FY 2024 Houston EMA/HSDA Ryan White Part A Service Definition **Substance Abuse Services - Outpatient** (Last Review/Approval Date: 6/3/16)	
HRSA Service Category Title: **RWGA Only**	Substance Abuse Services Outpatient
Local Service Category Title:	Substance Use Treatment/Counseling
Budget Type: **RWGA Only**	Fee-for-Service
Budget Requirements or Restrictions: **RWGA Only**	Minimum group session length is 2 hours
HRSA Service Category Definition (**do <u>not</u> change or alter**): **RWGA Only**	***Substance abuse services outpatient*** is the provision of medical or other treatment and/or counseling to address substance abuse problems (i.e., alcohol and/or legal and illegal drugs) in an outpatient setting, rendered by a physician or under the supervision of a physician, or by other qualified personnel.
Local Service Category Definition:	Treatment and/or counseling individuals with HIV with substance abuse disorders delivered in accordance with State licensing guidelines.
Target Population (age, gender, geographic, race, ethnicity, etc.):	Persons living with HIV and substance abuse disorders, residing in the Houston Eligible Metropolitan Area (EMA/HSDA).
Services to be Provided:	Services for all eligible HIV patients with substance abuse disorders. Services provided must be integrated with HIV-related issues that trigger relapse. All services must be provided in accordance with the Texas Department of Health Services/Substance Abuse Services (TDSHS/SAS) Chemical Dependency Treatment Facility Licensure Standards. Service provision must comply with the applicable treatment standards.
Service Unit Definition(s): **RWGA Only**	**Individual Counseling:** One unit of service = one individual counseling session of at least 45 minutes in length with one (1) eligible client. **A single session lasting longer than 45 minutes qualifies as only a single unit** – no fractional units are allowed. Two (2) units are allowed for initial assessment/orientation session. **Group Counseling:** One unit of service = 60 minutes of group treatment for one eligible client. A single session must last a minimum of 2 hours. Support Groups are defined as professionally led groups that are comprised of HIV-positive individuals, family members, or significant others for the purpose of providing Substance Abuse therapy.
Financial Eligibility:	Refer to the RWPC's approved *Current FY Financial Eligibility for Houston EMA/HSDA Services*.
Client Eligibility:	Individuals living with HIV with substance abuse co-morbidities/disorders.
Agency Requirements:	Agency must be appropriately licensed by the State. All services must be provided in accordance with applicable Texas Department of State Health Services/Substance Abuse Services (TDSHS/SAS) Chemical

	Dependency Treatment Facility Licensure Standards. Client must not be eligible for services from other programs or providers (i.e. MHMRA of Harris County) or any other reimbursement source (i.e. Medicaid, Medicare, Private Insurance) unless the client is in crisis and cannot be provided immediate services from the other programs/providers. In this case, clients may be provided services, as long as the client applies for the other programs/providers, until the other programs/providers can take over services. All services must be provided in accordance with the TDSHS/SAS Chemical Dependency Treatment Facility Licensure Standards. Specifically, regarding service provision, services must comply with the most current version of the applicable Rules for Licensed Chemical Dependency Treatment. Services provided must be integrated with HIV-related issues that trigger relapse. Provider must provide a written plan annually no later than March 31st documenting coordination with local TDSHS/SAS HIV Early Intervention funded programs if such programs are currently funded in the Houston EMA.
Staff Requirements:	Must meet all applicable State licensing requirements and Houston EMA/HSDA Part A/B Standards of Care.
Special Requirements: **RWGA Only**	Not Applicable.

FY 2025 RWPC "How to Best Meet the Need" Decision Process

Step in Process: **Council**		Date: **06/13/2024**
Recommendations:	Approved: Y:_____ No: _____ Approved With Changes:_____	If approved with changes list changes below:
1.		
2.		
3.		

Step in Process: **Steering Committee**		Date: **06/06/2024**
Recommendations:	Approved: Y:_____ No: _____ Approved With Changes:_____	If approved with changes list changes below:
1.		
2.		
3.		

Step in Process: **Quality Improvement Committee**		Date: **05/14/2024**
Recommendations:	Approved: Y:_____ No: _____ Approved With Changes:_____	If approved with changes list changes below:
2.		
2.		
3.		

Step in Process: **HTBMTN Workgroup #2**	Date: **04/16/2024**
Recommendations:	Financial Eligibility:
1.	
2.	
3.	

Barbie Robinson, MPP, JD, CHC
Executive Director
2223 West Loop South | Houston, Texas 77027
Tel: (832) 927-7500 | Fax: (832) 927-0237

Harris County Public Health
Building a Healthy Community

Michael Ha, MBA
Director, Disease Control & Clinical Prevention Division
2223 West Loop South | Houston, Texas 77027
Tel: (713) 439-6000 | Fax: (713) 439-6199

FY 2020 PERFORMANCE MEASURES HIGHLIGHTS

RYAN WHITE GRANT ADMINISTRATION

HARRIS COUNTY PUBLIC HEALTH (HCPH)

TABLE OF CONTENTS

HCPH is the local public health agency for the Harris County, Texas jurisdiction. It provides a wide variety of public health activities and services aimed at improving the health and well-being of the Harris County community.

Highlights from FY 2020 Performance Measures

Measures in this report are based on the *2021-2022 Houston Ryan White Quality Management Plan*, *Appendix B. HIV Performance Measures*. The document can be referenced here: https://publichealth.harriscountytx.gov/Services-Programs/Programs/RyanWhite/Quality

Substance Abuse Treatment

- During FY 2020, 9 (50%) clients utilized primary medical care after accessing Part A substance abuse treatment services.
- Among clients with viral load tests, 89% were virally suppressed during this time period.

Ryan White Part A
HIV Performance Measures
FY 2020 Report

Substance Abuse Treatment
All Providers

HIV Performance Measures	FY 2019	FY 2020	Change
*A minimum of 70% of clients will utilize Parts A/B/C/D primary medical care after accessing Part A-funded substance abuse treatment services	17 (70.8%)	9 (50.0%)	**-20.8%**
80% of clients for whom there is lab data in the CPCDMS will be virally suppressed (<200)	19 (82.6%)	16 (88.9%)	**6.3%**
90% of clients will complete substance abuse treatment program	See data below		

***Overall, the number of clients who received primary care in FY 2020 was 11, with 9 receiving the services through Ryan White and 2 receiving the services through other insurance such as Medicare.**

Number of clients engaged in substance abuse treatment program during FY20: **18**

Number of clients completing substance abuse treatment program during FY20 (March 2020 to February 2021): **7**

Number of clients completing substance abuse treatment during FY20 who entered treatment in FY19: **3**

Number of FY20 substance abuse treatment clients who are receiving primary care through other insurance, such as Medicare: **2**

Number of FY20 clients engaged in substance abuse treatment who completed treatment after FY20: **2**

HRSA
Ryan White & Global HIV/AIDS Programs

HRSA's Ryan White HIV/AIDS Program

The Intersection of HRSA's Ryan White HIV/AIDS Program and the Opioid Epidemic

A recent study has shown that the overall number of deaths in people with HIV in the United States is declining (12.7% decline from 2011 to 2015), yet the number of opioid overdose deaths in people with HIV is on the rise (47% increase from 2011 to 2015).[1] The Health Resources and Services Administration's (HRSA) Ryan White HIV/AIDS Program (RWHAP) recipients have spent decades building systems of care to meet the needs of people with HIV, including providing services to address individuals' medical and social needs. In consideration of the opioid crisis, RWHAP recipients are facing the need to redouble their efforts to provide services to the most vulnerable populations, meeting clients where they are and working to improve individual-level and overall public health.

[1] Bosh KA, Crepaz N, Dong X, et al. Opioid overdose deaths among persons with HIV infection, United States, 2011–2015. [Abstract number 147]. Abstract presented at the 2019 Conference on Retroviruses and Opportunistic Infections; March 7, 2019; Seattle, Washington.

To better understand the current impact of the opioid epidemic on the RWHAP, HRSA HIV/AIDS Bureau (HAB) hosted a Technical Expert Panel (TEP) on the "RWHAP Response to the Opioid Epidemic" in summer 2018. The TEP convened RWHAP recipients and other experts to discuss the intersection of the RWHAP and the opioid epidemic and how services for people with HIV who have substance use disorder could be bolstered to improve health outcomes. This technical assistance document provides examples from the TEP and follow-up phone interviews with TEP participants of activities RWHAP recipients are currently implementing for people with HIV who have substance use disorders; it also highlights how HRSA RWHAP providers can provide services to address clients' behavioral health needs, including those related to substance use.

> *"Like in the early years of HIV/AIDS, when homophobia led to responses of blame and fear, addiction is seen as a social problem rather than a defined disease. At the crux of another public health crisis, we need to take responsibility as a community, as providers, as human beings, for those who are living with addiction … This epidemic is a crisis that knows no geographic or economic boundaries. And the impact of it is felt across racial and ethnic minorities, and especially in disadvantaged populations. Like the HIV/AIDS epidemic, addiction touches just about every family in the U.S."*
>
> RADM Sylvia Trent-Adams, Ph.D., R.N. F.A.A.N., Principal Deputy Assistant Secretary for Health

CONSIDERATIONS FROM RWHAP PROVIDERS ON IMPLEMENTING SERVICES

RWHAP recipients are already engaging in work related to the intersection of HIV and the opioid epidemic, identifying the need in their jurisdiction and ways to implement work in what can be a challenging environment. The following overarching practices are important to consider when working to address the concomitant HIV and opioid epidemics in your jurisdiction.

- **Conduct training and provide technical assistance in all settings.** Consider a broad response to the opioid epidemic, with collaboration and program initiation from prevention, care, and treatment programs.
- **Explore opportunities to diversify funding.** Identify if funding is available from multiple sources (HIV prevention, RWHAP, Substance Abuse and Mental Health Services Administration [SAMHSA], etc.) to ensure that comprehensive services can be offered to clients. Within the evolving healthcare landscape, RWHAP funds can make it possible for "out-of-the-box thinking."

> *"When I asked them to come to the table, I asked as a partner. 'Let's do this together' instead of 'I'm doing this.' We need to collaborate and pull from our collective strengths."*
>
> Shannon Stephenson, Chief Executive Officer, Cempa Community Care

- **Use data to understand the needs of your client population.** Assess the data trends of clients accessing services at your site. Are there increases in the number of **new** clients who report injection drug use as a risk factor? Have the demographics of these clients changed or remained the same? What are the clinical outcomes of people with HIV who also have substance use needs? Understanding these questions can support program-planning activities.

- **Engage all providers.** Coordinate with local organizations to ensure that where a person initiates service does not define or limit the types of services they receive. Co-locate services when possible; for example, work to increase the co-location of medication-assisted treatment (MAT) and HIV treatment. Socioeconomic circumstances are at the core of linkage. Poverty, risk of HIV and other diseases, lack of jobs, and homelessness can be pervasive, ongoing, and unresolvable. Integrating services helps to treat the whole person.

- **Ensure warm hand-offs.** When possible, have a direct (i.e., in person) "hand-off" of a client from one service provider to another, helping to ensure the client successfully engages with the next provider.

> *"We need to better coordinate with local organizations to ensure that wherever patients land, we can ensure they get care."*
>
> Pamposh Kaul, Clinical Director, Ohio Regional AIDS Education and Training Centers

- **Encourage mainstreaming behavioral health services.** Work to incorporate behavioral health assessment and treatment into all RWHAP services. When all RWHAP clients are engaged in behavioral health, the engagement is destigmatized, and mental health and substance use risk factors can be assessed in a more consistent manner.

- **Assess and address emergent issues.** Inventory service systems to identify existing or emerging needs and issues. Consider if providers could establish and support mobile services to intensify efforts.

- **Understand the opioid epidemic and engage the community in which you are working.** Understand the type(s) of opioid epidemic in your jurisdiction (i.e., injection drug use, prescription drug use). There are different approaches to addressing the opioid epidemic, depending on the type of overuse experienced in a jurisdiction. Mobilize the broader community in which you are doing work to unify the effort. Develop a community action plan with a broad range of partners (e.g., military, tribal groups, homeless shelters, faith centers, emergency departments, barber shops/salons, police and other first responders, health department, etc.).

- **Ensure a client-centered approach to services.** Stigma toward substance users remains, even among some RWHAP recipients and subrecipients. RWHAP recipients have an opportunity to serve as leaders in implementing programs that meet substance users "where they are" without judgment, maintaining client rights, and ensuring that access to MAT and other interventions is not contingent on abstinence. The RWHAP has demonstrated high acuity in achieving viral suppression among people with HIV in general; however, reengagement and retention remain at the forefront of challenges when working with complex clients. Focusing on meeting clients where they are and embracing the challenges of individual circumstances could help increase access to and retention in the RWHAP systems of care for people with HIV who have substance use disorder.

> *"Many clients seem to be ready to be engaged—we will always offer resources and allow clients to know when they want to engage."*
>
> Tammy Miller, RWHAP Part C Clinic Manager

IMPLEMENTATION ACTIVITIES

RWHAP recipients have experienced successes in working with people with HIV who have substance use disorder. TEP participants are implementing the following strategies:

Community Engagement

- **Develop a community-level action plan.** The process of developing an action plan includes analysis of what exists within the community, what does not exist in the community, and where people are falling through service gaps. Implementation of the action plan helps to improve workflow.

- **Focus on relationships to gain trust.** Gather broad representation of community leadership and members to create a consortium to tackle the opioid problem in individual communities. This emboldens people to continue and further the work on their own.

- **Collaborate with health centers to establish an HIV, HCV, and substance use disease management portfolio.** Health centers have a wide range of services, eliminating the need for clients to be referred out to additional providers. Invest RWHAP funds in existing resources, like health centers, and work to bolster them. Coordinate with local providers and provide them with training and resources to assist them in furthering the services they are able to provide.
- Address and work to reduce **stigma.**

Development of Comprehensive and Integrated Services

- **Support syringe services programs (SSP).** RWHAP funds can be used to support SSPs, with the exception of needles/syringes and related equipment. The most effective SSP model is multi-tiered: for example, a full SSP that is open five days a week for 40 hours a week, with mobile clinics that go to various locations two hours a week.

> *"I would say that stigma and transportation are the biggest obstacles to any kind of care in rural communities—addiction, HIV, mental health. There is tremendous stigma around any of these topics. What that turns out to mean in the field is the work is slower than you would like, painstaking. You have to spend a lot of time gaining people's trust, and even then, they may not agree, but at least they would listen to you."*
>
> Judith Feinberg, Professor, Behavioral Medicine & Psychiatry, West Virginia University

- Establish **local treatment and prevention** for people who have substance use disorder.
- **Develop and support programs that distribute naloxone** at saturation levels directly to people in communities at high risk.
- Streamline **immediate access to medical care** to ensure that people with HIV do not have to wait for care.
- Investigate the ability of **MAT providers** to prescribe and/or administer HIV medications.

> *"Stigma is crosscutting, regardless of health care policy and financing landscapes."*
>
> Daniel Raymond, Deputy Director, Planning & Policy, Harm Reduction Coalition

- Develop a **case management model for people who have substance use disorder,** combining lessons learned from medical and nonmedical case management implementation. Establish and share coordinated care plans across RWHAP and behavioral health.

Systems Changes

- Explore opportunities to enact **policy changes** to make buprenorphine available in more settings, including SSPs, jails, emergency departments, and homeless shelters.

> *"Medicaid expansion has been critical because it opens up opportunity. [It] opens up people to a range of services beyond what Part A would fund. [It] opens up PrEP [pre-exposure prophylaxis]. It has been critical for people accessing services."*
>
> Coleman Terrell, Director, Philadelphia Part A

- **Educate** all team and support system members (RWHAP case managers, primary care providers, family, etc.) on addiction disease and management in an effort to enact change.
- **Provide training** on pain management, including dealing with both the pain people have and the reasons why people might be misusing substances. Give options for people who might be ready for harm reduction, not elimination.
- **Support frontline staff** who are directly impacted by trauma on a regular basis.

Although RWHAP recipients have implemented work related to the opioid crisis into their service structures, TEP participants noted that those efforts are just beginning to meet the needs. They indicated that much more effort is needed to fully address the HIV and opioid epidemics. HRSA HAB encourages recipients to consider ways to further their efforts to address the opioid epidemic in their existing and future service structures.

HOW HRSA'S RWHAP CAN SUPPORT PEOPLE WITH HIV WHO HAVE SUBSTANCE USE DISORDER

RWHAP recipients are funded to provide a range of services to support the HIV-related needs of eligible individuals. HRSA HAB Policy Clarification Notice (PCN) 16-02 details the allowable uses of RWHAP funds to provide services to both people with HIV and, in some instances, people who are affected by HIV. To be an allowable cost under the HRSA RWHAP, all services must—

- Relate to HIV diagnosis, care, and support,
- Adhere to established HIV clinical practice standards consistent with U.S. Department of Health and Human Services (HHS) Clinical Guidelines for the treatment of HIV and other related or pertinent clinical guidelines, and
- Comply with state and local regulations and be provided by licensed or authorized providers, as applicable.

Although PCN 16-02 specifically outlines the allowable activities under the Substance Abuse Outpatient Care and Substance Abuse Services (residential) service categories, all core medical and support services can be leveraged to assist RWHAP clients who have substance use disorder (refer to HRSA HAB PCN 16-02 for the complete service category definitions).

In March 2016, HHS released guidance on the use of federal funding to support SSPs. The guidance maintains the prohibition of the use of federal funds to purchase sterile needles or syringes for the purpose of injection of any illegal drug; however, it includes funding SSPs as an allowable use of federal funds. In April 2016, HRSA issued guidance specific to the use of HRSA funds (including RWHAP funds) to support certain components of SSPs. RWHAP recipients should coordinate with their project officers when considering implementation of SSP components as part of their RWHAP-funded work.

RESOURCES

The following resources are available for RWHAP recipients to explore how they can further implement behavioral health services for people with HIV who have substance use disorder.

amfAR. 2019. "Opioid Epidemic/Drug Policy." www.amfar.org/opioid-drug-policy.

Centers for Disease Control and Prevention. 2019. "Opioids Portal." www.cdc.gov/opioids.

Dawson, L., and J. Kates. 2018. "HIV and the Opioid Epidemic: 5 Key Points." Kaiser Family Foundation. www.kff.org/hivaids/issue-brief/hiv-and-the-opioid-epidemic-5-key-points.

