Review

Smoking Cessation for People Living With HIV/AIDS: A Literature Review and Synthesis

David M. Ledgerwood PhD, Russell Yskes MD

Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI

Corresponding Author: David M. Ledgerwood, PhD, Department of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Suite 2A, 3901 Chrysler Drive, Detroit, MI 48201, USA. Telephone: 313-993-1380; Fax: 313-993-1372; E-mail: dledgerw@med.wayne.edu

Abstract

Introduction: People living with HIV/AIDS (PLWHA) are more likely to smoke cigarettes than are individuals in the general population. The health implications of tobacco use are substantially more dire among PLWHA than among otherwise healthy smokers, including higher rates of various cancers, cardiovascular disease, inflammation, and lung infections. Efficacious behavioral and medication treatments for treating nicotine dependence have rarely been investigated in PLWHA.

Methods: We present a review of studies examining the efficacy of smoking cessation interventions.

Results and Conclusions: The literature reveals some limited evidence for the efficacy of behavioral interventions. However, the research literature on these interventions is sparse and the efficacy findings are mixed. Studies exploring the use of mobile technologies for reducing treatment barriers are becoming more prevalent. Few published trials have directly examined the efficacy of pharmacological smoking cessation interventions among PLWHA. Specific gaps in the treatment literature are discussed in detail, and a strategy is presented for developing a greater understanding of factors that contribute to the efficacy of smoking cessation among PLWHA.

Implications: This paper provides the most comprehensive review to date on smoking cessation intervention research conducted with PLWHA. It also discusses specific gaps in the literature that should be a priority for future research.

Introduction

As many as one in five deaths in the United States are due to smoking-related morbidity, and the financial burden of smoking related to illness and lost productivity exceeds \$289 billion each year.¹ Globally, tobacco use accounts for 12% of all deaths.² This high health burden of nicotine dependence is related to several factors. First, among the general population, cigarette smokers have significantly increased risk for numerous cancers (eg, lung, liver, larynx, esophagus, and colorectal cancers), chronic obstructive pulmonary disease, emphysema, stroke, diabetes mellitus, immune function deficits, rheumatoid arthritis, and many other diseases.¹ Second, about 18% of the adult population of the United States smokes cigarettes, meaning that the elevated health risks of smoking affect a large number of people.¹

As dire as the risk appears for the general population of smokers, the impact of cigarette smoking on people living with HIV/AIDS

(PLWHA) is substantially higher due to the overall health impact of HIV/AIDS and relatively high rates of smoking among this group. Recent studies reveal that nearly two-thirds of HIV+ smokers wish to quit smoking.^{3–5} However, despite the high-risk nature of smoking among PLWHA, relatively few studies have systematically examined treatment efforts to reduce smoking in this population. This dearth of studies might be a result of the nature of HIV/AIDS as an illness. Mortality from HIV/AIDS has dropped substantially in the past two decades due to the development of highly effective antiretroviral medications (ARTs), essentially making HIV/AIDS a chronic, manageable disease in many cases.⁶ Thus, behavioral factors such as smoking, diet, and exercise may have commanded diminished importance in the prior research climate. Furthermore, certain classes of ARTs may increase the risk for cardiovascular disease and myocardial infarction, particularly in combination with smoking.^{7,8}

Given the potential for reduced mortality using ARTs, there is an increasing focus on modifiable health risk factors such as smoking that have the potential to improve health and quality of life.⁹

The present review addresses the research gaps that have become more evident as a result of recent successes in reducing HIV/AIDS-related mortality. Specifically, this article reviews the current state of the literature on HIV/AIDS and tobacco use, including prevalence and health implications. The main emphasis of this paper is to present a thorough review of treatment efficacy/effectiveness studies, with attention to the substantial gaps in the literature and recommendations for further research.

Prevalence of Smoking Cessation in HIV

Compared with the general population, the prevalence of cigarette smoking among PLWHA is high. The most recent estimates place the prevalence of smoking among adults in the United States at 17.8%, a rate that has been falling precipitously since the 1964 Surgeon General Report when the prevalence rate was double today's rates.¹ By contrast, between 50% and 70% of PLWHA smoke cigarettes daily.^{3,5,10-13} On a positive note, one longitudinal study showed that smoking rates may be declining among women with HIV (to 39% in 2011 in the Women's Interagency HIV Study).¹⁴

Although the reasons for this high prevalence are not well understood, there are some factors that appear to distinguish nonsmoking from smoking PLWHA. Male PLWHA are more likely to be cigarette smokers than are women.^{13,15} Smokers also appear to be older, have less education, and are less likely to identify as Hispanic or Latino.¹³ Cigarette smoking among PLWHA is also associated with recent illicit substance use, particularly cocaine and marijuana use, as well as heavy or binge alcohol consumption.^{13,15}

There may also be psychological reasons for higher prevalence among PLWHA. For example, Grover et al.¹⁶ found that HIV+ cigarette smokers who experience greater levels of HIV-related symptom distress are more likely to expect smoking to relieve emotional distress and enhance positive mood (as well as being more likely to expect smoking to cause physical harm). PLWHA who smoke report doing so for numerous reasons, including improved concentration, relieving stress and worry, weight control, for socialization and enjoyment, and smoking out of habit.¹⁷ Some report that they smoke to help cope with depression, anxiety, and anger.⁴

Motivation to quit smoking may vary based on individual differences. For example, Peretti-Watel et al.¹⁷ reported that daily heavy smokers are less motivated to quit than occasional heavy smokers, and that strongly nicotine-dependent smokers and PLWHA who smoke for stress relief are less motivated to quit. Conversely, those with high perceived health risk report greater motivation to quit. Another large-scale study¹⁸ reported that PLWHA who were infected through intravenous drug use were less likely to attempt to quit smoking, but older patients, those with ≥ 15 years since initial diagnosis and those who had attempted to quit smoking previously, were more likely to engage in quit attempts.

