,71]=0.009$, $p=0.925$). Comparison and sensitivity Bayesian analysis showed moderate evidence in favor of the null hypothesis (BF_{01} 4.48 and 4.03 respectively). Median HIV DNA was 1132 copies/million cells for the popper group and 1187 copies/million cells for the comparison group. There was also no significant difference between groups for CD4+ or CD8+ T cell count or percentage.

Discussion

The HIV reservoir remains key to unlocking a cure, since HIV persists in the body despite viral suppression during antiretroviral therapy. Therefore, it is important to understand the potential impacts of substance use on the HIV reservoir. Previous studies from our group found an association between methamphetamine use and higher HIV DNA levels [142] and, conversely, between cannabis use and HIV DNA decay [138]; yet the biological impact of popper use on HIV persistence remains unknown.

Our study did not find an association between popper use and HIV DNA in people who reported recent popper use compared to those with no recent popper use. Although results were insignificant, the comparison group had a higher median HIV DNA than the popper group, which warrants further research. Repeated popper-related immune stimulation while on antiretroviral therapy may produce a ‘shock and kill’ effect [143], where poppers potentially

reactivate latent HIV which is then targeted and 'killed' by the immune system and antiretroviral therapy.

Limitations

While this study adds some important information about the impact of popper use on HIV DNA, given its exploratory nature there are several limitations. The small sample size and retrospective cross-sectional design do not allow for causal inference. Given that poppers are frequently used in the context of potentially confounding polysubstance use, it is difficult to isolate the effect of popper use on HIV DNA; our statistical methods attempted to control for this.

We limited our reservoir measure to total HIV DNA, which is an imperfect marker of HIV persistence and biomarkers of inflammation were not available. It is possible that other chronic conditions could confound results; while diabetes and hypertension were more prevalent in the comparison group, differences between groups were not statistically significant. Substance use was self-reported and interviewer administered, potentially introducing bias and error. However, given lack of availability of biological testing, self-report remains the most feasible means of measuring popper use. It is also possible an unknown selection bias may have been present contributing to popper users having lower median HIV DNA. Finally, establishment of the HIV reservoir may occur early in the course of infection, posing challenges for researchers seeking to measure the impact of variables on HIV DNA.

Conclusions

Although participants in this study represent a successful time point in terms of the HIV care continuum (e.g., virally suppressed), understanding poppers' impact at critical ends of the spectrum outside the continuum—HIV risk and HIV cure—is important, especially in groups

disproportionately impacted by HIV, like MSM, where popper and other substance use is high. While this study did not find any difference in HIV DNA levels by popper use, future research with a prospective, longitudinal design and larger sample size is needed to better establish the impact of popper use on HIV DNA. Recommendations for future research include inclusion of popper screening (distinct from general inhalants) in HIV research settings and use of more sophisticated assays to better characterize the HIV reservoir. A study design that accounts for the reality that poppers are often used in the context of polysubstance use and is able to tease out the individual and collective impact of popper and other drug use is warranted. Given time is of the essence in measuring HIV reservoir during early HIV infection, we recommend a strong pipeline to support linkage to research opportunities upon HIV diagnosis.

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Table 2. Participant characteristics of men who have sex with men (MSM) with virally suppressed HIV being assessed for the impact of popper use on HIV DNA

	Poppers (n=45)	Comparison (n=45)	*P*-Value[1]
Age (years), median [IQR]	47 [41-51]	47 [40-51]	0.897
Race/Ethnicity, n(%)			0.291
Non-Hispanic white	34 (75.6)	27 (60.0)	
Hisapnic/Latino	6 (13.3)	10 (22.2)	
Black/other	5 (11.1)	8 (17.8)	
Education (highest completed), n(%)			0.296
Did not complete high school	3 (6.7)	5 (11.1)	
High school completion	21 (46.7)	26 (57.8)	
College, masters or doctoral degree	21 (46.7)	14 (31.1)	
Lifetime Substance Use			
Alcohol	45 (100.0)	44 (97.8)	0.315
Cannabis	37 (82.2)	32 (71.1)	0.213
Tobacco	33 (73.3)	26 (57.8)	0.12
Stimulants	28 (62.2)	28 (62.2)	1
Opiates	3 (6.7)	6 (13.3)	0.292
Sedatives	14 (31.1)	14 (13.1)	1
Hallucinogens/dissociative drugs	17 (37.8)	21 (46.7)	0.393
Inhalants (non-popper)	6 (13.3)	6 (13.3)	1
HIV Outcomes			
AIDS diagnosis, n(%)	22 (48.9)	21 (47)	0.833
Years since diagnosis, median [IQR]	13 [3-20]	13 [5-19]	0.896
HIV DNA (copies/million cells), median [IQR]	1132 [2647.7]	1887 [2439.2]	0.364
Nadir CD4+ T cell counts (cell/μl), median [IQR]	236 [88-389]	248 [63-316]	0.793
CD4+ T cell counts (cell/μl), median [IQR]	744 [462-900]	616 [448-828]	0.331
CD4+%, median [IQR]	32.2 [23.7-38.6]	31.3 [23.8-35.3]	0.768
CD8+ T cell counts (cell/μl), median [IQR]	896 [766-1102]	867 [624-1026]	0.309
CD8%, median [IQR]	45.2 [35.8-52.6]	45.9 [35.0-53.2]	0.941
Ratio CD4/CD8, median [IQR]	0.7 [0.5-1.1]	0.7 [0.5-1.0]	0.809
Months exposure (all antiretrovirals) [IQR]	77 [22-173]	99 [52-165]	0.891
Antiretroviral Medications			0.513
Integrase-based	6 (13.3)	9 (20.0)	
Multi-class regimen	8 (17.8)	4 (8.9)	
NNRTI-based	13 (28.9)	18 (40.0)	
PI-based	17 (37.8)	13 (28.9)	
Missing	1 (2.2)	1 (2.2)	

[1]Chi square tests were used to analyze differences in categorical variables and Mann-Whitney U tests were used for continuous variables.
Note: Due to rounding error, may not sum to 100%.
μl: microliter, NNRTI: Non-nucleoside reverse transcriptase inhibitors, PI: Protease inhibitor

CHAPTER 3: Use of Nitrite Inhalants (Poppers) among Young Men Who Have Sex with Men with HIV: A Clinic-Based Qualitative Study

Abstract

Nitrite inhalants (poppers) are associated with HIV transmission and commonly used among young men who have sex with men (YMSM), a group at increased risk for HIV. Significant research gaps exist in understanding the context in which YMSM use poppers. Qualitative interviews were conducted with 15 YMSM (22-31 years) with HIV to better understand the context in which poppers are used and their impacts on HIV care outcomes, such as care retention and antiretroviral adherence. The Social Ecological Model (SEM) was applied to understand intrapersonal, interpersonal, community, and system level influences on popper use. Factors influencing popper use included: ubiquity of popper use in sexual settings, introduction to poppers by casual sexual partners, patient-HIV provider communication surrounding poppers, neighborhood, substance use and HIV care systems, and the legal status of poppers. Implications for clinical care, public health, policy, and future research are discussed.

