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Research Initiative / Treatment Action!

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Jonathan Shuter, MD
Step-by-step advice on helping HIV-positive smokers quit
with Mark Mascolini
Abstract: In the United States more than half of everyone who ever smoked has quit. Most people addicted to nicotine require several quit attempts to stop, but in some people with HIV a failed quit attempt predicts future success. People with HIV appear to have a harder time quitting than people without HIV. CDC analysis of nationally representative samples figured a quit ratio of 52% in the general population versus 32% in HIV-positive people. Studies in HIV populations indicate that those most likely to quit smoking include older people, pregnant women, and people with a high motivation to quit, a previous quit attempt, or recent pulmonary disease. US health authorities recommend that clinicians adopt the 5As approach to smoking cessation: ask, advise, assess, assist, and arrange. But only a little more than half of US clinicians assist smokers in picking a smoke-ending strategy, and only 10% arrange follow-up within the first week after a quit date. Smoking-cessation medications recommended and tested in people with HIV are varenicline, bupropion, and nicotine replacement in various forms. Success with these strategies generally ranges from 10% to 20% in HIV-positive people, with higher success rates in some subgroups. Successful nondrug strategies to support drug therapy in people with HIV include an Internet-based interactive program, cell-phone reminder calls, one-time 1-hour one-on-one counseling, and formal clinician education.

More people have quit smoking in the United States than still smoke. And more than half of everyone who ever smoked has stopped. Those eye-opening statistics from the Surgeon General may be the best way to challenge hardcore smokers—and reluctant clinicians—who say quitting is just too tough. The Surgeon General’s findings make it clear that many can—and do—break their dependence on nicotine.

Who quits smoking and who starts again?

Research reviewed in this article suggests that several standard strategies—and perhaps a few novel approaches—have helped HIV-positive people quit smoking. A steadfast few can stub out their last butt, resolve never to light up again, and free themselves for life. But most face a sterner challenge. And that challenge may prove greater for people with HIV. Analysis of a nationally representative sample of US residents with HIV ranked 42.4% as current smokers, 20.3% as former smokers, and 37.3% as never smokers.2 In the general-population National Health Interview survey, only 20.6% were current smokers, while 21.9% smoked in the past and 57.5% never smoked. Centers for Disease Control and Prevention (CDC) researchers calculated that the general-population group had a quit ratio* of 51.7%, compared with 32.4% in the HIV group.

And quitters can become relapers. A 1994-2011 study of 2961 HIV-positive and 981 HIV-negative women in the Women’s Interagency HIV Study (WIHS) found that smoking prevalence in this largely black and Hispanic cohort waned from a high of 57% in 1996 to a low of 39% in 2011. Among 1622 women who smoked at their first study visit, 316 (19.5%) quit for a hefty median of 16.5 years. But among 273 sustained quitters

*Quit ratio equals former smokers divided by former plus current smokers.
with follow-up data, 145 (53%) resumed smoking after an average 7.2 years without cigarettes.

Quitting and relapsing rates proved similar in a Swiss HIV Cohort Study (SHCS) analysis that included 4833 HIV-positive smokers, about one quarter of them women. Through 2012, 1261 smokers (26%) quit at least temporarily. Among 1167 quitters with follow-up data, 557 (48%) resumed smoking.

CDC researchers turned up several clues to which HIV-positive smokers are more or less likely to quit by analyzing quit ratios in a nationally representative sample of people in care for HIV infection in 2009 (Table 1). Quitting rates track with age, as people 50 or older—more concerned about mortality—had the highest quit ratio (42.6%) while 18- to 29-year-olds had the lowest (16.3%). Women with HIV had a substantially lower quit ratio than HIV-positive men.

Table 1. HIV-positive people likely to quit smoking or relapse after quitting

<table>
<thead>
<tr>
<th>More likely to quit</th>
<th>Less likely to quit</th>
<th>More likely to relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age²</td>
<td>Younger age²</td>
<td>Younger age³</td>
</tr>
<tr>
<td>Pregnancy³</td>
<td>On cART³</td>
<td>Not on cART³</td>
</tr>
<tr>
<td>Previous quit attempt⁴</td>
<td>CD4 count &lt;200 cells/mm³ (vs &gt;500)</td>
<td>Smoked more daily before quitting⁴</td>
</tr>
<tr>
<td>High motivation to quit³</td>
<td>Women vs men²</td>
<td>Poor motivation to quit⁴</td>
</tr>
<tr>
<td>Recent pulmonary disease¹</td>
<td>Blacks vs Hispanics or whites²</td>
<td>Not living in one's own home³</td>
</tr>
<tr>
<td>Lower income²,³</td>
<td>Marijuana use¹</td>
<td>Crack, cocaine, or heroin use¹</td>
</tr>
<tr>
<td>Less education²,³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having health insurance¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking longer³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use¹,⁵</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug dependence⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor self-reported health³</td>
<td></td>
<td></td>
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<tr>
<td>Recent hospital admission⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension³</td>
<td></td>
<td></td>
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<tr>
<td>Psychiatric comorbidities⁴</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nationally representative US sample,² Women’s Interagency HIV Study,¹ Swiss HIV Cohort Study,⁴ Veterans Aging Cohort Study.⁵

cART, combination antiretroviral therapy.
(27.0% versus 34.2%), and blacks had a lower quit ratio (26.2%) than Hispanics (35.4%) or whites (38.2%). Quitting proved significantly more likely in HIV-positive people with more than a high school education (quit ratio 39.6%) than in those who only completed high school (26.8%) or didn’t finish high school (25.1%). HIV-positive people at or above the poverty level were significantly more likely to quit than people below the poverty levels (quit ratio 39.9% versus 24.3%). For every category listed, people with HIV had quit ratios significantly below those of smokers in the general population comparison group.

Analysis of 2961 HIV-positive women and 981 demographically similar HIV-negative women in WIHS identified several factors independently linked to longer time to quit smoking: less than high school education, only high school education (versus more), having health insurance, smoking for more than 10 years, 1 to 6 alcoholic drinks weekly or more (versus none), fair to poor self-reported health (versus good to excellent), and hypertension (Table 1). Limiting the analysis to women with HIV, the WIHS team pinpointed four additional risk factors for longer time to quitting smoking: household income at or below $12,000 yearly, use of combination antiretroviral therapy (cART), CD4 count below 200 cells/mm³ (versus 500 or higher), and use of crack, cocaine, or heroin. Pregnant women were more likely to quit smoking sooner.

To single out predictors of quitting and relapse, SHCS investigators built two models. The smoking cessation model classified smokers into highly, poorly, and typically motivated people based on common-sense predictors of high motivation (like a previous quit attempt or a recent cardiovascular diagnosis) (Figure 1). The relapse model incorporated nicotine dependence level (maximum cigarettes smoked daily before quitting), the three motivational groups, age, and gender.

The Swiss team found that smokers who stopped were more likely to be highly motivated and to have tried stopping before. Smokers were less likely to stop if they were poorly motivated, had a recent hospital admission, had psychiatric comorbidities, or had a history of alcohol or drug dependence.

Figure 1. Simple models for high or low motivation to quit smoking provided bases for more complex models to predict quitting and relapse from abstention in the Swiss HIV Cohort Study. The analysis found that “simple prediction models are nearly as discriminatory as complex models.” CVD, cardiovascular disease.
A Veterans Aging Cohort Study (VACS) team probed for predictors of quitting in 1027 HIV-positive and 794 HIV-negative veterans in care between 2005 and 2007. More than half of both groups, 56%, had tried to quit before, and two thirds of both groups were contemplating another attempt to quit. Among HIV-positive smokers, those with recent pulmonary disease proved almost 5 times more likely to have tried quitting recently (adjusted odds ratio [aOR] 4.93, 95% confidence interval [CI] 1.41 to 17.17). Unhealthy alcohol use cut odds that HIV-positive or negative veterans were contemplating quitting (aOR 0.66, 95% CI 0.49 to 0.90 for HIV positive).

Certainly, clinicians should not refrain from encouraging patients to stop smoking because they have one or more predictors of lower quitting likelihood. For example, the SHCS study found people with psychiatric comorbidity less likely to stop smoking. But the WIHS study of mostly black and Hispanic US women found no evidence that depression made women less likely to quit or more likely to relapse. People who inject drugs may seem poor candidates for smoke-ending interventions, but some are readier than others. A study of 267 HIV-positive current or former injection drug users who smoked found that older age and having a supporter who used medication to quit smoking doubled the odds of using smoke-ending medication.

Among HIV-positive and negative WIHS women who stopped smoking for more than 12 months, marijuana use and not living in one’s own home independently predicted a shorter time to resumed smoking (Table 1). Limiting the analysis to HIV-positive women identified two more predictors of a shorter time to relapse—enrollment in 2001-2002 (versus 1994-1995) and use of crack, cocaine, or heroin. Older age and cART use predicted a longer time to relapse. In the SHCS study, relapsers smoked more in the three follow-up visits before quitting and had poor motivation to quit (Figure 1).

Clinicians should tell smokers who quit and relapse that many people try to quit several times before succeeding, so they shouldn’t give up if the first few tries fail. Previous quit attempts predicted later success in the Swiss HIV Cohort Study.

The WIHS team speculates that HIV-positive women with a CD4 count below 200 cells/mm³ may be less likely to stop smoking because their more advanced HIV disease presents more immediate health challenges and robs them of motivation. That may also explain why women taking cART (who probably had more advanced disease) were less likely to quit in that analysis. But this WIHS study also linked taking cART to a longer time to relapse among women who quit at least 12 months. That could mean women doing well on cART have more motivation to improve their overall health, the authors propose. The surprising finding that women with health insurance took a longer time...
to quit, the WIHS team suggests, may mean women without insurance worry more about behaviors that threaten their health. But the insurance finding seems to be at odds with the link between lower income and lower probability of quitting.

The SHCS investigators found that their complex statistical models did no better than simple models (Figure 1) in picking HIV patients more likely to quit. “As a rough rule of thumb for clinicians,” they suggest, “patients in our highly motivated group, especially those with a history of attempting to stop, and those known to have stopped recently are the best candidates for an intervention.”

**First steps in getting HIV patients to quit**

US health authorities urge clinicians to adopt the 5As approach to smoking cessation (Figure 2). Research indicates that primary care providers do a good job on the first two As—ask every patient whether they smoke and advise smokers to stop. But dwindling proportions of clinicians implement the more time-consuming third, fourth, and fifth As. That falloff became clear in a study of 3336 people enrolled in the National Lung Screening Trial, which found lower lung cancer mortality in participants randomized to screening by low-dose computed tomography than in those randomized to chest x-ray. Participants reported that three quarters of their providers asked them about smoking and advised them to stop (Figure 3). But fewer than two thirds of providers assessed whether patients were willing to quit, only 56% assisted them in picking a smoke-ending strategy, and a mere 10% arranged follow-up after the patient began to quit.

Veterans Administration (VA) clinicians may not represent all HIV providers in the United States, but a VA study indicates that clinicians caring for veterans often do not know which patients smoke, and this gap in care is worse with HIV-positive veterans. The study compared reports of 801 HIV-positive and 602 HIV-negative veterans with reports of 72 HIV providers and 71 non-HIV providers. While 82% of non-HIV providers correctly identified current smokers, only 65% of HIV providers knew which of their patients smoked.