U.S. Department of Health and Human Services. August 2012. *Training Manual: Integration of Buprenorphine into HIV Primary Care Settings*. Available at www.targethiv.org/sites/default/files/file-upload/resources/HRSA.%20SPNS.%20IHIP%20buprenorphine%20training%20manual.%20508%20compliant.pdf.

U.S. Department of Health and Human Services. 2018. "Substance Use and HIV Risk." www.hiv.gov/hiv-basics/hiv-prevention/reducing-risk-from-alcohol-and-drug-use/substance-use-and-hiv-risk.

U.S. Department of Health and Human Services. 2019. "Help, Resources and Information: National Opioids Crisis." www.hhs.gov/opioids.

JAMA Network Open

Original Investigation | Substance Use and Addiction

Effect of Implementation Facilitation to Promote Adoption of Medications for Addiction Treatment in US HIV Clinics

A Randomized Clinical Trial

E. Jennifer Edelman, MD, MHS; Geliang Gan, MPH; James Dziura, PhD; Denise Esserman, PhD; Elizabeth Porter, MBA; William C. Becker, MD; Philip A. Chan, MD; Deborah H. Cornman, PhD; Christian D. Helfrich, MPH, PhD; Jesse Reynolds, MS; Jessica E. Yager, MD; Kenneth L. Morford, MD; Srinivas B. Muvvala, MD; David A. Fiellin, MD

Abstract

IMPORTANCE Medications for addiction treatment (MAT) are inconsistently offered in HIV clinics.

OBJECTIVE To evaluate the impact of implementation facilitation (hereafter referred to as "facilitation"), a multicomponent implementation strategy, on increasing provision of MAT for opioid use disorder (MOUD), alcohol use disorder (MAUD), and tobacco use disorder (MTUD).

DESIGN, SETTING, AND PARTICIPANTS Conducted from July 26, 2016, through July 25, 2020, the Working with HIV Clinics to adopt Addiction Treatment using Implementation Facilitation (WHAT-IF?) study used an unblinded, stepped wedge design to sequentially assign each of 4 HIV clinics in the northeastern US to cross over from control (ie, baseline practices) to facilitation (ie, intervention) and then evaluation and maintenance periods every 6 months. Participants were adult patients with opioid, alcohol, or tobacco use disorder. Data analysis was performed from August 2020 to September 2022.

INTERVENTIONS Multicomponent facilitation.

MAIN OUTCOMES AND MEASURES Outcomes, assessed using electronic health record data, were provision of MAT among patients with opioid, alcohol, or tobacco use disorder during the evaluation (primary outcome) and maintenance periods compared with the control period.

RESULTS Among 3647 patients, the mean (SD) age was 49 (12) years, 1814 (50%) were Black, 781 (22%) were Hispanic, and 1407 (39%) were female; 121 (3%) had opioid use disorder, 126 (3%) had alcohol use disorder, and 420 (12%) had tobacco use disorder. Compared with the control period, there was no increase in provision of MOUD with facilitation during the evaluation period (243 patients [27%; 95% CI, 22%-32%] vs 135 patients [28%; 95% CI, 22%-35%]; $P = .59$) or maintenance period (198 patients [29%; 95% CI, 22%-36%]; $P = .48$). The change in provision of MAUD from the control period to the evaluation period was not statistically significant (251 patients [8%; 95% CI, 5%-12%] vs 112 patients [13%; 95% CI, 8%-21%]; $P = .11$); however, the difference increased and became significant during the maintenance period (180 patients [17%; 95% CI, 12%-24%]; $P = .009$). There were significant increases in provision of MTUD with facilitation during both the evaluation (810 patients [33%; 95% CI, 30%-36%] vs 471 patients [40%; 95% CI, 36%-45%]; $P = .005$) and maintenance (643 patients [38%; 95% CI, 34%-41%]; $P = .047$) periods.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, facilitation led to increased provision of MTUD, delayed improvements in MAUD, and no improvements in MOUD in HIV clinics.

(continued)

Key Points

Question Does implementation facilitation promote increased adoption of medications for opioid, alcohol, and tobacco use disorder in HIV clinics?

Findings In this randomized clinical trial of 3647 patients with opioid, alcohol, or tobacco use disorder, during short-term follow-up compared with the control period, implementation facilitation was not associated with a statistically significant increase in observed provision of medication for opioid use disorder (27% vs 28%) or alcohol use disorder (8% vs 13%). There was a significant increase in provision of medication for tobacco use disorder (33% vs 40%).

Meaning These findings suggest that implementation facilitation can increase provision of medications for alcohol and tobacco use disorder in HIV clinics, although additional efforts may be needed to improve its impact, especially for medications for opioid use disorder.

+ Visual Abstract

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

Enhanced strategies, potentially including clinic and patient incentives, especially for MOUD, may be needed to further increase provision of MAT in HIV clinics.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02907944

JAMA Network Open. 2022;5(10):e2236904. doi:10.1001/jamanetworkopen.2022.36904

Introduction

Substance use disorders (SUDs), including opioid use disorder (OUD), alcohol use disorder (AUD), and tobacco use disorder (TUD), are major factors associated with morbidity and mortality among individuals with HIV. Furthermore, untreated SUDs are associated with risk behaviors and ongoing HIV transmission to threaten public health. Medications for addiction treatment (MAT) for OUD (MOUD), AUD (MAUD), and TUD (MTUD) are safe, effective, and recommended by clinical guidelines for individuals with HIV.[1] It is recommended that MAT is offered with HIV care to maximize reach to patients and improve clinical outcomes.[1]

Despite the urgent need to intervene to prevent harms associated with SUD, individuals with HIV are infrequently prescribed MAT.[2,3] This is due, in part, to lack of training and comfort among HIV clinicians.[4,5] Implementation facilitation (hereafter referred to as "facilitation"), is defined as "a multi-faceted process of enabling and supporting individuals, groups, and organizations in their efforts to adopt and incorporate clinical innovations in routine practices"[6] and is an effective implementation strategy for improving treatment of chronic conditions in primary care settings.[7,8] To our knowledge, only a few prior studies have applied facilitation[9] or any of its components (ie, academic detailing)[10,11] to promote MAT provision, and there are no published studies in HIV clinics specifically.[12]

Thus, we conducted the Working with HIV clinics to adopt Addiction Treatment using Implementation Facilitation (WHAT-IF?) study to examine the impact of facilitation on promoting MAT provision and increasing clinician, staff, and organizational readiness to promote MAT in 4 diverse HIV clinics in the northeastern US. We hypothesized that facilitation would improve MAT provision among patients with OUD, AUD, or TUD.

Methods

Study Design Overview

As described elsewhere,[13,14] the WHAT-IF? study used a hybrid type 3 effectiveness-implementation design[15] with a stepped wedge approach[16] to evaluate the impact of facilitation on promoting provision of MAT and counseling to address OUD, AUD, and TUD in HIV clinics. Study outcomes included provision of MAT (primary) and clinician, staff, and organizational readiness to provide such treatments (secondary). The study was approved by institutional review boards at Yale University and each of the participating universities and health care sites. A waiver of informed consent was obtained because the study involved minimal risk to patients and obtaining consent would have not been practical. The study protocol is shown in Supplement 1. This randomized clinical trial follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for trial studies (eFigure 1 in Supplement 2).[17]

Study Context and Participants

The study was conducted within the Yale CIRA (Center for Interdisciplinary Research on AIDS) New England HIV Implementation Science Network.[18] The coordinating center is located at Yale School of Medicine in New Haven, Connecticut, and the Yale Center for Analytic Science coordinated the data

management and analytic support. Study activities occurred at 4 urban HIV clinics intentionally selected given their variability in terms of affiliations (ie, academic vs community-based hospital clinic), infrastructure (eg, on-site behavioral health programs), and resources (eg, external grant funding).

Patient Participants

We extracted electronic health record (EHR) data on all patients with HIV receiving care in the participating clinics from July 26, 2016, through July 25, 2020. Patients were considered to be receiving care if they had a scheduled visit at the clinic during the time period of interest, regardless of attendance, and they were eligible to enter the cohort (ie, open cohort design) at any point during the study period upon meeting these inclusion criteria. Patients were considered to have OUD, AUD, or TUD according to documentation on the problem list, encounter reason, or international diagnostic codes (*International Classification of Diseases, Ninth Revision* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*). Data on patient race and ethnicity were obtained from the EHRs and were evaluated in this study to characterize the patient population receiving care in the participating sites.

Clinician and Staff Participants

All clinicians, including prescribing (ie, physicians, nurse practitioners, and physician assistants) and nonprescribing (eg, psychologists and social workers) clinicians, as well as staff (eg, nurses and community health workers) who had been employed at the given site for 6 months or longer, were invited to complete a survey at study initiation and then every 6 months for a total of 6 follow-up surveys. Responses from individuals who did not have a role involving provision of clinical services (ie, administrative staff or data coordinator) and/or were missing all responses on outcomes of interest (ie, readiness rulers and Organizational Readiness to Change Assessment [ORCA][19]) on relevant surveys were excluded. The decision to complete the survey was considered consent to study participation.

Randomization and Blinding

Given concerns for potential contamination by a different National Institute on Drug Abuse–funded project at 1 of the sites (which was not ultimately implemented at this site), 1 site was assigned to receive facilitation last. The remaining 3 sites were randomized by the statistician to the date when facilitation would begin at their site. Members of the investigative team and study sites remained blinded to the sequence until approximately 6 weeks before the start of facilitation to allow for planning activities.

Procedures

Informed by prior efforts to promote integration of mental health treatment into primary care,[6] the approach and details of our manualized facilitation have been published previously.[13] Facilitation started with a baseline mixed-methods formative evaluation of barriers and facilitators to promoting addiction treatments in HIV clinics.[14] The external facilitators, including a team of 4 physicians (E.J.E., K.L.M., S.B.M., and D.A.F.) with expertise in addiction medicine, addiction psychiatry, and/or HIV, worked with each of the sites to identify local champions and promote site engagement. Then during 2 follow-up visits to each site over the 6-month facilitation period, the external facilitators (E.J.E., K.L.M., S.B.M., and D.A.F.) conducted academic detailing and facilitated networking opportunities across disciplines within the same institution with the goal of building relationships and training opportunities. The external facilitators also had ongoing communications (via email and telephone) with the sites to facilitate additional facilitation activities. Upon initiation of the facilitation period, sites were invited to join learning collaborative activities, which included a monthly webinar with a mix of didactics and case-based learning and receipt of a monthly newsletter with resources (eg, journal articles, addiction-focused scientific conferences, and training opportunities). Sites were

encouraged to conduct program marketing (eg, pens, pads, posters, and pins with the phrase "WHAT IF?" designed to engage patients and clinicians in a conversation about substance use) and to develop processes for performance monitoring and feedback, and they were provided site-specific data on prevalence of OUD, AUD, and TUD based on the EHR data and rates of treatment at 2 time points. After crossing over from the control period to 6-month facilitation, sites were then considered to be in the 6-month evaluation period, followed by the maintenance period that lasted the duration of the study. Before facilitation onset and then every 6 months thereafter for the duration of the study, EHR data were extracted and confidential web-based Qualtrics surveys were administered.

Outcomes

Implementation outcomes included change in the proportion of patients with one of the 3 targeted SUDs who received MAT during the evaluation (primary) and maintenance periods compared with the control period. We specifically examined receipt of MAT, measured using EHR data, that may be prescribed through HIV clinics (eTable 1 in Supplement 2) and provision of counseling. A patient was considered to have an active prescription in a given 6-month study period if they had medication coverage during the period of interest based on the days supplied and assuming the medication was taken as prescribed; for injectable naltrexone, we assumed coverage lasted for 30 days and was administered on schedule as prescribed. In secondary analyses, we also assessed provision of counseling as documented on the basis of encounters with a clinician, social worker, or psychologist and including psychiatric and substance use assessments, individual and group psychotherapy, individual counseling, case management, crisis intervention, prolonged services, family services, and health and behavior education.

Additional secondary implementation outcomes included clinician, staff, and organizational readiness to promote MAT and counseling for OUD, AUD and TUD. Clinician and staff readiness were measured on a readiness ruler (eg, "How ready are you to prescribe or refer patients for medications [i.e., nicotine replacement therapy, bupropion, and varenicline] for the treatment of tobacco use disorder?"), where response options ranged from 0 (not ready) to 10 (ready) on a continuous scale. This assessment was collected during all survey waves except when inadvertently not collected during 1 period (July 26, 2019, to January 25, 2020).

Organizational readiness was assessed with a modified ORCA[19] with which participants were asked to rate the evidence supporting each evidence-based practice and the context as a setting for delivering addiction treatments. Subscale response options also included a 5-point Likert scale, ranging from 1 (very infrequently) to 5 (very frequently). Subscale response options also included do not know or not applicable, which were recoded as neither agree nor disagree or neither frequently nor infrequently to allow computation of subscale scores.[20]

Statistical Analysis

On the basis of prior work,[7,21-23] we hypothesized we would detect an 11% and 19% absolute increase in provision of MAT during the evaluation period and maintenance period, respectively, compared with the control period. Accounting for the stepped wedge design with a cross-sectional analytic approach with 4 steps of 6 months each, 1 baseline measurement, and an intraclass correlation coefficient of 0.01,[24] we estimated that a sample size of 375 across the 4 clinics would be necessary to detect these differences with at least 90% power and a type I error rate of 5%.

We used descriptive statistics to characterize the baseline characteristics of the clinic populations. For all analyses, we used an intention-to-treat approach based on the time clinics were intended to cross over from control condition to facilitation. For the primary implementation outcomes and other measurements in this study, including readiness to provide MAT, ORCA evidence ratings for MAT, and ORCA context ratings for MAT, we used generalized estimating equation models with study phase, site, and natural time to generate adjusted odds ratios or mean differences and associated 95% CIs measuring the effect of facilitation compared with the control period at each

study period. Compound symmetry working correlation matrix was specified to control for correlation of repeated measures within subjects. In secondary analyses, we assessed provision of MAT with counseling. In sensitivity analyses, we included all clinic patients regardless of SUD diagnosis given concerns that SUD diagnoses may not be uniformly captured and separately reran primary analyses excluding the final study period when the first wave of COVID-19 pandemic started (January 26 to July 25, 2020). We applied a similar approach to describe clinician and staff participants and then evaluated the impact of facilitation on the readiness ruler and ORCA subscale scores. Two-sided $P < .05$ was considered significant. All analyses were performed using SAS statistical software version 9.4 (SAS Institute). Data analysis was performed from August 2020 to September 2022.

Results

Clinic Patient Populations

At study start, a total of 3647 patients were engaged in care across the 4 clinics (range, 366-1548 patients per clinic). Among 3647 patients, the mean (SD) age was 49 (12) years, 1814 (50%) were Black, 781 (22%) were Hispanic, and 1407 (39%) were female; 121 (3%) had opioid use disorder, 126 (3%) had alcohol use disorder, and 420 (12%) had tobacco use disorder (**Table 1**).

Impact of Facilitation on Provision of MAT Alone and With Counseling

Among patients with OUD, compared with the control period (243 patients [27%; 95% CI, 22%-32%]), we did not observe an increase in provision of MOUD with facilitation during the evaluation period (135 patients [28%; 95% CI, 22%-35%]; $P = .59$) or maintenance period (198 patients [29%; 95% CI, 22%-36%]; $P = .48$) (**Table 2** and **Figure 1**). Among patients with AUD, compared with the control period (251 patients [8%; 95% CI, 5%-12%]), there was an increase in provision of MAUD with facilitation during the evaluation period, although the difference was not significant (112 patients [13%; 95% CI, 8%-21%]; $P = .11$); however, the difference from the control period increased and became significant during the maintenance period (180 patients [17%; 95% CI, 12%-24%]; $P = .009$) (Table 2 and Figure 1). Among patients with TUD, compared with the control period (810 patients [33%; 95% CI, 30%-36%]), we observed significant increases in provision of MTUD with facilitation during both the evaluation (471 patients [40%; 95% CI, 36%-45%; $P = .005$) and maintenance (643 patients [38%; 95% CI, 34%-41%]; $P = .047$) periods (Table 2 and Figure 1). The findings were not substantially different in secondary analyses focused on MAT with counseling, with sensitivity analyses including all clinic patients regardless of the presence of a SUD diagnosis or when excluding the period impacted by COVID-19 .

Clinician and Staff Populations

Among 131 invited participants, 85 completed the baseline survey (65% response rate). We excluded 8 administrative staff and 7 with missing data on all readiness rulers and ORCA subscales. Clinician and staff participant characteristics are reported in **Table 3**.

Clinician, Staff, and Organizational Readiness to Provide MAT

Compared with the control period, we did not observe an increase in readiness to provide MOUD, MAUD, or MTUD with facilitation during the evaluation or maintenance periods (**Figure 2** and eTable 2 in Supplement 2). Compared with the control period, we observed an increase in evidence subscale scores for MAUD with facilitation during the maintenance period; we did not observe any other changes during the evaluation or maintenance periods otherwise (eTable 3 and eFigure 2 in Supplement 2). Similarly, we did not observe any changes in the context subscale scores over the study periods (eTable 4 and eFigure 3 in Supplement 2).