Smoking-Related Morbidity and Mortality Among PLWHA

Compared with PLWHA who are nonsmokers, smokers have substantially greater prevalence of several illnesses, including increased respiratory symptoms, chronic obstructive pulmonary disease, and bacterial pneumonia.¹⁹ Smoking among PLWHA is associated with

at least a threefold increased risk of cancers of the lung, trachea, and bronchus,²⁰ and PLWHA diagnosed with smoking-related lung cancer face much higher mortality rates than do HIV negative smokers with a similar lung cancer diagnosis.²¹ HIV+ smokers also have lower CD4 cell counts, higher HIV viral loads, and lower self-reported quality of life than HIV+ nonsmokers.¹⁹⁻²² Smokers are also more likely to progress to an AIDS diagnosis,²³ have poorer response to ART,¹² and are more likely to be nonadherent to ART.²⁴ Importantly, longer duration of abstinence from smoking substantially reduces HIV symptom burden.²⁵ This finding is increasingly important as HIV shifts from being a largely deadly disease to a chronic illness that can be managed with increasing efficacy.

Lifson et al.²⁶ reported smoking data from a large ($N = 5472$) sample from the Strategies for Management of Antiretroviral Therapy clinical trial. Overall mortality was significantly higher for current than never-smokers. Additionally, compared with nonsmokers, current smokers had significantly higher rates of cardiovascular disease, non-AIDS cancers, and bacterial pneumonia. The most common non-AIDS cancers were nonmelanoma skin cancers and lung cancer, but only lung cancer was significantly more prevalent among current smokers.

In a study examining respondents to the Swiss HIV Cohort Study, all instances of cancers of the lip, mouth, pharynx, trachea, bronchus, and lung occurred among smokers in the cohort.²⁰ Lung cancer rates were insensitive to CD4 counts in this study, suggesting that higher rates are directly attributable to smoking in this population. Smoking also appears to have a compounding effect on chronic systemic inflammation associated with HIV, and this exaggerated inflammation may increase the risk for chronic illnesses such as chronic obstructive pulmonary disease, atherosclerotic disease, and others.²⁷

Health Benefits of Quitting Smoking

Health benefits of smoking cessation are well documented among the general population, with quitting smoking before age 40 resulting in years of life gained compared with those who do not quit.²⁸ Among HIV patients, quitting smoking also appears to convey substantial health benefits. For example, Lifson et al.²⁶ reported that mortality among HIV patients in their sample was significantly higher throughout the follow-up period for current smokers than for former smokers. Current smokers were also more likely than former smokers to experience AIDS-related events (which include diseases meeting the revised CDC AIDS case definition as well as other conditions associated with HIV-related immunodeficiency, such as esophageal candidiasis), cardiovascular disease, non-AIDS cancers, and bacterial pneumonia.

Benard et al.²⁹ reported that PLWHA who had at least 1 year of abstinence from smoking experienced substantial reductions in the rates of bacterial pneumonia compared with individuals who continued to smoke. Furthermore, although rates of bacterial pneumonia were higher among individuals who had greater HIV-related immunodeficiency (as measured by HIV RNA and CD4 count), there was no interaction between immunodeficiency and smoking status on incidence of infection. Thus, smoking cessation can be beneficial even in patients who experience greater risk via HIV-related vulnerability. Additional studies have demonstrated significantly reduced rates of cardiovascular disease (including instances of myocardial infarction and coronary heart disease) among HIV patients who quit smoking compared to current smokers.^{30,31} However, some studies

have not demonstrated a decrease in mortality rates in past smokers compared with current smokers.³¹

Smoking Cessation Efforts in Community Treatment of HIV/AIDS

To date, a relatively small number of studies have examined the attitudes and preparation of HIV treatment providers with regard to administering smoking interventions. Most HIV treatment providers rate smoking among their patients as a high-priority problem in need of clinical intervention.³² Further, there is evidence that a majority of HIV health care providers advise their patients to quit smoking, but these interventions are not universal.^{4,5} Among those who provide cessation services, the most frequent interventions include brief advice to quit, recommending nicotine replacement, and providing print self-help materials.³² Treatment providers cite both patient resistance to smoking cessation interventions, as well as systemic barriers (eg, lack of reimbursement for pharmacotherapy, lack of time, and lack of provider confidence in their abilities to provide smoking cessation) as barriers to effective implementation of smoking cessation treatments in HIV care.^{5,32} Importantly, however, PLWHA who smoke are significantly more likely to engage in a quit attempt if a treatment provider provides smoking intervention.³³

Research on Treatment Efficacy

Search Strategy

The primary aim of this article is to review efficacy studies for smoking cessation interventions used with PLWHA. We searched PubMed and ISI Web of Science using the terms (HIV or AIDS) and (nicotine or tobacco or smoking) and (treatment or clinical trial or cessation) to obtain all of the published English language articles on the topic. We also reviewed reference sections of published articles to obtain references missed in our database searches. We limited our searches to articles published in peer-review journals. In total, our searches returned 2314 articles on PubMed and 2340 articles on Web of Science. Thorough review of these abstracts revealed 22 trials that: (1) included a discernable treatment; (2) included application of treatment to human subjects diagnosed with HIV or AIDS; and (3) reported outcome data related to cigarette smoking. We considered limiting our search only to well-controlled clinical trials. However, examination of the literature revealed that there are relatively few controlled trials. Thus, we also report results from other trials with less rigorous designs (eg, open-label, nonrandom assignment).

We organized the studies into behavioral (eg, psychotherapy) and pharmacological interventions. However, we noted that several studies also used technology (eg, cellular telephones), and we added technologically assisted interventions as a subgroup within the behavioral treatments. All treatment studies published to date are presented in [Supplementary Tables 1](#) (behavioral), [2](#) (technology-based), and [3](#) (pharmacological).

Behavioral Treatments

Face-to-face interventions typically include brief (1–8 sessions) counseling directed toward smoking cessation, and the studies are often based on recent standard of care guidelines for smoking cessation.³⁴ The methodologies of these studies are varied. Some studies are rigorous with random assignment to treatments, intent-to-treat analysis of data, and follow-up assessment up to 1-year posttreatment.