![Figure 2. US health authorities recommend that providers use the 5As approach to help patients stop smoking.](image-url)
Models adjusted for age, gender, race, and other factors determined that having HIV doubled the odds that the provider failed to identify current smoking (aOR 2.28, 95% CI 1.48 to 3.53). And compared with general practitioners, infectious diseases specialists proved almost 3 times more likely to miss current smokers (aOR 2.71, 95% CI 1.79 to 4.11). Providers did not identify current smokers more often when patients reported “bothersome” shortness of breath or cough, or when patients had smoking-related diseases like chronic obstructive pulmonary disease (COPD), coronary artery disease, or bacterial pneumonia. While 62% of non-HIV providers felt confident about influencing smoking cessation, only 39% of HIV providers did ($P = 0.049$).

A reasonable way to start encouraging HIV-positive people to forsake smoking is to count off the key benefits of quitting. The CDC highlights several major documented benefits of quitting, and research involving people with HIV confirms these benefits and adds others:

**Overall benefits of quitting smoking**

- Smoking-related mortality plunges up to 90% in smokers who quit when younger than 40.1
- When smokers over 50 years old quit, their excess cardiovascular disease risk disappears within 5 years.11
- Two to 5 years after quitting, risk of stroke may fall to the same level as someone who never smoked.12
- Within 5 years of quitting, risk of several cancers—mouth, throat, esophagus, and bladder—drops by half.12
- Ten years after quitting, lung cancer risk drops by half.12
**HIV-specific benefits of quitting smoking**

- Overall mortality risk is lower in former smokers than current smokers with HIV.\(^{13}\)
- Risk of cardiovascular disease, including myocardial infarction, is lower in former smokers than current smokers\(^{13}\) and decreases with longer time since quitting.\(^{14}\)
- Non-AIDS cancer risk is lower in former smokers than current smokers with HIV.\(^{13}\)
- Giving up cigarettes cuts risk of bacterial pneumonia, a frequent and serious complication of HIV infection.\(^{13,15-17}\)

In the interview on page 29 of this issue, HIV smoking expert Jonathan Shuter underlines the importance of building a quit plan before trying to stop smoking. The National Cancer Institute’s SmokeFree.gov offers a step-by-step interactive guide to help people design their personal quit plan ([http://smokefree.gov/build-your-quit-plan](http://smokefree.gov/build-your-quit-plan)). Creating a quit plan involves seven steps:

1. Set a quit date.
2. List your reasons for quitting.
3. Identify smoking triggers you should avoid.
4. Build a “quit kit” to help you fight tobacco cravings.
5. Get rid of smoking reminders.
6. Pick a smoke-ending medication with your provider and line up support.
7. Tell friends and family you plan to quit.

See pages 25 and 27 of this issue for 10-point summaries of long-term smoking risks and quitting benefits. At the same time, clinicians should not overlook the short-term benefits of quitting that may spark the interest of patients who want to see immediate gains from their abstinence. In a useful review article, Barcelona HIV experts Marta Calvo-Sánchez and Esteban Martínez note that short-term gains include having more money, tasting food better, and having better skin and less dyspnea.\(^{18}\)

**Smoke-ending drug therapy options**

In their comprehensive review of smoking and HIV, Barcelona clinicians Calvo-Sánchez and Martínez note “significant resistance among the general population and the HIV-positive community” against taking drugs to help quit smoking.\(^{18}\) Fewer than half of HIV clinicians responding to a nationwide survey reported frequently prescribing antismoking drugs.\(^{19}\) But relying on will power alone to quit, they observe, results in repeated failure to escape nicotine addiction and in quit rates below 10%.

Calvo-Sánchez and Martínez list three first-line medication options—various forms of nicotine-replacement therapy, varenicline (Chantix), and bupropion (Zyban).\(^{18}\) They relegate nortriptyline and clonidine to second-line status because of their side effects. These HIV smoking experts bluntly advise that “before a smoking cessation attempt, one of the first-line drugs should be prescribed in combination with health advice.”\(^{18}\) The reason for this exhortation is simple: These drugs work. The Cochrane Database of Systematic Reviews lists 53 trials of nicotine replacement gum in the general population, 41 trials of replacement patches, and 14 studies of replacement tablets, inhalers, or nebulizers.\(^{18}\) Cochrane counts 19 bupropion trials in the general population, 7 varenicline

continued...
trials, 6 clonidine trials, and 4 nortriptyline trials. With each of these options, odds ratios for successful cessation versus comparison interventions range from 1.43-fold (nicotine gum) to 2.33-fold (varenicline), and odds of success are always significant.

**Varenicline.** By blocking nicotinic acetylcholine receptors, varenicline blunts the craving for nicotine. Results of two small pilot trials\(^{20,21}\) and a larger placebo-controlled trial\(^{22}\) found at least short-term success with varenicline in people with HIV. The first study involved 22 people who took varenicline for an average 30 days.\(^{20}\) Abstinence could be confirmed by cotinine levels in 6 people (27%) after 3 months and in 5 (23%) after 6 months. One person stopped varenicline after 1 week because of vomiting, headache, and discomfort. In an open-label nonrandomized study of 36 people averaging 29 pack-years of smoking (for example, 2 packs a day for 14.5 years), 6 people (17%) stopped varenicline because of side effects.\(^{21}\) No one had grade 3 or 4 lab abnormalities or serious side effects. Fifteen of these 36 people (42%) had cotinine-confirmed continuous smoking abstinence in weeks 9 to 12 of treatment.

ANRS, the French national HIV trials group, conducted the placebo-controlled trial in 250 HIV-positive people who smoked at least 10 cigarettes daily and said they wanted to quit.\(^{22}\) The researchers excluded people with current psychoactive drug dependence, a suicide attempt, or ongoing depression. US prescribing information warns of “serious neuropsychiatric events,” including depression and suicide, in some people using varenicline.\(^{23}\) HIV-smoking mavens Calvo-Sánchez and Martinez suggest that “depression or psychiatric disorders at baseline are not contraindications [to varenicline] but great caution is recommended when depressive symptoms appear.”\(^{18}\)

Participants in the placebo-controlled trial smoked a median of 20 cigarettes daily, and more than 80% tried to quit at least once before.\(^{22}\) Their age averaged about 45, and 83% were men. Enrollees started varenicline at a dose of 0.5 mg once daily on days 1 to 3, followed by 0.5 mg twice daily on days 4 to 7, then two 0.5-mg tablets twice daily through week 12. The researchers confirmed self-reported quitting by measuring exhaled carbon monoxide. All participants received counseling on quitting throughout the study.

A modified intention-to-treat analysis involving 102 people who started varenicline and 111 who started placebo calculated continuous abstinence from weeks 9 through 12 in 34.3% randomized to varenicline and 12.6% randomized to placebo, rates that yielded 3.6-fold higher odds of quitting with varenicline (95% CI 1.8 to 7.2, \(P = 0.0003\)).\(^{22}\) From week 9 through week 48, the quit rate dwindled to 17.6% with varenicline versus 7.2% with placebo, results yielding still nearly tripled odds of quitting with varenicline (OR 2.8, 95% CI 1.1 to 6.7, \(P = 0.024\)). Grade 3 or 4 adverse events developed in 25% in the varenicline arm and 13% in the placebo group. Grade 3 or 4 drug-related adverse events affected 10% taking varenicline, while grade 3 or 4 drug-related psychiatric events affected 6%.

A nonrandomized US study of 228 HIV-positive smokers found that varenicline outdid nicotine-replacement therapy in helping people stop smoking\(^{24}\) as handily as it outdid placebo in the French trial.\(^{22}\) Study participants had enrolled in the Lung HIV study of respiratory complications; they smoked at least five cigarettes daily and expressed interest in quitting in the next 30 days. Researchers encouraged them to try varenicline for 12 weeks, and those who could not or opted not to received nicotine replacement therapy. Everyone got 12 weeks of telephone counseling. The
investigators confirmed 7-day abstinence by saliva cotinine levels or exhaled carbon monoxide.

Age averaged 43, and 85% of participants were men. While 118 took varenicline, 110 used a nicotine patch (with gum as needed). Rates of confirmed abstention at the end of treatment were 25.6% with varenicline and 11.8% with nicotine replacement, results that translated into 2.54-fold greater odds of abstention with varenicline (95% CI 1.43 to 4.49). About 14% taking varenicline switched to nicotine replacement because of adverse events, which included nausea, abnormal dreams, agitation, insomnia, and depression. One person taking varenicline reported suicidal ideation, a problem that resolved when varenicline stopped.

**Bupropion.** Bupropion may help people stop smoking via two mechanisms. First, the drug selectively inhibits reuptake of the addiction drivers dopamine and norepinephrine. Bupropion also blocks nicotine receptors. Prescribing information for bupropion warns that people taking the drug may feel hostility, agitation, or depression and may have suicidal thoughts. Protease inhibitors and efavirenz may lower bupropion concentrations.

Because bupropion is also prescribed as an antidepressant, Weill Cornell Medical College HIV experts call it “an attractive option” for some HIV-positive smokers. But bupropion remains poorly studied as a smoking stopper in people with HIV. In a Spanish case series of 21 HIV-positive smokers who took bupropion, 8 (38%) gave up cigarettes for more than 1 year. No one had clinically significant interactions with antiretrovirals.

**Nicotine replacement.** Nicotine replacement remedies now come in five formats—patch, gum, nasal spray, oral inhaler, and lozenge. Scores of studies in the general population confirm that tapering smokers off nicotine with nicotine replacement can help them quit smoking. In the larger studies of nicotine replacement in people with HIV, quit rates have been as high as 26%.

Researchers at six US clinics randomized 444 HIV-positive smokers to 8 weeks of nicotine patch replacement plus standard care (two brief counseling sessions) or to nicotine patch plus more intensive motivation (four counseling sessions plus a quit-day call). Study participants smoked an average 18 cigarettes daily, 63% were men, 52% European American, 18% African American, and 16% Hispanic. Almost two thirds had at least a high school education, but 79% were unemployed.

Intention-to-treat analysis determined carbon monoxide-confirmed 7-day abstinence rates of 13% at 2 months after enrollment and 10% at 4 months and 6 months in the standard care group versus 12% and 9% in the enhanced-counseling group. Six-month abstinence rates were significantly higher in Hispanics, people with low nicotine dependence, and people with high motivation to quit. Statistical analysis adjusted for these factors determined that more patch use boosted abstinence odds by one third (OR 1.32, 95% CI 0.99 to 1.75).

Another US study involved 209 HIV-positive smokers in care at three clinics and randomized to 10 weeks of nicotine patch or gum plus (1) individual counseling, (2) Internet-based counseling, or (3) self-help. Study participants averaged 45 years in age, 82% were men, 53% white, 27% black, and 14% Hispanic. More than three quarters of participants (79%) had at least a high school education, and 35% had education beyond high school. Only 14% had a job, while 11% were retired. They smoked an average 18 cigarettes a day.