Table 1. Baseline Patient Characteristics by Substance Use Disorder

Characteristic	Patients, No. (%)			
	Opioid use disorder (n = 121)	Alcohol use disorder (n = 126)	Tobacco use disorder (n = 420)	Total (N = 3647)
Age, mean (SD), y	52 (9)	50 (11)	51 (11)	49 (12)
Race				
Asian	0	1 (1)	0	19 (1)
Black	39 (32)	61 (48)	219 (52)	1814 (50)
White	46 (38)	42 (33)	121 (29)	1118 (31)
Other[a]	36 (30)	22 (18)	80 (19)	689 (19)
Missing[b]	0	0	0	7
Ethnicity				
Hispanic	39 (32)	34 (27)	87 (21)	781 (22)
Non-Hispanic	82 (68)	92 (73)	333 (79)	2859 (79)
Missing[b]	0	0	0	7
Sex				
Female	41 (34)	31 (25)	161 (38)	1407 (39)
Male	80 (66)	95 (75)	259 (62)	2240 (61)
Public insurance				
Yes	47 (61)	69 (81)	252 (81)	1725 (70)
No	30 (39)	16 (19)	61 (20)	740 (30)
Missing[b]	44	41	107	1182
Self-pay				
Yes	0	0	5 (2)	21 (1)
No	77 (100)	85 (100)	308 (98)	2444 (99)
Missing[b]	44	41	107	1182
Private or commercial insurance				
Yes	35 (46)	29 (34)	89 (28)	985 (40)
No	42 (55)	56 (66)	224 (72)	1480 (60)
Missing[b]	44	41	107	1182
Income in the ZIP code, $				
Median (range)	68 035 (59 805-98 187)	68 035 (45 063-98 187)	62 276 (45 063-110 485)	62 276 (45 063-172 243)
Missing[b]	0	0	0	2
Completed visits, median (range), No.	3 (0-14)	2 (0-15)	2 (0-13)	2 (0-17)
Prescribed antiretroviral therapy				
Yes	115 (95)	119 (94)	404 (96)	3430 (94)
No	6 (5)	7 (6)	16 (4)	217 (6)
Detectable HIV viral load (>200 copies/mL)				
Yes	16 (16)	19 (18)	43 (11)	325 (11)
No	83 (84)	84 (82)	349 (89)	2774 (90)
Missing[b]	22	23	28	548
Hepatitis C virus infection				
Yes	70 (59)	40 (32)	110 (26)	522 (15)
No	49 (41)	86 (68)	307 (74)	3072 (86)
Missing[b]	2	0	3	53
CD4 cell count, cells/μL				
<50	0	0	2 (1)	31 (1)
50-99	3 (4)	2 (2)	7 (2)	42 (2)
100-199	9 (11)	10 (11)	27 (8)	154 (6)
200-349	14 (17)	16 (18)	39 (11)	336 (12)
350-499	19 (22)	21 (23)	54 (15)	480 (18)
>500	40 (47)	42 (46)	225 (64)	1697 (62)
Missing[b]	36	35	66	907

[a] Other refers to American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, or any other race not specified.

[b] Missing data were not included in calculations of percentages.

Discussion

To our knowledge, this randomized clinical trial is the first study to evaluate the impact of facilitation on promoting evidence-based addiction treatment to address OUD, AUD, and TUD in HIV clinics, and it generated several key findings. First, facilitation yielded improvements in clinician and staff self-rated readiness to provide MAUD and a corresponding increase in provision of these medications. Second, facilitation was not sufficient to result in measurable or consistent changes in readiness or actual provision of MOUD. Third, facilitation resulted in improvements in provision of MTUD without measurable change in clinician or staff readiness in the context of high baseline readiness. Fourth, clinician and staff consistently reported high readiness to provide MAT for these life-threatening conditions, but this did not translate into actual provision of these medications. Our findings suggest that facilitation as implemented, with a primary focus on clinician and staff-level factors, was insufficient for promoting high-levels of provision of MOUD, MAUD, and MTUD in HIV clinics.

Prior studies[7,8] have demonstrated benefits of facilitation on promoting chronic disease management in general medical settings, yet these studies have generally not targeted addiction treatment. Instead, previous studies to promote addiction treatment have focused on evaluating academic detailing (a potential component of facilitation or stand-alone intervention) to improve treatment of a specific use disorder and demonstrated greatest benefits in the context of low baseline prescribing and high density of treatment-eligible patients.[10,11] Our study extends this literature by applying facilitation in HIV clinics to simultaneously promote provision of treatment of the 3 SUDs for which effective medication and behavioral interventions are available.

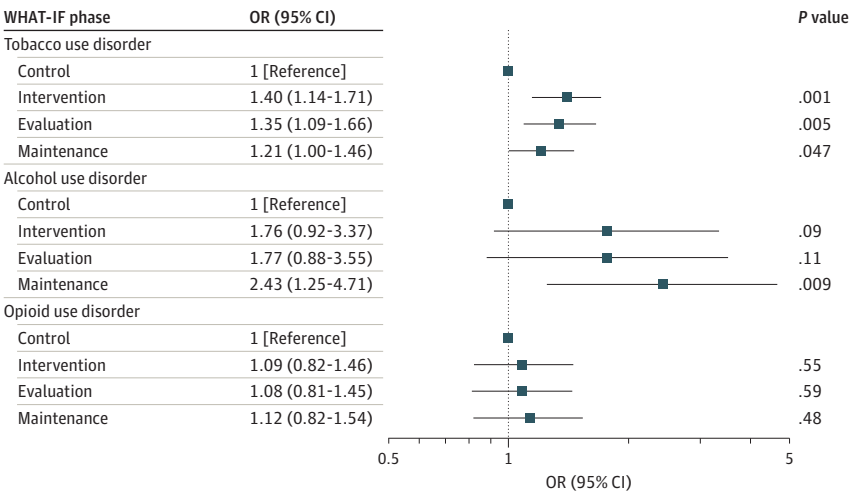
Table 2. Provision of Medications for Addiction Treatment Among Treatment-Eligible Patients Across All Sites by Study Period, Results From Generalized Estimating Equation

	Provision of MOUD[a]		Provision of MAUD		Provision of MTUD	
Study period	Patients, No. (%) [95% CI]	*P* value	Patients, No. (%) [95% CI]	*P* value	Patients, No. (%) [95% CI]	*P* value
Control	243 (27) [22-32]	Reference	251 (8) [5-12]	Reference	810 (33) [30-36]	Reference
Intervention	117 (28) [22-35]	.55	122 (13) [8-21]	.09	444 (41) [37-46]	.001
Evaluation	135 (28) [22-35]	.59	112 (13) [8-21]	.11	471 (40) [36-45]	.005
Maintenance	198 (29) [22-36]	.48	180 (17) [12-24]	.009	643 (38) [34-41]	.047

Abbreviations: MAUD, medications for alcohol use disorder; MOUD, medications for opioid use disorder; MTUD, medications for tobacco use disorder.

[a] MOUD exclusively included buprenorphine products.

Figure 1. Provision of Medications for Addiction Treatment Among Treatment-Eligible Patients Across Sites by Study Period



OR indicates odds ratio; WHAT-IF, Working with HIV Clinics to adopt Addiction Treatment using Implementation Facilitation.

Our findings that facilitation resulted in increased provision of MTUD, delayed improvements in MAUD, and no observed improvements in MOUD correspond with observed patterns in clinician and staff readiness. In the context of high baseline clinician and staff readiness to prescribe MTUD treatment, with some focused clinician education and academic detailing coupled with clinic-level processes stimulated by facilitation (eg, nurse-led protocols), it was possible to change practices to promote MTUD in a short time. On the other hand, the observed delayed increases in MAUD may be explained by the fact that higher levels of education and academic detailing (ie, more interactions) may be required to enhance clinician and staff readiness, particularly in the absence of a local champion. Finally, the fact that we did not observe increases in clinician and staff readiness to provide MOUD or increased provision of MOUD may be explained, at least in part, by the fact that all sites had at least 1 clinician who prescribed buprenorphine at the time the study was initiated, perhaps contributing to a lower perceived need and sufficient MOUD services.

Although it is encouraging that facilitation resulted in some increases in provision of MAT, our findings suggest that additional strategies may be needed. First, facilitation may have been more

Table 3. Baseline Clinician and Staff Participant Characteristics

Characteristic	Participants, No. (%)				
	Site A (n = 24)	Site B (n = 11)	Site C (n = 12)	Site D (n = 23)	Total (N = 70)
Age, mean (SD), y	63 (54)	57 (5)	48 (10)	60 (46)	58 (41)
Sex					
Female	16 (67)	6 (55)	10 (83)	19 (83)	51 (73)
Male	8 (33)	5 (45)	2 (17)	4 (17)	19 (27)
Race					
Asian	2 (9)	2 (18)	1 (8)	1 (4)	6 (9)
Black	7 (30)	2 (18)	0	1 (4)	10 (14)
White	12 (52)	7 (64)	7 (58)	19 (83)	45 (65)
Other[a]	2 (9)	0	4 (33)	2 (9)	8 (12)
Ethnicity					
Hispanic	3 (13)	0	7 (58)	2 (9)	12 (17)
Non-Hispanic	17 (74)	10 (91)	5 (42)	20 (87)	52 (75)
Other[a]	3 (13)	1 (9)	0	1 (4)	5 (7)
Missing[b]	1	0	0	0	1
Clinician (physicians, physician assistant, nurse practitioner)					
Yes	11 (46)	7 (64)	4 (33)	12 (52)	34 (49)
No	13 (54)	4 (36)	8 (67)	11 (48)	36 (51)
Time working at this clinic, mean (SD), y	5 (5)	12 (10)	7 (8)	7 (8)	7 (8)
Time per week spent working at HIV clinic, median (range), h	25 (3-55)	40 (4-40)	36 (12-40)	18 (4-50)	31 (3-55)
Ever prescribed medications to treat tobacco use disorder (ie, nicotine replacement therapy, bupropion, varenicline), yes	9 (82)	7 (100)	4 (100)	12 (100)	32 (94)
Ever provided counseling to treat tobacco use disorder, yes	11 (100)	7 (100)	4 (100)	12 (100)	34 (100)
Ever prescribed medications to treat unhealthy alcohol use (ie, disulfiram, acamprosate, oral or injectable naltrexone, other), yes	3 (27)	3 (43)	1 (25)	7 (58)	14 (41)
Ever provided counseling to treat unhealthy alcohol use, yes	11 (100)	7 (100)	4 (100)	12 (100)	34 (100)
Ever provided counseling to treat opioid use disorder, yes	9 (82)	7 (100)	4 (100)	12 (100)	32 (94)
Hold a waiver that allows buprenorphine (eg, Suboxone) prescribing, yes	4 (36)	1 (14)	1 (25)	5 (42)	11 (32)
Ever prescribed oral or injectable (eg, Vivitrol) naltrexone to treat opioid use disorder, yes	1 (9)	1 (14)	1 (25)	2 (17)	5 (15)

[a] Other refers to American Indian or Alaska Native, Native Hawaiian or Pacific Islander, or any other race not specified.

[b] Missing data were not included in calculations of percentages.

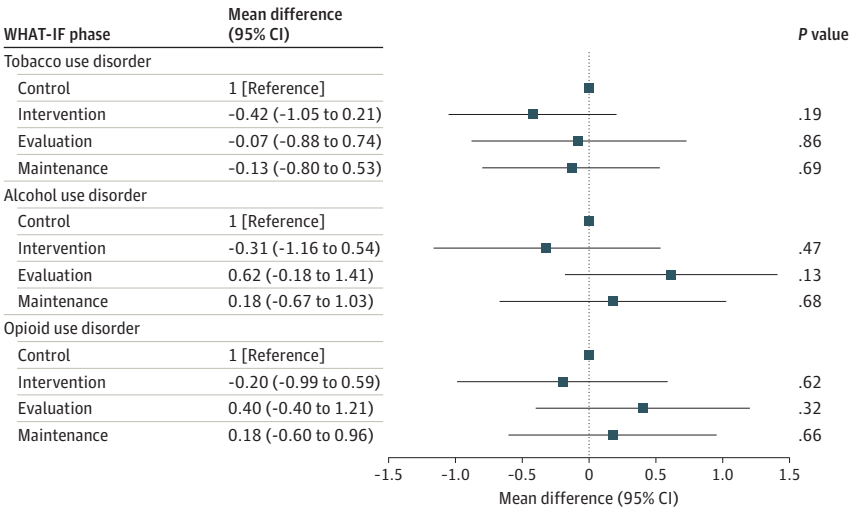
effective by sequentially focusing on different use disorders rather than 3 simultaneously. Second, facilitation may have been more effective if provided over a longer time or with higher intensity of contacts and support. Third, clinician and staff may have benefited from further training in motivational interviewing techniques to engage patients in care. Finally, efforts to more directly link provision of MAT to reimbursement may be required to help prioritize MAT in these settings given the multiple, complex existing demands.[25]

Limitations and Strengths

Our study has limitations. First, our primary outcome focused on provision of any treatment during a given period among treatment-eligible patients within the given clinic; we did not distinguish between treatment initiation and continuation or assess treatment duration, nor were we focused on medications that may have been provided elsewhere (eg, opioid treatment programs). Second, treatment eligibility relied on clinician coding of SUD, which undercounts true prevalence.[26] Third, we are unable to determine whether counseling as measured in the EHR was specifically provided to address a given SUD. Fourth, self-reported outcomes are subject to social desirability bias, survey fatigue, and assessment reactivity.[27] Fifth, we had missing data on readiness scales during 1 period. Sixth, our study was conducted in HIV clinicals all located in the northeastern US and thus may not be generalizable to other settings. Given their willingness to participate in a study focused on promoting addiction treatment, these sites may have had higher baseline readiness to provide addiction treatment than the typical HIV clinic. Seventh, our findings may have been impacted by temporal trends, a time when there has been greater focus on enhancing treatment of OUD, and also threatened by the COVID-19 pandemic.

Our study also has important strengths. First, for our primary outcome, we relied on EHR data to assess MAT provision that were routinely collected, thus minimizing selection bias and allowing for robust ascertainment of our primary outcome.[28] Second, our study was conducted in both community and academically affiliated HIV clinics with varying levels of resources and infrastructure to enhance generalizability. Third, with the exception of 1 site, site personnel and study investigators were blinded as to when each site would receive the intervention to minimize prefacilitation activities.

Figure 2. Clinician and Staff Readiness Across All Sites to Provide Medications for Addiction Treatment by Study Period



WHAT-IF indicates Working with HIV Clinics to adopt Addiction Treatment using Implementation Facilitation.

Conclusions

In this randomized clinical trial, facilitation resulted in improvements in MTUD and MAUD with no measurable change in MOUD provision. Given the importance of these treatments to people with HIV and observed treatment gaps, robust implementation strategies are needed to reach individuals with HIV engaged in care.

ARTICLE INFORMATION

Accepted for Publication: August 30, 2022.

Published: October 17, 2022. doi:10.1001/jamanetworkopen.2022.36904

Corresponding Author: E. Jennifer Edelman, MD, MHS, Department of Internal Medicine, Yale School of Medicine, 367 Cedar St, ESH A, New Haven, CT 06510 (ejennifer.edelman@yale.edu).

Author Affiliations: Program in Addiction Medicine, Yale School of Medicine, New Haven, Connecticut (Edelman, Becker, Morford, Muvvala, Fiellin); Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut (Edelman, Porter, Becker, Morford, Fiellin); Center for Interdisciplinary Research on AIDS, Yale School of Public Health, New Haven, Connecticut (Edelman, Fiellin); Yale Center for Analytic Sciences, Yale School of Public Health, New Haven, Connecticut (Gan, Dziura, Esserman, Reynolds); Department of Emergency Medicine, Yale School of Medicine, New Haven, Connecticut (Dziura, Fiellin); Department of Biostatistics, Yale School of Public Health, New Haven, Connecticut (Esserman); VA Connecticut Healthcare System, West Haven (Becker); Department of Medicine, Brown University, Providence, Rhode Island (Chan); Institute for Collaboration on Health, Intervention, and Policy (InCHIP), University of Connecticut, Storrs (Cornman); University of Washington and VA Puget Sound, Seattle (Helfrich); SUNY Downstate, Brooklyn, New York (Yager); Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut (Muvvala).

Author Contributions: Drs Edelman and Fiellin had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Edelman, Dziura, Esserman, Cornman, Helfrich, Reynolds, Fiellin.

Acquisition, analysis, or interpretation of data: Edelman, Gan, Dziura, Esserman, Porter, Becker, Chan, Cornman, Reynolds, Yager, Morford, Muvvala, Fiellin.

Drafting of the manuscript: Edelman, Dziura, Chan, Muvvala.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Gan, Dziura, Esserman, Reynolds.

Obtained funding: Fiellin.

Administrative, technical, or material support: Porter, Cornman, Helfrich, Reynolds, Yager, Morford, Fiellin.

Supervision: Edelman, Esserman, Cornman, Fiellin.

Conflict of Interest Disclosures: Dr Muvvala reported receiving personal fees from Alkermes for participating in an advisory board meeting in 2020 outside the submitted work. No other disclosures were reported.

Funding/Support: This work was funded by the National Institute on Drug Abuse (grant R01DA041067) and partially funded by the Yale Clinical and Translational Science Award (grant UL1TR001863).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: Susan Holman, MS, RN (SUNY Downstate, Brooklyn, New York), Stephen Thompson, MS (University of Connecticut, Storrs), Caitlin Partridge (Yale School of Medicine, New Haven, Connecticut), and Fizza Gillani, PhD (The Miriam Hospital, Providence, Rhode Island), assisted with extracting the electronic medical record data. They were not compensated for this work beyond their normal salaries.