Smoking outcomes frequently include 7-day point prevalence for smoking abstinence at specific timepoints (eg, posttreatment, 6- and 12-month follow-up). Modality varies with some studies testing individual counseling and others using group treatment. Most studies also use treatment techniques that have an evidence base in the broader smoking cessation literature; these often include cognitive behavioral therapy which involves having patients change perceptions of smoking and developing strategies for coping with urges to smoke, and motivational interviewing techniques which are geared toward helping individuals to address their ambivalence about smoking cessation, resulting in increased motivation and self-efficacy to quit. Further, in most of these studies, behavioral treatments are augmented by nicotine replacement therapy (NRT), usually in the form of nicotine patch.

In one study, PLWHA who wanted to quit smoking were randomly assigned to receive either two sessions of standard brief counseling or four sessions (plus one telephone session on the participant's quit day) of motivational enhancement therapy (with similar goals to motivational interviewing approaches).³⁵ Follow-up abstinence rates for the 2-, 4-, and 6-month assessments were 13%, 10%, and 10%, respectively, for the standard care condition, and 12%, 9%, and 9%, respectively, for the motivational enhancement condition. Groups did not differ significantly at these timepoints. Examination of race/ethnicity data revealed that African American participants were least likely to quit smoking, followed by European American participants, and Hispanic/Latino participants who demonstrated the highest likelihood of quitting. Another trial comparing self-guided reading of smoking cessation materials (plus NRT) to motivational interviewing (single session plus NRT) revealed no significant group differences at 3-month follow-up.³⁶

One pilot study randomized PLWHA to either a combined 8-week NRT and SBIRT (Screening, Brief Intervention, and Referral for Treatment) counseling or a usual care condition which involved standard HIV medical care and no smoking cessation treatment (although participants in standard care did participate in smoking assessments on the same schedule as the SBIRT group).³⁷ SBIRT resulted in fewer self-reported cigarettes smoked per day, lower physical nicotine dependence, lower smoking urge, and lower nicotine withdrawal symptoms than participants in an assessment-only condition. Another randomized study with a small sample ($N = 30$) compared women with HIV who received a single session of motivational interviewing or a brief prescribed advice condition.³⁸ All participants were encouraged to use nicotine replacement. Smoking outcomes assessed at 1-month follow-up revealed no difference between the two groups in 7-day point prevalence abstinence rates (self-report confirmed by urine cotinine scores) but found that motivational interview treated participants reported smoking significantly fewer cigarettes.

Moadel et al.³⁹ randomly assigned 145 PLWHA to receive either standard care (including brief advice to quit and NRT) or an enhanced program that included standard care and eight group therapy sessions that incorporated social support. Although there appeared to be stronger 3-month quit rates for those receiving group therapy (19.2% vs. 9.7%), these differences were not statistically significant. Multivariate analysis revealed that Latino ethnicity, lower scores on a loneliness scale, and attending seven or more sessions were associated with more successful quit attempts.

Several other small, uncontrolled pilot studies have examined various counseling programs for quitting smoking in PLWHA. Cummins et al.⁴⁰ combined NRT with motivationally based counseling, finding

that 44% of self-selected treatment enrollees self-reported quitting smoking by the end of the 8- to 12-week NRT administration period, and 22% of enrollees maintained self-reported abstinence through the end of 5-month follow-up. Elzi et al.⁴¹ compared smoking cessation rates in 34 self-selected PLWHA who participated in a nurse-delivered smoking cessation program that included cognitive behavioral counseling and NRT to 383 patients who did not participate in the program. They noted that posttreatment and 12-month self-reported abstinence rates for smoking program participants were 50% and 38%, respectively, compared with rates of 15% and 7%, respectively, for the control group.

In another similarly designed study, PLWHA who were motivated to quit smoking were provided with counseling and pharmacotherapy (NRT, bupropion, or varenicline decided on a case-by-case basis).³⁰ Among those who received treatment, 39.4%, 30.3%, and 25% were abstinent from smoking (determined by self-report verified by expired carbon monoxide [eCO] readings of <5 ppm) at the 3-, 6-, and 12-month follow-up assessments, respectively. Participants also evidenced significant cardiovascular benefits from quitting, including reduced systolic blood pressure and Regicor (cardiovascular risk) scale score. Wewers et al.⁴¹ examined cessation rates of randomized patients enrolled in a treatment that combined NRT and counseling by a peer counselor. They found that patients enrolled in this treatment were likely to exhibit abstinence at treatment week 8 and 8-month posttreatment, compared to none of the participants enrolled in a control condition that included only self-help materials were abstinent at either of these timepoints.

Matthews et al.⁴² examined outcomes of PLWHA who underwent a seven-session, group-based intervention plus NRT. They found the intervention to be feasible and highly acceptable by participants. eCO-verified 7-day point prevalence rate at 1 month was 16%, and at 3 months was only 6%. NRT adherence was poor with 68% initiating any patch use, and an average use of only 11 out of 28 possible days of use. Browning et al.⁴³ conducted a nonrandomized trial in which all participants received 12 weeks of telephone-based cognitive behavioral counseling and pharmacotherapy (NRT or varenicline). Seven-day point prevalence abstinence rates (confirmed by negative cotinine test) were 19.4% at the 3-month follow-up and 10.2% at the 12-month assessment. Abstinence was associated with adherence to medication and counseling at the 3-month assessment, and adherence to counseling at the 12-month assessment. Chew et al.⁴⁴ reported 16% self-reported 7-day point prevalence rates at their 6-month follow-up for PLWHA who participated in a single counseling session and were prescribed pharmacotherapy. Finally, Cropsey et al.⁴⁵ noted that smokers who underwent brief counseling and an algorithm-based intervention designed to provide appropriate level of care based on patient motivation to quit and indications for medication treatments reported greater reductions in self-reported cigarettes smoked per day and a greater number of 24-hour quit attempts over treatment and 1-month follow-up compared with patients who received usual care.

By and large, these studies demonstrate that PLWHA are able to reduce their smoking, but that abstinence rates are generally modest, particularly at long-term follow-up points. Assessment methods for smoking abstinence are inconsistent with some studies using only self-report, some using eCO (a method with short half-life), and few using cotinine tests. Abstinence rates tend to be lower when biological tests (CO and cotinine) are used for confirmation of self-report. Additionally, several of these studies are hampered by lack of randomization, comparison conditions, and treatment fidelity

assessments. Thus, any conclusions regarding their efficacy should be made cautiously.