About one quarter of participants in each study arm achieved carbon monoxide-verified 7-day abstinence continued...
12 weeks after treatment began. One year after treatment began, quit rates remained near that level—20% with self-help, 20% with individual counseling, and 26% with Internet-based counseling, and these differences between groups were not significant. Employment, greater desire to quit, and lower mood disturbance scores favored quitting.

- **Which smoke-stopping drug to use.** In the general population nicotine replacement therapy plus other interventions yielded 1-year quit rates of 15% to 31%—results not too different from those recorded in the 209-person HIV trial. In the Cochrane Database review by Calvo-Sánchez and Martínez, nicotine replacement therapy efficacy compared with control arms ranged from 1.43-fold higher with gum to 2.02-fold higher with nasal spray. Odds of success with bupropion were similar (1.94-fold), while odds of success with varenicline were slightly higher (2.33-fold). In a nonrandomized study in Madrid involving 12 smokers who took bupropion, 8 who used nicotine replacement, and 6 who took varenicline—all with four to six psychological support sessions—12-month quit rates were similar with the three interventions: 25% (3 of 12) with bupropion, 25% (2 of 8) with nicotine replacement, and 17% (1 of 6) with varenicline.

University of Alabama at Birmingham researchers devised and tested an algorithm to help HIV clinicians figure whether varenicline, bupropion, or nicotine replacement suits an individual patient best. Providers should find and copy this useful algorithm in the cited article. The algorithm rests on a few simple decision drivers:

- **Is patient willing to take an oral medication twice daily?**
  - Yes → consider contraindications to varenicline, then bupropion (Table 2).
  - No → consider contraindications to nicotine replacement (Table 2).

- Contraindications to one medication drive patients to another medication.

- **Has patient unsuccessfully tried that medication before?**
  - Yes with varenicline → consider bupropion.
  - Yes with bupropion → consider nicotine replacement.
  - Yes with nicotine replacement → prescribe two nicotine replacement methods.

- **Has patient quit after 4 weeks on medication?**
  - No with varenicline → varenicline plus nicotine replacement.
  - No with bupropion → bupropion plus nicotine replacement.
  - No with one nicotine replacement → two nicotine replacements.

The algorithm study involved 100 adults in care for HIV who smoked at least 5 cigarettes daily and were not pregnant or nursing. They got randomized to algorithm-driven treatment or treatment as usual (smoking cessation assistance from their provider when they were ready to quit). All participants received one standard 20-minute smoke-ending session in which staff discussed behavioral methods to reduce smoking. The authors picked varenicline as the preferred oral agent because of an eight-trial general-population analysis demonstrating its superiority to bupropion or placebo.
The 100 study participants averaged 46 years in age; 71% were men, 75% black, and 25% white; 70% had at least a high school education. Two thirds of participants had received treatment for substance abuse and 57% for mental health. Enrollees smoked an average 16 cigarettes daily and had smoked for an average 27 years. The algorithm group and the usual-care group did not differ in any of these measures. Of the 50 people randomized to the algorithm group, 38% used the nicotine patch, 36% varenicline, 12% nicotine patch plus lozenge, and 10% bupropion. Twenty-six people randomized to the algorithm cluster had not tried to quit in 4 weeks and were offered the nicotine lozenge to ease acute cravings. More people randomized to the algorithm than to usual care took a smoke-ending medication (81% versus 23%, \( P < 0.001 \)). Through 16 weeks of follow-up, people in the algorithm group lowered their smoking rate more than people in the control group (10 versus 6 fewer cigarettes daily, \( P = 0.021 \)). Throughout follow-up, a higher proportion in the algorithm arm made at least a 24-hour quit attempt (50% versus 38%, \( P = 0.006 \)). The researchers argue that this algorithm “provides clinicians with a brief and succinct pathway for treatment selection decisions and thereby lends itself to being utilized during even brief clinical encounters.”

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**Table 2.** Pluses and minuses of three first-line smoke-ending medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Contraindications and cautions*</th>
<th>Drug interactions*</th>
<th>Quit rate in general population</th>
<th>Quit rate in people with HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varenicline (Chantix)</td>
<td>Suicide attempt, depression or psychiatric disorders, kidney impairment, pregnancy</td>
<td>None</td>
<td>21% to 23% at 1 year(^{34})</td>
<td>18% at 1 year(^{22})</td>
</tr>
<tr>
<td>Bupropion (Zyban)</td>
<td>Epilepsy, seizures, intracranial lesion, suicide attempt, mania, eating disorders, alcohol or benzodiazepine withdrawal, MAOI antidepressants, serious hepatic disease, pregnancy</td>
<td>Ritonavir-boosted protease inhibitor may decrease concentration; efavirenz or rifabutin may increase concentration; avoid linezolid and ciprofloxacin</td>
<td>20% to 30% at 1 year with other interventions(^{36})</td>
<td>38% at 1 year in small case series(^{27})</td>
</tr>
<tr>
<td>Nicotine replacement</td>
<td>MI within 2 weeks, pregnancy, latex allergy (with patch)</td>
<td>Possible interactions with tricyclic antidepressants, theophylline</td>
<td>15% to 31% at 1 year with other interventions(^{39})</td>
<td>From 10% at 6 months(^{28}) up to 26% after 12 months(^{29})</td>
</tr>
</tbody>
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MAOIs, monoamine oxidase inhibitors; MI, myocardial infarction.

*Adapted from Calvo-Sánchez and Martinez,\(^{19}\) Cropsey,\(^{12}\) and product information.
Are e-cigarettes an option for smokers with HIV?

Makers of e-cigarettes (electronic nicotine delivery systems, conveniently shortened to ENDS) promote their ability to ease nicotine addiction and thus put smokers on the road to quitting. A few studies (none of them in people with HIV) found that e-cigarettes can help people reduce nicotine intake, perhaps on a level equivalent to nicotine patches. But the potential value—and risks—of e-cigarettes remain largely unknown.

E-cigarettes have three parts: a cartridge containing a liquid solution of nicotine and other chemicals, a heating element that vaporizes the liquid, and a power source, usually a battery. Proponents of e-cigarettes say they are safer than cigarettes because don’t produce tar and other chemicals that come from burning tobacco. But e-cigarette vapors do contain substances other than nicotine, including some carcinogens and toxic substances such as formaldehyde, acetaldehyde, and derivatives of benzene and benzodiazepine.

The FDA does not regulate e-cigarettes but the agency has begun to study them. Quality-control of processes used to make e-cigarettes, the FDA found, “are substandard or non-existent.” Cartridges labeled as containing no nicotine did contain nicotine, and three cartridges with the same label produced markedly different nicotine levels. The FDA sent warning letters to three e-cigarette makers accusing them of unsubstantiated claims and poor manufacturing processes.

The National Institute on Drug Abuse cautions that “very little data exists on the safety of e-cigarettes, and consumers have no way of knowing whether there are any therapeutic benefits or how the health effects compare to conventional cigarettes.” Calvo-Sánchez and Martinez say “reasons for skepticism about the potential benefits of ENDSs” include “paradoxical hindering of tobacco smoking cessation, inhalation of propylene glycol, unexpectedly high plasma nicotine levels, and inadequate information about the contents of ENDSs and the chemical environmental contamination they may produce.”

The three parts of a standard e-cigarette (fitted together at top to resemble an actual cigarette) are the mouthpiece cartridge containing liquid nicotine solution, a heating element, and a power source. (Source: FDA, public domain.)
**Non-drug smoke-ending strategies for people with HIV**

As HIV smoking maven Jonathan Shuter observes in the interview on page 29, writing a prescription for smokers and wishing them good luck are not enough. Medication-based smoking cessation attempts must be backed by counseling and some form of structured support. The most basic non-drug support may be provider follow-up within the first week of a scheduled quit attempt, as called for in the 5As approach to smoking cessation (Figure 2), or referral to a smoke-ending support line. A national quit line (1-800-QUIT-NOW) routes callers to state smoke-ending call lines (see Quit by Phone box). Non-drug support can be considerably more extensive than that. Most of the drug intervention trials reviewed above included at least one non-drug element. This article reviews four non-drug strategies that complement pharmacotherapy and have been studied in people with HIV: an Internet-based approach smokers can start today, a cell-phone reminder strategy, a physician-training program, and a one-session counseling strategy.

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**Quit by Phone: 1-800-QUIT-NOW**

A national quit line, 1-800-784-8669, refers callers to state phone lines that may provide an array of services:

- Free support, advice, and counseling from experienced quitline coaches
- A personalized quit plan
- Practical information on how to quit, including ways to cope with nicotine withdrawal
- The latest information about stop-smoking medications
- Free or discounted medications (available for at least some callers in most states)
- Referrals to other resources
- Mailed self-help materials

The CDC offers online quitting tips at [http://www.cdc.gov/tobacco/quit_smoking/how_to_quit/resources/index.htm](http://www.cdc.gov/tobacco/quit_smoking/how_to_quit/resources/index.htm).

SmokeFree.gov guides smokers through designing their own quit plan at [http://smokefree.gov/build-your-quit-plan](http://smokefree.gov/build-your-quit-plan) or [http://espanol.smokefree.gov/preparacion-de-un-plan-para-dejar-de-fumar](http://espanol.smokefree.gov/preparacion-de-un-plan-para-dejar-de-fumar)

Internet-based program. PositivelySmokeFreeMe (PSFM) is an 8-session 7-week interactive program that any smoker with Internet access can start today (https://www.positivelysmokefreeme.com/). In the pilot trial described here, 18% of HIV-positive smokers who completed all 8 sessions stopped smoking. Almost one third of women who viewed all 8 sessions quit. All participants were offered the nicotine patch and could use other cessation-aiding drugs.

The study took place at Montefiore Medical Center in the Bronx, which serves more than 2800 HIV-positive people in a poor to middle-class part of New York City. Between March 2012 and April 2013, the Montefiore team recruited HIV-positive smokers who said they wanted to quit and had access to an Internet-linked computer. They excluded pregnant women and people with low English or Spanish literacy. Participants got randomized to standard care (under 5 minutes of counseling and a self-help brochure) or to PSFM. Everyone got a prescription for a 3-month supply of nicotine patches, and everyone had full insurance for patch therapy. PSFM includes 8 separate sessions of 4 to 7 interactive Web pages that become available over 7 weeks. These pages aim to educate, motivate, and increase self-efficacy to quit smoking. The primary efficacy endpoint was carbon monoxide-verified 7-day abstinence 3 months after participants were supposed to complete the 8 sessions.

Among 138 people who entered the study, 134 completed follow-up, including 68 of 69 in the PSFM group. Age averaged 46, about 40% of participants were women, three quarters black, and almost half Hispanic. Although 90% had stable housing, 86% were unemployed. These people smoked an average 11 cigarettes daily. None of these factors differed significantly between study groups.

Of the 51 study participants who used any smoke-ending drug, 24 were in the PSFM group and 27 in the control group. Two thirds of people randomized to PSFM visited six or more online sessions, 41% visited all eight, and one third viewed all 41 Web pages. Almost everyone in the PSFM group, 94%, needed phone calls reminding them to view their next Web session.