REFERENCES

1. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescents with HIV. February 2021. Accessed September 12, 2022. https://health.gov/healthypeople/tools-action/browse-evidence-based-resources/guidelines-use-antiretroviral-agents-adults-and-adolescents-living-hiv

2. Oldfield BJ, McGinnis KA, Edelman EJ, et al. Predictors of initiation of and retention on medications for alcohol use disorder among people living with and without HIV. *J Subst Abuse Treat*. 2020;109:14-22. doi:10.1016/j.jsat.2019.11.002

3. Shahrir S, Crothers K, McGinnis KA, et al. Receipt and predictors of smoking cessation pharmacotherapy among veterans with and without HIV. *Prog Cardiovasc Dis*. 2020;63(2):118-124. doi:10.1016/j.pcad.2020.01.003

4. Chander G, Monroe AK, Crane HM, et al. HIV primary care providers: screening, knowledge, attitudes and behaviors related to alcohol interventions. *Drug Alcohol Depend*. 2016;161:59-66. doi:10.1016/j.drugalcdep.2016.01.015

5. Bold KW, Deng Y, Dziura J, et al. Practices, attitudes, and confidence related to tobacco treatment interventions in HIV clinics: a multisite cross-sectional survey. *Transl Behav Med*. 2022;12(6):726-733. doi:10.1093/tbm/ibac022

6. Ritchie MJ, Dollar KM, Miller CJ, et al. Using implementation facilitation to improve care in the Veterans Health Administration (version 2). 2017. Accessed September 12, 2022. https://www.queri.research.va.gov/tools/Facilitation-Manual.pdf

7. Baskerville NB, Liddy C, Hogg W. Systematic review and meta-analysis of practice facilitation within primary care settings. *Ann Fam Med*. 2012;10(1):63-74. doi:10.1370/afm.1312

8. Wang A, Pollack T, Kadziel LA, et al. Impact of practice facilitation in primary care on chronic disease care processes and outcomes: a systematic review. *J Gen Intern Med*. 2018;33(11):1968-1977. doi:10.1007/s11606-018-4581-9

9. D'Onofrio G, Edelman EJ, Hawk KF, et al. Implementation facilitation to promote emergency department-initiated buprenorphine for opioid use disorder: protocol for a hybrid type III effectiveness-implementation study (Project ED HEALTH). *Implement Sci*. 2019;14(1):48. doi:10.1186/s13012-019-0891-5

10. Williams EC, Matson TE, Harris AHS. Strategies to increase implementation of pharmacotherapy for alcohol use disorders: a structured review of care delivery and implementation interventions. *Addict Sci Clin Pract*. 2019;14(1):6. doi:10.1186/s13722-019-0134-8

11. Leone FT, Evers-Casey S, Graden S, Schnoll R, Mallya G. Academic detailing interventions improve tobacco use treatment among physicians working in underserved communities. *Ann Am Thorac Soc*. 2015;12(6):854-858. doi:10.1513/AnnalsATS.201410-466BC

12. NIH Research Portfolio Online Reporting Tools (RePORT). Implementation to motivate physician response to opioid dependence in HIV setting. Accessed September 7, 2021. https://reporter.nih.gov/search/Z9RxTlyRvOyPQ__0ft3Kkg/project-details/9656986#publications

13. Edelman EJ, Dziura J, Esserman D, et al. Working with HIV clinics to adopt addiction treatment using implementation facilitation (WHAT-IF?): rationale and design for a hybrid type 3 effectiveness-implementation study. *Contemp Clin Trials*. 2020;98:106156. doi:10.1016/j.cct.2020.106156

14. Edelman EJ, Gan G, Dziura J, et al. Readiness to provide medications for opioid, alcohol and tobacco use disorder in HIV clinics: a multi-site mixed-methods formative evaluation. *J Acquir Immune Defic Syndr*. 2021;87(3):959-970. doi:10.1097/QAI.0000000000002666

15. Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. *Med Care*. 2012;50(3):217-226. doi:10.1097/MLR.0b013e3182408812

16. Beard E, Lewis JJ, Copas A, et al. Stepped wedge randomised controlled trials: systematic review of studies published between 2010 and 2014. *Trials*. 2015;16:353. doi:10.1186/s13063-015-0839-2

17. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Ann Intern Med*. 2010;152(11):726-732. doi:10.7326/0003-4819-152-11-201006010-00232

18. van den Berg JJ, O'Keefe E, Davidson D, et al. The development and evaluation of an HIV implementation science network in New England: lessons learned. *Implement Sci Commun*. 2021;2(1):64. doi:10.1186/s43058-021-00165-2

19. Helfrich CD, Li YF, Sharp ND, Sales AE. Organizational readiness to change assessment (ORCA): development of an instrument based on the Promoting Action on Research in Health Services (PARIHS) framework. *Implement Sci*. 2009;4:38. doi:10.1186/1748-5908-4-38

20. Hawk KF, D'Onofrio G, Chawarski MC, et al. Barriers and facilitators to clinician readiness to provide emergency department–initiated buprenorphine. *JAMA Netw Open*. 2020;3(5):e204561. doi:10.1001/jamanetworkopen.2020.4561

21. Garner BR. Research on the diffusion of evidence-based treatments within substance abuse treatment: a systematic review. *J Subst Abuse Treat*. 2009;36(4):376-399. doi:10.1016/j.jsat.2008.08.004

22. Knudsen HK, Ducharme LJ, Roman PM. Early adoption of buprenorphine in substance abuse treatment centers: data from the private and public sectors. *J Subst Abuse Treat*. 2006;30(4):363-373. doi:10.1016/j.jsat.2006.03.013

23. Kirchner JE, Ritchie MJ, Pitcock JA, Parker LE, Curran GM, Fortney JC. Outcomes of a partnered facilitation strategy to implement primary care-mental health. *J Gen Intern Med*. 2014;29(suppl 4):904-912. doi:10.1007/s11606-014-3027-2

24. Woertman W, de Hoop E, Moerbeek M, Zuidema SU, Gerritsen DL, Teerenstra S. Stepped wedge designs could reduce the required sample size in cluster randomized trials. *J Clin Epidemiol*. 2013;66(7):752-758. doi:10.1016/j.jclinepi.2013.01.009

25. HRSA. HIV/AIDS Bureau performance measures. November 2, 2019. Accessed September 12, 2022. https://hab.hrsa.gov/sites/default/files/hab/clinical-quality-management/adolescentadultmeasures.pdf

26. Holt SR, Ramos J, Harma M, et al. Physician detection of unhealthy substance use on inpatient teaching and hospitalist medical services. *Am J Drug Alcohol Abuse*. 2013;39(2):121-129. doi:10.3109/00952990.2012.715703

27. Heishman SJ, Saha S, Singleton EG. Imagery-induced tobacco craving: duration and lack of assessment reactivity bias. *Psychol Addict Behav*. 2004;18(3):284-288. doi:10.1037/0893-164X.18.3.284

28. Hemming K, Taljaard M, Grimshaw J. Introducing the new CONSORT extension for stepped-wedge cluster randomised trials. *Trials*. 2019;20(1):68. doi:10.1186/s13063-018-3116-3

SUPPLEMENT 1.

Trial Protocol

SUPPLEMENT 2.

eFigure 1. CONSORT Flow Diagram
eTable 1. Medications Available for HIV Clinic-Based Addiction Treatment by Substance Use Disorder
eTable 2. Clinician and Staff Readiness to Provide MAT by Study Period, Results From GEE
eTable 3. Clinician and Staff ORCA Evidence Ratings for MAT by Study Period, Results From GEE
eFigure 2. Clinician and Staff ORCA Evidence Ratings for Medications for Addiction Treatment by Study Period
eTable 4. Clinician and Staff ORCA Context Ratings for MAT by Study Period, Results From GEE
eFigure 3. Clinician and Staff ORCA Context Ratings for Medications for Addiction Treatment by Study Period

SUPPLEMENT 3.

Data Sharing Statement

scientific reports

Check for updates

OPEN

Combined effects of smoking and HIV infection on the occurrence of aging-related manifestations

Laurent Boyer[1,2,4,5,7]✉, Sonia Zebachi[2,7], Sébastien Gallien[2,3,4], Laurent Margarit[1], Bruno Ribeiro Baptista[2], José-Luis Lopez-Zaragoza[2], Thomas D'Humières[1,2], Françoise Zerah[1], Sophie Hue[2,4,6], Geneviève Derumeaux[1,2], Serge Adnot[1,2], Etienne Audureau[2,4,6] & Jean-Daniel Lelièvre[2,3,4]

Both HIV-1 infection and smoking may contribute to the development of ageing-related manifestations affecting the prognosis of people living with HIV, but it is unclear whether HIV and smoking exert their effects independently or interact by potentiating each other. We conducted a cross-sectional study in 192 people living with HIV aged- and gender-matched with 192 HIV-uninfected controls, assessing the relative effect of HIV-1/smoking status on lung function (FEV1), bone mineral density (BMD), appendicular skeletal muscle mass index (ASMI), aortic pulse-wave velocity (PWV), insulin resistance (HOMA-IR) and renal function. In both unadjusted and adjusted analyses, FEV1, BMD and ASMI significantly differed according to smoking/HIV status, with the worst parameters found in HIV-1 infected patients currently smoking, and BMD and ASMI decreased to a lesser extent in HIV-1 infected patients formerly smoking (> 10 pack-years). Values in people living with HIV with < 10 pack-years exposure were of similar magnitude to those from controls. Regarding PWV, HOMA-R and eGFR, no significant differences were found, with the exception of eGFR values which were globally lower in HIV-1 infected patients. In conclusion HIV infection and smoking acted synergistically and were associated with a wasting phenotype combining muscle mass and bone mineral reduction.

Clinical Trial Registration (registrar, website, and registration number), where applicable: CPP 10-023, 09-027, 10-034.

With the advent of combined antiretroviral therapy (ART), people living with HIV (PLWH) live longer, currently reaching a median age higher than 50 years[1]. However, PLWH still die earlier than non-infected patients, mainly due the development of aging related comorbidities that adversely affect the prognosis of the disease, such as chronic obstructive pulmonary diseases, cardiovascular diseases, diabetes, renal insufficiency, or osteoporosis. These comorbidities are each individually associated with worse quality of life or increased mortality[2–7]. Decreased limb muscle and increased central adiposity are associated with 5-year all-cause mortality in HIV infection[8]. However, whether such systemic effects are ascribable directly to HIV disease and ART, or to other factors such as aging, environmental or behavioral determinants is still in debate. Among these factors, several are modifiable risk factors for comorbidities and it is crucial to determine whether actions reducing these risk factors may be sufficient to prevent or reverse the development of these comorbidities.

Tobacco smoking is the main modifiable risk that has a strong impact on age related comorbidities in the general population, in particular regarding lung and cardiovascular disease or osteoporosis. The systemic effects of smoking are mainly represented by pulmonary alterations such as emphysema and chronic obstructive pulmonary disease[9–12]. The higher prevalence of smoking among PLWH compared to the general population has led to an increasing cumulative exposure to tobacco in this population[13,14]. However, whether smoking is the main driver of age related diseases and comorbidities in PLWH is still a subject of debate[14,15]. If the relationship between smoking and cardiovascular diseases such as atherosclerosis and myocardial infarction, may be stronger

[1]Département de Physiologie-Explorations Fonctionnelles, FHU Senec, APHP Hôpital Henri Mondor, 1 rue Gustave Eiffel, 94010 Créteil, France. [2]Univ Paris Est Creteil, INSERM IMRB, UMR U955, 94010 Créteil, France. [3]Service de maladies infectieuses et immunologie clinique, APHP Hôpital Henri Mondor, 94010 Créteil, France. [4]Faculté de médecine, Université Paris Est (UPEC), 94010 Créteil, France. [5]Service d'Immunologie Biologique, APHP Hôpital Henri Mondor, 94010 Créteil, France. [6]Service de Santé Publique, APHP Hôpital Henri Mondor, 94010 Créteil, France. [7]These authors contributed equally: Laurent Boyer and Sonia Zebachi. ✉email: Laurent.boyer@aphp.fr

in PLWH than in uninfected subjects[16], we do not know how HIV affects the relationship between smoking and the other systemic manifestations associated with cigarette smoke exposure. Similarly, we do not know whether HIV and smoking may exert their effects independently or may interact by potentiating each other.

To further our understanding of the impact of tobacco smoking to the age-related systemic manifestations in HIV-infected individuals, we investigated the association between smoking and several parameters such as arterial stiffness, bone mineral density, muscle mass, insulin resistance and kidney function, in PLWH and uninfected individuals and determined whether these relationships differed depending on HIV status. Because smoking may gradually exert its potential systemic effects within a continuum, relevant associations may be overlooked when only focusing on clinically established diseases. We consequently investigated these complex associations using continuous biological and functional parameters operating also at earlier stages of disease development.

Methods

Study design and participants

Participants living with HIV were recruited from the CARDAMONE study, a cross-sectional monocentric study of adult PLWH enrolled from the HIV outpatient clinic of the Henri Mondor Teaching hospital, France, between 2009 and 2012. To be included, patients had to have plasma HIV RNA below 50 copies/ml under c-ART and no past major cardiovascular event (i.e. myocardial infarction/chronic heart failure). HIV-uninfected individuals were recruited from the Clinical Investigation Center of the Henri Mondor Teaching hospital, as previously described[9,10,17]. For the present analysis, HIV-infected patients were 1:1 gender- and age-matched (using 5-years classes) to HIV-uninfected patients. A comparison of the main characteristics of subjects matched with those unmatched and discarded from the present analysis is shown in Supplemental Tables 1 and 2, indicating notable age-related differences between (un)matched subjects, with the youngest PLWH and the oldest controls being left out of the analysis. All studies were approved by the ethical committee of the Henri-Mondor Teaching Hospital (CARDAMONE: CPP 10-023; uninfected individuals: CPP 09-027 and 10-034). All participants provided written informed consent before inclusion. All research was performed in accordance with the Declaration of Helsinki.

Variables and data measurement

Demographic, clinical and lifestyle factors were collected for all participants from medical records, including age, gender, smoking, body mass index, waist circumference and blood pressure. Smokers were defined as individuals who had smoked more than 100 cigarettes in their lifetime[18], distinguishing between current and former (≥ 1 year) smokers who had quit smoking at the time of the study.

Each participant underwent spirometry, plethysmography measurement according to ATS/ERS consensus guidelines[19]. In each participant, arterial stiffness (aortic pulse-wave velocity, PWV) was measured as the carotid-femoral pulse-wave velocity using the Complior Analyse device (Alam Medical, Vincennes, France). Bone mineral density (BMD) at the hip (femoral neck) and lumbar spine was determined using dual-energy X-ray absorptiometry (Lunar iDXA, GE Healthcare, UK). BMD is reported as the absolute value (g/cm^2). T-scores were computed to classify participants as having normal BMD or osteoporosis (defined as T-score < -2.5 at either site). To assess muscle mass, appendicular skeletal muscle mass (ASM) was measured as the fat-free soft-tissue masses of the arms and legs divided by height squared and ASM index (ASMI) was then computed as ASMM divided by height squared. The cutoff for defining sarcopenia was two standard deviations below the mean sex-specific ASMI values in the Rosetta Study of young adults (5.45 for females and 7.26 for males), as proposed by Baumgartner et al.[20]. Insulin resistance was assessed by calculating the homeostasis model assessment of insulin resistance (HOMA-IR) (insulin·glucose)/22.5), and renal function by estimating the glomerular filtration rate (eGFR) using the Cockcroft-Gault formula. Other biological data included hemoglobin, white blood cell count (WBC), fasting glycemia, Hba1c, cholesterol (total, HDL, LDL), triglycerides, CRP and specifically in PLWH T lymphocytes parameters (i.e. Nadir $CD4^+$ cell count, $CD4^+$ and $CD8^+$ cell counts, $CD4^+/CD8^+$ ratio).

Statistical analysis

Qualitative variables are reported as numbers and percentages, and quantitative variables as means (± standard deviation, SD) or medians [interquartile range, IQR], depending on the normality of variable distributions as assessed by Shapiro–Wilk tests. Unadjusted between-groups comparisons were performed by means of mixed effects regression models to account for the 1:1 matching between PLWH and HIV-uninfected patients, using linear regression for continuous parameters and logistic regression for binary variables. Mixed effects linear multivariate models adjusted for age and gender were secondarily conducted to assess the relative effects of smoking and HIV-infection on aging-related systemic manifestations (i.e. arterial stiffness, bone mineral density, muscle mass, insulin resistance and kidney function). To assess the potential effect of the combination between smoking status and HIV, a composite 6-categories variable was entered in to the model, as follows: controls who were (i) never smokers or < 10 pack-years, (ii) former smokers with > 10 pack-years or (iii) current smokers with > 10 pack-years; and HIV-1-infected patients who were (iv) never smokers or < 10 pack-years, (v) former smokers with > 10 pack-years or (vi) current smokers with > 10 pack-years. No adjustment for multiple testing was done in the present study. Analyses of the effects of smoking and HIV-1 status were exploratory by nature and performed on prespecified ageing parameters of interest.

For illustrative purposes, a Gabriel's biplot was created to project the subjects along the principal components axes from a principal components analysis (PCA) based on their individual aging-related characteristics[21]. HIV/smoking 6-categories status was then mapped on the biplot by attributing different colors to patient's groups. Missing data for the main outcomes and covariates ranged from 0 to 13% (ASMI); all analyses were performed on complete cases using Stata v16.0 (StataCorp, College Station, TX, USA) and data visualizations using R v3.6.2 (R Foundation, Vienna, Austria).

Ethics approval and consent to participate

All studies were approved by the ethical committee of the Henri-Mondor Teaching Hospital (CARDAMONE: CPP 10-023; uninfected individuals: CPP 09-027 and 10-034). All participants provided written informed consent before inclusion.

Results

HIV-infected and matched controls differed on key baseline characteristics

From an initial total of 629 patients (N = 239 PLWH and N = 390 HIV-uninfected controls), 1:1 age- and gender-matching was possible for 378 patients (189 patients in each subgroup). Main characteristics of the participants are described in Table 1. In addition to age (overall mean 49.8 ± 8.2 years) and gender (overall 21.2% women), matched participants were also comparable regarding systolic blood pressure, pulse-wave velocity, HOMA-IR, and the ratio forced expiratory volume in one second (FEV1)/forced vital capacity (FVC). Overall, PLWH were characterized by a higher proportion of current smokers and sarcopenia, lower body mass index (BMI), eGFR

	N completed	Controls N = 189	People living with HIV N = 189	p-value*
Age, years	378	50.0 ± 8.4	49.6 ± 8.0	0.644
Gender, women (%)	378	40 (21.2%)	40 (21.2%)	1.000
Smoking status	378			0.043
Never smoker (%)	180	100 (52.9%)	80 (42.3%)	
Former smoker (%)	78	40 (21.2%)	38 (20.1%)	
Current smoker (%)	120	49 (25.9%)	71 (37.6%)	
Pack-years of cigarettes	378	12.7 (± 18.3)	12.3 (± 14.9)	0.793
Smoking/Pack-years status	378			0.445
Never smokers or < 10 Pack-years	214	111 (58.7%)	103 (54.5%)	
> 10 Pack-years, former smokers	61	32 (16.9%)	29 (15.3%)	
> 10 Pack-years, current smokers	103	46 (24.3%)	57 (30.2%)	
BMI, kg/m^2	376	26.9 (± 3.6)	24.1 (± 3.9)	< 0.001
Obesity	376	35 (18.6%)	18 (9.6%)	0.013
Dyslipidemia	355	53 (30.5%)	76 (42.0%)	0.024
Diabetes	369	3 (1.6%)	8 (4.4%)	0.126
Systolic blood pressure, mmHg	346	120.3 (± 14.4)	121.7 (± 14.2)	0.392
Diastolic blood pressure, mmHg	346	78.4 (± 8.6)	76.7 (± 9.7)	0.080
HTA	345	19 (11.7%)	27 (14.8%)	0.387
FEV1, % predicted	347	101.5 (± 15.3)	98.4 (± 17.3)	0.078
FEV1/FVC	347	81.8 (± 6.5)	81.5 (± 7.8)	0.750
Pulse-wave velocity, m/s	341	10.5 (9.4; 11.6)	10.2 (9.5; 11.6)	0.892
BMD total lumbar, g/cm^2	348	1.2 (± 0.2)	1.1 (± 0.2)	0.002
BMD hip (lowest), g/cm^2	347	1.0 (± 0.2)	1.0 (± 0.2)	0.002
ASMI, kg/m^2	330	8.2 (± 1.3)	7.7 (± 1.3)	0.001
Sarcopenia (%)	330	4 (2.7%)	41 (22.8%)	< 0.001
HOMA-IR	353	2.0 (1.3; 3.5)	2.3 (1.5; 3.3)	0.593
Glomerular flow rate, mL/min	362	98.2 (86.5; 116.1)	92.5 (81.4; 110.9)	0.026
Time since HIV diagnosis, years	189	–	12.6 (8.7; 18.4)	–
History of AIDS (%)	189	–	51 (27.0%)	–
Nadir CD4$^+$ cell count, cells/mm^3	185	–	142.0 (35.0; 244.0)	–
CD4$^+$ cell count, cells/mm^3	174	–	237.5 (79.0; 404.0)	–
CD8$^+$ cell count, cells/mm^3	188	–	645.0 (478.0; 842.0)	–
CD4$^+$/CD8$^+$ ratio	188	–	0.8 (0.6; 1.1)	–
ART use at enrollment	182			
PI-based therapy		88 (48.4%)		–
INI-based triple therapy		10 (5.5%)		–
RTI-based triple therapy		77 (42.3%)		–
Others		3 (1.6%)		
No treatment		4 (2.2%)		–

Table 1. Baseline characteristics of the study population. *p-values from mixed effects linear or logistic regression model accounting for matching between HIV-infected and HIV-uninfected patients. Results are mean (± standard deviation), median (interquartile range) or N (%).

and musculoskeletal parameters (i.e. hip and lumbar BMD, ASMI) compared to non HIV-infected subjects. No statistically significant difference was found between groups regarding mean past cigarette smoke exposure as expressed in pack-years.