Introduction

Young men who have sex with men (YMSM) experience elevated rates of substance use compared to their heterosexual peers [144-147] and in 2018, 21% of new HIV diagnoses in the United States (U.S.) were among youth, with black and Latino YMSM at greatest risk [4]. Alarmingly, youth are the least likely of any age group to be aware of their HIV status, retained in care and have an undetectable HIV viral load [4]. The science is clear: individuals who receive timely HIV diagnosis, are retained in HIV medical care and achieve sustained viral suppression on antiretroviral medication do not transmit HIV [134]. Given that substance use negatively impacts each stage of the HIV care continuum (diagnosis, entry into care, treatment initiation,

and viral suppression), it is essential that substance use is assessed and addressed in vulnerable populations in order to reduce HIV transmission [148].

Nitrite inhalants (poppers) are commonly used by men who have sex with men (MSM) [5, 52] and are associated with HIV acquisition [90]—likely due to their association with serodiscordant anal intercourse [63] and condomless sex [149]. Poppers are potent rapid-onset short-acting vasodilators which produce a head rush and are often used during sexual encounters to enhance pleasure and facilitate intercourse by relaxing smooth muscle tissue. They are legal to purchase under the guise of commercial use (e.g., cleaners and odorizers), are widely available online and at adult bookstores and have potential for abuse. Popper use is concentrated in the MSM community; representative U.S. data from 2015-2017 indicated that over one-third of men who identified as gay and approximately 11% of men who identified as bisexual had used poppers in their lifetime compared with less than 4% of men who identified as heterosexual [5]. Among MSM with HIV who met criteria for drug abuse, 56.6% were using inhalants [150]. Popper use is often reported broadly as ‘inhalant use’ in representative data, and available literature on popper use is often focused specifically on MSM populations. Available literature comes predominantly from the 1900s and 2000s, posing challenges to understanding the current potential scope of popper abuse.

Significant gaps persist in our understanding of the implications of popper use on HIV risk and outcomes for YMSM. In particular, information is lacking on the individual and social experience of young popper users with HIV and whether poppers play a role in determining HIV care outcomes (such as viral suppression). The limited availability of current data indicates that poppers are often overlooked, minimized or under assessed by researchers and clinicians as drugs of abuse and little is understood about social and environmental contexts for use. Even

medical providers with experience providing HIV and addiction care to MSM may not be aware of the risks of popper use [31]. Speculation early in the epidemic that popper use caused AIDS or Kaposi sarcoma has been disproven [17, 151], but gaps remain in our knowledge of their mechanism for HIV risk. There is some evidence that popper use among persons living with HIV is associated with immunosuppression [18, 75] and elevated cancer risk [23], but a richer understanding of the context for behavioral risks associated with popper use is needed and represents an unmet opportunity to reduce new HIV transmissions. Further, the impact of popper use on HIV care engagement (e.g., attending medical visits) and treatment adherence is unknown.

Qualitative research on poppers [152, 153], which could serve to elucidate these research gaps, is limited, was conducted in the 1990s and does not focus on implications of popper use for individuals with HIV. Researchers have identified the need for qualitative research to better understand quantitative findings regarding the influence of popper use on sexual risk behaviors (e.g., condom usage) among MSM [154]. To address this gap in knowledge, the aims of the current qualitative study are to: 1) contextualize the experiences of popper use among YMSM with HIV, particularly as they relate to HIV care and treatment and 2) describe perceptions of how individual, social and environmental factors impact YMSM's ability to stay healthy, manage HIV and influence harms related to popper use.

To best address study aims, the Social Ecological Model was applied (SEM) [34, 35] (Figure 4). SEM provides a rich context for understanding substance use, associated risks and protective factors which acknowledge the complex interplay of micro, mezzo and macro factors influencing substance use, sexual practices and health behaviors. An important feature of the SEM is that levels are nested and interconnected rather than mutually exclusive. YMSM with

and at-risk for HIV and substance abuse represent a group in need of tailored interventions at the individual, community and system level to promote their health and wellbeing, as well as support optimal adherence to antiretroviral treatment to reduce HIV transmission in the community. These findings may be useful for clinical, public health, and policy efforts supporting YMSM [155-157].

Methods

From January 2020 to February 2021, in-depth, semi-structured interviews were conducted using an interview guide with open-ended questions and probes designed to explore individual, social and environmental contexts of popper use among YMSM with HIV (Table 3). Inquiry was guided by four levels of the Social Ecological Model: *intrapersonal*, *interpersonal*, *community*, *systems*. Interviews lasted approximately 60 minutes and were audio recorded. Due to the COVID-19 pandemic, most interviews were conducted via HIPAA-compliant Zoom for Healthcare. Participants were compensated with a $30 gift card for their time. This study was approved by the University of California San Diego Human Research Protections Program. All individuals provided written informed consent, including consent for audio recording.

A brief demographic survey which included demographic information and basic HIV outcomes (e.g., last HIV care visit, use of antiretroviral treatment and HIV viral load) and a substance use history assessment were completed prior to qualitative interviews. The substance use history assessed lifetime use, age of first use, most recent use, frequency of use, amount used, mode of administration, and concurrent use with poppers for the following substances (in addition to poppers): alcohol, cannabis (including synthetic), cocaine/crack, methamphetamine, opiates (heroin, fentanyl, prescription medications), 3,4-methylenedioxymethamphetamine (MDMA)/ecstasy, lysergic acid diethylamide (LSD), other hallucinogens (e.g., psilocybin,

mescaline, ayahuasca, N,N-dimethyltryptamine/DMT), non-popper inhalants (e.g., whippets, spray paint, glue), prescription stimulant medications (e.g., Adderall), erectile dysfunction medications (e.g., Viagra), 'club drugs' (e.g., ketamine, gamma hydroxybutyrate/GHB and gamma-butyrolactone/GBL), steroids, and other. For prescription medications, participants were asked if the medications were prescribed to them and used as prescribed.

Participants

Participants were recruited via flyers which were posted and shared electronically with HIV clinics, programs and service providers in San Diego, California. Eligible participants were between the ages of 18-30 years old, HIV-positive, identified as a male who had sex with other men, used poppers in the past six months, were able to provide informed consent, and able to read and speak English. Exclusion criteria included cognitive impairment or currently experiencing symptoms of serious mental illness. If a participant presented with signs or symptoms of impairment or serious mental illness (e.g., confusion, psychosis), established protocol was for the interviewer (a licensed clinical social worker with experience working with youth with co-occurring disorders) to provide clinical assessment and, if needed, referral to emergent services. Additional protocol included requesting to reschedule the interview if the participant presented with acute substance intoxication. No individuals required assessment, referral or study exclusion based on cognitive impairment, serious mental illness or acute intoxication.

Analysis

Interviews were audio recorded and transcribed verbatim. Personally-identifiable information was not transcribed and interviews were identified only with a unique identifier. Qualitative software (NVivo) was used to conduct analysis. A phenomenological approach [158,

159] was used to explore and describe the lived experiences of YMSM with HIV who had used poppers. Sample size was determined by a priori thematic saturation [160]. Researchers determined a high degree of saturation was reached when each level of the SEM was thoroughly explored, as evidenced by ample data reflecting both diverse experiences and similar perspectives to illustrate each level, and when interviews were not producing new information. Thematic saturation was reached with 15 participants. Transcribed interviews were reviewed thoroughly and coded by theme within the four levels of the SEM by NP. Analysis was also considered within the context of existing literature about popper use among YMSM. Final analysis was conducted with discussion and consensus between researchers. Compelling quotes which illustrate themes were selected from the coded data.