In an intention-to-treat analysis, the 3-month 7-day quit rate measured 10.1% in the PSFM arm versus 4.3% in the control arm, a nonsignificant difference (Figure 5). But among 28 Internet users who logged into all 8 sessions, the quit rate came to 17.9%. Quit rates were higher for women overall than men (11.7% versus 2.7%, P = 0.08) and higher still for women who logged into all 8 sessions (30.8%) and women who viewed all 41 Web pages (40%) (Figure 5).

Although adherence in this trial required frequent phone-call reminders, adherence might be better in a population that spends more time online and enjoys interactive programs. Because PositivelySmokeFreeMe is free and immediately available, HIV providers may consider recommending it to motivated smokers. A new and enhanced version of PositivelySmokeFreeMe, including a moderated social network, will be online in the first half of 2016. (See the interview with Jonathan Shuter on page 29 for more details about PositivelySmokeFreeMe.)

Cell-phone reminder calls. Three months of counseling via cell phone improved 3-month quit rates compared with usual care in a randomized trial of HIV-positive smokers in Houston. But that advantage waned over the next 9 months and overall quit rates were low, perhaps because few study participants used nicotine replacement therapy, as recommended.

The study involved 474 adult smokers willing to set a quit date within 7 days. Researchers randomized 238 people to standard care (written smoke-ending materials and instructions on how to get nicotine patches at the study clinic) and 236 to the cell-phone
Perspectives

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Figure 5. An Internet-based smoking-cessation program helped up to 40% of HIV-positive people prescribed the nicotine patch to quit smoking 3 months after the online program ended.49

Quitting rates with an online program versus standard care

<table>
<thead>
<tr>
<th></th>
<th>Standard care</th>
<th>Online overall</th>
<th>All 8 Web sessions</th>
<th>All 41 Web pages</th>
<th>Women overall</th>
<th>Women all 8 sessions</th>
<th>Women all 41 pages</th>
</tr>
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<tr>
<td>3 months</td>
<td>4.3%</td>
<td>10.1%</td>
<td>17.9%</td>
<td>21.7%</td>
<td>11.7%</td>
<td>30.8%</td>
<td>40%</td>
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The cell-phone group was significantly younger than the control group (43.9 versus 45.7 years), but the groups were balanced in proportion of women (about 30%), blacks (about 75%), whites (about 12%), Hispanics (about 10%) and in years of education (about 11), employment (about 20%), not working because of illness (about 63%), cigarettes smoked daily (about 19), illicit drug use in the past 30 days (40%), and major depressive symptoms (67%). Three quarters of participants in both groups completed 12 months of follow-up.

In an intention-to-treat analysis about 12% in the cell-phone group and 4% in the control group quit at 3 months.40 Among people who completed all 12 months, respective quit rates at 3 months were about 15% and 5%. Quit rates remained stable through 6 and 12 months in the control group while dropping in the cell-phone group to levels equivalent to control participants. Multivariate analysis determined that people randomized to get cell-phone reminders had quadrupled odds of quitting at 3 months (OR 4.3, 95% CI 1.9 to 9.8, \( P < 0.001 \)). Through 12 months chances of quitting remained significantly higher in the cell-phone arm (OR 2.41, 95% CI 1.01 to 5.76, \( P = 0.049 \)).

The researchers suggested high nicotine dependence coupled with low nicotine patch use could explain the low quit rates in both study arms. Trial investigators did not give participants nicotine patches but instead told them how to get patches through the clinic. But county requirements that people getting patches take smoke-ending classes may have discouraged patch use in this study group. The waning impact of cell-phone counseling after 3 months, the authors suggest, could mean a longer intervention may be needed for smokers like these.

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Clinician training program. Instead of making smokers the initial target of cessation efforts, Swiss HIV Cohort Study (SHCS) researchers in Zurich aimed at HIV providers in a half-day session on patient smoking counseling and drug therapy. This nonrandomized study comparing Zurich smokers with smokers at other SHCS sites found that those cared for in Zurich were about 25% more likely to stop smoking and 25% less likely to relapse.

All physicians at the University Hospital Zurich HIV outpatient clinic took a half-day smoking-cessation course between November 2007 and December 2009. The course included information on identifying smokers, rating nicotine dependence and motivation, counseling, and prescribing drugs to help smokers quit. During the study period these physicians completed a checklist documenting the smoking status of each patient and physician support offered (counseling, explaining medications available, arranging follow-up appointments, and if appropriate setting a quit date). The SHCS investigators defined quitting as a study visit in which a patient smoked followed by at least two consecutive visits without smoking. Relapse meant consecutive study visits in which a patient had quit followed by a visit with smoking.

The analysis involved 11,056 SHCS cohort members across the country, including 1689 seen at the Zurich clinic during the intervention period. The smoking cessation analysis considered 5805 smokers with at least three follow-up visits, while the relapse analysis involved 1953 smokers who quit. Zurich cohort members were older than SHCS members at other centers (median 44 versus 38), and Zurich had a lower proportion of women (25% versus 34%).

Overall smoking prevalence in SHCS members plunged from 60% in 2000 to 43% in 2010. The overall drop was greater in Zurich (−22.5%) than in other SHCS centers (−16.5%) or private practices (−14.5%). Logistic regression analysis determined that during the provider training period Zurich smokers were almost 25% more likely to quit smoking than SHCS smokers at other centers (OR 1.23, 95% CI 1.07 to 1.42, \( P = 0.004 \)), and Zurich quitters were 25% less likely to relapse (OR 0.75, 95% CI 0.61 to 0.92, \( P = 0.007 \)). The effect of the intervention was stronger than the effect of calendar time (OR 1.19 versus 1.04 per year).

The Zurich team proposed that “our approach of an institution-wide training programme for infectious diseases physicians to improve smoking cessation counselling can be well integrated into routine HIV care, was well accepted by patients and physicians, and can support patients’ efforts to stop smoking.” A 2008 survey of 363 HIV clinicians across the United States found that only 23% ever had formal tobacco treatment training. Only 29% of these US clinicians said they would be interested in attending a brief smoking cessation session, another 29% said they might be interested, and 40% claimed no interest. The Zurich HIV group now provides clinicians a yearly 1-hour smoking cessation class. Other SHCS centers around the country have not adopted that practice.
One-hour one-time smoker counseling. A 1-hour individualized smoke-ending session with a physician, other health professional, or peer helped 16% of HIV-positive smokers in Newark quit through 6 months, a rate similar to results reported in other studies of more complex and time-consuming strategies.43

The Infectious Disease Practice in Newark, New Jersey43 cares for a largely minority, low-income HIV population similar to those in the Bronx39 and Houston40 studies. The Newark analysis involved HIV-positive adult smokers interested in quitting. Prospective participants were referred to the smoking program by their clinic provider, by clinic staff, or by themselves in response to fliers in waiting rooms and exam rooms. The hour-long counseling session with
a physician, case manager, peer navigator, or mental health counselor (all trained in smoking cessation) focused on practical problem solving, withdrawal symptoms, and coping strategies. Clinicians prescribed smoke-ending therapy either at the counseling session or at a follow-up visit. Participants self-reported smoking cessation at 6 months at a follow-up visit or by phone.

Among 1545 adults cared for at the HIV clinic, 774 (50%) smoked. Of these 744 people, 123 (16%) had counseling and 651 did not. Age averaged 50 years in counseled smokers and 47 in uncounseled smokers ($P = 0.01$). Respective proportions of women were 47% and 43%, blacks 85% and 85%, and uninsured 29% and 40% ($P = 0.03$). Among all patients analyzed, 52% had a history of mental illness, 58% had used cocaine, and 41% had used heroin. The study group smoked 11 cigarettes daily and had tried to quit an average of 2 times.

Among the 123 counseled smokers, 101 (82%) got prescribed a smoke-ending drug, usually nicotine replacement therapy (96% of 101), though 54% got a combination prescription. Most people with a prescription (83%) reported nonadherence at least once during follow-up, and 48% said insurance did not fully cover their prescription.

Twenty of 123 people (16%) who received counseling reported quitting at 6 months. (The study did not confirm quitting biochemically.) Multivariate analysis determined that past or current heroin or cocaine use lowered chances of quitting 80% (aOR 0.20, 95% CI 0.07 to 0.56, $P = 0.002$). Being in the preparation stage to quit rather than the precontemplation stage or the contemplation stage boosted odds of quitting more than 8 times (aOR 8.26, 95% CI 1.02 to 66.67, $P = 0.048$). Factors that did not influence quitting in this analysis were age, gender, race, mental illness history, and nicotine dependence level.

- **Pluses and minuses of four nondrug interventions.**

Each of the four just-reviewed nondrug interventions has its pluses and minuses (Table 3). PositivelySmokeFreeMe is free and immediately available to all smokers with Internet access. This 8-session Web-based program may be particularly well-suited to people who enjoy interactive online programs. But unless clinicians or staff can check patient progress through the eight online segments, many smokers may not have the motivation needed to complete the program. The inner-city study group in a randomized trial required regular prodding to access each new session that came online. So PositivelySmokeFreeMe will probably work best for more highly motivated individuals. Clinicians will have to work with motivated patients to select and prescribe an appropriate medication and to promote adherence.

Cell-phone counseling calls offer a reliable platform to bolster patient commitment to quitting, to remind patients to use their antismoking medication, and to address concerns that arise. But such a program requires some planning at the clinic level, commitment of time from capable staff or perhaps trained peer volunteers, and occasional interaction with the clinician. Houston researchers who tested this approach found that quit rates waned when the calls stopped.

The half-day clinician training program designed by the Zurich unit of the Swiss HIV Cohort Study (SHCS) provides the foundation for any successful smoking cessation program by ensuring that providers understand the principles of nicotine addiction, counseling, and treatment. After the Zurich researchers launched this program, which included a smoking checklist for each patient, they recorded higher quit rates and lower relapse rates than other SHCS units across Switzerland. Program success clearly depends on clinicians implementing what they learn in the session, as a large majority of clinicians in
after publishing their report, the Zurich group began providing a 1-hour smoking cessation course for HIV clinicians once a year. Other SHCS centers have not adopted such a program. Updated numbers show that smoking prevalence in HIV-positive people remains lower in Zurich than at other centers.42

The primary advantage of the one-time, 1-hour, one-on-one smoke-ending session is its focus on individual smokers in a single session that can be performed by a nonphysician health professional or even a peer counselor.43 The Newark researchers who ran this study observe that this “low-intensity” approach yielded a 6-month quit rate similar to rates recorded in studies of more complicated and lengthy interventions. Yet the authors note that prior or current illicit drug use cut chances of success, a finding suggesting some smokers “may benefit from more intensive cessation approaches or strategies that incorporate substance use counseling and mental health services into cessation interventions.”43

The three US studies all involved low-income heavy smokers with high rates of alcohol and drug abuse and psychiatric comorbidities.39,40,43 All achieved similar short-term quit rates around 15%. Although that rate may sound low, it is comparable to rates in some general population studies, which often include people with fewer addiction and dependence risk factors. And getting 3 of every 20 HIV-positive people to quit will certainly have a profound impact on the health of those quitters—an impact that easily justifies the health worker effort.