All PLWH had plasma HIV RNA below 50 copies/ml, of whom 98% were receiving ART. The median nadir $CD4^+$ T-cell count was 142 cells/mm^3 (IQR, 35; 244 cells/mm^3), the current $CD4^+$ T-cell count was 237.5 (IQR, 79; 404), the baseline median $CD4^+/CD8^+$ ratio was 0.82 (IQR 0.58; 1.14) and 27% had a history of AIDS.

Effects of combined smoking and HIV status on ageing-related parameters

Results from unadjusted and age–gender adjusted linear regression modeling are shown in Table 2 (FEV1, BMD, ASMI) and Table 3 (PWV, HOMA-R, eGFR).

In both unadjusted and adjusted analyses, FEV1, BMD and ASMI significantly differed according to smoking/HIV status (Table 2), with the worst parameters significantly found in PLWH currently smoking (adjusted regression coefficients compared to controls never smokers or < 10 pack-years: FEV1 − 8.03, p = 0.003; BMD − 0.12, p < 0.0001; ASMI − 1.05, p < 0.0001). BMD and ASMI were also significantly decreased in HIV-1 infected patients formerly smoking, but to a lesser extent (BMD − 0.08, p = 0.014; ASMI − 0.72, p = 0.001). Of note, values for these parameters did not substantially differ in controls according to smoking status. Likewise, values in PLWH who were never smokers or with < 10 pack-years were of similar magnitude to those from controls.

Regarding PWV, HOMA-R and eGFR (Table 3), no significant differences were found between smoking/HIV categories in all unadjusted and adjusted analyses, to the exception of eGFR values which were substantially lower in PLWH to those from controls.

To further illustrate these findings, Fig. 1 shows as boxplots the age–gender adjusted comparisons of the ageing-related parameters values according to the composite smoking-HIV status, confirming the decreased FEV, BMD and ASMI values found in PLWH currently smoking and, to a lesser extent, formerly smoking for BMD and ASMMI. Detailed statistics including raw and adjusted means are given in Supplemental Table 3.

Figure 2 shows the 2-dimensional biplot representation of patients' characteristics according to the composite smoking and HIV+ status variable. PLWH currently or, to a lesser extent, formerly smoking were distinctively projected in the left area of the plot, indicating lower values in ASMI and BMD, while controls and PLWH who were never smokers or with < 10 pack-years were all closely located in the middle-right area, indicating a global overlap in characteristics.

Conclusion

The main finding of this study is that HIV infection and smoking interact by potentiating each other's negative effects on ageing. This deleterious effect concerns lung function, bone mineral density and muscle mass, with worse parameters found in PLWH currently smoking. Our findings strongly suggest that smoking acts synergistically with HIV infection to develop aging-related complications.

The synergic effect of cigarette smoke and HIV infection is particularly observed on bone mineral density and muscle mass, that is also linked with low BMI. As others, we observed that bone density and muscle mass were lower in PLWH[22–25]. In large cohort studies, HIV infection was shown to be independently associated with low

Ageing-related parameter	Group			Unadjusted analysis			Adjusted analysis*		
				Beta coefficient (CI 95%)	p-value	p-value (overall)	Beta coefficient (CI 95%)	p-value	p-value (overall)
FEV_1	Controls	< 10 PY		0 (ref)	–	**0.044**	0 (ref)	–	0.054
		> 10 PY	Former smokers	1.53 (− 5.36; 8.43)	0.663		1.31 (− 5.62; 8.23)	0.712	
			Current smokers	− 1.83 (− 7.64; 3.98)	0.537		− 1.83 (− 7.75; 4.10)	0.545	
	HIV	< 10 PY		− 1.47 (− 5.92; 2.98)	0.518		− 1.39 (− 5.86; 3.08)	0.542	
		> 10 PY	Former smokers	− 0.26 (− 7.00; 6.49)	0.940		− 0.56 (− 7.37; 6.24)	0.871	
			Current smokers	− 8.11 (− 13.36; − 2.85)	**0.003**		− 8.03 (− 13.29; − 2.77)	**0.003**	
BMD Hip	Controls	< 10 PY		0 (ref)	–	**0.0002**	0 (ref)	–	**< 0.0001**
		> 10 PY	Former smokers	0.00 (− 0.07; 0.07)	0.999		0.01 (− 0.06; 0.07)	0.868	
			Current smokers	− 0.05 (− 0.10; 0.01)	0.110		− 0.02 (− 0.07; 0.04)	0.524	
	HIV	< 10 PY		− 0.03 (− 0.07; 0.01)	0.180		− 0.03 (− 0.07; 0.02)	0.230	
		> 10 PY	Former smokers	− 0.09 (− 0.15; − 0.02)	**0.007**		− 0.08 (− 0.14; − 0.01)	**0.015**	
			Current smokers	− 0.11 (− 0.16; − 0.06)	**< 0.0001**		− 0.12 (− 0.17; − 0.07)	**< 0.0001**	
ASMI	Controls	< 10 PY		0 (ref)	–	**< 0.0001**	0 (ref)	–	**< 0.0001**
		> 10 PY	Former smokers	0.26 (− 0.31; 0.83)	0.363		0.27 (− 0.23; 0.77)	0.285	
			Current smokers	− 0.44 (− 0.89; 0.00)	0.051		− 0.09 (− 0.48; 0.31)	0.659	
	HIV	< 10 PY		− 0.31 (− 0.64; 0.01)	0.061		− 0.23 (− 0.53; 0.07)	0.136	
		> 10 PY	Former smokers	− 0.68 (− 1.17; − 0.19)	**0.007**		− 0.72 (− 1.16; − 0.28)	**0.001**	
			Current smokers	− 0.96 (− 1.34; − 0.58)	**< 0.0001**		− 1.05 (− 1.40; − 0.70)	**< 0.0001**	

Table 2. Effects of smoking and HIV-1 status on aging-related parameters: FEV1, BMD and ASMMI. *Mixed effects linear regression model adjusted for age and gender. Significant values are in bold.

Ageing-related parameter	Group			Unadjusted analysis			Adjusted analysis*		
				Beta coefficient (CI 95%)	p-value	p-value (overall)	Beta coefficient (CI 95%)	p-value	p-value (overall)
PWV	Controls	< 10 PY		0 (ref)	–	0.148	0 (ref)	–	0.684
		> 10 PY	Former smokers	0.64 (−0.14; 1.43)	0.108		0.42 (−0.33; 1.16)	0.274	0
			Current smokers	0.38 (−0.30; 1.07)	0.272		0.19 (−0.47; 0.85)	0.576	
	HIV	< 10 PY		0.22 (−0.31; 0.74)	0.414		0.19 (−0.32; 0.70)	0.472	
		> 10 PY	Former smokers	0.94 (0.14; 1.74)	**0.022**		0.60 (−0.17; 1.37)	0.126	
			Current smokers	−0.07 (−0.70; 0.55)	0.820		0.06 (−0.54; 0.66)	0.836	
HOMA-R	Controls	< 10 PY		0 (ref)	–	0.101	0 (ref)	–	0.193
		> 10 PY	Former smokers	0.96 (−0.28; 2.20)	0.129		0.82 (−0.41; 2.06)	0.192	
			Current smokers	−0.63 (−1.76; 0.49)	0.271		−0.72 (−1.86; 0.41)	0.212	
	HIV	< 10 PY		−0.14 (−0.97; 0.70)	0.748		−0.15 (−0.98; 0.69)	0.730	
		> 10 PY	Former smokers	0.77 (−0.48; 2.02)	0.226		0.55 (−0.71; 1.81)	0.393	
			Current smokers	−0.66 (−1.65; 0.33)	0.191		−0.62 (−1.60; 0.36)	0.217	
eGFR (Cockcroft)	Controls	< 10 PY		0 (ref)	–	0.110	0 (ref)	–	**0.027**
		> 10 PY	Former smokers	6.67 (−3.10; 16.44)	0.181		7.40 (−1.49; 16.29)	0.103	
			Current smokers	3.07 (−5.89; 12.03)	0.502		7.56 (−0.66; 15.78)	0.071	
	HIV	< 10 PY		−5.24 (−11.49; 1.01)	0.100		−3.50 (−9.46; 2.47)	0.250	
		> 10 PY	Former smokers	−2.14 (−11.92; 7.65)	0.668		0.43 (−8.70; 9.57)	0.926	
			Current smokers	−2.72 (−10.35; 4.91)	0.485		−4.00 (−11.11; 3.11)	0.270	

Table 3. Effects of smoking and HIV status on aging-related parameters: PWV, HOMA-R and eGFR. *Mixed effects linear regression model adjusted for age and gender. Significant values are in bold.

bone mineral density, and this association remained despite adjustment for traditional risk factors, in particular smoking status[23]. However, whether smoking and HIV-1 infection effects are cumulative and/or whether smoking effects may differ between PLWH and HIV non-infected individuals was not determined in these different studies. We observed that low bone density and low muscle mass are features of the same group of patients, suggesting a common phenomenon leading to a progressive wasting of muscle tissue and bone minerals, and a wasting profile[26,27]. This observation may be due to the lower BMI observed in PLWH compared to the others and may depend on the choice of the control population that has higher BMI. Moreover, as in smokers with or without chronic obstructive pulmonary disease (COPD), low bone mineral density and muscle mass are associated with a lower diffusion capacity and probably with emphysema[11].

Our results are a new piece of evidence of the synergistic effect of HIV-1 and cigarette smoke on lung function as suspected by the multiple biological changes described along the pulmonary tree when these two factors are combined[28]. This may partially explain the higher decline of lung function described in HIV current smokers than HIV non-smokers[29], in a population of patient with an already known higher prevalence of airways obstruction than non-HIV infected subjects[30,31].

Regarding arterial stiffness, no differences were found between smoking and HIV categories in all unadjusted and adjusted analyses. Arterial stiffness assessed by PWV is a sub-clinical marker of atherosclerosis that is associated with increased of cardiovascular events and death both in the general population and in PLWH[3]. Whether people chronically living with HIV have a higher level of pulse wave velocity than non-HIV subjects is object of debate and may depend on the population[32]. However, patients receiving ART and with a suppressed viral replication at the time of pulse wave velocity measurement as in our study, did not present a higher arterial stiffness than non-infected individuals[32]. Our data contrasts with previous studies showing that smoking was more strongly associated with carotid intima-media thickness and myocardial infarction in PLWH compared with HIV-uninfected subjects[16,33]. These differences may be essentially linked to our inclusion criteria: we explored our population at a preclinical stage under the level of cardiovascular disease, since none of the PLWH had presented any cardiovascular events.

One of the strengths of our study is the evaluation of several systemic manifestations concomitantly and objectively quantified. To date, most studies on the impact of comorbidities in PLWH used data on self-reported concurrent chronic conditions or assessed individually. Most systemic manifestations have been studied separately, whereas most HIV infected patients may have two or more chronic morbidities[15]. Interestingly we observed that the expression of manifestations induced by cigarette smoking differed depending on the HIV status, some were amplified and other were not modulated by the chronic infection. More interestingly, smoking combined with HIV was mainly associated with a special cluster of systemic manifestations combining a bone and muscle wasting profile with lung alterations. Similarly, bone, muscle and lung profile in response to cigarette smoke exposure seemed not to be associated with increase arterial stiffness suggesting a different pathophysiological process leading to this alteration in this population, and that different mechanism may be involved in this different manifestation. Our study has also limitations worth mentioning. Sample sizes in HIV/smoking subgroups were somewhat low (ranging from 29 to 111), thus potentially limiting the statistical power of the study to identify statistically significant relationships. It should also be noticed that PLWH included in our study were restricted to those patients with undetected viral load and without overt cardiac comorbidity, and that some

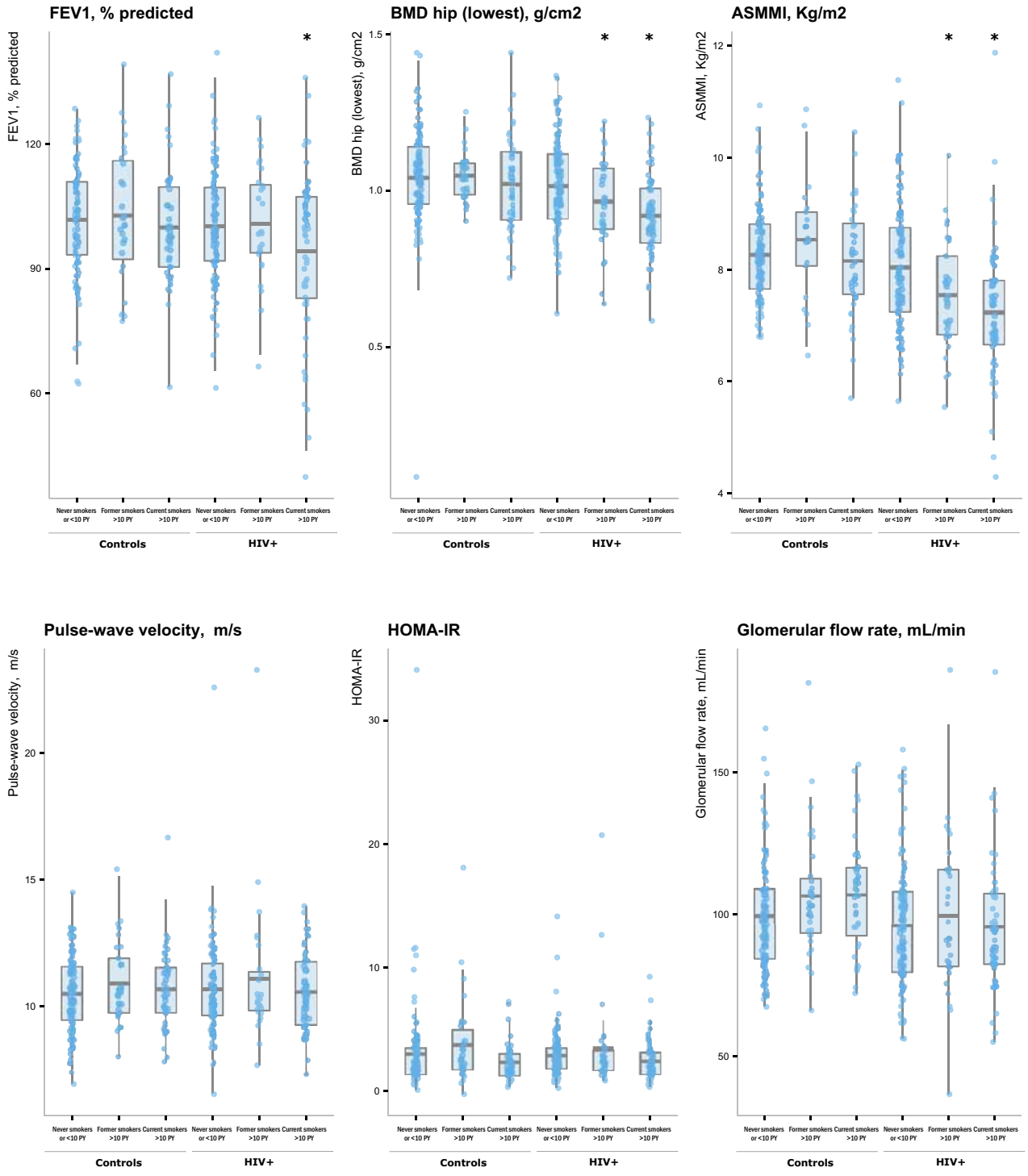


Figure 1. Boxplots of ageing-related parameters according to smoking and HIV+ status. Results are shown as boxplots, with each box representing the interquartile range (1st to 3rd quartile, IQR), the line within the box indicating the mean, and the whiskers extending to 1.5 times the IQR above and below the box; the dots represent individual values for each subject as predicted from mixed effects linear regression modeling adjusted for age and gender. Asterisks (*) indicate subgroups statistically significantly different from never smoker controls.