Results

Participant demographics are shown in Table 4. All but one participant identified as gay and one participant identified as pansexual. Participants predominantly identified as Hispanic/Latino, had completed high school, were unemployed and/or students, and living below the Federal Poverty Level. Average age was 26 (range 22-31 years, SD=3). Eighty percent of the sample considered themselves stably housed, but a significant number of these participants lived with family or friends or were in time-limited residential treatment or sober living. All participants were engaged in HIV care (attended a visit with their HIV provider within the past six months) and virally suppressed. The average age of first drug use (including cannabis) was 15 (range 8-28 years, SD=5) and average age of first popper use was 20 (range 12-28, SD=4). Median days since last popper use was 11 (range 0-178, mean = 45, SD=64).

Patterns of Popper Use

All participants reported primarily inhaling poppers nasally directly from the bottle. A few participants described oral inhalation via bagging or huffing, typically either because of tolerance or skin irritation around their nose from repeated nasal inhalation. Less common routes of administration included crushing and snorting poppers after drying the liquid, smoking the liquid from a bong, mixing with alcoholic beverages, and accidental ingestion. Participants reported paying between $10 and $30 dollars per 10mL bottle. Most participants reported using "spray poppers" (aerosol solvents) and noted these were very common in their community. These inhalants were described as more intense than poppers, and in some cases, a progression from conventional poppers to aerosol solvents (and sometimes used simultaneously).

Frequency and amount of popper use varied in this sample. At the time of the interview, some participants disclosed that they were in recovery and among them were individuals who reported not using poppers currently. However, participants were asked to categorize how often they typically used poppers during periods of use in the past six months. Nearly all participants reported at least monthly use and more than half reported using poppers at least weekly. Four participants used daily or almost daily. Use varied from periods of total abstinence to moderate to heavy use. Periods of abstinence were attributed to intentional efforts to reduce substance use, participation in substance use recovery services or being abstinent from sex. Moderate (occasional) use was attributed to use as a sexual tool based on sexual positioning (e.g., receptive versus insertive) and partner anatomy and in the absence of polysubstance use. Periods in which heavy use occurred included initiation of popper use, HIV diagnosis, and frequent sexual activity or use of other drugs ("being in my addiction"). Some participants described initial fear of popper use followed by increasing comfort level with continued use. Typical use ranged from

one to four sniffs to 15-20 sniffs in a three to four hour period. The high was typically perceived to have lasted a short time--between 10 seconds to a minute.

Although poppers were used almost exclusively during sexual encounters with partners, a number of individuals used poppers by themselves, primarily for masturbation and to a lesser degree "for fun" and to alleviate boredom and stress. Less common settings for popper use included clubs, parties and for kissing. *"Personally, I enjoy poppers when it's not in a sexual interaction. It doesn't give me pleasure or it makes it hard to stay erect...Once I tried it on the dance floor and I tend to enjoy it the most either when I'm making out or partying or dancing (Middle Eastern, 31 years old)."*

Benefits and Side Effects

Participants were mostly aligned about the benefits, side effects and risks of popper use. The primary reported benefits were intensifying sexual experiences, a head and/or body "rush", and a relaxing of smooth muscle tissue which facilitated anal and oral sex and reduced pain for the receptive partner. Other benefits included stress reduction, relaxation and enhanced intimacy. *"The feeling that I got was fast blood flow throughout my body and relaxation...The rush that it gives, the enhanced sensations, kind of gives me a calmness (Middle Eastern, 31 years old)." "It's like a head rush. It's just--I don't know. It's just, I guess at a certain point I like the feeling, like, how disoriented--and it's not really disoriented--but it's just like, you just got dropped in the middle of the ocean I guess (Latino, 24 years old)."*

Overall, participants perceived poppers to be relatively low risk, sometimes citing their short duration, and participants noted they lacked factual information about poppers and risks of use. *"I've never really put thought into [poppers], you know, just because it's so normalized. But it does leave me questioning, you know? Like, to be honest, I don't even know what poppers are.*

I don't know. This whole time I've been putting them in my body, you know, and using them...If they're chemical and they're like a cleaning kind of way...well that's about all I know about them. Other than that I don't know anything (Latino, 24 years old)."

All participants experienced headache as a common side effect and oftentimes it was the side effects that caused participants to wonder about popper safety and prompted participants to research poppers. Others reported feeling dizzy, nauseous, lightheaded, dehydrated, and having dry mouth. One participant reported having passed out and experienced auditory hallucinations while using poppers. *"It just always has the same effect on me. I never really liked it. It just gives me a headache instantly and I ask myself why I did that 'cause I know how it affects me...some of them have been like where I sniff it and then immediately it's like a truck hits me...it's like a 15-pound weight at like in the front of my skull and it's like dragging me down everywhere I go. And it's a splitting headache (Latino, 27 years old)." "The headache that I experience is not very pleasurable afterwards so I know it's not a healthy substance (Middle Eastern male, 31 years old)."* Participants reported learning more about poppers online, through friends or sexual partners, from adult bookstore employees, or through popper-specific pornography and Reddit boards. Several participants reported that poppers made it difficult to maintain an erection. Participants expressed mixed opinions regarding whether they developed a tolerance to poppers or experienced a progression of abuse. *"It's like the feeling can be different every time you do it because depending on the poppers, depending on everything like that, on how you're feeling--it's just like every time can be different, but I feel like the rush is always the same. Like with methamphetamine, I feel like I have a tolerance with that, but with poppers, it's like I don't have a tolerance, like every time I use it it's the same, you know (Latino, 22 years old)."*

Contextualization of Popper Use and HIV Risk and Outcomes in the Social Ecological Model

Intrapersonal

Initiation. For most participants, popper use preceded their HIV diagnosis. Common personal factors influencing popper initiation included general experimentation with substance use and disclosing sexual orientation ("coming out"). Other factors included increased freedom (e.g., moving away from home, getting their own apartment, graduating college) and adverse life events (e.g., personal loss, family difficulties, break-ups). Several participants described the time in their life surrounding popper use as "self-destructive" or a "downward spiral." *"I was more experimental. I had just joined a dating app, or not even dating, it's like Grindr. I was just putting myself more out there. I had come out. I was meeting people. It was just, like, a new chapter. Like my whole world was really like unfolding cause I'd just graduated college (Latino, 26 years old)."* HIV diagnosis was also identified as a factor that led to popper initiation or increased use. *"Yes, it [popper use] increased a lot [after my HIV diagnosis]. It increased a lot (Non-Hispanic white, 29 years old)." "I had just gotten diagnosed with HIV...and at that point, I just didn't care about life anymore so I was willing to try anything (Latino, 29 years old)."*

Polysubstance use. Polysubstance use with poppers was consistently reported by participants. Table 5 describes lifetime substance use and whether the individual reported having used a substance simultaneously with poppers. Nearly all participants had used methamphetamine with poppers and nearly three quarters (73%) of participants had used poppers with club drugs, like ketamine and GHB, and/or with erectile dysfunction medications (e.g., Viagra, Cialis).