References

continued from page 23

23. CHANTIX (varenicline) tablets. https://www1.pfizerpro.com/hcp/chantix
1. Life expectancy is rising in people with HIV, but not if they smoke.  
2. Tobacco and tobacco smoke contain nicotine, carbon monoxide, arsenic, formaldehyde, benzene, and other toxic substances. (Formaldehyde is an embalming agent and is known to cause cancer; benzene is found in emissions from burning coal and oil, and in motor vehicle exhaust.)
3. In animal studies nicotine is as deadly as strychnine and three times more deadly than arsenic.
4. Feeling a strong urge to smoke first thing in the morning, after a meal, or when drinking alcohol probably means you’re addicted to nicotine.
5. Nicotine addiction leads all preventable causes of death across the world, and more than 60% of deaths in people with HIV can be attributed to smoking.
6. Smokers with HIV can quit: An estimated one third of HIV-positive US smokers have stopped.
7. Don’t quit quitting! Many people must try to quit several times before they succeed.
8. Ten years after someone quits smoking, their risk of lung cancer drops by half.
9. Someone who quits smoking before age 40 cuts their risk of death from a smoking-related disease by 90%.
10. A study of 5472 people with HIV found that former smokers had significantly lower risk of death from any cause and lower risks of AIDS, major heart disease, cancer, and bacterial pneumonia than current smokers.
References

1. In HIV-positive North Americans and Europeans, smoking decreases survival more than HIV itself.1
2. Analysis of 18,000 HIV-positive people in Europe and North American determined that smokers have a twice higher death rate than nonsmokers. But former HIV-positive smokers and never-smokers have equivalent death rates.5
3. In a study of 2000 US veterans, all-cause mortality was more than 80% higher in in HIV-positive smokers than HIV-positive never-smokers whether they smoked under 20 pack-years* or over 20 pack-years.2
4. A nationwide study in Denmark found that HIV-positive smokers run a 6 times higher risk of myocardial infarction than HIV-positive people who never smoked.3
5. Compared with HIV-negative smokers in the United States, HIV-positive smokers who had AIDS pneumonia run a 3.5-fold higher risk of lung cancer.4
6. A large proportion of US smokers manage to quit. In fact, the United States has more ex-smokers than current smokers.5
7. US clinicians don’t do as well getting HIV-positive smokers to quit as they do with HIV-negative smokers. The CDC figures a quit ratio† of 52% in the general population, compared with 32% in people with HIV.6
8. Fewer than half of US HIV clinicians frequently prescribe any of the three medications recommended for smoking cessation: nicotine replacement, varenicline (Chantix), or bupropion (Zyban).7
9. Studies in people with HIV show that quit rates can reach as high as 1 in 5 to 2 in 5 with varenicline,8 bupropion,9 or nicotine replacement.10
10. SMART trial analysis of people with HIV determined that current smokers had a higher risk of five outcomes than people who had quit smoking: all-cause mortality, AIDS-related disease, major cardiovascular disease, non-AIDS cancer, and bacterial pneumonia.11

* A pack-year measures the number of packs smoked daily for life. Twenty pack-years could mean smoking 1 pack daily for 20 years or smoking 2 packs daily for 10 years.
† Quit ratio = former smokers/(former + current smokers).

Ten things every HIV clinician should know about smoking
References

Step-by-step advice on helping HIV-positive smokers quit

An interview with Jonathan Shuter, MD

Professor, Department of Medicine
Division of Infectious Diseases
Montefiore Medical Center and
the Albert Einstein College of Medicine
Bronx, New York

Dr. Shuter ranks among the top researchers on smoking in people with HIV infection. Together with several collaborative teams, he developed Positively Smoke Free, a smoking cessation program designed for people with HIV for use in group therapy, individual therapy, and online computer and smartphone applications. Dr. Shuter is a clinician who has been caring for people with HIV since 1985 and a researcher with multiple NIH grants to study tobacco treatment strategies for HIV-positive smokers. Working with low- to middle-income minority populations in the Bronx, he has conducted and published research on conditions that affect inner-city HIV populations, including tuberculosis, overweight, and poor antiretroviral adherence. Dr. Shuter reviews articles for The Lancet, PLoS One, JAIDS, Clinical Infectious Diseases, and a half-dozen other leading journals.

Motivating the unmotivated, then closing the deal

Mascolini: Why does smoking have a greater negative impact in people with HIV?

Shuter: There are a few answers to that question. Much recent attention is focused on the additive impact of the direct damage of tobacco use plus the inflammatory state that is part of living with HIV. These two factors have additive effects on the cardiovascular damage that we associate with cigarette smoking. Tobacco use also compromises lung function by impairing mucociliary function of the respiratory epithelium, and patients with HIV are at uniquely high risk for pulmonary infection because of their compromised immunity. All these factors plus the infectious disease component of HIV infection pose additive risks for tobacco use in patients with HIV.

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**Mascolini:** Research shows that high motivation to quit smoking predicts success in quitting. How should HIV clinicians start with people who have low motivation?

**Shuter:** Clinicians can start by trying to get them to understand the damage that tobacco use is doing to them and the prospect that they can quit if they really try. Patients with low motivation should understand that long-time smokers can be successful in quitting and it’s not hopeless to try. It’s also useful to emphasize how much better they’ll feel both in the short term and the long term if they’re able to quit.

**Mascolini:** What do you tell people with HIV about their chances of success in quitting?

**Shuter:** Here statistics are probably not your friend. At best, studies are getting 15% or 20% quit rates. I certainly wouldn’t stress that. But I do tell smokers that I’ve had many patients successfully quit and that they can too.

**Mascolini:** When an HIV-positive person is highly motivated to quit, how should clinicians close the deal?

**Shuter:** We’re not trying to reinvent the wheel here. There’s an awful lot of data available on the best strategies to promote cessation. [See “Helping people with HIV quit smoking: what works for whom?” on page 5.]

One thing I’ve learned over time as a clinician is that patients with HIV often have such complicated and stressful lives that simply prescribing a medication—whether it’s nicotine patches or varenicline—generally is not enough. You have to remember that many patients live in a medical world where they believe the solution to a problem comes in a bottle. These patients may have a mindset that says, “I’m ready to quit now, I’ll get some nicotine patches or Chantix, and that’ll do it for me.” I certainly support medication as part of the attempt to quit. The medications we have really do help, and they’re necessary for many patients.

But I try very hard to convince patients that they need a multipronged approach. Besides pharmacotherapy, social support is very important. Patients should try to find someone who’s going to support them though this, and they should stay away from people who are going to discourage the cessation process. A roommate or housemate who smokes can pose a particular challenge. If someone lives with another smoker, try to get them motivated to quit together because it’s really hard to quit if you live with another smoker.

The support person may be a family member or friend, or someone at the end of a telephone, like a quitline counselor. There are online resources too. More and more patients like to go online and seek support that way. There are social networks one can go to as well. [See box “Quitlines and online: Tools to help smokers stop.”]
## Quitlines and online: Tools to help smokers stop

<table>
<thead>
<tr>
<th>Quitlines</th>
<th>Online resources</th>
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| **US National Quitlines**  
Calling one of the following three toll-free numbers will connect you to your state quitline, where trained coaches can provide information and help with quitting. Specific services and hours vary by state.  
**English:** 1-800-QUIT-NOW (1-800-784-8669)  
**Español:** 1-800-Dejelo-Ya (1-800-335-3569)  
**TTY (text telephone):** 1-877-777-6543 | **Centers for Disease Control and Prevention. Smoking & tobacco use.**  
[http://www.cdc.gov/tobacco/](http://www.cdc.gov/tobacco/)  
The comprehensive CDC site for tobacco use includes links to the TipsCampaign to help people quit, FactSheets, and state and community resources.  
**Centers for Disease Control and Prevention. How to quit.**  
[http://www.cdc.gov/tobacco/quit_smoking/how_to_quit/index.htm](http://www.cdc.gov/tobacco/quit_smoking/how_to_quit/index.htm)  
The CDC “How to quit” site includes five basic tips all quitters should know, tips from former smokers, and information on the short- and long-term benefits of quitting smoking.  
In English and Spanish, SmokeFree.gov helps smokers build a quit plan, provides a quitSTART app to get support via your phone, and offers a sign-up for SmokeFreeTXT messages.  
**American Cancer Society Guide to Quitting Smoking**  
The American Cancer Society answers 20 basic questions about why to quit, how to quit, and how to stay smoke-free, including getting help with the mental and physical parts of nicotine addiction.  
**PositivelySmokeFreeMe**  
[https://www.positivelysmokefreeme.com](https://www.positivelysmokefreeme.com)  
This 7-week 8-part program, detailed in this interview, is designed specifically for HIV-positive smokers who want to quit. A new and improved version, which will incorporate a social network, will be available in late spring or early summer 2016. |

*continued...*
Someone who’s really serious about quitting should also pick a quit day and get ready for that quit day.\textsuperscript{1} A patient who decides impulsively, “I’m quitting today,” is probably not going to succeed. Planning a quit day means getting a support person, getting your pharmacotherapy in order, getting rid of all your cigarettes and getting secret stashes of cigarettes out of the house, throwing all ashtrays away—and doing all this in a thoughtful and methodical way. Patients who are willing to take those steps have a higher chance of succeeding.

**Mascolini:** Do you see certain mistakes that many HIV clinicians make when addressing smoking in their patients?

**Shuter:** I think the biggest problem is that time is limited. The typical patient in my clinic has multiple medical problems; he might be on 5, 10, 15 medications. When you’re seeing patients like that and writing their notes, you realize you’re dealing with 7 or 8 problems, and tobacco use can fall to the bottom of the list. I think that’s the biggest challenge.

An additional challenge is that HIV providers don’t have a lot of training in tobacco cessation. A survey we did showed that only one quarter of HIV providers in a national US sample reported ever receiving formal teaching in tobacco treatment.\textsuperscript{2} That means many HIV clinicians don’t really know how to treat tobacco use, and they don’t often get to it during smokers’ visits.

Personally I think this is a very destructive scenario. It means if you’re a smoker you can walk into your provider’s office and deal with your HIV and your high blood pressure and your diabetes and asthma. So tobacco use falls off the list. It’s never even addressed. Subliminally, that patient can walk out of that office after 15 minutes with a net-neutral view of smoking. But an HIV provider should be communicating a negative view toward tobacco use at every visit.

**Positively Smoke Free: an 8-module intervention**

**Mascolini:** What’s the status of Positively Smoke Free, the smoking-cessation intervention for people with HIV?

**Shuter:** Positively Smoke Free is a suite of different options, including an eight-module group therapy intervention led by a counselor and an eight-module self-administered online intervention, PositivelySmokeFreeMe (https://www.positivelysmokefreeme.com) (Figure 1). In New York State a Positively Smoke Free brochure has been disseminated statewide. We offer on-site Positively Smoke Free group therapy in the setting of a clinical trial. But outside the centers participating in the trial, Positively Smoke Free group therapy is not yet available. Positively Smoke Free individual therapy is starting at the University of Maryland in Baltimore, but that is not yet available outside of a clinical trial.