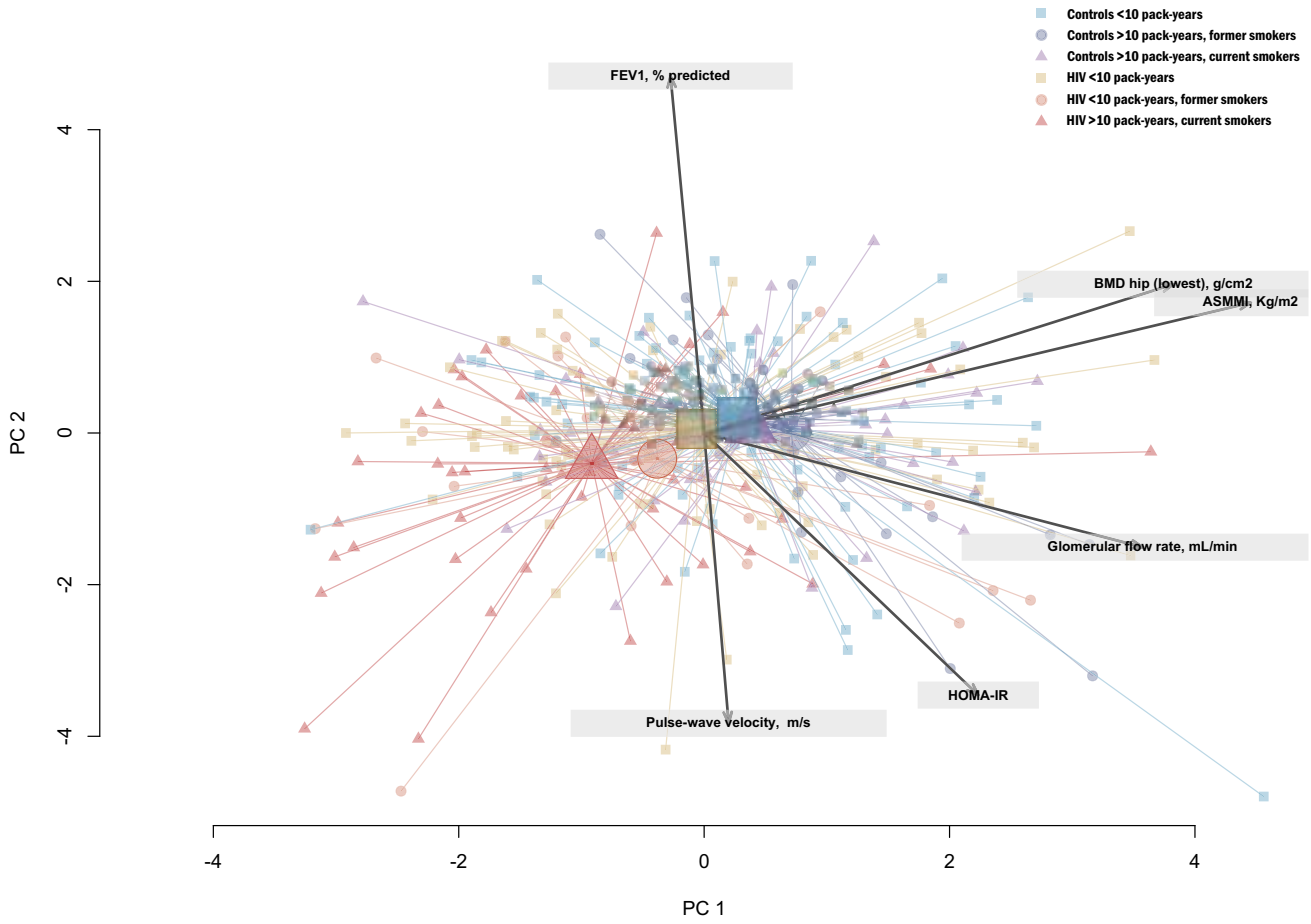


Figure 2. 2-dimensional biplot representation of patients' characteristics according to smoking and HIV+ status. Biplot representation allows the visualization of relationships between ageing parameters (arrows) while simultaneously displaying the patients (dots), based on their individual characteristics. Results are projected onto the two first dimensions generated by principal component analysis. Colors for observations correspond to one of the six groups according to HIV and smoking status (i.e. controls who were (i) never smokers or < 10 pack-years, (ii) former smokers with > 10 pack-years or (iii) current smokers with > 10 pack-years; and people living with HIV who were (iv) never smokers or < 10 pack-years, (v) former smokers with > 10 pack-years or (vi) current smokers with > 10 pack-years). Highlighted markers of increased size within each group represent the group centroid of the group.

individuals from the youngest and oldest age groups were discarded from the analysis due to the age–gender matching procedure, thus potentially limiting the generalizability of our results to broader populations. Finally, adjustment for BMI or other cardiovascular risk factors was not performed considering their potential high level of correlations with ageing parameters (e.g. BMI and ASMMI/sarcopenia; HOMA-IR and diabetes. Given their potential intermediate role in the causal chain between smoking/HIV and ageing parameters, a mediation analysis would have been of interest but was not performed due to the limited sample size of our study to test such more complex relationships.

In conclusion, we find a combined effect of smoking and HIV infection on age related systemic manifestations and HIV appeared as an additive risk factor for some cigarette smoke induced systemic manifestations. Smoking and HIV may be mainly associated with a wasting phenotype associated with lung alterations in HIV infected individuals. These data emphasize again the need to integrate actively smoking cessation in health policies for PLWH, but also to personalize the HIV smoker's health management with nutrition and exercise to prevent or reverse the bone and muscle loss.

More globally, these emphasize the need to target modifiable risk factors to prevent comorbidities in PLWH. Given the high prevalence of tobacco use in people living with HIV in both high-income and low or middle-income countries, policies and practices to promote tobacco cessation have to be a central strategy to improve the health outcomes in this population.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Received: 13 July 2022; Accepted: 1 August 2023
Published online: 08 December 2023

References

1. UNAIDS: Global HIV and AIDS statistics. https://www.unaids.org/en/resources/fact-sheet (2020).
2. Triplette, M. *et al.* Markers of chronic obstructive pulmonary disease are associated with mortality in people living with HIV. *AIDS* **32**, 487–493 (2018).
3. Hanna, D. B. *et al.* Carotid artery atherosclerosis is associated with mortality in HIV-positive women and men. *AIDS* **32**, 2393–2403 (2018).
4. Feinstein, M. J. *et al.* Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. *Am. J. Cardiol.* **117**, 214–220 (2016).
5. Walker Harris, V. & Brown, T. T. Bone loss in the HIV-infected patient: Evidence, clinical implications, and treatment strategies. *J. Infect. Dis.* **205**(Suppl 3), S391–S398 (2012).
6. Mocroft, A. *et al.* Deteriorating renal function and clinical outcomes in HIV-positive persons. *AIDS* **28**, 727–737 (2014).
7. Putcharoen, O. *et al.* New-onset diabetes in HIV-treated adults: Predictors, long-term renal and cardiovascular outcomes. *AIDS* **31**, 1535–1543 (2017).
8. Scherzer, R. *et al.* Decreased limb muscle and increased central adiposity are associated with 5-year all-cause mortality in HIV infection. *AIDS* **25**, 1405–1414 (2011).
9. Boyer, L. *et al.* Are systemic manifestations ascribable to COPD in smokers? A structural equation modeling approach. *Sci. Rep.* **8**, 8569 (2018).
10. Boyer, L. *et al.* Aging-related systemic manifestations in COPD patients and cigarette smokers. *PLoS One* **10**, e0121539 (2015).
11. Bon, J. *et al.* Radiographic emphysema predicts low bone mineral density in a tobacco-exposed cohort. *Am. J. Respir. Crit. Care Med.* **183**, 885–890 (2011).
12. Sabit, R. *et al.* Arterial stiffness and osteoporosis in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **175**, 1259–1265 (2007).
13. Tron, L., Lert, F., Spire, B., Dray-Spira, R., The ANRS-Vespa2 study group. Tobacco smoking in HIV-infected versus general population in France: Heterogeneity across the various groups of people living with HIV. *PLoS One* **9**, e107451 (2014).
14. Helleberg, M. *et al.* Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. *AIDS* **29**, 221–229 (2015).
15. Schouten, J. *et al.* Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: The AGEhIV cohort study. *Clin. Infect. Dis.* **59**, 1787–1797 (2014).
16. Rasmussen, L. D. *et al.* Myocardial infarction among Danish HIV-infected individuals: Population-attributable fractions associated with smoking. *Clin. Infect. Dis.* **60**, 1415–1423 (2015).
17. Boyer, L. *et al.* Telomere shortening in middle-aged men with sleep-disordered breathing. *Ann. Am. Thorac. Soc.* **13**, 1136–1143 (2016).
18. Statistics NCfH. National Health Interview Survey Glossary. https://www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm
19. Quanjer, P. H. *et al.* Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur. Respir. J. Suppl.* **16**, 5–40 (1993).
20. Baumgartner, R. N. *et al.* Epidemiology of sarcopenia among the elderly in New Mexico. *Am. J. Epidemiol.* **147**, 755–763 (1998).
21. Gabriel, K. R. The biplot graphic display of matrices with application to principal component analysis. *Biometrika* **58**, 453–467 (1971).
22. Brown, T. T. & Qaqish, R. B. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: A meta-analytic review. *AIDS* **20**, 2165–2174 (2006).
23. Cotter, A. G. *et al.* Relative contribution of HIV infection, demographics and body mass index to bone mineral density. *AIDS* **28**, 2051–2060 (2014).
24. Hawkins, K. L. *et al.* Abdominal obesity, sarcopenia, and osteoporosis are associated with frailty in men living with and without HIV. *AIDS* **32**, 1257–1266 (2018).
25. Guerri-Fernandez, R. *et al.* HIV infection is strongly associated with hip fracture risk, independently of age, gender, and comorbidities: A population-based cohort study. *J. Bone Miner. Res.* **28**, 1259–1263 (2013).
26. van den Borst, B., Gosker, H. R. & Schols, A. M. Central fat and peripheral muscle: Partners in crime in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **187**, 8–13 (2013).
27. van den Borst, B. & Schols, A. M. Low bone mineral density in emphysema: Epiphenomenon of a wasting phenotype?. *Am. J. Respir. Crit. Care Med.* **184 (author reply 8–9)**.
28. Chand, H. S. *et al.* Cigarette smoke and HIV synergistically affect lung pathology in cynomolgus macaques. *J. Clin. Investig.* **128**, 5428–5433 (2018).
29. MacDonald, D. M. *et al.* Smoking and accelerated lung function decline in HIV-positive individuals: A secondary analysis of the START pulmonary substudy. *J. Acquir. Immune Defic. Syndr.* **79**, e85–e92 (2018).
30. Crothers, K. *et al.* Increased COPD among HIV-positive compared to HIV-negative veterans. *Chest* **130**, 1326–1333 (2006).
31. Bigna, J. J., Kenne, A. M., Asangbeh, S. L. & Sibetcheu, A. T. Prevalence of chronic obstructive pulmonary disease in the global population with HIV: A systematic review and meta-analysis. *Lancet Glob. Health* **6**, e193–e202 (2018).
32. Echeverria, P. *et al.* Pulse wave velocity as index of arterial stiffness in HIV-infected patients compared with a healthy population. *J. Acquir. Immune Defic. Syndr.* **65**, 50–56 (2014).
33. Fitch, K. V. *et al.* Effects of aging and smoking on carotid intima-media thickness in HIV-infection. *AIDS* **27**, 49–57 (2013).

Author contributions

L.B., J.D.L., B.R.B., S.A., S.H., S.G., E.A., S.Z. contributed to the study design. L.M., F.Z., J.-L.L.-Z., S.A., L.B., J.D.L., S.G. contributed to the data acquisition. S.Z., E.A., L.B., J.D.-L., S.G. contributed to the data analysis and interpretation. L.B., S.Z., E.A., J.D.-L. participated in the initial drafting and all authors substantially revised the manuscript. All authors have approved the manuscript prior to submission.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-023-39861-5.

Correspondence and requests for materials should be addressed to L.B.

AJPM FOCUS
INCLUSIVITY IN PEOPLE, METHODS, AND OUTCOMES
RESEARCH ARTICLE

E-Cigarette Use Among Persons With Diagnosed HIV in the U.S.

Stacy L. Thorne, PhD, MPH,[1] Ralph S. Caraballo, PhD,[2] Yunfeng Tie, PhD,[1] Norma S. Harris, PhD,[1] R. Luke Shouse, MD, MPH,[1] John T. Brooks, MD[1]

Introduction: E-cigarettes emerged in the U.S. market in the late 2000s. In 2017, E-cigarette use among U.S. adults was 2.8%, with higher use among some population groups. Limited studies have assessed E-cigarette use among persons with diagnosed HIV. The purpose of this study is to describe the national prevalence estimates of E-cigarette use among persons with diagnosed HIV by selected sociodemographic, behavioral, and clinical characteristics.

Methods: Data were collected between June 2018 and May 2019 as part of the Medical Monitoring Project, an annual cross-sectional survey that produces nationally representative estimates of behavioral and clinical characteristics of persons with diagnosed HIV in the U.S. Statistically significant differences ($p<0.05$) were determined using chi-square tests. Data were analyzed in 2021.

Results: Among persons with diagnosed HIV, 5.9% reported currently using E-cigarettes, 27.1% had ever used them but were not using them currently, and 72.9% had never used them. Current use of E-cigarettes was highest among persons with diagnosed HIV who currently smoke conventional cigarettes (11.1%), those with major depression (10.8%), those aged 25–34 years (10.5%), those who reported injectable and noninjectable drug use in the past 12 months (9.7%), those diagnosed <5 years ago (9.5%), those who self-reported sexual orientation as other (9.2%), and non-Hispanic White people (8.4%).

Conclusions: Overall, findings suggest that a greater proportion of persons with diagnosed HIV used E-cigarettes than the overall U.S. adult population and that higher rates were observed among certain subgroups, including those who currently smoke cigarettes. E-cigarette use among persons with diagnosed HIV warrants continued attention because of its potential impact on HIV-related morbidity and mortality.

INTRODUCTION

In the late 2000s, E-cigarettes emerged in the U.S. market and were initially advertised as a cessation aid to those who smoke cigarettes.[1] These battery-powered devices deliver nicotine, flavoring, and other additives through an inhaled aerosol.[1] Since the emergence of E-cigarettes in the U.S. and world markets, minimal information exists about potential long-term health effects.

From the [1]Division of HIV/AIDS Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia; and [2]Office on Smoking and Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

Address correspondence to: Stacy L. Thorne, Division of HIV/AIDS Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, Mail Stop US8-5, Atlanta GA 30329. E-mail: sthorne@cdc.gov.

2773-0654/$36.00
https://doi.org/10.1016/j.focus.2022.100056

However, there are studies on the short-term effects of E-cigarettes.[2] Studies have linked E-cigarette use to adverse cardiovascular and respiratory outcomes.[3,4] Notably, ingredients in E-cigarettes vary, including various nicotine concentrations, carcinogens, and toxic substances found in tobacco cigarettes.[1] Although there are some common carcinogens in E-cigarettes and cigarettes, overall, E-cigarettes appear to contain fewer amounts of carcinogens[5–8] and may benefit those trying to quit smoking, if used as a complete substitute for combustible tobacco products.[9]

Over time, the use of E-cigarettes has increased among various population groups, especially youth (aged 13–18 years), young adults (aged 18–24 years), and those who currently smoke cigarettes.[10,11] During 2018–2019, E-cigarette use among U.S. adults was 2.3% and was higher among some population groups.[12] About 39% of adults who currently use E-cigarettes also currently smoke cigarettes (dual users),[12,13] which may lead to increased nicotine dependency and higher risks of tobacco-related morbidity and mortality.[3,14]

Since 2009, cigarette smoking among persons with diagnosed HIV (PWH) has decreased; however, usage remains significantly higher, and PWH are less likely to quit than the general U.S. population (33.6% vs. 16.8%).[15] Risks of HIV- and non-HIV–related morbidity and mortality due to cigarette smoking are higher for PWH, including those taking antiretroviral medications (ARTs).[16] Even though E-cigarettes can serve as a bridge to tobacco cessation among persons who currently smoke cigarettes, the health effects, such as lung diseases, associated with their use may pose similar health risks among PWH, similar to that of the general population.[3,6,14] At present, estimates of E-cigarette use among PWH are scarce. The purpose of this study is to describe the national estimates of E-cigarette use among PWH by selected sociodemographic, behavioral, and clinical characteristics.

METHODS

Study Population

Data were obtained from the Medical Monitoring Project (MMP), an annual cross-sectional survey designed to produce nationally representative estimates of behavioral and clinical characteristics of U.S. adults diagnosed with HIV. Briefly, the 2018 and 2019 MMP data cycles used a 2-stage sampling method that has been described elsewhere.[17] MMP data collection has been determined to be nonresearch.[18] Participating states or territories obtained local IRB approval, when necessary, on the basis of local requirements to collect data and obtained informed consent from all participants. Data were weighted on the basis of known probabilities of selection at state/territory and person levels and to adjust for person-level nonresponse and were poststratified to National HIV Surveillance System population totals.[17] Data were combined from participant interviews and medical record abstraction collected during MMP's 2018 and 2019 data cycles (n=8,150) to assess the prevalence of E-cigarette use among PWH.

Measures

Persons who currently use E-cigarettes were defined as persons who reported having used ≥1 E-cigarettes in their lifetime and in the past 30 days. *Persons who have ever tried E-cigarettes* were defined as individuals who had used ≥1 E-cigarettes in their lifetime but not in the past 30 days. *Persons who have never tried E-cigarettes* were defined as individuals who had never used an E-cigarette.

Self-reported information on sociodemographic and behavioral characteristics from participants was included. Sociodemographic variables included sex, sexual orientation, race/ethnicity, age, educational attainment, health insurance or other coverage for medical expenses, and annual household income. Household income and the number of household dependents were used to determine participants' poverty level on the basis of guidelines and thresholds published by the HHS, Census Bureau for 2017–2019.[19] Health insurance was categorized on the basis of participant's self-report regarding the type of coverage during the 12 months before the interview. Behavioral characteristic variables included the use of cigarettes, alcohol, and other substances as well as diagnosis of depression. Utilizing an established definition for smoking,[15] persons who currently smoke were individuals who smoked at least 100 cigarettes in their lifetime and currently smoked daily, weekly, monthly, or less than monthly. Persons who formerly smoked were individuals who reported that they had smoked ≥100 cigarettes in their lifetime and currently did not smoke, whereas persons who never smoke were individuals who reported that they had smoked 0 to <100 cigarettes in their lifetime. *Any alcohol use* was defined as having consumed ≥1 alcoholic beverage during the 12 months before the interview. *Any drug use* was defined as having used injected or noninjected drugs during the past 12 months. Drugs assessed include both illicit and prescription drugs. Prescription drugs could have been nonprescribed or prescribed but taken more than directed. As described elsewhere, self-reported responses to the Patient Health Questionnaire depression scale were used to determine whether participants had major, other, or no depression.[20]

Also included were HIV clinical variables abstracted from participants' medical records. These variables included time since HIV diagnosis, HIV disease stage at diagnosis, prescribed ART, and recent or sustained viral suppression. *Recent viral suppression* was defined as the most recent viral load measurement in the past 12 months <200 copies/mL. *Sustained viral suppression* was defined as having viral load measurements <200 copies/mL on all viral load measurements in the past 12 months.

Statistical Analysis

Weighted percentages and associated 95% CIs were computed. Statistical estimations were suppressed if the sample size was <30 or the relative coefficient of variation was >0.30. Statistically significant differences (p<0.05) were determined using chi-square tests. All analyses accounted for complex sample design and unequal selection probabilities and were conducted using SAS, Version 9.4. Data were analyzed in 2021.