Participants in this study resoundingly shared that popper use was more likely when other substances were being used. *"Your body turns into just some chemical power plant. There's meth, there's poppers, there's Viagra, you know? There's alcohol. It's just a wreck waiting to happen. Usually with meth use it [popper use] would increase a lot (Non-Hispanic white, 29 years old)." "When I started using meth about three years ago, where I would just do them [poppers] every time that I was high on meth, like I'd just be on poppers all the time...I wouldn't necessarily go out of my way to get 'em, you know what I mean?...I would do [ketamine] every day, along with GHB, meth and poppers. It was all part of my combo--my, like, routine at that moment in my life (Latino, 30 years old)." "It [poppers] adds another level to it [co-use of GHB, methamphetamine and Viagra], so it makes it a little bit more fun and intense and it makes it last a little bit longer. It's just, like, it just makes it stronger, to be honest, whatever you're feeling (Latino, 22 years old)."*

Some mentioned co-use of other drugs to mask the unpleasant side effects of popper use, like headaches. *"If I'm sober, I don't really want to [use poppers], 'cause I just don't really like how they make me feel...I mostly only use them when I'm on other substances (Non-Hispanic white, 23 years old)." "Pretty much they [methamphetamine and poppers] always went together. I remember a bunch of occasions in, like, sober sex, when you know, they usually give you a headache, so I wouldn't usually use them outside of using meth (Non-Hispanic white, 29 years old)."* Poppers were also used in the context of polysubstance use in an effort to restore an erection when methamphetamine use resulted in impotence. *"You know, where like the methamphetamine kicked in and you're, you know, you got 'T-dick' or whatever, and it's like well there's really nothing to do so you'll just use poppers, you know, to help rebuild your erection (Latino, 24 years old)."* It was very common to report concurrent use of poppers and

unprescribed erectile dysfunction medications and some participants were aware of the contraindication. *"There's usually, like, Viagra involved. Meth, viagra, poppers, other inhalants. So you know, like there's so much. I am aware that it's a high-risk--risk for like heart attack or, you know, cardio issues that could happen (Non-Hispanic white, 29 years old)."*

It was common for participants to minimize popper use in the context of other drug use. Not all participants abstained from poppers during periods of sobriety, although many did, and several identified popper use as a risk factor for relapse with other drugs. *"I never saw it [popper use] as, like, really a problem, just 'cause, like, I was on other drugs so I never really...thought about it in that way, but I feel like they go hand in hand with drug use...but I never really thought that, like, poppers were an issue (Latino, 29 years old)." "I've literally relapsed before over, you know, I went and I hooked up with someone and they had poppers...led me to a few days later doing meth (Non-Hispanic white, 29 years old)."*

Perceived risk. Most participants shared a low perception of risk and expressed ambivalence about use; individual factors noted by participants to influence risk perception included lack of knowledge about poppers, the short duration of effects, perceived lack of overdose risk, and the perception that poppers weren't addictive or weren't "hard drugs." *"'Cause, I mean, I did like the way it made me feel, but sometimes I didn't like how they made me feel (Latino, 24 years old)." "To me they're not really a drug. I mean, they are definitely a drug, but they don't last long, you know?...I use them...in sexual situations. I use them as a tool, 'cause sometimes they are necessary...I don't include poppers in my sobriety. I don't think that they should. They don't show up on a drug test and, like I said, I mean, I don't use them outside of sexual contact and context...I don't think that poppers really affect my judgment...it's not like a hard drug to me...to me they're not addictive. Like I definitely want to use them less. I do know*

they have a pretty big effect on...my health in general... so I will probably start using them less. (Non-Hispanic white, 27 years old).” The interconnectedness of SEM levels is exemplified in this quote. The combined effect of individual (e.g., duration of effects), interpersonal (contextual use as a sexual tool versus a drug of abuse) and system level influences (not showing up on a drug test) combine to shape perception that risks associated with use are low and influencing behavior (continued use during sexual encounters).

Despite the perception of relative low risk associated with popper use, participants described heavy use and a progressive relationship with poppers. *“I had an issue with inhalants and I needed to stay away from them, ‘cause it was progressive (Non-Hispanic white, 29 years old).” “If they [poppers] were there, I was gonna use them and I was gonna use them a lot. Until, like, my nose hurts, I couldn’t breathe anymore. And then I would still try to use them with my mouth...I would hit that point a lot (Latino, 30 years old).”*

Popper use and HIV risk and treatment adherence. Few participants had considered a direct connection between popper use and HIV and did not feel that popper use impacted their ability to be adherent to antiretroviral treatment or remain engaged in HIV care, again citing the short duration of their effects. One participant alone expressed concern that poppers might decrease the effectiveness of his HIV medication. *“They may, you know, decrease the effectiveness of my medication or whatever. I do realize that…, but as far as them causing me to not take the medication or, like, condom use, I don't think that they have an effect on that (Non-Hispanic white, 27 years old).”* Participants attributed poor medication adherence and care retention to other drugs they often used with poppers, primarily methamphetamine. On the other hand, some participants were intentional about taking their HIV medication and prioritizing their health during periods of drug use. *“When I use poppers or when I use any kind of substance, I’m*

responsible. I take my meds, I make sure after I'm done I go get tested [for sexually transmitted infections]...even when I'm using drugs or poppers, I take my meds every day (Latino, 24 years old)."

Interpersonal

Interpersonal influences, primarily through sexual partners, were a major factor contributing to popper use. Interpersonal influences on popper use were identified as contributing to HIV risk in several ways: initiation of popper use with sexual partners, increased sexual arousal and prolonged sexual encounters, disorientation, inhibiting conversations about condom use or HIV status, multiple partners and group sex, polysubstance use with drugs associated with sex (e.g. methamphetamine, GHB, Viagra), popper use based on the anatomy of the insertive partner (potentially leading to increased tearing or bleeding), masking pain, rougher sex, and sexual assault. *"I feel like poppers are related to HIV because sometimes it takes out that conscience that you have in your head when you're with, like, a sexual partner in the room, and once you take that whiff, it's like, it's like a drug where like all bets are off...so all you're there for is basically sex and if that's on your mind once you whiff poppers, there's not typically a conversation about HIV or anything, you know what I'm saying? It just throws that out the window (Latino, 24 years old)."*

Popper use in the context of sexual relationships. All participants had used poppers during a sexual encounter, most almost exclusively in this context. Increased sexual activity heavily influenced popper initiation and frequency of use. *"I was having a lot a lot of sex...my whole life revolved around sex. I finally had freedom, I had a place [to live], it was what I did for work, it was what I did for everything...So it was like poppers poppers poppers (Latino, 30 years old)."* Some participants defined frequency of popper use in relation to sexual activity

(e.g., using poppers "like 90%" or "70%" of sexual encounters).*"The more sex I had, the more I would use poppers, I guess, cause they were always around...so I would always just, just use poppers cause I was having sex (Latino, 24 years old)."*