A small number of studies have also focused on training HIV care physicians to provide smoking cessation counseling and treatment. In one study, one center from the Swiss HIV Cohort Study implemented a structured smoking cessation training program for medical staff.⁴⁶ All physicians participated in a half-day workshop on treatment for nicotine dependence. Subsequently, all patients underwent assessment and treatment for smoking at their semiannual appointments. This treatment center experienced significantly increased smoking cessation and reduced smoking relapse relative to patients at comparison institutions. Further, smoking cessation was higher among individuals with cardiovascular risk, and negatively associated with being middle-aged, intravenous drug use, psychiatric difficulties, and heavier alcohol consumption.

Technology Assisted Interventions

A small but growing literature has begun to explore the use of interventions that have a broader reach for PLWHA who smoke. Often, these individuals are challenged by lower socioeconomic status, which results in difficulties accessing care via transportation, social support, and other constraints. Nevertheless, a majority of PLWHA who smoke also appear to use cellular phones, and about half access the Internet.⁴⁷ Studies have begun to explore the use of technology to reduce these barriers and improve access to treatment for PLWHA who also face socioeconomic difficulties. For example, one pilot study examined the feasibility and acceptability of providing a cellular phone-based smoking cessation counseling to low-income PLWHA.⁴⁸ In total, 19 out of 20 participants completed the intervention and 75% self-reported smoking abstinence at assessments 1 and 2 weeks after their quit dates.

In a series of well-designed studies, Vidrine et al.^{25,48-51} have also demonstrated the value of cellular phone-delivered smoking cessation for PLWHA. In an initial randomized trial, PLWHA were randomly assigned to receive usual care (involving brief advice on quitting, self-help materials, and nicotine replacement) or a cellular phone-based counseling (involving the same usual care plus eight proactive counseling sessions across 2 months on a prepaid cellular phone and access to a hotline number for additional support).⁵⁰ Three-month intent-to-treat outcomes revealed that cellular phone treated participants were significantly more likely to be abstinent (biochemically verified 7-day point prevalence 16.7% vs. 6.4%) and had longer durations of abstinence (mean 24.4 vs. 10.2 days) than those who received only usual care.

Based on this initial study, this group conducted a randomized, intent-to-treat clinical trial in which 474 PLWHA were randomized to receive either usual care (similar to ref.⁵⁰ except that NRT was recommended, not provided) or a cellular phone counseling intervention (11 sessions across 3 months).^{49,51} Outcomes revealed that participants receiving the cellular phone intervention were 4.33 times more likely to be abstinent at 3-month follow-up (based on 7-day point prevalence confirmed using CO testing) than those in the usual care condition.⁵¹ Similarly, positive outcomes were found for the cellular phone condition when considering other smoking outcomes at 3 months (24-hour abstinence, 30-day abstinence, and continuous abstinence); however, the authors caution that a fairly small proportion of their sample actually quit smoking at this point (12% in the cellular phone condition vs. 3% in usual care). In a separate report, the authors noted that group differences diminished and

were no longer significant at 6- and 12-month follow-up timepoints with the exception of 7-day point prevalence at 12-months.⁴⁹

Few studies have examined Internet-based interventions for smoking cessation among PLWHA. In one such study, Shuter et al.⁵² randomly assigned PLWHA to receive either standard brief advice or an eight-session, web-based counseling intervention (both groups also were offered 3 months of NRT). Adherence and engagement in the web-based intervention was good (eg, subjects logged on to a mean 5.5 out of eight sessions, and 26.2 of 41 available web pages were accessed). Three-month, biochemically verified smoking abstinence did not differ significantly between treatment conditions (10.1% in the web-based intervention compared with 4.3% in the control group). However, among those who were randomized to the web-based intervention, quit rate among those who logged on to all eight sessions was 17.9%, and 21.7% for those who accessed all 41 web pages. Satisfaction ratings were also high across the sample for the Internet intervention.

Another study compared participants randomized to receive six face-to-face sessions of cognitive behavioral therapy for smoking, a six-module Internet-based intervention, or a self-help condition.⁵³ All participants received NRT. Cessation rates at the end of treatment ranged from 15% to 29% across conditions, but treatment differences in abstinence were not statistically significant. Smoking cessation was associated with greater baseline desire to quit, lower mood disturbance, and being employed.

Medication Treatments

Nicotine replacement treatments (NRT), including nicotine patch, gum, inhalers, lozenges, and other forms, have demonstrated significant efficacy in numerous clinical trials with healthy smokers and other nicotine-dependent groups (see Cahill et al.⁵⁴ for a recent meta-analysis). However, no double-blind, placebo-controlled trials have been conducted with PLWHA. Many of the psychosocial intervention studies described above included either prescription for or encouragement to obtain NRT. Further, a few smaller, uncontrolled, and open-label trials have shown smoking reduction among PLWHA using NRT and behavioral interventions.^{11,36,40} Compliance with NRT tends to be poor across studies.^{36,42} Further, it appears that psychological variables, including self-efficacy and motivation (decisional balance) around quitting, may mediate the relationship between NRT use and smoking abstinence.⁵⁵

Bupropion, a norepinephrine-dopamine reuptake inhibitor that is also used to treat depression, has similarly demonstrated efficacy across numerous smoking cessation trials in a number of different patient groups,⁵⁴ but no randomized trials have examined the efficacy of bupropion in PLWHA. Bupropion has demonstrated efficacy and tolerability among PLWHA being treated for depression (eg, ref.⁵⁶). Some have suggested that ritonavir may reduce the availability of bupropion treatment through inhibition of cytochrome P450 2B6-mediated hydroxylation of bupropion.⁵⁷ However, research on healthy volunteers found that short-term ritonavir use has only a minimal impact (<20%) on the pharmacokinetic effect of a single dose of bupropion.⁵⁷ Subsequent research has demonstrated that the pharmacokinetic clearance of bupropion is pronounced at exposure to high doses of ritonavir (600mg twice daily), and substantially less so at lower doses, possibly requiring adjustments of bupropion dose (100mg twice daily).⁵⁸ Further, the protease inhibitor combination of lopinavir and ritonavir (400/100mg) was found to decrease bupropion maximum plasma concentration by 57% with similar reductions in hydroxybupropion concentrations among healthy

volunteers.⁵⁹ Similarly, there is evidence that efavirenz can result in decreased bupropion plasma concentrations; however, the clinical implications remain unclear.⁶⁰