The Positively Smoke Free Web site is an eight-module program that parallels the eight modules in the Positively Smoke Free live sessions. That is now available in the public domain at www.PositivelySmokeFreeMe.com. HIV specialists, behavioral psychologists, graphic artists, software engineers, and smokers with HIV collaborated to design this 8-session, 7-week program.\textsuperscript{3} Each session includes 4 to 7 Web pages with interactive features. The sessions aim to educate, motivate, and increase patient self-efficacy to quit.
Mascolini: Have people been using the online PositivelySmokeFreeMe?

Shuter: We’re just beginning to track use because it hasn’t been available continuously. Originally it was restricted to clinical trials, but now it’s in the public domain. The American Legacy Foundation, which very recently changed its name to The Truth Initiative (http://truthinitiative.org/), has taken this up and now maintains PositivelySmokeFreeMe on its server.

The Web site will incorporate a social network with contributions from users on topics of interest to HIV-positive smokers. The social network will be kicking into gear soon and will be fully active by late spring or early summer of 2016. It will be available in the public domain for at least several years. If it’s successful, we hope it can sustain itself after that. We’re planning a clinical trial to assess the effect of the social network.

Mascolini: What will be the thrust of the social network?

Shuter: There will be discussion threads pertaining to topics of particular interest to HIV-infected smokers and former smokers—probably including the impact of stress on smoking and as an impediment to quitting, whether smoking interferes with adherence to medications, whether smoking cessation medications have interactions with HIV medicines, and anything else users want to bring up. The social network will be guided by a professional Web site social network moderator. We plan to design a very modern type of site with the bells and whistles that our patients expect in 2016.

Mascolini: Do you plan other versions of Positively Smoke Free?

continued...
Shuter: Yes. In concert with the University of Michigan Center for Health Communications Research, we’re developing another version of Positively Smoke Free specifically for smartphones. Positively Smoke Free Mobile has been alpha- and beta-tested and it’s ready to go. This smartphone version is faithful to the original 8-session Positively Smoke Free intervention. But instead of having a live counselor conducting a group therapy session or individual therapy, and instead of the mostly written presentation on the Web site, the smartphone version uses an actor and cartoon characters in video sessions. We distilled the content into 8 bite-size pieces available as video via smartphone.

Positively Smoke Free Mobile includes some innovative and hopefully useful resources not possible in the other formats. For example, the mobile version includes a HELP button. When someone trying to quit craves a cigarette, that craving usually lasts for 3 to 5 minutes. The Positively Smoke Free group therapy counselor can’t help you if you’re out on the street away from your group therapy. You might be able to apply some of the lessons you learned in group therapy, but there’s none of the immediacy you have with your cell phone. You have your cell phone in your pocket, you go to the site, and you hit the HELP button. Doing that will send you to a place where you hear one of your favorite songs, where you play a game, or where you get directed to a quitline. All these things could distract you for 5 or 10 minutes until your craving passes. We’re very eager to see how that works.

Another major element of Positively Smoke Free Mobile is a text-messaging intervention. We plan frequent texts with encouragement, motivational messages, and tips to help you quit. All of those things together make up the Positively Smoke Free Mobile intervention.

**Picking the best cessation therapy for your patient**

Mascolini: Do you always recommend medication for HIV-positive smokers who want to quit?

Shuter: The answer is a qualified yes. You could imagine a scenario where someone has a contraindication to every single medicine out there. That would be extremely rare. Barring that, the answer is yes, I would always recommend pharmacotherapy.

Mascolini: How do you decide which medication to use?

Shuter: The decision rests on discussion with the patient and review of the medical and psychiatric history. The default medication is usually the nicotine patch or another form of nicotine replacement therapy. There is very little downside with nicotine replacement options, and they do help. Even though we haven’t had great success with nicotine patches at our center in the Bronx, other investigators have found them to be effective and predictive of successful cessation in the HIV population. And many patients are familiar with this strategy and not scared of it.

The potential negative aspect of nicotine patches is that many of our patients have used them already, failed with them, and feel they don’t help. So we have many patients who just say no to nicotine replacement. For many of those patients, varenicline—Chantix—is a terrific choice. Product information cautions about psychiatric morbidities and complications with Chantix, but I believe those risks are exaggerated.
We’ve used Chantix many, many times in patients with a history of depression or anxiety—as long as they’re psychiatrically stable at the time. They usually tolerate Chantix very well, and I’ve had good experience with it.

The last major option is bupropion—Wellbutrin or Zyban—which we use fairly frequently because it is an antidepressant and many of our patients have depression. In some patients, Wellbutrin can kill two birds with one stone.

**Mascolini:** Are there any other important issues you would like to stress about smoking cessation in people with HIV?

**Shuter:** I would like to give an extra plug to PositivelySmokeFreeMe.com. Clearly, the long-term success of a social network depends on how much people use it and how much they like it. There’s nothing that bodes worse for a social network than underutilization. So we encourage HIV-positive smokers and quitters to visit that site (Figure 1). I think it will be a great resource where none exists right now. The site and the social network component are professionally moderated and administered. It’s really exciting that anyone with a computer and WiFi who’s interested in getting help can use this site to quit and to stay engaged with other HIV-positive people.

Finally, I want to say I appreciate the attention the mainstream media and the public health and medical community are beginning to pay to cigarette smoking in people with HIV infection. I’ve been taking care of HIV-infected patients since the early 1980s. I certainly remember the day when smoking was completely ignored in the HIV population because they were dying from something else so much sooner than cardiovascular disease or lung cancer. They were dying from direct complications of HIV. Now we live in an era when patients are surviving much longer with HIV. Tobacco use has emerged as one of the most important treatable medical issues in this population. It still doesn’t get enough attention, but it’s getting more and more. I appreciate the opportunity to speak about this issue, because help is available today for smokers with HIV who want to quit. But more work needs to be done.
References


4. The Truth Initiative ([http://truthinitiative.org/](http://truthinitiative.org/)) “is dedicated to achieving a culture where all youth and young adults reject tobacco. We speak, seek and spread the truth about tobacco through education, tobacco control research and policy studies, and community activism and engagement.”
Abstract. Smoking exacts a huge toll on the health of everyone who becomes addicted to nicotine. That toll is greater in people with HIV, and not only because as a group they smoke more than the general population. Research shows that smoking subtracts more years from the life of a middle-aged person with HIV than HIV itself. Nicotine addiction raises the risk of all-cause mortality more in HIV-positive smokers than in HIV-negative smokers. A nationwide study in Denmark found that HIV-positive smokers run a 6 times higher risk of myocardial infarction than HIV-positive never-smokers, but current smoking only doubled the MI risk in HIV-negative people. Research in HIV-positive and negative men and women in the United States found that HIV-positive smokers who had prior AIDS pneumonia had a 3.5-fold higher risk of lung cancer than HIV-negative smokers. Meta-analysis of 18 studies involving more than 625,000 people with HIV found significantly higher rates of smoking-related cancer and infection-related cancer in HIV-positive people than in the general population. People who quit smoking enjoy rapid declines in their risk of smoking-related disease. In the US general population, people who quit by age 40 cut their risk of smoking-related death by 90%. Analysis of almost 5500 SMART trial participants determined that current HIV-positive smokers had a higher risk of five outcomes than former smokers with HIV: all-cause mortality, AIDS-related disease, major cardiovascular disease, non-AIDS cancer, and bacterial pneumonia. In a large DAD study analysis, cardiovascular disease incidence fell steadily as time since quitting rose. A CDC study of a nationally representative HIV population identified numerous factors independently linked to higher smoking prevalence: younger age, white or black race versus Hispanic ethnicity, less education, incarceration, poverty, noninjection drug use, binge alcohol drinking, major depression, and a viral load above 200 copies/mL.

Smoking leads all preventable causes of death across the world. And it’s more deadly in people with HIV than in HIV-negative people. That’s not a surprise, because smoking causes deadly diseases—like continued...
myocardial infarction\(^1\) and lung cancer\(^4\)—more in people with than without HIV. In North Americans and Europeans with HIV, smoking subtracts more years of life than HIV itself.\(^5\)

Health professionals need no convincing that smoking imperils health by ravaging one organ after another, from top (stroke) to bottom (peripheral vascular disease). But it’s easy to forget the prodigious scope of this assault. In the general population, smoking chops off at least 10 years of life, the CDC estimates,\(^6\) and smokers who quit by age 40 limit their risk of a smoking-related death by 90%. In the United States smoking causes more deaths every year than HIV infection, illegal drugs, alcohol, guns, and automobile accidents combined.\(^7\) Smoking has killed more than 10 times as many US citizens as all the wars in the history of this country.\(^7\)

The news gets worse for people with HIV infection. A 2000-veteran study found that smoking raised the all-cause death risk more in HIV-positive veterans than in HIV-negative veterans, and lighter smokers ran a death risk just as high as heavier smokers.\(^2\) This Veterans Aging Cohort Study (VACS) analysis involved 1034 HIV-positive veterans matched by age, sex, and study site to 739 veterans without HIV. Through a median follow-up of 5.3 years, 200 veterans with HIV (19.3%) and 72 without HIV (9.7%) died.

Compared with HIV-positive veterans who never smoked, HIV-positive current smokers had more than a doubled risk of all-cause death (adjusted incidence rate ratio [aIRR] 2.31, 95% confidence interval [CI] 1.53 to 3.49).\(^2\) In contrast, HIV-negative current smokers did not have an independently higher death risk than HIV-negative never-smokers (aIRR 1.32, 95% CI 0.67 to 2.61). And HIV-positive former smokers did not run a higher death risk than never-smokers (aIRR 1.29, 95% CI 0.81 to 2.04). All-cause death risk was more than 80% higher in HIV-positive smokers than in HIV-positive never-smokers whether they smoked under 20 pack-years (aIRR 1.82, 95% CI 1.20 to 2.76) or more pack-years (aIRR 1.87, 95% CI 1.21 to 2.89). (Pack-years equal the number of cigarettes smoked daily times the number of years a person has smoked. Twenty pack-years means smoking 1 pack a day for 20 years or a half-pack a day for 40 years. (See http:// smokingpackyears.com.)

Analysis of almost 18,000 HIV-positive people in Europe and the United States figured that smoking shortens life expectancy more than HIV itself in the years after people start antiretroviral therapy.\(^5\) In a study population that excluded injection drug users, 60% smoked. Through 4 years of follow-up, smokers had a twice higher death rate than nonsmokers (mortality rate ratio [MRR] 1.94, 95% CI 1.56 to 2.41) and (in a separate analysis) a 70% higher death rate than never-smokers (MRR 1.70, 95% CI 1.23 to 2.34) (Figure 1). But mortality among former smokers proved similar to mortality in never-smokers (MRR 0.92, 95% CI 0.64 to 1.34). Compared with nonsmokers, current smokers had 6 times higher mortality from cardiovascular disease (MRR 6.28, 95% CI 2.19 to 18.0) and almost 3 times higher mortality from non-AIDS cancers (MRR 2.67, 95% CI 1.60 to 4.46).