Perceived benefits of popper use during sex included intensifying pleasure, facilitating anal and oral sex by relaxing smooth muscle tissue and reducing pain and bleeding. Some participants described poppers not as a drug, but as a "tool" or "accessory" for sex. Easing tension or anxiety, emotional numbing, and artificial intimacy were also cited as reasons for using poppers in sexual settings. *"Everything rushed, I felt like my--I felt a rush in my head, just got warm and 'ooh', just like all my muscles got relaxed for a second and then it was easier for the guy to, you know, for us to have sex. It helps you loosen up (Latino, 22 years old)." "When you use poppers, it relaxes your sphincter muscles. That way, it makes it easier for them to be able to penetrate you and not be as painful (Latino, 22 years old)." "There was once when I didn't use them [poppers] and they [my partner] were very big and I did bleed (Latino, 26 years old)."" "It's just, like, so it wouldn't hurt I guess...I mean...it all depends--like on size, you know? 'Cause...if it's big, it's gonna hurt and I just didn't want to feel it (Latino, 22 years old)." "Intimacy, I guess. [Poppers] makes it...feel real, not just like a hook-up (Latino, 29 years old)." "If I just really don't want to do it [have sex], it helps me, like, not be so tense (Latino, 22 years old)."*

The majority of participants used poppers for the first time during a sexual encounter with a casual partner and some had never heard of poppers prior to the experience. Poppers were usually supplied at the suggestion of their partner as a way to make anal sex more comfortable. *"The first time I tried poppers it was kind of like a suggestion from the man I was having sexual intercourse with. It would relax my body...They suggested, they offered. They just said, 'Take one*

sniff, you'll feel relaxed.' (Latino, 24 years old)." Participants discussed popper use almost exclusively in the context of "hook-ups" or casual partners (primarily met via applications such as Grindr and Adam4Adam) and few participants reported using with primary partners.

There was a perception that poppers were used primarily by the receptive partner--both because they relaxed muscle tissue and made it easier and less painful for receptive sex and also because insertive partners experienced difficulty maintaining an erection with popper use. *"I would try to use more poppers to continue my erection...to pretty much continue staying in that elevated state so I can maintain the erection, but that only lasted for so long and yeah, like I'd get soft (Latino, 29 years old)."* However all but one participant reported being versatile (receptive and insertive) and having used poppers regardless of sexual position. Overall participants reported that in their experience, both partners used poppers during a sexual encounter. Despite this, the idea that poppers were used primarily for receptive partners persisted. *"Usually both [use poppers]. Like if my partner is using it, then I'll use it or he'll ask me if I want to use it...A lot of my friends, they mostly use it when they bottom (Latino, 24 years old)." "I would say that's not true [that poppers are used only for the receptive partner], because you still get the rush. But it's usually mostly for bottoms, because it's, like, I guess, more painful to be a bottom, but I mean, it's as pleasurable for the top too (Latino, 22 years old)." "I typically bottom, but I've in recent times topped more and, I mean, I still use them in those situations...but it makes it difficult if you are topping to use them. They are kind of an erection killer (Non-Hispanic white, 27 years old)."*

Risk for assault (both sexual and physical) and theft were identified as safety concerns related to popper use. Two participants had experiences during which popper use was not consensual. *"You can do too much and, like, pass out and that can be unsafe for anyone because*

you don't know where you're at or who you're with...and they could fully take advantage of you either sexually or just rob you (Latino, 24 years old)." "It affects my awareness, you know? 'Cause you get that head rush, you know, you're kind of, like, dizzy, spinny and there are some guys out there that kind of took advantage of me and in some situations, you know?...I became less aware and conscious of what was really going on around me, which is dangerous (Non-Hispanic white, 29 years old)."

Few participants considered a direct risk between popper use and HIV, but participants did speak to popper use enabling sexual risk taking. Few participants felt that popper use impacted condom use, because few participants reported using condoms regardless of substance use. *"As for taking sexual risks, I have taken sexual risks because of poppers (Latino, 26 years old)." "I've had a couple friends that have been raped or, like you know, influenced, probably persuaded into having sex and, you know, poppers are always part of it. So it's, you know, I could see maybe a link [to HIV] somewhere (Latino, 24 years old)?" "I go back to awareness, you know? What's going on lowers inhibitions...I'm in like some head high...I am literally mentally distracted...I know for a fact, that there's a correlation between [poppers] and...less protected sex and getting HIV. Like the correlation is so strong, it's crazy (Non-Hispanic white, 29 years old)." "I really don't think that they [poppers] have had an effect on me not using condoms (Non-Hispanic white, 22 years old)." "The euphoria, the disorientation, you know, it affected my judgment a hundred percent. So I can easily see myself, you know, doing poppers and not being as cautious to use a condom for sure (Non-Hispanic white, 29 years old)."*

Participants articulated protective factors they associated with popper use (e.g., reducing other substance use, supporting medication adherence and reducing bleeding during sex). *"It [poppers] actually helps, because I feel like I don't need to smoke [meth] to, you know, not hurt*

[during sex] (Latino, 29 years old).” Several participants strengthened their commitment to medication adherence during periods of substance use as a way to reduce risk of HIV transmission to their partners. *“Knowing that I was going to use poppers again kind of made me want to...make sure that I took my medication, you know? Just in case that accident happened again where I forgot to put on a condom or the person did or whatever...that I was as close to not being able to infect the person as possible, you know? So the poppers kind of got me into taking my medication more frequently and to make sure I was taking it (Latino, 24 years old).”*

Provider relationships. Participants in this study reported positive and supportive relationships with their HIV providers and welcomed discussions about substance use. *“[When my doctor asks about substance use] I feel like they care and I see that they care and I’m happy that they do care. I do not mind, you know, I like to hear it ‘cause then it’s like, shows that they still care (Latino, 22 years old).”* Many felt that HIV providers were more knowledgeable and nonjudgmental about substance use than general practitioners. Having a provider who was a member of the gay community was also cited as a factor increasing trust and comfort level. Interestingly, although nearly all participants discussed substance use in general with their provider, and felt comfortable doing so, none had discussed popper use. Participants reported their providers had never asked about poppers. *“We haven’t really talked about poppers. I don’t think she’s asked me. We’ve talked about meth. She’s given me resources; she set up an appointment with, like, their drug counseling. I’m pretty comfortable with her. She’s, you know, pretty open-minded. I mean, she’s an HIV specialist (Non-Hispanic white, 27 years old).”* For some, providers not asking about poppers reinforced the perception that poppers were not dangerous or addictive and others attributed lack of assessment of popper use to prioritizing other substance use (e.g., methamphetamine) or focusing on HIV outcomes. *“Since they don’t*

make a big deal about it at the doctor--all they care about is my T cell count and all that, you know? They don't really care about what drug I'm using (Latino, 22 years old)."

Community

Community factors influencing popper use included: local availability of poppers, neighborhood, peer group, perceived norms around condom and substance use, gay culture, use of applications like Grindr and Adam4Adam, and community awareness and risk perception.