Varenicline is a relatively newer medication that has demonstrated efficacy in treating otherwise healthy smokers.^{54,61} Varenicline is a partial agonist at alpha 4/beta 2 subtype of the nicotinic acetylcholine receptor, and it is believed that this is the physiological mechanism that results in reduced craving and psychogenic effects of nicotine. One open-label study has examined the safety, tolerability, and initial effectiveness of varenicline among PLWHA.⁶² This study reported that adverse events associated with varenicline use tended to be mild (including nausea, abnormal dreams, affect lability, and insomnia) and tended to be similar to those reported by otherwise healthy individuals on this medication. The exception was that participants in this study experienced more abnormal dreams and a higher medication discontinuation rate than that published for HIV negative, generally healthy smokers. Positive effects were noted for smoking cessation including increased continuous abstinence rates throughout weeks 9–12 (42%) and weeks 9–24 (28%) of participation, as well as increased 7-day point prevalence abstinence rates (39% in the first 3 weeks, 50% at study week 12, and 42% at study week 24). Other changes noted in this sample included increased CD4 count by week 24, no increases in viral load detection and some weight gain, but there were also increases in alanine transaminase (ALT) and diastolic blood pressure that prompted the authors to caution that physicians should closely monitor liver enzymes and blood pressure of patients on varenicline.

Another open-label study compared varenicline to nicotine replacement (NRT).⁶³ Participants in this study were encouraged to take varenicline but were offered NRT if they had contraindications for or preferred not to take this medication. At 3-month posttreatment, more participants in the varenicline condition were abstinent (25.6%) than were NRT-treated participants (11.8%). Ferketich et al.⁶³ reported similar adverse events for varenicline, as well as specific adverse effects for NRT (including rash around patch site, nausea, vivid dreams, and insomnia). These authors also noted a single case of suicidal ideation that resolved after discontinuation of varenicline, and one case of myocardial infarction in a patient receiving NRT. About 14% discontinued varenicline or switched to NRT because of adverse effects. Overall, the adverse effects profiles were similar (only minor differences found) for those on ART and those not on ART.

Finally, a small open-label trial of varenicline among 22 PLWHA revealed that six patients were smoking abstinent at 3-months, and five were abstinent at 6-months.⁶⁴ Some patients discontinued the trial because of poor motivation (three patients) or adverse effects of varenicline (one patient). Only the first 15 days of varenicline was free to patients, and the authors noted that a majority of patients did not complete treatment because of medication cost. Although these studies are promising, it is important to note that no published, blinded, randomized trials have been conducted to establish the efficacy of varenicline in PLWHA.

Gaps in the Literature

Although there have been more studies examining the efficacy of smoking cessation interventions over the past two decades, several gaps in the literature are clear on the basis of this review. First, and most importantly, there are very few clinical trials examining the efficacy of smoking cessation treatment for PLWHA. Furthermore, the

studies that do examine the efficacy of behavioral and medication interventions have several methodological limitations. Many behavioral studies do not use a randomized assignment to treatment. The pharmacological trials tend to be open-label, with one study comparing NRT to varenicline based on patient factors (self-selection and clinical considerations). Although some studies use an intent-to-treat approach, this is the exception rather than the rule, and in some cases there is little or no long-term follow-up, meaning the longevity of benefits of smoking interventions is difficult to determine.

Among the studies that examine behavioral interventions, biologically confirmed smoking cessation rates tend to be modest, with many studies reporting follow-up abstinence rates that frequently do not differ significantly from treatment as usual. This finding is similar to the rates of abstinence found among several other populations of smokers (eg, refs. ^{65,66}). Thus, there is a need to improve the success of smoking cessation interventions for PLWHA by either (1) developing more efficacious interventions or (2) testing interventions that have a broader reach. Cell phone- and Internet-based interventions represent options that may improve the overall reach and availability of treatment to a larger proportion of the HIV population who are ready to quit smoking. Although cell phone and Internet interventions may not be any more effective than face-to-face interventions, there is a significant potential to reach a much larger number of people and to reduce barriers to treatment (eg, transportation) that are often faced by PLWHA. Given the challenges of developing highly effective smoking interventions that are provided on a face-to-face basis, it may be worthwhile to expand research into interventions using widely available technology in order to reduce barriers to care inherent in face-to-face approaches.

Future studies that are designed to test established treatments that have not been examined among PLWHA may demonstrate improved outcomes over treatment that have been tested to date. Contingency management approaches, for example, that use tangible rewards for successful completion of a behavioral target (such as a negative CO test) have been shown to directly reduce cigarette smoking in numerous challenging populations.⁶⁷ This intervention, which is typically used as an adjunct to other behavioral or medication approaches, has also been used to improve attendance to group therapy⁶⁸ and ART medication compliance⁶⁹ among PLWHA. Thus, contingency management may demonstrate efficacy for improving both initial quit rates as well as adherence to treatment if tested in HIV+ smokers.

Finally, very few studies have examined the implementation of smoking cessation strategies on a broad scope across multiple treatment settings (eg, infectious disease and primary care clinics). One study found that, although identification of smokers among case-loads was generally high, HIV treatment providers were more likely to fail to recognize smokers among their cases than were non-HIV providers.⁷⁰ Female providers and nurse practitioners/physician's assistants were more likely to correctly identify smokers than were male providers and physicians, respectively. Further, infectious disease providers were more likely to identify smokers than were general medicine providers. These differences may stem from differential training or confidence in providing smoking cessation services, meaning that greater emphasis should be placed on these services in HIV care. There is evidence that treatment policy implementation focusing on increasing screening, treatment, and follow-up of smoking cessation among PLWHA can increase the extent to which this issue is addressed by medical personnel.⁹

In conclusion, there is an imminent need to develop and test the efficacy of smoking cessation interventions among PLWHA.