The researchers calculated that 35-year-old men with HIV would lose 7.9 life-years if they smoked (95% CI 7.1 to 8.7). In comparison, HIV infection would subtract 5.9 years from a 35-year-old man’s life (95% CI 4.9 to 6.9).\(^5\)

HIV-positive current smokers ran a 6 times higher risk of myocardial infarction (MI) than HIV-positive never-smokers in a nationwide Danish analysis (aIRR 6.06, 95% CI 2.99 to 12.25).\(^2\) In contrast, current smoking only doubled the MI risk among HIV-negative people compared with HIV-positive never-smokers (aIRR 2.22, 95% CI 1.44 to 3.44). MI risk in HIV-positive former
smokers also proved much lower than in HIV-positive current smokers compared with HIV-positive never-smokers (aIRR 2.64, 95% CI 1.16 to 6.01).

The Danish investigators calculated that 72% of MIs in people with HIV could be attributed to smoking, compared with only 24% of MIs in the HIV-negative comparison group (Figure 2). That means 3 of 4 heart attacks in people with HIV could be prevented if these people never smoked. Among current HIV-positive smokers, smoking accounted for 42% of MIs. In other words, 42% of MIs could be prevented if all current HIV-positive smokers quit. If all current smokers in the general population quit, it would prevent only 21% of MIs.

As with heart attacks, so with lung cancer: Your chances of getting it run higher if you smoke and have HIV than if you smoke and don’t have HIV. That finding comes from a comparison of 2546 HIV-positive and negative women smokers in the Women’s Interagency HIV Study (WIHS) and 4274 HIV-positive and negative men smokers in the Multicenter AIDS Cohort Study (MACS). Compared with HIV-negative smokers, HIV-positive smokers who had AIDS pneumonia in the past had more than a 3.5-fold higher risk of lung cancer (aIRR 3.56, 95% CI 1.67 to 7.61). Heavier smoking boosted lung cancer risk in women and men with and without HIV. Compared with people who smoked fewer than 10 pack-years, those who smoked 10 to 30 pack-years had almost a 5-fold higher risk of lung cancer (aIRR 4.75, 95% CI 1.62 to 13.96), and those who smoked more than 30 pack-years had an 11-fold higher risk (aIRR 11.09, 95% CI 3.72 to 33.11).

Rigorous research from around the world shows how thoroughly smoking assails the already-vulnerable health of people with HIV—in lung, larynx, bone, bladder, and beyond.
Figure 2. If no HIV-positive people ever smoked, 72% of myocardial infarctions would be prevented in people with HIV, according to results of a nationwide Danish study. If all current HIV-positive smokers quit, 42% of MIs would be prevented. Proportions of preventable MIs would be much lower in a comparison group of HIV-negative people.

Lung disease

- Current smoking more than doubled the risk of bacterial pneumonia in a 5-year study of 4942 people starting antiretroviral therapy in Italy at a median age of 36 (adjusted hazard ratio [aHR] 2.623, 95% CI 2.060 to 3.3339, P < 0.0001). Smoking in the past did not independently boost pneumonia risk (aHR 1.64, 95% CI 0.94 to 2.86, P = 0.08). This study group had a median age of 43, and all entered the trial with a CD4 count above 350 cells/mm³.

- Meta-analysis of 14 cohort or case-control studies in HIV-positive adults determined that current smokers had more than a 70% higher risk of bacterial pneumonia than current nonsmokers (HR 1.73, 95% CI 1.44 to 2.06) and almost a 40% higher risk than former smokers (HR 1.37, 95% CI 1.06 to 1.78). Former smokers did not run a higher pneumonia risk than never-smokers (HR 1.24, 95% CI 0.96 to 1.60).

- In a 176-person comparison of people with and without HIV in Italy, current smoking was the only independent predictor of chronic obstructive pulmonary disease (COPD). HIV-positive participants had a significantly higher COPD
prevalence than HIV-negative controls matched for age, sex, and smoking status.

- In the young (median age 36), antiretroviral-naive, international START trial population—all with a CD4 count above 500—every 10 pack-years of smoking independently raised the risk of COPD.12

- A cross-sectional study of 1446 HIV patients in Italy who had thoracic computed tomography found that 48% had emphysema, bronchiolitis, or both.13 Smoking more than tripled the odds of either diagnosis (adjusted odds ratio [aOR] 3.48, 95% CI 2.58 to 4.71) and proved a stronger predictor than age, injection drug use, body mass index, leukocyte count, or gender.

**Invasive pneumococcal disease**

- A nationwide 1995-2012 study in Denmark determined that smoking independently boosted the risk of invasive pneumococcal disease by one third in people with HIV (adjusted relative risk [aRR] 1.34, 95% CI 1.26 to 1.42).14

**Cancer**

- Comparing rates of non-AIDS cancers in people with HIV and the general population, meta-analysis of 18 studies involving 625,716 people with HIV found higher rates of smoking-related cancers (lung standardized incidence ratio [SIR] 2.6, 95% CI 2.1 to 3.1; kidney SIR 1.7, 95% CI 1.3 to 2.2; laryngeal SIR 1.5, 95% CI 1.1 to 2.0) and infection-related cancer (anal SIR 28, 95% CI 21 to 35; liver SIR 5.6, 95% CI 4.0 to 7.7; Hodgkin lymphoma SIR 11, 95% CI 8.8 to 15) in people with HIV.15

- Smoking doubled the risk of non-AIDS cancers (anal, basal cell carcinoma, Hodgkin lymphoma, lung cancer) in a 3.8-year analysis of 3158 HIV-positive people starting antiretroviral therapy in AIDS Clinical Trials Group (ACTG) studies at a median age of 37 years (aRR 2.12, 95% CI 1.1 to 4.08).16

- Compared with never smoking, current smoking and former smoking more than doubled the risk of death from non-AIDS cancer in a 33,308-person 3-year DAD cohort analysis (aRR 2.20, 95% CI 1.48 to 3.26 for current smoking; aRR 2.52, 95% CI 1.73 to 3.67 for former smoking).17

- Comparison of 3503 HIV-positive people in Denmark and 12,979 people in the general population found almost a tripled risk of smoking-related cancers in the HIV group (aIRR 2.8, 95% CI 1.6 to 4.9) and an 11.5 time higher risk of virus-related cancers (aIRR 11.5, 95% CI 6.5 to 20.5).18 HIV-positive nonsmokers did not run a higher risk of nonvirus-related cancers than general population controls (aIRR 1.2, 95% CI 0.7 to 2.1).

- Compared with HIV-positive people who never smoked, current smokers had nearly a doubled risk of non-AIDS cancer in a 33-month SMART trial analysis (aHR 2.1, 95% CI 1.2 to 2.8, P = 0.008).19 Compared with former smoking, current smoking more than doubled the risk of non-AIDS cancer (aHR 2.3, 95% CI 1.5 to 3.6, P < 0.001).

- In 2010 lung cancer displaced non-Hodgkin lymphoma as the leading cancer cause of death among people with HIV in a nationwide French study.20 Among 728 deaths, lung cancer accounted for 61 (8.4%), non-Hodgkin lymphoma for 53 (7.3%), and hepatitis-related cancer for 31 (4.3%).

- Current smoking upped the odds of lung cancer in a Swiss HIV Cohort Study comparison of 68 HIV-positive people with lung cancer and 337 matched controls without lung cancer (aOR for current versus never-smokers 14.4, 95% CI 3.6 to 62.1).21 Neither CD4 count nor antiretroviral therapy predicted lung cancer in this analysis.

- In a 6820-person comparison of HIV-positive and negative men and women in MACS and WIHS, HIV-positive smokers with AIDS pneumonia in the past had more than a 3 times higher risk of lung cancer than HIV-negative smokers (aIRR 3.56, 95% CI 1.67 to 7.61).4
Mortality after lung cancer proved more than twice higher in HIV patients than in matched HIV-negative controls in a nationwide Danish study (MRR 2.33, 95% CI 1.51 to 3.61). All 29 HIV-positive people diagnosed with lung cancer were current or former smokers.

In a matched comparison of HIV-positive and negative adults in California’s Kaiser Permanente healthcare system, 5-year cancer-free survival was significantly lower with lung cancer in the HIV group than in the HIV-negative group (10% versus 19%, \( P = 0.002 \)) but not in comparisons of HIV-positive and negative people with four other non-AIDS cancers—anal, prostate, colorectal, or Hodgkin lymphoma.

**HPV infection and related cancers**

- A study of 1797 US women with HIV linked smoking to higher prevalence and incidence of human papillomavirus (HPV) infection, including more than a 2-fold higher prevalence of cancer-causing HPV-18 (OR 2.45, 95% CI 1.86 to 3.22).
- Smoking correlated with cumulative HPV detection in an 11-year Women’s Interagency HIV Study of 2543 women with HIV and 895 without HIV.
- In a 30-month comparison of 328 US women with HIV and 325 without HIV, current cigarette smoking doubled the risk of squamous intraepithelial lesions—an invasive cervical cancer precursor—in HIV-positive women (aRR 2.1, 95% CI 1.0 to 4.4, \( P = 0.06 \)).
- A study of 2835 US men with and at risk for HIV infection found that smoking independently raised chances of HPV-related external genital warts (aRR 1.2, 95% CI 1.0 to 1.4).
- A case-control study of Swiss HIV Cohort Study members (85% men) with or without anal cancer found that current smoking more than doubled the odds of anal cancer (aOR 2.59, 95% CI 1.25 to 5.34).
- A cross-sectional study of 500 Australian men who have sex with men (half with HIV) determined that current smoking doubled the odds of oral HPV (aOR 2.2, 95% CI 1.2 to 3.9), a cause of oropharyngeal squamous cell carcinoma. Men with HIV had a significantly higher prevalence of any oral HPV type (19% versus 7%, \( P < 0.001 \)).
- A 2-year study of US women and men with and at risk for HIV infection found that HIV infection independently raised the risk of incident oral HPV infection, while current smoking increased the risk of oral HPV persistence.

**Cardiovascular disease**

- Follow-up of 33,308 HIV-positive DAD cohort members for 3 years linked smoking to a doubled risk of cardiovascular death in current smokers (aRR 1.90, 95% CI 1.29 to 2.80) and former smokers (aRR 1.98, 95% CI 1.36 to 2.88).
- A 5472-person 33-month SMART trial analysis determined that current smoking doubled the risk of major cardiovascular disease compared with never smoking in people with HIV (aHR 2.0, 95% CI 1.3 to 3.1, \( P = 0.002 \)). Compared with former smoking, current smoking raised the risk of major cardiovascular disease 60% (aHR 1.6, 95% CI 1.1 to 2.4, \( P = 0.02 \)).
- A comparison of 3251 HIV-positive people in Denmark and 13,004 general-population controls matched for age and gender found that current HIV-positive smokers had almost a tripled risk of myocardial infarction compared with current general-population smokers (aIRR 2.83, 95% CI 1.71 to 4.70). Previous HIV-positive smokers had almost a doubled risk compared with previous general-population smokers, but that association lacked statistical significance (aIRR 1.78, 95% CI 0.75 to 4.24). MI risk was equivalent in HIV-
positive and general-population never-smokers (aIRR 1.01).

- Smoking and family history of cardiovascular disease—but not diabetes or hypertension—individually boosted the odds of acute coronary syndrome in a case-control study of people with HIV infection. In people with HIV, more than half of acute coronary syndrome diagnoses could be attributed to smoking (54.35%), while lower proportions could be attributed to diabetes (30.58%) or hypertension (6.57%).