Table 1. Sociodemographic and HIV Clinical Characteristics of Adults With Diagnosed HIV, MMP, 2018–2019

Demographics	n[a]	%[b] (95% CI[c])
Sex		
Male	5,888	74.7 (73.0, 76.5)
Female	2,090	23.3 (21.6, 25.1)
Transgender[d]	165	2.0 (1.6, 2.3)
Sexual orientation		
Heterosexual or straight	3,866	46.3 (43.6, 49.0)
Homosexual or gay	3,266	41.3 (38.6, 43.9)
Bisexual	715	9.3 (8.3, 10.2)
Other	238	3.1 (2.5, 3.7)
Race/ethnicity[e]		
White, non-Hispanic	2,320	29.1 (25.1, 33.2)
Black, non-Hispanic	3,459	41.4 (34.8, 48.0)
Hispanic/Latino	1,816	22.3 (16.8, 27.9)
Other	555	7.1 (5.8, 8.4)
Age at the time of interview (years)		
18–24	173	2.2 (1.7, 2.6)
25–34	1,109	14.5 (13.3, 15.6)
35–44	1,364	18.4 (17.2, 19.5)
45–54	2,265	27.6 (26.6, 28.6)
≥55	3,239	37.5 (36.0, 38.9)
Education		
Less than HS, no diploma	1,403	16.6 (15.4, 17.8)
HS diploma or GED	2,191	26.9 (25.6, 28.2)
More than HS	4,533	56.5 (54.6, 58.4)
Combined yearly household income ($)[d]		
0–19,999	3,965	52.0 (50.1, 53.9)
20,000–39,999	1,625	22.7 (21.4, 24.0)
40,000–74,999	1,035	14.6 (13.6, 15.6)
≥75,000	822	10.7 (9.2, 12.2)
Poverty guidelines[d]		
Above poverty level	4,200	57.8 (55.6, 59.9)
At or below poverty level	3,244	42.2 (40.1, 44.4)
Time since HIV diagnosis (yr)		
<5	1,132	14.5 (13.5, 15.5)
5–9	1,416	17.9 (16.9, 19.0)
≥10	5,594	67.6 (66.5, 68.7)
Health Insurance or coverage type[d]		
Private insurance	2,771	34.1 (32.0, 36.2)
Public insurance (excluding RW/ADAP only)	4,507	54.3 (51.2, 57.4)
RW/ADAP only or no insurance coverage	769	11.2 (9.1, 13.3)
Unspecified insurance	46	0.5 (0.2, 0.7)
HIV clinical characteristics[d]		
HIV disease Stage 3 (AIDS)	4,734	55.8 (54.3, 57.2)
Prescribed ART	7,032	81.9 (80.6, 83.2)
Currently taking ART	7,758	93.7 (92.8, 94.6)
Viral suppression		
Sustained viral suppression	5,409	61.6 (58.9, 64.2)
Recent viral suppression	5,974	67.7 (64.7, 70.6)
Had at least one VL (past 12 months)	6,603	75.3 (71.9, 78.7)
Geometric mean CD4 count ≥200	6,037	92.4 (91.6, 93.1)

(continued on next page)

Table 1. Sociodemographic and HIV Clinical Characteristics of Adults With Diagnosed HIV, MMP, 2018–2019 (*continued*)

Demographics	n[a]	%[b] (95% CI[c])
Behavioral characteristics		
Cigarette use[f]		
Never	3,751	47.0 (44.6, 49.4)
Former	1,756	21.0 (19.5, 22.6)
Current	2,563	32.0 (30.0, 33.9)
E-cigarette use[g]		
Never	5,982	72.9 (70.3, 75.4)
Ever	2,105	27.1 (24.6, 29.7)
Current	448	5.9 (5.2, 6.5)
Any alcohol use (past 12 months)[d]		
No alcohol use	3,091	37.9 (35.8, 40.1)
Alcohol use	4,991	62.1 (59.9, 64.2)
Any drug use (past 12 months)[h]		
No injection or noninjection drug use	5,395	67.0 (65.0, 69.1)
Injection or noninjection drug use	2,659	33.0 (30.9, 35.0)
Depression[d]		
No depression	6,664	83.2 (82.0, 84.3)
Other depression	605	7.5 (6.8, 8.1)
Major depression	742	9.4 (8.5, 10.3)
Total	8,150	

[a]Numbers are unweighted. Numbers might not add to total because of missing data.
[b]Percentages are weighted column percentages. Percentages might not sum to 100 because of rounding.
[c]CIs incorporate weighted percentages.
[d]Variable definition has been described in detail in the study Centers for Disease Control and Prevention. Behavioral and Clinical Characteristics of Persons with Diagnosed HIV Infection: Medical Monitoring Project, United States 2016 Cycle (June 2016 – May 2017). In: HIV Surveillance Special Report 21; Revised edition. https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published June 2019.
[e]Non-Hispanic White: participants who self-identify as non-Hispanic and White only. Non-Hispanic Black: participants who self-identify as non-Hispanic and Black/African American only—Hispanic participants who self-identify as Hispanic, even if other race/ethnicity categories were selected. Other participants include those who selected Asian, Native Hawaiian/other Pacific Islander, American Indian/Alaska Native, or multiple race/ethnicity categories.
[f]Never smoker: respondents who said that they have not smoked at least 100 cigarettes in their entire life. Current smokers: respondents who said that they have smoked at least 100 cigarettes in their entire life and who now smoke daily, weekly, monthly, and less than monthly. Former smoker: respondents who said that they have smoked at least 100 cigarettes in their entire life and who now never smoke.
[g]*E-cigarette ever use* was defined as respondents who said that they have used an E-cigarette even just 1 time in their entire life. *Current E-cigarette use* was defined as respondents who said that they have used an E-cigarette even just 1 time in their entire life and have used E-cigarettes during the past 30 days.
[h]Includes all drugs that were injected and not injected (i.e., administered by any route other than injection), including legal drugs that were not used for medical purposes.
ART, antiretroviral therapy; HS, high school; MMP, Medical Monitoring Project; RW/ADAP, Ryan White HIV/AIDS or AIDS Drug Assistance Coverage; VL, viral load.

RESULTS

Descriptive data for the 8,150 MMP participants included in this analysis are shown in Table 1. During 2018–2019, 74.7% of the study population was male (CI=73.0, 76.5), 46.3% were heterosexual (CI=43.6, 49.0), and 41.4% were Black Americans (CI=34.8, 48.0). The median age was 50 years, and 54.3% had public insurance (CI=51.5, 57.0) other than Ryan White HIV/AIDS or AIDS Drug Assistance Coverage. In addition, 67.6% had HIV for >10 years (CI=66.5, 68.7), 93.7% were currently taking ART (CI=92.8, 94.6), 67.7% were virally suppressed at the time of their most recent viral load test (CI=64.7, 70.6), and 61.6% had sustained viral suppression (CI=58.9, 64.2). At least 32% of the study population were persons who currently smoke cigarettes (CI=30.0, 33.9), 62.1% used alcohol in the last 12 months (CI=59.9, 64.2), and 33.0% used injection or noninjection drugs in the last 12 months (CI=30.9, 35.0). In the study population, 5.9% currently used E-cigarettes (CI=5.2, 6.5), 27.1% ever used (but not currently) an E-cigarette (CI=24.6, 29.7), and 72.9% had never used E-cigarettes (CI=70.3, 75.4).

Current E-cigarette use among PWH was about 2 times higher among males (6.7%, CI=5.9, 7.5) than among females (3.3%, CI=2.3, 4.2). Current E-cigarette use among PWH was also about 2 times higher among those who reported being homosexual or gay (8.0%,

CI=6.8, 9.1) or bisexual (6.4%, CI=4.4, 8.4) than among those who reported being heterosexuals (3.7%, CI=2.9, 4.5) (Table 2). Current E-cigarette use was about 2 times higher among White Americans and others than among Black Americans (8.4%, CI=7.3, 9.6, 7.3% and CI=5.0, 9.6 vs 3.9%, CI=3.0, 4.7, respectively). Estimates of current E-cigarette use decreased with age; among the age groups with sufficient sample size for robust statistical estimation, use was highest among those aged 25−34 years (10.5%, CI=8.5, 12.5). Estimate of current E-cigarette use increased with education attainment; use was highest among those with more than a high school diploma (6.5%, CI=5.7, 7.4, $p<0.05$). Current E-cigarette use was also highest among participants whose HIV diagnosis was <5 years ago (9.5%, CI=7.6, 11.4) compared with among those who were diagnosed >10 years ago (4.7%, CI=4.0, 5.4).

Among the HIV clinical characteristics, current E-cigarette use was almost 2 times higher among PWH who were not in HIV disease Stage 3 than among those who were (7.1%, CI=6.1, 8.0 vs. 4.9%, CI=4.1, 5.7). Current E-cigarette use was also high among PWH who did not have sustained viral suppression (6.7%, CI=5.6, 7.8, $p<0.05$).

Current E-cigarette use was about 5 times higher among those who currently smoke cigarettes (11.1%, CI=9.7, 12.4) and 2 times higher among those who formerly smoked cigarettes (6.5%, CI=5.1, 7.9) than among those who never smoked cigarettes (2.0%, CI=1.4, 2.7). Current E-cigarette use was higher among people who used substances than among people who did not. Among persons who had used any alcohol or who used injectable and noninjectable drugs in the past 12 months, E-cigarette use was 7.2% (CI=6.3, 8.0) and 9.7% (CI=8.5, 11.0), respectively. Current use of E-cigarettes was higher among PWH who had major depression (10.8%, CI=8.1, 13.6) and other forms of depression (6.1%, CI=3.7, 8.6) than among PWH who did not have depression (5.3%, CI=4.6, 6.0).

Demographic characteristic estimates for persons who have ever tried E-cigarettes mimicked estimates for persons who are currently using E-cigarettes. These estimates can be found in Table 2. Ever use of E-cigarettes was higher among PWH whose diagnosis was not at disease Stage 3 (31.8%, CI=28.8, 34.7) than among those who were (23.4%, CI=23.8, 26.0). Ever use of E-cigarettes among PWH who were not prescribed (30.7%, CI=27.0, 34.4) or not currently taking ART (34.3%, CI=28.8, 39.8) was higher than among those who were prescribed (26.3%, CI=23.7, 28.9, $p<0.05$) or currently taking ART (26.6%, CI=24.1, 29.2, $p<0.05$). Ever use of E-cigarettes was higher among those who did not have sustained viral suppression (31.4%, CI=27.8, 35.0) than among those who had sustained viral suppression (24.5%, CI=22.2, 26.7). Ever use was higher among persons who had not achieved viral suppression (31.0%, CI=27.2, 34.9) than among those who had (25.3%, CI=23.1, 27.5) (Table 2).

Ever E-cigarette use was higher among persons who currently smoke cigarettes (51.0%, CI=47.2, 54.8) and persons who formerly smoked cigarettes (30.2%, CI=27.4, 32.9) than among persons who never smoked cigarettes (9.5%, CI=8.1, 11.0). Ever E-cigarette use was higher among people who used substances than among people who did not. Among persons who had used any alcohol or who used injectable and noninjectable drugs in the past 12 months, E-cigarette use was 31.7% (CI=29.2, 34.1) and 44.8% (CI=42.0, 47.6), respectively. Ever use of E-cigarettes was higher among those who had major depression (41.9%, CI=37.5, 46.4) than among those who had no depression (25.0%, CI=22.4, 27.6).

DISCUSSION

To our knowledge, these are the first nationally representative prevalence estimates of E-cigarette use among U.S. PWH. These findings suggest that current and ever use of E-cigarettes among PWH is higher than among the general U.S. population.[12] Findings showed that nearly 1 in 4 PWH had tried using E-cigarettes and that 1 in 20 PWH were current users. Even though E-cigarettes have only been in the U.S. market for about 10 years, evidence is emerging that E-cigarette use may cause deleterious health effects, especially for young users.[3,4]

Although this study group was an older cohort, with a median age of 50 years, only 2% were between the ages of 18 years and 24 years; we also found that current E-cigarette use varied among subgroups of PWH. Specifically, current and ever usage was higher among PWH who self-identified as bisexual, homosexual, or gay; males; non-Hispanic white people or others; those aged 25−34 years; those who had more than a high-school diploma; those who used any alcohol or drugs in the past 12 months; and those who have not sustained viral suppression.

Even though E-cigarettes were originally marketed as effective cessation aids to persons who smoke conventional cigarettes, they contain nicotine, the main ingredient, and other toxic ingredients also found in conventional cigarettes.[1] While the emissions from E-cigarettes generally contain lower levels of harmful ingredients than the smoke from regular cigarettes, they are not necessarily safer.[21] Research shows that dual use of E-cigarettes and conventional cigarettes increases nicotine exposure and intake, which may prolong tobacco substance use disorder and negate cessation efforts.[6,14] The finding that approximately 11% of PWH who currently smoke conventional cigarettes had also tried E-

Table 2. Sociodemographic and HIV Clinical Characteristics Among E-cigarette Adult Users With Diagnosed HIV, MMP 2018–2019

Demographics	Current E-cigarette use[a]			Ever E-cigarette use[a]			Never E-cigarette use[a]		
	n[b]	%[c] (95% CI[d])	*p*-Value[e]	*n*[b]	%[c] (95% CI[d])	*p*-Value[e]	*n*[b]	%[c] (95% CI[d])	*p*-Value[e]
Sex			**<0.0001**			**<0.0001**			**<0.0001**
Male	367	6.7 (5.9, 7.5)		1,639	29.1 (26.7, 31.5)		4,201	70.9 (68.5, 73.3)	
Female	69	3.3 (2.3, 4.2)		411	20.5 (16.8, 24.1)		1,666	79.5 (75.9, 83.2)	
Transgender[f]	12	NA		52	31.0 (22.1, 39.9)		111	69.0 (60.1, 77.9)	
Sexual orientation			**0.001**			**<0.0001**			**<0.0001**
Heterosexual or straight	138	3.7 (2.9, 4.5)		738	19.9 (16.8, 23.0)		3,110	80.1 (77.0, 83.2)	
Homosexual or gay	246	8.0 (6.8, 9.1)		1,049	33.1 (30.8, 35.4)		2,205	66.9 (64.6, 69.2)	
Bisexual	42	6.4 (4.4, 8.4)		222	32.6 (27.1, 38.0)		485	67.4 (62.0, 72.9)	
Other	20	9.2 (4.2, 14.2)		89	41.0 (31.6, 50.5)		147	59.0 (49.5, 68.4)	
Race/ethnicity[g]			**<0.0001**			**<0.0001**			**<0.0001**
White, non-Hispanic	193	8.4 (7.3, 9.6)		829	37.4 (34.3, 40.4)		1,477	62.6 (59.6, 65.7)	
Black, non-Hispanic	117	3.9 (3.0, 4.7)		698	21.7 (19.3, 24.0)		2,732	78.3 (76.0, 80.7)	
Hispanic/Latino	96	5.8 (4.3, 7.2)		384	21.4 (17.8, 25.0)		1,416	78.6 (75.0, 82.2)	
Other	42	7.3 (5.0, 9.6)		194	34.7 (29.3, 40.1)		357	65.3 (59.9, 70.7)	
Age at the time of interview (years)			**<0.0001**			**<0.0001**			**<0.0001**
18–24	16	NA		56	34.2 (25.9, 42.6)		116	65.8 (57.4, 74.1)	
25–34	109	10.5 (8.5, 12.5)		467	44.7 (40.0, 49.4)		632	55.3 (50.6, 60.0)	
35–44	104	8.0 (6.3, 9.7)		430	32.2 (29.0, 35.5)		921	67.8 (64.5, 71.0)	
45–54	120	5.1 (4.0, 6.2)		592	26.9 (23.6, 30.2)		1,658	73.1 (69.8, 76.4)	
≥55	99	3.3 (2.5, 4.1)		560	17.6 (15.0, 20.2)		2,655	82.4 (79.8, 85.0)	
Education			**0.006**			**<0.001**			**<0.001**
Less than HS, no diploma	50	3.7 (2.5, 4.8)		293	21.2 (17.8, 24.6)		1,102	78.8 (75.4, 82.2)	
HS diploma or GED	126	5.8 (4.5, 7.1)		564	27.0 (22.4, 31.5)		1,612	73.0 (68.5, 77.6)	
More than HS	272	6.5 (5.7, 7.4)		1,248	29.0 (26.8, 31.1)		3,264	71.0 (68.9, 73.2)	
Combined yearly household income ($)[f]			**0.045**			0.728			0.728
0–19,999	204	5.3 (4.3, 6.2)		1,046	27.7 (24.1, 31.4)		2,905	72.3 (68.6, 75.9)	
20,000–39,999	95	6.8 (5.4, 8.2)		436	28.2 (25.0, 31.5)		1,177	71.8 (68.5, 75.0)	
40,000–74,999	74	7.9 (6.0, 9.9)		275	27.4 (23.4, 31.3)		758	72.6 (68.7, 76.6)	
≥75,000	52	6.3 (4.3, 8.3)		198	25.3 (21.4, 29.2)		622	74.7 (70.8, 78.6)	
Poverty guidelines[f]			**0.023**			0.629			0.629
Above poverty level	258	6.8 (5.9, 7.7)		1,114	27.8 (25.2, 30.5)		3,064	72.2 (69.5, 74.8)	
At or below poverty level	167	5.2 (4.3, 6.2)		840	27.1 (23.4, 30.7)		2,396	72.9 (69.3, 76.6)	

(*continued on next page*)

Table 2. Sociodemographic and HIV Clinical Characteristics Among E-cigarette Adult Users With Diagnosed HIV, MMP 2018–2019 (*continued*)