Local availability. Poppers were widely available in the community. *"It's something that you can get, like, practically around the city anywhere, you know (Latino, 24 years old)?"* The most common means of acquiring poppers was through sex partners and purchasing at adult bookstores. *"I mean, I wouldn't buy 'em, they would just be there--like, my sex partner would have them. I only used poppers when it was just around, if they offered it (Latino, 22 years old)."* Participants also purchased poppers at liquor stores and online (e.g., eBay, Amazon, Craigslist). Most participants resided in Central San Diego, inclusive of Hillcrest which is known for being a lesbian, gay, bisexual, transgender (LGBT) neighborhood. Several participants mentioned Hillcrest specifically in reference to poppers. One participant shared that in his experience, popper use was more common in San Diego than other places he had lived. *"A lot more common than [name of state] for sure...I had never tried it out there at all and then when I got out here [San Diego], it's everybody is doing it, everybody has it (Latino, 29 years old)."* Peer group was also mentioned as a factor influencing popper initiation. *"I was hanging out with the wrong crowd (Latino, 22 years old)."*

Perception of poppers and gay culture. Participants shared a perception that popper and other substance use was common in the local gay community, contributed to HIV risk and that poppers were associated with gay culture and subcultures (e.g., the leather community). *"It*

was almost like gay culture to have poppers (Latino, 24 years old).” “It’s [use of poppers] built into the gay party scene I guess, the culture...People that use poppers are more likely to have HIV, you know? It’s ‘cause, like, those type of crowd and scene that they’re all into (Latino, 22 years old).” Meanwhile, participants shared a sense that awareness about the risks of popper use in the community was low. *“The lack of education, the lack of social awareness. I think people, in my perception, I think that people rationalize it, like ‘Oh I mean, it’s only poppers. It’s just, like,--you know--a sex accessory (Non-Hispanic white, 29 years old).” “A lot of my friends--maybe like 90% of my friend group--is straight, so like, when they heard about it [poppers], they didn’t know what I was talking about. So it’s really limited to, in my world at least, the gay community...I’m not educated enough on [poppers], nor have I done enough research. I think mostly because I just relied on the information that I’ve received from the community (Latino, 26 years old).”*

Participants shared about a normalization of condomless sex and drug use associated with “hook-up culture” and use of social networking applications (most commonly Grindr and Adam4Adam) to meet sexual partners with whom they used poppers. Mention of drug use on these applications was ubiquitous and in some cases the applications even allowed for users to filter results to identify partners who used drugs. Sometimes poppers would be discussed prior to meeting in person. Meeting sexual partners on social networking applications, especially around the time of coming out as gay, was identified as an important part of the context for popper initiation. *“[On social networking applications] a few times I would be like, ‘What are you into?’ You know? And people would say, like ‘Oh poppers, are you okay with poppers?’ It’s very seldom [that we would discuss it] ‘cause it’s such a common thing. So you know, it’s almost, like, so socially normal for, like, everything--or it seems like, a lot like for the gays to be okay*

with that (Latino, 24 years old)." "It's pretty common [in the gay community], yeah. I will see on profiles, like 'Poppers Plus' or something like that. It's like--it's like a thing, like, to talk about if you're going to have sex (Latino, 26 years old)."

Systems

The primary system level influences on popper use were the legal status of poppers and drug treatment and HIV health care systems.

Legal status of poppers. The fact that poppers are legal to purchase was frequently cited as influencing perception of low risk, yet participants were confused about the legal status of poppers. Most were aware that poppers were legal to purchase, but less clear on whether they were legal to possess or use. Poppers were typically displayed near the entrance of the store, in a refrigerated case that was accessed by employees. Participants were aware that there was a specific way to purchase them and that they would be denied if they asked for "poppers", but were not clear on the rationale. Instead, participants asked for specific brand names (e.g., "Rush" or "Jungle Juice"), cleaners (e.g., video head cleaner) or "nail polish remover." Participants shared that no identification was requested to enter stores or purchase poppers and that websites where poppers are purchased did not ask for age verification.

"I don't think they're supposed to be used the way that they are used. I don't know if it's legal (Non-Hispanic white, 23 years old)." "You want to make sure you ask for the right thing, because if you ask for poppers--they say they, like, don't have poppers...you have to ask for something like video head cleaner or something like that. I would just ask for the brand sometimes (Latino, 30 years old)." "So from my understanding, when you go into sex shops, if you say, like, 'poppers', they can't legally sell them to you, I think. You know, which is horrible, because no one is using video head cleaner that's shopping at a sex shop (Non-Hispanic white,

29 years old).” “Well because they’re being sold for a purpose other than what you’re using them for and the terminologies or the verbiage that you use would indicate that you know you’re going to use them to get high off them. So in order to, you know, superficially look like you’re buying them for the intended purpose of them, you have to use the language that they use on the bottle (Latino, 27 years old).”

Systems of care. All participants were engaged in HIV medical care (had attended a medical visit and completed HIV monitoring labs within the past six months) and 87% had at least one substance use treatment episode. Despite heavy popper use, few identified poppers as one of the substances for which they sought treatment. Participants had received substance use assessments (e.g. questionnaires and urine tests) in the context of their medical care, but they did not include poppers and participants pointed out that poppers were not detected on urine toxicologies.

With few exceptions, participants said that popper use was not discussed in their substance use treatment programs and that there was hesitancy to define sobriety as inclusive of abstinence from poppers. Although some participants did not include abstaining from poppers as part of sobriety, others felt that popper use should be better addressed in treatment noting that they led to relapse of other drugs. *“No, I don’t think we ever talk about poppers here [in residential substance use treatment]. I mean, it’s such a gray area because it’s legal. I guess it gets overshadowed. It gets overlooked by a lot of people in recovery are like, ‘Well poppers are okay for me to use,’ you know? And then that becomes like the gateway back again to their active addiction. People relapse, you know? I know I used poppers before and then I relapsed, like, within the next few days (Latino, 24 years old).” “I feel like sometimes counselors don’t want to tiptoe or, you know, create hard lines in the sand of what’s considered relapse because*

they don't want to, you know, scare people off. But, you know, it's how I define sobriety is, anything that affects me, my body from the neck up, my mind--literally any mind altering substance. But I don't think it's talked about. I think education around, you know, the effects that poppers and other inhalants can have, you know, on your body, especially like the toxicity of it on your brain and your lungs, I think that would benefit a lot of LGBT rehabs (Non-Hispanic white, 19 years old)."

Discussion

Following we consider our findings illuminating novel and critical aspects of popper use in relation to their ability to inform clinical care, public health strategies, policies, and future research to reduce harms and promote the health of YMSM with and at-risk for HIV.

HIV Care and Substance Use Treatment

Most participants were not well informed about poppers' potential adverse effects, especially more serious risks, and expressed a desire to be more informed. Adverse effects of poppers range from mild to potentially life-threatening and include contact dermatitis, neurotoxicity, vision problems, methemoglobinemia, and serious hypotension [87, 161]. Ingestion [28] and/or concurrent use with other substances can elevate risk for serious side effects. Most participants had used poppers with Viagra, which is contraindicated [162], and concurrent use represents potential correlates of other risk behaviors like condomless sex, polysubstance use and assault. Viagra also interacts with some antiretroviral medications (protease inhibitors) [87], causing it to be metabolized more slowly. Individuals on protease inhibitors using Viagra and poppers are at potentially increased risk for serious hypotension [87]. Since most participants did not have a prescription for erectile dysfunction medications, medical

providers should include screening and counseling about these medications during substance use assessments.

Popper use was not perceived as impacting HIV care engagement or antiretroviral treatment adherence. While participants did not directly attribute HIV risk to popper use, they described popper use as part of a constellation of other sex and drug risk behaviors--offering multiple potential avenues for intervention and education. Several participants indicated that popper (and other drug) use increased after HIV diagnosis; this has been attributed to coping with HIV-related stigma, denial and false information about the morbidity and mortality of HIV [163]. Substance use assessment and counseling may be an important part of supporting YMSM at the point of HIV testing and diagnosis, as a way to promote their health, link to needed support services and reduce risk of transmission.