Smokers with HIV are at substantially elevated risk for several smoking-related diseases, and there is evidence that quitting smoking can result in improved health outcomes. However, the state of smoking cessation intervention research in the area of HIV lags behind the field, generally. In particular, there is a need for controlled clinical trials to examine the efficacy of pharmacological interventions in this population. There is also a need to develop new interventions designed to bolster both the effectiveness and reach of current behavioral smoking cessation treatments, including those that may be delivered through technology-based measures.

Supplementary Material

Supplementary Tables 1–3 can be found online at <http://www.ntr.oxfordjournals.org>

Funding

Supported by National Institutes of Health grants R01 DA034537 and R21 DA021839 and supported by the Helene Lycaki/Joe Young Sr. Fund (State of Michigan) and Detroit Wayne Mental Health Authority.

Declaration of Interests

None declared.

Acknowledgments

We thank Dr. Brenda Davie for her editorial assistance.

References

1. U.S. Department of Health and Human Services. *The Health Consequences of Smoking – 50 Years of Progress: 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; 2014.
2. World Health Organization. *WHO Global Report: Mortality Attributable to Tobacco*. Geneva, Switzerland: WHO; 2012.
3. Mamary EM, Bahrs D, Martinez S. Cigarette smoking and the desire to quit among individuals living with HIV. *AIDS Patient Care STDS*. 2002;16(1):39–42. doi:10.1089/108729102753429389.
4. Shuter J, Bernstein SL, Moadel AB. Cigarette smoking behaviors and beliefs in persons living with HIV/AIDS. *Am J Health Behav*. 2012;36(1):75–85. doi:10.5993/AJHB.36.1.8.
5. Tesoriero JM, Gieryic SM, Carrascal A, Lavigne HE. Smoking among HIV positive New Yorkers: prevalence, frequency, and opportunities for cessation. *AIDS Behav*. 2010;14(4):824–835. doi:10.1007/s10461-008-9449-2.
6. The Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372(9635):293–299. doi:10.1016/S0140-6736(08)61113-7.
7. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003;349(9):1993–2003. doi:10.1056/NEJMoa030218.
8. Friis-Møller N, Weber R, Reiss P, et al.; DAD Study Group. Cardiovascular disease risk factors in HIV patients – association with antiretroviral therapy. Results from the DAD study. *AIDS*. 2003;17(8):1179–1193.
9. Zwiebel MA, Hughes V. Smoking cessation efforts in one New York City HIV clinic. *J Assoc Nurses AIDS Care*. 2010;21(1):11–15. doi:10.1016/j.jana.2009.10.001.
10. Burkhalter JE, Springer CM, Chhabra R, Ostroff JS, Rapkin BD. Tobacco use and readiness to quit smoking in low-income HIV-infected persons. *Nicotine Tob Res*. 2005;7(4):511–522. doi:10.1080/14622200500186064.