Demographics	Current E-cigarette use[a]			Ever E-cigarette use[a]			Never E-cigarette use[a]		
	n[b]	%[c] (95% CI[d])	*p*-Value[e]	*n*[b]	%[c] (95% CI[d])	*p*-Value[e]	*n*[b]	%[c] (95% CI[d])	*p*-Value[e]
Time since HIV diagnosis (year)			**<0.0001**			**<0.0001**			**<0.0001**
<5	97	9.5 (7.6, 11.4)		375	35.4 (31.6, 39.2)		743	64.6 (60.8, 68.4)	
5–9	95	7.3 (5.9, 8.8)		430	31.2 (27.7, 34.8)		974	68.8 (65.2, 72.3)	
≥10	256	4.7 (4.0, 5.4)		1,298	24.3 (21.7, 26.8)		4,259	75.7 (73.2, 78.3)	
Health insurance or coverage[f]			0.050			0.421			0.421
Private insurance	172	6.9 (5.7, 8.0)		681	25.9 (23.4, 28.4)		2,076	74.1 (71.6, 76.6)	
Public insurance (excluding RW/ADAP only)	219	5.2 (4.3, 6.0)		1,195	27.7 (24.3, 31.0)		3,294	72.3 (69.0, 75.7)	
RW/ADAP Only or No insurance coverage	55	6.5 (4.6, 8.4)		212	28.5 (25.0, 32.0)		553	71.5 (68.0, 75.0)	
Unspecified insurance	2	NA		12	24.1 (12.3, 35.9)		34	75.9 (64.1, 87.7)	
HIV clinical characteristics[f]									
HIV disease Stage 3 (AIDS)			**<0.001**			**<0.0001**			**<0.0001**
No	226	7.1 (6.1, 8.0)		1,041	31.8 (28.8, 34.7)		2,354	68.2 (65.3, 71.2)	
Yes	222	4.9 (4.1, 5.7)		1,063	23.4 (20.8, 26.0)		3,628	76.6 (74.0, 79.2)	
Prescribed ART			0.900			**0.009**			**0.009**
No	59	6.0 (4.3, 7.7)		309	30.7 (27.0, 34.4)		789	69.3 (65.6, 73.0)	
Yes	389	5.8 (5.1, 6.6)		1,796	26.3 (23.7, 28.9)		5,193	73.7 (71.1, 76.3)	
Currently taking ART			0.882			**0.001**			**0.001**
No	19	5.7 (2.7, 8.6)		105	34.3 (28.8, 39.8)		221	65.7 (60.2, 71.2)	
Yes	429	5.9 (5.2, 6.6)		1,996	26.6 (24.1, 29.2)		5,741	73.4 (70.8, 75.9)	
Viral suppression									
Sustained viral suppression			**0.044**			**<0.0001**			**<0.0001**
No	175	6.7 (5.6, 7.8)		810	31.4 (27.8, 35.0)		1,895	68.6 (65.0, 72.2)	
Yes	273	5.4 (4.6, 6.1)		1,295	24.5 (22.2, 26.7)		4,087	75.5 (73.3, 77.8)	
Most recent viral suppression			0.607			**<0.0001**			**<0.0001**
No	126	6.1 (4.9, 7.3)		636	31.0 (27.2, 34.9)		1,509	69.0 (65.1, 72.8)	
Yes	322	5.7 (5.0, 6.5)		1,469	25.3 (23.1, 27.5)		4,473	74.7 (72.5, 76.9)	
Had at least 1 VL (past 12 months)			0.850			**0.013**			**0.013**
No	83	6.0 (4.6, 7.3)		437	30.4 (25.8, 35.1)		1,080	69.6 (64.9, 74.2)	
Yes	365	5.8 (5.1, 6.6)		1,664	25.9 (23.7, 28.2)		4,899	74.1 (71.8, 76.3)	
Geometric mean CD4 count ≥200			0.064			0.820			0.820
No	20	4.0 (2.4, 5.6)		125	25.9 (21.0, 30.8)		384	74.1 (69.2, 79.0)	
Yes	336	5.9 (5.0, 6.7)		1,548	26.3 (23.8, 28.8)		4,452	73.7 (71.2, 76.2)	
Behavioral characteristics									

(*continued on next page*)

Table 2. Sociodemographic and HIV Clinical Characteristics Among E-cigarette Adult Users With Diagnosed HIV, MMP 2018–2019 (*continued*)

Demographics	Current E-cigarette use[a]			Ever E-cigarette use[a]			Never E-cigarette use[a]		
	n[b]	%[c] (95% CI[d])	*p*-Value[e]	*n*[b]	%[c] (95% CI[d])	*p*-Value[e]	*n*[b]	%[c] (95% CI[d])	*p*-Value[e]
Cigarette use[h]			**<0.0001**			**<0.0001**			**<0.0001**
Never	72	2.0 (1.4, 2.7)		347	9.5 (8.1, 11.0)		3,403	90.5 (89.0, 91.9)	
Former	104	6.5 (5.1, 7.9)		503	30.2 (27.4, 32.9)		1,253	69.8 (67.1, 72.6)	
Current	271	11.1 (9.7, 12.4)		1,251	51.0 (47.2, 54.8)		1,312	49.0 (45.2, 52.8)	
Any alcohol use (past 12 months)[f]			**<0.0001**			**<0.0001**			**<0.0001**
No alcohol use	115	3.8 (2.8, 4.7)		591	19.8 (16.7, 22.8)		2,498	80.2 (77.2, 83.3)	
Alcohol use	333	7.2 (6.3, 8.0)		1,514	31.7 (29.2, 34.1)		3,476	68.3 (65.9, 70.8)	
Any drug use (past 12 months)[i]			**<0.0001**			**<0.0001**			**<0.0001**
No injection or noninjection drug use	199	4.0 (3.3, 4.7)		946	18.4 (16.0, 20.8)		4,448	81.6 (79.2, 84.0)	
Injection or noninjection drug use	248	9.7 (8.5, 11.0)		1,148	44.8 (42.0, 47.6)		1,511	55.2 (52.4, 58.0)	
Depression[f]			**0.002**			**<0.0001**			**<0.0001**
No depression	335	5.3 (4.6, 6.0)		1,621	25.0 (22.4, 27.6)		5,041	75.0 (72.4, 77.6)	
Other depression	38	6.1 (3.7, 8.6)		183	31.7 (27.4, 36.0)		421	68.3 (64.0, 72.6)	
Major depression	71	10.8 (8.1, 13.6)		279	41.9 (37.5, 46.4)		463	58.1 (53.6, 62.5)	
Total	448	5.9 (5.2, 6.5)		2,105	27.1 (24.6, 29.7)		5,982	72.9 (70.3, 75.4)	

Note: Boldface indicates statistical significance ($p<0.05$).

[a]*E-cigarette ever use* was defined as respondents who said that they have used an E-cigarette even just 1 time in their entire life. *Current E-cigarette use* was defined as respondents who said that they have used an E-cigarette even just 1 time in their entire life and have used E-cigarettes during the past 30 days.

[b]Numbers are unweighted.

[c]Percentages are weighted row percentages.

[d]CIs incorporate weighted percentages.

[e]Statistical significance within demographic, HIV clinical, and behavior characteristics using chi-square tests.

[f]Variable definition has been described in detail in the study Centers for Disease Control and Prevention. Behavioral and Clinical Characteristics of Persons with Diagnosed HIV Infection: Medical Monitoring Project, United States 2016 Cycle (June 2016 – May 2017). In: HIV Surveillance Special Report 21; Revised edition. https://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published June 2019.

[g]Non-Hispanic White: participants who self-identify as non-Hispanic and White only. Non-Hispanic Black: participants who self-identify as non-Hispanic and Black/African American only; Hispanic participants who self-identify as Hispanic, even if other race/ethnicity categories were selected. Other participants include those who selected Asian, Native Hawaiian/other Pacific Islander, American Indian/Alaska Native, or multiple race/ethnicity categories.

[h]Never smoker: respondents who said that they have not smoked at least 100 cigarettes in their entire life. Current smokers: *respondents* were defined as those who said that they have smoked at least 100 cigarettes in their entire life and who now smoke daily, weekly, monthly, and less than monthly. Former smoker: respondents who said that they have smoked at least 100 cigarettes in their entire life and who now never smoke.

[i]Includes all drugs that were injected and not injected (i.e., administered by any route other than injection), including legal drugs that were not used for medical purposes.

NA estimates are not presented because the coefficient of variance ≥30%.

ART, antiretroviral therapy; HS, high school; MMP, Medical Monitoring Project; NA, not applicable; RW/ADAP, Ryan White HIV/AIDS or AIDS Drug Assistance Coverage; VL, viral load.

cigarettes is consistent with general population studies regarding the dual use of E-cigarettes and conventional cigarettes.[12,13] It is noteworthy that persons with HIV who smoke make fewer quit attempts and have lower rates of smoking cessation success than the general population.[15] Similar to that of the general population, several behavioral risk factors such as alcohol, substance use, and mental health issues have been identified as barriers to successful smoking cessation among PWH.[22] These barriers combined with perceptions that E-cigarettes are effective cessation aids may partially explain the higher prevalence of E-cigarette use among persons with HIV who currently smoke than among the general population. Despite the fact that E-cigarettes are not Food and Drug Administration approved for smoking cessation coupled with the uncertainty of long-term health impacts, PWH are interested in their use.[23] E-cigarettes may have the potential to benefit non-pregnant adults who smoke conventional cigarettes if used as a complete substitute for regular cigarettes and other smoked tobacco products.[21] In order for adults who smoke conventional cigarettes to achieve any meaningful health benefits from e-cigarettes, they must fully switch to E-cigarettes and completely stop smoking conventional cigarettes and other tobacco products.[21] Even though less harmful cessation aids exist (e.g., nicotine replacement, pharmaceutical treatment, and cessation counseling),[24] there is literature to suggest that PWH may use them as a bridge to tobacco cessation or a safer substitute for combustible tobacco products.[23]

Over the past 30 years, achievements in the HIV epidemic resulting in PWH living longer and healthier lives have occurred.[25] Considering amplified health effects caused by the use of conventional cigarettes for PWH compared with that for persons in the general population,[16,24] E-cigarette use among PWH merits close attention. To avoid a rapid increase in E-cigarette use among PWH and to sustain PWH living longer and healthier lives, monitoring efforts for E-cigarette use among PWH and interventions to deter tobacco use for PWH should continue.

Limitations

This study has limitations. First, the analysis is limited to persons diagnosed with HIV in the U.S.; the results do not provide E-cigarette estimates among persons with undiagnosed HIV in the U.S. Second, our estimates of E-cigarette and conventional cigarette use were based on self-report and were not biochemically validated; however, studies have shown good correlation between self-reported tobacco use behaviors and biochemical measures such as cotinine.[26] Third, although MMP used data-weighting methods to mitigate nonresponse bias, nonresponse bias is still possible. In addition, there are differences between MMP and general population surveys (e.g., National Health Interview Survey) in the definition of current E-cigarette use. Fourth, owing to population sample size and unstable estimates, we were unable to perform a multivariable regression.[27] For example, for current E-cigarette use by age, the estimate of the proportion of current E-cigarette use in the age group 18−24 years had a coefficient variation >0.30, so it is suppressed for reporting and cannot be modeled.[27]

CONCLUSIONS

These findings suggest that current and ever use of E-cigarettes among PWH was at a greater proportion than among the general U.S. population,[12] suggesting that E-cigarette use may be a potential issue for PWH if they are being used with other tobacco products and not solely used as a substitute for conventional cigarettes and other smoked tobacco products. It is unclear at this time whether health effects related to E-cigarettes are amplified in the presence of HIV infection as it is for cigarette smoking.[16] E-cigarette use may be a preventable health threat; therefore, usage should be discouraged among adults who do not smoke conventional cigarettes. Persons interested in quitting smoking should be encouraged to first try Food and Drug Administration–approved smoking cessation aids, especially among PWH.

DECLARATIONS OF INTEREST

None.

ACKNOWLEDGMENTS

The authors thank participating Medical Monitoring Project providers, facilities, and project area staff.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Funding for the Medical Monitoring Project is provided by a cooperative agreement from CDC. CDC reviewed and approved the final submission.

CREDIT AUTHOR STATEMENT

Stacy L. Thorne: Conceptualization; Methodology; Writing - original draft; Visualization; Writing - review & editing. Ralph S. Caraballo: Methodology; Writing - review & editing; Supervision. Yunfeng Tie: Formal Analysis; Data curation; Writing - review & editing. Norma S. Harris: Writing - review & editing; Supervision. R. Luke Shouse: Writing - review & editing; Supervision. John T. Brooks: Writing - review & editing; Supervision.

REFERENCES

1. HHS. E-cigarette use among youth and young adults: a report of the Surgeon General. Atlanta, GA: U.S: Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016. https://e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Full_Report_non-508.pdf Accessed June 30, 2018.
2. George J, Hussain M, Vadiveloo T, et al. Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes. *J Am Coll Cardiol.* 2019;74(25):3112–3120. https://doi.org/10.1016/j.jacc.2019.09.067.
3. Reidel B, Radicioni G, Clapp PW, et al. E-cigarette use causes a unique innate immune response in the lung, involving increased neutrophilic activation and altered mucin secretion. *Am J Respir Crit Care Med.* 2018;197(4):492–501. https://doi.org/10.1164/rccm.201708-1590OC.
4. Osei AD, Mirbolouk M, Orimoloye OA, et al. Association between E-cigarette use and cardiovascular disease among never and current combustible-cigarette smokers. *Am J Med.* 2019;132(8). 949−954.e2. https://doi.org/10.1016/j.amjmed.2019.02.016.
5. Goniewicz ML, Leigh NJ, Gawron M, et al. Dual use of electronic and tobacco cigarettes among adolescents: a cross-sectional study in Poland. *Int J Public Health.* 2016;61(2):189–197. https://doi.org/10.1007/s00038-015-0756-x.
6. Glantz SA, Bareham DW. E-cigarettes: use, effects on smoking, risks, and policy implications. *Annu Rev Public Health.* 2018;39:215–235. https://doi.org/10.1146/annurev-publhealth-040617-013757.
7. Malas M, van der Tempel J, Schwartz R, et al. Electronic cigarettes for smoking cessation: a systematic review. *Nicotine Tob Res.* 2016;18(10):1926–1936. https://doi.org/10.1093/ntr/ntw119.
8. Rahman MA, Hann N, Wilson A, Mnatzaganian G, Worrall-Carter L. E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. *PLoS One.* 2015;10(3):e0122544. https://doi.org/10.1371/journal.pone.0122544.
9. Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. *N Engl J Med.* 2019;380(7):629–637. https://doi.org/10.1056/NEJMoa1808779.
10. Gentzke AS, Creamer M, Cullen KA, et al. Vital signs: tobacco product use among middle and high school students - United States, 2011−2018. *MMWR Morb Mortal Wkly Rep.* 2019;68(6):157–164. https://doi.org/10.15585/mmwr.mm6806e1.
11. Olfson M, Wall MM, Liu SM, Sultan RS, Blanco C. E-cigarette use among young adults in the U.S. *Am J Prev Med.* 2019;56(5):655–663. https://doi.org/10.1016/j.amepre.2018.12.004.
12. Mayer M, Reyes-Guzman C, Grana R, Choi K, Freedman ND. Demographic characteristics, cigarette smoking, and e-cigarette use among US adults. *JAMA Netw Open.* 2020;3(10):e2020694. https://doi.org/10.1001/jamanetworkopen.2020.20694.
13. Bao W, Xu G, Lu J, Snetselaar LG, Wallace RB. Changes in electronic cigarette use among adults in the United States, 2014−2016. *JAMA.* 2018;319(19):2039–2041. https://doi.org/10.1001/jama.2018.4658.
14. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med.* 2016;4(2):116–128. https://doi.org/10.1016/S2213-2600(15)00521-4.
15. Frazier EL, Sutton MY, Brooks JT, Shouse RL, Weiser J. Trends in cigarette smoking among adults with HIV compared with the general adult population, United States - 2009−2014. *Prev Med.* 2018;111:231–234. https://doi.org/10.1016/j.ypmed.2018.03.007.
16. Helleberg M, May MT, Ingle SM, et al. Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America [published correction appears in *AIDS.* 2015;29(14):1909]. *AIDS.* 2015;29(2):221–229. https://doi.org/10.1097/QAD.0000000000000540.
17. Behavioral and clinical characteristics of persons with diagnosed HIV infection: medical monitoring project, United States 2019 cycle. Centers for Disease Control and Prevention. https://www.cdc.gov/hiv/library/reports/hiv-surveillance-special-reports/no-28/index.html. Updated February 9, 2022. Accessed June 30, 2018.
18. Centers for Disease Control and Prevention. Distinguishing public health res public health nonresearch. Atlanta, GA: Centers for Disease Control and Prevention; 2010. https://stacks.cdc.gov/view/cdc/24235 Published July 29, Accessed October 26, 2022.
19. Poverty guidelines 2017-2019. U.S. Census Bureau. https://aspe.hhs.gov/topics/poverty-economic-mobility/poverty-guidelines/prior-hhs-poverty-guidelines-federal-register-references. Updated December 2022. Accessed June 30, 2022.
20. Do AN, Rosenberg ES, Sullivan PS, et al. Excess burden of depression among HIV-infected persons receiving medical care in the united states: data from the medical monitoring project and the behavioral risk factor surveillance system. *PLoS One.* 2014;9(3):e92842. https://doi.org/10.1371/journal.pone.0092842.
21. About electronic cigarettes (e-cigarettes). Centers for Disease Control and Prevention. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/about-e-cigarettes.html. Updated November 10, 2022. Accessed May 28, 2022.
22. Cioe PA. Smoking cessation interventions in HIV-infected adults in North America: a literature review. *J Addict Behav Ther Rehabil.* 2013;2(3):1000112. https://doi.org/10.4172/2324-9005.1000112.
23. Pacek LR, Rass O, Johnson MW. Positive smoking cessation-related interactions with HIV care providers increase the likelihood of interest in cessation among HIV-positive cigarette smokers. *AIDS Care.* 2017;29(10):1309–1314. https://doi.org/10.1080/09540121.2017.1330532.
24. HHS. The health consequences of smoking−50 years of progress: a report of the Surgeon General. Atlanta, GA: HHS, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014. https://www.hhs.gov/sites/default/files/consequences-smoking-exec-summary.pdf Accessed June 30, 2018.
25. Effectiveness of prevention strategies to reduce the risk of acquiring or transmitting HIV. Centers for Disease Control and Prevention. https://www.cdc.gov/hiv/risk/estimates/preventionstrategies.html. Updated June 17, 2022. Accessed June 10, 2019.
26. Connor Gorber S, Schofield-Hurwitz S, Hardt J, Levasseur G, Tremblay M. The accuracy of self-reported smoking: a systematic review of the relationship between self-reported and cotinine-assessed smoking status. *Nicotine Tob Res.* 2009;11(1):12–24. https://doi.org/10.1093/ntr/ntn010.
27. Jenkins DG, Quintana-Ascencio PF. A solution to minimum sample size for regressions. *PLoS One.* 2020;15(2):e0229345. https://doi.org/10.1371/journal.pone.0229345.