Screening for popper use should occur as part of HIV primary care and, ideally, in primary care settings serving sexual minorities. Despite trusting and supportive relationships with HIV care providers, including open dialogue about other substance use, participants had not been asked by their providers about popper use. This represents a critical missed opportunity for risk reduction and health education and reinforced participants' perception of poppers as relatively low-risk substances. Positive relationships with HIV care providers and existing conversations about substance use are an excellent foundation on which to build in assessment and education about popper use and related sexual behaviors. Assessment of legal substances (e.g., cannabis and alcohol) is also important since the legal status of poppers influences use and risk perception and studies have identified a strong association between cannabis and popper use [5]. Participants in this study had all used cannabis--in most cases prior to popper use.

In this sample of YMSM with HIV, most had received substance use services (e.g., outpatient and/or residential care) and shared positive experiences with treatment. This is encouraging and potentially points to service systems that enable YMSM to connect to treatment and effective referral partnerships between HIV care and substance use systems. One participant specifically mentioned that his HIV provider referred to substance use treatment, which was coordinated within the same health care system. Recovery services that were tailored to the needs of young adults, individuals with HIV and sexual minorities and were centrally located (and/or integrated into their HIV care) in areas frequented by YMSM promoted engagement in substance use services. Participants identified a need for substance use treatment to address poppers specifically and in the context of polysubstance use, as well as for interventions that considered the role sex and popper use played in relapse on other substances (e.g., methamphetamine).

Participants expressed considerable ambivalence about popper use--their risk, context, effects, and connection to HIV. This ambivalence presents a ripe opportunity for interventions aimed at reducing potential harms. Evidence informed interventions for substance abuse, like motivational enhancement approaches and Screening Brief Intervention and Referral to Treatment (SBIRT), are brief interventions that have been successfully implemented in various settings (e.g., primary care, emergent care, substance use treatment) and by various disciplines (e.g., medical providers, social workers, case managers, peers, and alcohol and drug counselors) [164]. While no evidence informed treatments currently exist specifically for popper or inhalant abuse, basic screening, brief intervention (e.g., health education) enhanced by motivational approaches and, when needed, referral to substance use programs could be of great benefit.

SBIRT is beneficial as both an intervention and as prevention, since it provides an opportunity for a dialogue between provider and patient and provision of basic educational information.

Public Health

Popper use among YMSM with HIV impacts public health due to their potential to increase HIV transmission. There is a need for enhanced population level screening and dissemination of information related to potential risks, especially given study participants' perspective that popper use is part of gay culture. Unfortunately, poppers are often absent from validated screening tools or included generally under the category of inhalants. Other inhalants (e.g., spray paint, whippets, glue) have very different contextual risks. In order to effectively address popper use, service systems should also incorporate assessment of gender identity and sexual orientation as part of routine standard care.

Participants perceived that overall community knowledge about potential risks of poppers was lacking. Studies on popper use from 1978 [165] and 1997 [153] similarly found that participants felt ill-informed about side effects, demonstrating that community health education (e.g., public service announcements and campaigns) is long overdue. Specific public health efforts are needed to clarify the specific harms associated with use of "spray poppers", which are in fact a distinct group of aerosol solvent or propellant inhalants and are more dangerous than nitrite inhalant poppers--both in formulation and mode of administration (huffing) [31]. Participants in this study shared that use was common in their communities and many inaccurately considered these aerosol inhalants in the category of poppers.

The importance of neighborhood and social networks as influences on substance use in the urban gay community has been supported by previous research [166, 167]. Public health opportunities for dissemination of information about poppers exist at the intrapersonal level (e.g.,

websites), interpersonal level (e.g., through healthcare providers, peer educators and sexual networks) and the community level (e.g., public health campaigns focusing on neighborhoods where popper users live and socialize).

Policy

The vague legal status of poppers (i.e., being legal to purchase but not for their intended use) potentially contributes to low perceived risk, ubiquity of use in some communities and inhibition of the provision of information about risks. This perspective, however, runs in contrast to participant lived experiences, which expressed addictive behavior and negative consequences of popper use, as well as the desire to be better informed about risks. The legal status of alcohol, cannabis and tobacco products, for example, have enabled label warnings, dissemination of health information about risks and public health campaigns aimed at reducing harms related to use.

There is also a clear need for policies and funding that support integrated and/or co-located substance use and HIV services. YMSM experience multiple barriers to accessing needed services, such as navigating complex applications for health insurance or Medicaid and having to receive care in multiple systems and locations to address their comprehensive health and wellness needs. Funding systems are often siloed and/or create barriers with restrictive eligibility requirements (e.g., the need to have a detectable HIV viral load in order to receive medical case management that can support youth with navigating systems and staying retained in care). YMSM in this study experienced high rates of unemployment, poverty and unstable housing, which is commensurate with the challenges faced by other urban YMSM [168]; it's essential that strategies to promote substance use treatment and HIV prevention and care include support with employment and housing.

Research

This study had a high representation of Latino participants, perhaps a result of San Diego's location near the U.S.-Mexico border. This unplanned representation of Latino participants is unique in the popper literature, where the voices of Latinos who are highly impacted by HIV and substance use are underrepresented in research. Among YMSM (18-30 years old) diagnosed in San Diego County between 2016-2020, 52.5% identified as Hispanic/Latino (S. Tweeten, County of San Diego, personal communication, May 17, 2021) and further research describing the perspectives of Latino YMSM is warranted, especially among YMSM who may be binational.

The majority of participants in this study were introduced to poppers by a sexual partner and used poppers for the first time during a casual sexual encounter; these findings differ from other recent research indicating that poppers were commonly used among YMSM prior to sexual debut [51]. Further research is needed to learn about the context in which poppers are initiated and the temporal relationships between popper and other substance use, as a potential opportunity to develop interventions that support linkage to pre-exposure prophylactic treatment (PrEP) or other health education that could reduce risk for HIV transmission. Future research should focus on developing validated screening tools for poppers and seeking a better understanding of the perspectives of providers serving YMSM about popper use. This study presented the perspectives of YMSM with HIV, however perspectives of YMSM without and at-risk for HIV should also be assessed. Finally, any effective research on poppers should account for their use in the context of polysubstance use.

Limitations

While this study offers important information about context and potential influences on popper use, it was designed to explore the lived experiences of English-speaking YMSM with HIV who use poppers in San Diego and thus may not be generalizable to other populations. This sample reflected a group who was engaged in HIV care and experienced with substance use treatment. Individuals not receiving HIV care and substance use treatment may be especially vulnerable and possess unique needs. It is also important to acknowledge that 'saturation' in qualitative research is a matter of degree, not a fixed point. Substance use often develops as a strategy to cope with stress and adversity; however, this study did not thoroughly assess mental health or traumatic experiences that may precede use. Information from this study was self-reported and explored stigmatized topics, potentially leading to response bias. However we note two important aspects that would likely attenuate this potential bias: 1) the interviewer was a Licensed Clinical Social Worker with extensive experience and training working with YMSM with HIV and substance use; and 2) detailed and thoughtful participant descriptions of popper use, context of use and articulation of life experiences and sincere uncertainties surrounding use would indicate that respondents felt comfortable providing honest answers. Additionally, because all but one participant identified as gay, the extent that findings are applicable to men who identify as bisexual or have a different minority sexual orientation is not known.