11. Elzi L, Spoerl D, Voggensperger J, et al.; Swiss HIV Cohort Study. A smoking cessation program in HIV-infected individuals: a pilot study. *Antivir Ther.* 2006;11(6):787–795.
12. Feldman JG, Minkoff H, Schneider MF, et al. Association of cigarette smoking with HIV prognosis among women in the HAART era: a report from the women's interagency HIV study. *Am J Public Health.* 2006;96(6):1060–1065. doi:10.2105/AJPH.2005.062745.
13. Gritz ER, Vidrine DJ, Lazev AB, Amick BC, Arduino RC. Smoking behavior in a low-income multiethnic HIV/AIDS population. *Nicotine Tob Res.* 2004;6:71–77. doi:10.1080/14622200310001656885.
14. Hessel NA, Weber KM, D'Souza G, et al. Smoking cessation and recidivism in the Women's Interagency Human Immunodeficiency Virus Study. *Am J Prevent Med.* 2014;47(1):53–69. doi:10.1016/j.amepre.2014.02.010.
15. Pacek LR, Harrell P, Martins SS. Cigarette smoking and drug use among a nationally representative sample of HIV-positive individuals. *Am J Addict.* 2014;23(6):582–90. doi:10.1111/j.1521-0391.2014.12145.x.
16. Grover KW, Gonzalez A, Zvolensky MJ. HIV symptom distress and smoking outcome expectancies among HIV+ smokers: a pilot test. *AIDS Patient Care STDs.* 2013;27(1):17–21. doi:10.1089/apc.2012.0333.
17. Peretti-Watel P, Garelik D, Baron G, Spire B, Ravaud P, Duval X; EVIT Study Group. Smoking motivations and quitting motivations among HIV-infected smokers. *Antivir Ther.* 2009;14(6):781–787. doi:10.3851/1292.
18. Encrenaz G, Benard A, Rondeau V, et al.; ANRS CO3 Aquitaine Study Group (Groupe d'Epidémiologie Clinique du Sida en Aquitaine). Determinants of smoking cessation attempts among HIV-infected patients: results from a hospital-based prospective cohort. *Curr HIV Res.* 2010;8(3):212–217. doi:10.2174/157016210791111089.
19. Crothers K, Griffith TA, McGinnis KA, et al. The impact of cigarette smoking on mortality, quality of life and comorbid illness among HIV-positive veterans. *J Gen Intern Med.* 2005;20(12):1142–1145. doi:10.1111/j.1525-1497.2005.0255.x.
20. Clifford GM, Polesel J, Rickenbach M, et al.; Swiss HIV Cohort. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst.* 2005;97(6):425–432. doi:10.1093/jnci/dji072.
21. Sridhar KS, Flores MR, Raub WA, Saldana M. Lung cancer in patients with human immunodeficiency virus infection compared with historic control subjects. *Chest.* 1992;102(6):1704–1708.
22. Turner J, Page-Shafer K, Chin DP, et al.; Pulmonary Complications of HIV Infection Study Group. Adverse impact of cigarette smoking on dimensions of health-related quality of life in persons with HIV infection. *AIDS Patient Care STDs.* 2001;15(12):615–624. doi:10.1089/108729101753354617.
23. Page-Shafer K, Delorenze GN, Satariano WA, Winkelstein W. Comorbidity and survival in HIV-infected men in the San Francisco Men's Health Survey. *Ann Epidemiol.* 1996;6(5):420–430. doi:10.1016/S1047-2797(96)00064-6.
24. Shuter J, Bernstein SL. Cigarette smoking is an independent predictor of nonadherence in HIV-infected individuals receiving highly active antiretroviral therapy. *Nicotine Tob Res.* 2008;10(4):731–736. doi:10.1080/14622200801908190.
25. Vidrine DJ, Arduino RC, Gritz ER. The effects of smoking abstinence on symptom burden and quality of life among persons living with HIV/AIDS. *AIDS Patient Care STDs.* 2007;21(9):659–666. doi:10.1089/apc.2007.0022.
26. Lifson AR, Neuhaus J, Arribas JR, van den Berg-Wolf M, Labriola AM, Read TR; INSIGHT SMART Study Group. Smoking-related health risks among persons with HIV in the Strategies for Management of Antiretroviral Therapy clinical trial. *Am J Public Health.* 2010;100(10):1896–1903. doi:10.2105/AJPH.2009.188664.
27. Shirley DK, Kaner RJ, Glesby MJ. Effects of smoking on non-AIDS-related morbidity in HIV-infected patients. *Clin Infect Dis.* 2013;57(2):275–282. doi:10.1093/cid/cit207.
28. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med.* 2013;368(4):341–350. doi:10.1056/NEJMsa1211128.
29. Benard A, Mercié P, Alioum A, et al. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000–2007. *PLoS One.* 2010;5(1):e8896. doi:10.1371/journal.pone.0008896.
30. Fuster M, Estrada V, Fernandez-Pinilla MC, et al. Smoking cessation in HIV patients: rate of success and associated factors. *HIV Med.* 2009;10(10):614–619. doi:10.1111/j.1468-1293.2009.00735.x.
31. Petoumenos K, Worm S, Reiss P, et al.; D:A:D Study Group. Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study(*). *HIV Med.* 2011;12(7):412–421. doi:10.1111/j.1468-1293.2010.00901.x.
32. Horvath KJ, Eastman M, Prosser R, Goodroad B, Worthington L. Addressing smoking during medical visits: patients with Human Immunodeficiency Virus. *Am J Prevent Med.* 2012;43(5 suppl 3):S214–S221. doi:10.1016/j.amepre.2012.07.032.
33. Berg CJ, Nehl EJ, Wang X, et al. Healthcare provider intervention on smoking and quit attempts among HIV-positive versus HIV-negative MSM smokers in Chengdu, China. *AIDS Care.* 2014;26(9):1201–1207. doi:10.1080/09540121.2014.892565.
34. Fiore MC, Jaen CR, Baker TB, et al. *Treating Tobacco Use and Dependence: 2008 Update.* Rockville, MD: Agency for Healthcare Research and Quality; 2008.
35. Lloyd-Richardson EE, Stanton CA, Papandonatos GD, et al. Motivation and patch treatment for HIV+ smokers: a randomized controlled trial. *Addiction.* 2009;104(11):1891–1900. doi:10.1111/j.1360-0443.2009.02623.x.
36. Ingersoll KS, Cropsey KL, Heckmann CJ. A test of motivational plus nicotine replacement interventions for HIV positive smokers. *AIDS Behav.* 2009;13(3):545–554. doi:10.1007/s10461-007-9334-4.
37. Cropsey KL, Hendricks PS, Jardin B, et al. A pilot study of screening, brief intervention, and referral for treatment (SBIRT) in non-treatment seeking smokers with HIV. *Addict Behav.* 2013;38(10):2541–2546. doi:10.1016/j.addbeh.2013.05.003.
38. Manuel JK, Lum PJ, Hengl NS, Sorensen JL. Smoking cessation interventions with female smokers living with HIV/AIDS: a randomized pilot study of motivational interviewing. *AIDS Care.* 2013;25(7):820–827. doi:10.1080/09540121.2012.733331.
39. Moadel AB, Bernstein SL, Mermelstein RJ, Arnsten JH, Dolce EH, Shuter J. A randomized controlled trial of a tailored group smoking cessation intervention for HIV-infected smokers. *J Acquir Immune Defic Syndr.* 2012;61(2):208–215. doi:10.1097/QAI.0b013e3182645679.
40. Cummins D, Trotter G, Moussa M, Turham G. Smoking cessation for clients who are HIV-positive. *Nurs Stand.* 2005;20(12):41–47.
41. Wewers ME, Neidig JL, Kihm KE. The feasibility of a nurse-managed, peer-led tobacco cessation intervention among HIV-positive smokers. *J Assoc Nurses AIDS care.* 2000;11(6):37–44. doi:10.1016/S1055-3290(06)60353-1.
42. Matthews AK, Conrad M, Kuhns L, Vargas M, King AC. Project exhale: preliminary evaluation of a tailored smoking cessation treatment for HIV-positive African American smokers. *AIDS Patient Care STDs.* 2013;27(1):22–32. doi:10.1089/apc.2012.0253.
43. Browning KK, Wewers ME, Ferketich AK, Diaz P, Koletar SL, Reynolds NR. Adherence to Tobacco Dependence Treatment Among HIV-Infected Smokers. *AIDS Behav.* 2016;20(3):608–621. doi:10.1007/s10461-015-1059-1.
44. Chew D, Steinberg MB, Thomas P, Swaminathan S, Hodder SL. Evaluation of a smoking cessation program for HIV infected individuals in an urban HIV clinic: challenges and lessons learned. *AIDS Res Treat.* 2014;1–8. doi:10.1155/2014/237834.
45. Cropsey KL, Jardin BF, Burkholder GA, Clark CB, Raper JL, Saag MS. An algorithm approach to determining smoking cessation treatment for persons living with HIV/AIDS: results of a pilot trial. *J Acquir Immune Defic Syndr.* 2015;69(3):291–298. doi:10.1097/QAI.0000000000000579.
46. Huber M, Ledergerber B, Sauter R, et al.; Swiss HIV Cohort Study Group. Outcome of smoking cessation counselling of HIV-positive persons by HIV care physicians. *HIV Med.* 2012;13(7):387–397. doi:10.1111/j.1468-1293.2011.00984.x.
47. Chander G, Stanton C, Hutton HE, et al. Are smokers with HIV using information and communication technology? Implications for

- behavioral interventions. *AIDS Behav.* 2012;16(2):383–388. doi:10.1007/s10461-011-9914-1.
48. Lazev AB, Vidrine DJ, Arduino RC, Gritz ER. Increasing access to smoking cessation treatment in low-income, HIV-positive population: the feasibility of using cellular telephones. *Nicotine Tob Res.* 2004;6(2):281–286. doi:10.1080/14622200410001676314.
 49. Gritz ER, Danysh HE, Fletcher FE, et al. Long-term outcomes of a cell phone-delivered intervention for smokers living with HIV/AIDS. *Clin Infect Dis.* 2013;57(4):608–615. doi:10.1093/cid/cit349.
 50. Vidrine DJ, Arduino RC, Gritz ER. Impact of a cell phone intervention on mediating mechanisms of smoking cessation in individual living with HIV/AIDS. *Nicotine Tob Res.* 2006;8(suppl 1):S103–S108. doi:10.1080/14622200601039451.
 51. Vidrine DJ, Marks RM, Arduino RC, Gritz ER. Efficacy of cell phone-delivered smoking cessation counseling for persons living with HIV/AIDS: 3-month outcomes. *Nicotine Tob Res.* 2012;14(1):106–110. doi:10.1093/ntr/ntr121.
 52. Shuter J, Morales DA, Considine-Dunn SE, An LC, Stanton CA. Feasibility and preliminary efficacy of a web-based smoking cessation intervention for HIV-infected smokers: a randomized controlled trial. *J Acquir Immune Defic Syndr.* 2014;67(1):59–66. doi:10.1097/QAI.0000000000000226.
 53. Humfleet GL, Hall SM, Delucchi KL, Dilleay JW. A randomized clinical trial of smoking cessation treatments provided in HIV clinical care settings. *Nicotine Tob Res.* 2013;15(8):1436–1445. doi:10.1093/ntr/ntr121.
 54. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis (review). *Cochrane Database Syst Rev.* 2013;5:CD009329. doi:10.1002/14651858.
 55. Stanton CA, Lloyd-Richardson EE, Papandonatos GD, de Dios MA, Niaura R. Mediators of the relationship between nicotine replacement therapy and smoking abstinence among people living with HIV/AIDS. *AIDS Educ Prev.* 2009;21(3 suppl):65–80. doi:10.1521/aeap.2009.21.3_suppl.65.
 56. Currier MB, Molina G, Kato M. A prospective trial of sustained-release bupropion for depression in HIV-seropositive and AIDS patients. *Psychosomatics.* 2003;44(2):120–125.
 57. Hesse LM, Greenblatt DJ, von Moltke LL, Court MH. Ritonavir has minimal impact on the pharmacokinetic disposition of a single dose of bupropion administered to human volunteers. *J Clin Pharmacol.* 2006;46(5):567–576. doi:10.1177/0091270006286981.
 58. Park J, Vousden M, Brittain C, et al. Dose-related reductions in bupropion plasma concentrations by ritonavir. *J Clin Pharmacol.* 2010;50(10):1180–1187. doi:10.1177/0091270009359524.
 59. Hogeland GW, Swindells S, McNabb JC, Kashuba ADM, Yee GC, Lindley CM. Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects. *Clin Pharm Ther.* 2006;81(1):69–75. doi:10.1038/sj.clpt.6100027.
 60. Robertson SM, Maldarelli F, Natarajan V, Formentini E, Alfaro RM, Penzak SR. Efavirenz induces CYP2B6-mediated hydroxylation of bupropion in healthy subjects. *J Acquir Immune Defic Syndr.* 2008;49(5):513–519. doi:10.1097/QAI.0b013e318183a425.
 61. Jorenby DE, Hays JT, Rigotti NA, et al.; Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA.* 2006;296(11):56–63. doi:10.1001/jama.296.1.56.
 62. Cui Q, Robinson L, Elston D, et al. Safety and tolerability of varenicline tartrate (Chantix/Chantix) for smoking cessation in HIV-infected subjects: a pilot open-label study. *AIDS Patient Care STDs.* 2012;26(1):12–19. doi:10.1089/apc.2011.0199.
 63. Ferketich AK, Diaz P, Browning KK, et al. Safety of varenicline among smokers enrolled in the Lung HIV study. *Nicotine Tob Res.* 2013;15(1):247–254. doi:10.1093/ntr/nts121.
 64. Tornero C, Mafé C. Varenicline and antiretroviral therapy in patients with HIV. *J Acquir Immune Defic Syndr.* 2009;52(2):656. doi:10.1097/QAI.0b013e3181ba1beb.
 65. Heckman CJ, Egleston BL, Hofmann MT. Efficacy of motivational interviewing for smoking cessation: a systematic review and meta-analysis. *Tob Control.* 2010;19(5):410–416. doi:10.1136/tc.2009.033175.
 66. Mottillo S, Filion KB, Bélisle P, et al. Behavioural interventions for smoking cessation: a meta-analysis of randomized controlled trials. *Eur Heart J.* 2009;30(6):718–730. doi:10.1093/eurheartj/ehn552.
 67. Ledgerwood DM. Contingency management for smoking cessation: where do we go from here? *Curr Subst Abuse Rev.* 2008;1(6):340–349. doi:10.2174/1874473710801030340.
 68. Petry NM, Martin B, Finocche C. Contingency management in group treatment: a demonstration project in an HIV drop-in center. *J Subst Abuse Treat.* 2001;21(2):89–96. doi:10.1016/S0740-5472(01)00184-2.
 69. Rosen MI, Dieckhaus K, McMahon TJ, et al. Improved adherence with contingency management. *AIDS Patient Care STDs.* 2007;21(1):30–40. doi:10.1089/apc.2006.0028.
 70. Crothers K, Goulet JL, Rodriguez-Barraas MC, et al. Decreased awareness of current smoking among health care providers of HIV-positive compared to HIV-negative veterans. *J Gen Intern Med.* 2007;22(6):749–754. doi:10.1007/s11606-007-0158-8.