Conclusions

In this sample of YMSM with HIV, poppers were frequently used during sexual encounters, often concurrently with other substances (especially methamphetamine and unprescribed erectile dysfunction medications). Participants were introduced to poppers by casual sex partners, frequently met on 'apps' like Grindr, and motivations for use included enhanced pleasure and intimacy, facilitation of anal sex and reduced pain during sex. Perceived

risk of popper use was low; contributing factors included their legal status, short duration, contextual use (e.g., as a tool or accessory for sex), lack of health care provider assessment, and relative severity in the context of other drug use (primarily methamphetamines). Participants were not educated about the potential risks of using poppers and desired more information. Participants were engaged in both HIV care and substance use treatment and had positive, trusting relationships with their providers. Despite these supportive relationships, popper use was not addressed in either the HIV care or substance use setting. Protective factors identified included the belief that poppers could reduce tearing and bleeding during sex, support reduced use of other substances (like methamphetamine), and reinforce commitment to antiretroviral medication adherence and testing for sexually transmitted infections. Participants did not articulate a direct connection between popper use and HIV risk, but were able to identify associated risks such as impaired decision-making, impacts on condom use and discussions about HIV status with sexual partners, and use of poppers associated with other risk factors such as polysubstance use and multiple partners. YMSM with HIV in this study prioritized their health through engagement in HIV care and antiretroviral medication adherence demonstrated by viral suppression. HIV care providers and substance use clinicians are trusted by YMSM and can promote their health by assessing for popper use and providing health education about related risks. Public health interventions can disseminate information at a community level through focused campaigns, which could influence social norms. Clarification of poppers' legal status could support the availability of information about risks at point of purchase and shape YMSM's perceptions about the risks of popper use. Future research opportunities exist to support the development of effective HIV prevention strategies among YMSM who use poppers.

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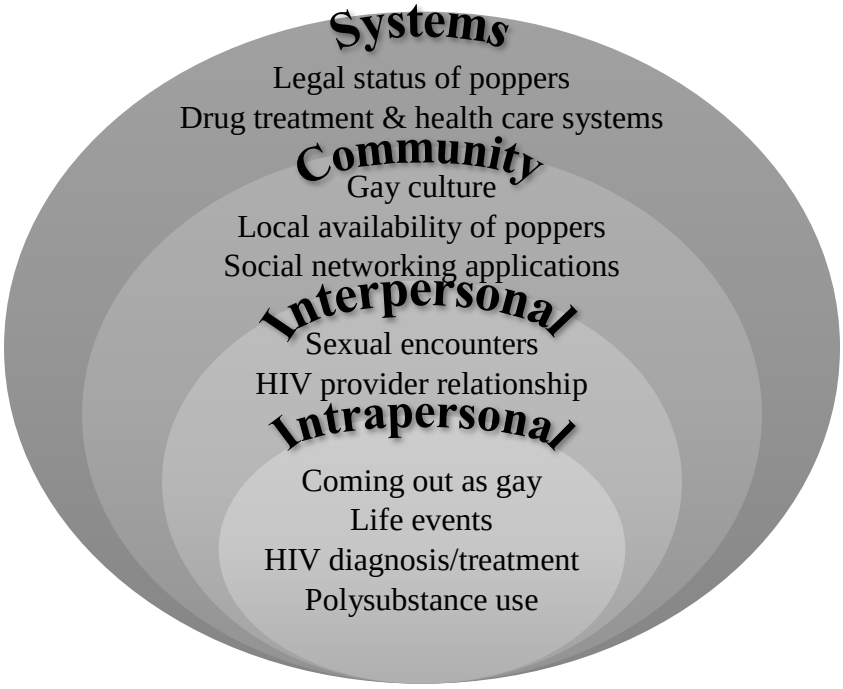

Figure 4. Selected examples illustrating influences on popper use among young men who have sex with men (YMSM) with HIV contextualized in the Social Ecological Model

Table 3. Sample interview guide questions organized by the Social Ecological Model to describe the context of popper use among young men who have sex with men (YMSM) with HIV

SEM Level	Interview Topics	Sample Questions
Intrapersonal	Popper initiation	Can you tell me about the first time you tried poppers?
	Polysubstance use	I'm wondering if you ever use poppers with other substances.
	Effects	Oftentimes people report both good and sometimes bad experiences while using drugs. What are the positive things that you experience using poppers? How about any negative experiences or side effects?
	HIV health outcomes	Sometimes people report that using substances impacts their health (for example, taking medications on time) or taking sexual risks when they're high. How has this been for you with popper use?
Interpersonal	Popper use during sexual encounters	In what situations do you typically use poppers? Can you tell me about your use of popper when you're having sex?
	Medical provider relationship	What conversations has your medical provider had with you about popper use?
Community	Availability of poppers	Can you tell me about how you usually get poppers?
	Social networks	Who else do you know, like friends, partners or acquaintances, that uses poppers?
Systems	Cost	About how much do you usually pay for poppers?
	Legal status of poppers	Are poppers legal to purchase and use?

Table 4. Characteristics of young men who have sex with men (YMSM) with HIV participating in a clinic-based qualitative study on popper use

Variable	N=15
Years of age, mean±SD (range)	26±3 (22-31)
Hispanic/Latino descent, n (%)	
Yes	11* (73.3)
No	4 (26.7)
Which group best describes you?, n (%)	
White	14 (93.3)
Other†	1 (6.7)
Sexual Orientation	
Gay	14 (93.3)
Pansexual	1 (6.7)
Education (highest completed), n (%)	
Did not complete high school	5 (33.3)
High school completion	3 (20)
Some college	5 (33.3)
Bachelors Degree	2 (13.3)
Employment Status	
Employed full-time	5 (33.3)
Employed part-time	2 (13.3)
Unemployed	5 (33.3)
Student	3 (20)
Housing	
Stable	12 (80)
Unstable	2 (13.3)
Homeless	1 (6.7)
Income	
Below Federal Poverty Level	8 (53.3)
Above Federal Poverty Level	7 (46.7)
HIV Outcomes	
Years since HIV diagnosis, mean± (range)	5±3 (0-10)
Medical visit in the past 6 months	15 (100)
On antiretroviral therapy	15 (100)
Virally suppressed	15 (100)

SD= Standard Deviation
* 10 participants identified as Mexican and 1 as Central or Southern American
† Middle Eastern

Table 5. Lifetime substance use (including concurrent use with poppers) among young men who have sex with men (YMSM) with HIV participating in a clinic-based qualitative study on popper use

	Lifetime Substance Use n (%)	**Used with Poppers n (%)**
Alcohol	15 (100)	8 (53)
Cannabis	15 (100)	8 (53)
Cocaine	9 (60)	3 (20)
Methamphetamine	13 (87)	13 (87)
Heroin	6 (40)	1 (7)
Fentanyl	4 (27)	1 (7)
MDMA, Ecstasy	12 (80)	6 (40)
LSD	8 (53)	1 (7)
Hallucinogens	10 (67)	2 (13)
Other Inhalants	10 (67)	3 (20)
Stimulant Pills	8 (53)	2 (13)
Pain Pills	7 (47)	1 (7)
Sedative Pills	10 (67)	3 (20)
Erectile Dysfunction Medications	12 (80)	11 (73)
Club Drugs (e.g. ketamine, GHB)	12 (80)	11 (73)

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