- Among 27,136 HIV-positive current smokers in the DAD cohort study, cardiovascular disease risk dropped from an adjusted incidence rate ratio of 2.32 compared with never-smokers in the first year after stopping to 1.46 after more than 3 years since quitting.

- A 2000-2004 Women’s Interagency HIV Study of 1725 women with HIV and 668 women at risk for HIV identified smoking as an independent predictor of metabolic syndrome in the HIV group (aOR 1.31, 95% CI 1.06 to 1.61) and the HIV-negative group (aOR 2.19, 95% CI 1.46 to 3.26).

### Osteoporosis and fracture

- Meta-analysis of 13 studies of incident fracture in HIV-positive people identified five studies in which smoking independently predicted any fracture or fragility fractures.

- Meta-analysis of 15 studies involving bone mineral density or fracture in people with HIV or HIV/HCV found that smoking predicted osteoporosis in univariate analysis in four studies, and smoking predicted fracture in univariate analysis in three studies.

### Chronic and advanced kidney disease

- A case-control study of 75 HIV-positive people admitted to the hospital for chronic kidney disease (CKD) and 461 HIV-positive people admitted without CKD determined that smoking independently tripled the odds of hospital admission for CKD (aOR 3.0, 95% CI 1.4 to 5.6, P = 0.005). There was a dose-response relationship between packs smoked per day and CKD risk.

- A 35,192-person DAD study analysis determined that current smoking nearly doubled the risk of advanced CKD or end-stage renal disease compared with never smoking (aIRR 1.79, 95% CI 1.08 to 2.97).

### Oral disease

- Smoking quadrupled the risk of oropharyngeal candidiasis in a cross-sectional US study of 215 people with HIV (OR 4.07, 95% CI 1.18 to 14.08, P = 0.027).

- A 1995-2000 US study of 631 adults with HIV linked smoking to higher odds of prevalent oral candidiasis (OR 2.5, 95% CI 1.3 to 4.8) and incident oral candidiasis (OR 1.9, 95% CI 1.1 to 3.8).

- A cross-sectional US study 152 people with HIV identified more smoking pack-years as a risk factor for periodontitis.

- A US study of 415 people with HIV correlated smoking with higher prevalence of oral lesions (including oral candidiasis, salivary gland enlargement, and oral hairy leukoplakia), independently of CD4 count.

### Birth outcomes

- The impact of smoking on pregnant women and their neonates is well appreciated. In a 1998-2007 study of 1.6 million women with and without HIV across Florida, HIV infection and smoking independently predicted low birth weight, preterm birth, and infants small for gestational age.
Quitting turns the tables clinically

Compared with SMART trial participants who never smoked, current smokers in this six-continent study had higher risks of all-cause mortality, major cardiovascular disease, non-AIDS cancer, and bacterial pneumonia.19 This 5472-person analysis also found that current smokers ran a higher risk of five clinical outcomes than former smokers—all-cause mortality (aHR 1.5, 95% CI 1.0 to 2.1, \( P = 0.04 \)), AIDS-related disease (aHR 1.6, 95% CI 1.0 to 2.3, \( P = 0.03 \)), major cardiovascular disease (aHR 1.6, 95% CI 1.1 to 2.4, \( P = 0.02 \)), non-AIDS cancer (aHR 2.3, 95% CI 1.5 to 3.6, \( P < 0.001 \)), and bacterial pneumonia (aHR 1.5, 95% CI 1.1 to 2.1, \( P = 0.01 \)). These findings indicate that quitting confers a decided morbidity and mortality advantage.

Aquitaine cohort investigators set out to gauge the impact of quitting smoking on bacterial pneumonia risk.43 The analysis involved 3336 HIV-positive people who made at least two study visits from 2000 through 2007 and did not have bacterial pneumonia at their first visit. Compared with current smokers, people who never smoked had a 50% lower risk of bacterial pneumonia in an analysis adjusted for CD4 count, age, gender, HIV transmission category, antiretroviral therapy, cotrimoxazole prophylaxis, statin treatment, viral load, and previous AIDS diagnosis (aHR 0.5, 95% CI 0.29 to 0.86, \( P = 0.01 \)). When the Aquitaine team compared people who had quit smoking for at least 1 year with current smokers, the decrease in bacterial pneumonia risk was almost exactly the same (aHR 0.48, 0.26 to 0.90, \( P = 0.02 \)). A 14-study meta-analysis determined that current HIV-positive smokers had a 37% higher risk of bacterial pneumonia than HIV-positive people who kicked the habit (aHR 1.37, 95% CI 1.06 to 1.78, \( P = 0.02 \)).20

DAD study investigators conducted a detailed analysis to assess the impact of quitting smoking on cardiovascular disease.32 They considered three cardiovascular outcomes, myocardial infarction (MI), coronary heart disease (CHD, including MI, invasive coronary procedures, or death from other CHD), and cardiovascular disease (CVD, including CHD plus carotid artery endarterectomy or stroke). Poisson regression analysis to figure incidence rate ratios adjusted for age, sex, cohort, calendar year, family history of CVD, diabetes, lipids, blood pressure, and antiretroviral treatment.

Compared with people who never smoked, incidence rate ratios for MI fell from 3.73 per 100 person-years within the first year of quitting to 2.07 more than 3 years after quitting (Figure 3).32 Respective drops in incidence rate ratio were 2.93 to 1.83 for CHD and 2.32 to 1.49 for CVD (Figure 3). Compared with current smokers, people who had quit for more than 3 years had a 39% lower MI risk (IRR 0.61, 95% CI 0.36 to 1.04, \( P = 0.068 \)), a 26% lower CHD risk (IRR 0.74, 95% CI 0.48 to 1.15, \( P = 0.176 \)), and a 32% lower CVD risk (IRR 0.68, 95% CI 0.46 to 1.01, \( P = 0.058 \)). The declines in risk for MI and CVD approached statistical significance.

Smoking, adherence, and viral load

Smoking imperils adherence to antiretroviral therapy and—probably largely in consequence—can threaten viral control and CD4 response. A SMART study analysis including 5295 people, 38% of them smokers, determined that current smoking independently raised the odds of suboptimal adherence (missing any pills by self-report) more than 50% (aOR 1.54, 95% CI 1.41 to 1.68, \( P < 0.0001 \)).44 Current smoking also independently lowered MEMS-measured adherence in a 24-week study of 64 people taking lopinavir/ritonavir.45 Nonsmokers took 84.8% of prescribed doses, while current smokers took 63.5% (\( P < 0.001 \)). Former smokers did not differ from never-smokers in adherence.

A study of 333 HIV-positive people in Boston found lower medication adherence and appointment keeping in smokers than in nonsmokers, and higher odds of a detectable viral load (OR 2.85, 95% CI 1.53 to 5.30)
Figure 3. In the 3 or more years after DAD study members stopped smoking, rates of myocardial infarction (MI), coronary heart disease (CHD), and cardiovascular disease (CVD) (defined in text) declined steadily when compared with study members who never smoked.32 (Incidence rate ratios calculated per 100 person-years.)

and recent hospital admission (OR 1.89, 95% CI 0.99 to 3.57).46 In New York City a comparison of smoking and nonsmoking HIV-positive gay men 50 and older found that current smokers were 68% less likely to have an undetectable viral load than never-smokers in an analysis adjusted for age, income, and illicit drug use (aOR 0.32, 95% CI 0.13 to 0.81).47 Current smokers proved 75% less likely to have an undetectable load than former smokers (aOR 0.25, 95% CI 0.10 to 0.62). But former smokers did not differ significantly from never-smokers in chances of having an undetectable viral load.

Women’s Interagency HIV Study investigators assessed virologic and immunologic responses and risk of AIDS or death in 924 HIV-positive women starting antiretroviral between July 1995 and September 2003.48 More than half of the women, 57%, smoked. The WIHS team defined virologic response as the first viral load below 80 copies/mL after treatment began and immunologic response as the first CD4-cell gain of 100 cells/mm³. Virologic failure meant a rebound from below 80 copies/mL to above 1000 copies/mL, and immunologic failure meant a CD4 count below the pretreatment nadir. An analysis adjusted for age, race, HCV status, illicit drug use, and other variables determined that, compared with nonsmokers, smokers had:

- A lower chance of a virologic response: aHR 0.79, 95% CI 0.67 to 0.93, P = 0.006
- A lower chance of an immunologic response: aHR 0.85, 95% CI 0.73 to 0.99, P = 0.041

continued...
A higher chance of virologic failure: aHR 1.39, 1.06 to 1.69, \(P = 0.013\)

A higher chance of immunologic failure: aHR 1.52, 95% CI 1.18 to 1.96, \(P = 0.001\)

**Why so many HIV-positive people smoke**

Smoking prevalence runs higher in people with HIV than in uninfected people. In high-income countries between 40% to 60% of HIV-positive people smoke.\(^49\) And people with HIV often supplement their cigarette smoking with other tobacco products, usually cigars or snuff. In a US smoking-cessation trial that enrolled 474 people with HIV, 22% of them used at least one tobacco product besides cigarettes, a rate far higher than the 1% to 6% recorded in recent general-population studies.\(^50\)

The most comprehensive recent US analysis of smoking prevalence in people with HIV comes from a 2009 Medical Monitoring Project study by the Centers for Disease Control and Prevention (CDC).\(^51\) According to these nationally representative cross-sectional surveys, 42% of HIV-positive adults in care smoke, twice the 21% rate in the adult US population. Figuring the quit rate as the ratio of former smokers to the sum of former and current smokers, the CDC found a steeply lower ratio in adults with HIV than in the general population—32% versus 52%. Still, a one-third quit ratio in the US HIV population should encourage providers to continue pressing people with HIV to abandon tobacco.

Why do so many people with HIV smoke? An equally valid and perhaps more enlightening question is why so many smokers get HIV infection. A 2007 systematic review identified six studies probing the role of tobacco in HIV risk.\(^52\) Five of those six studies pinpointed smoking as an independent predictor of HIV acquisition, with adjusted odds ratios ranging from 1.6 to 3.5. But the authors of this review caution that residual confounding may explain that finding. In other words, smokers may have demographic and lifestyle traits that predispose them to HIV infection but did not get factored into the statistical analyses of these studies. Sifting some of the same data, a 2009 review “found little evidence that cigarette smoking increases the risk for acquiring HIV.”\(^53\)

No matter how one interprets the risk data, demographic and behavioral factors that incline one toward smoking clearly may also boost chances of picking up sexually transmitted infections like HIV. In a 2013 analysis of smoking and non-AIDS morbidity in people with HIV, workers from New York’s Weill Cornell Medical Center observed that reasons for high smoking prevalence in HIV populations reflect links between smoking and factors routinely observed in HIV groups, such as “low socioeconomic and education levels, psychiatric comorbidity, concurrent illicit drug and alcohol use, and mental stress.”\(^49\) To be sure, the CDC smoking prevalence study identified all or those factors—and a few more—as independent predictors of greater smoking prevalence in people with HIV; “older age, non-Hispanic white or non-Hispanic black race, lower educational level, poverty, homelessness, incarceration, substance use, binge alcohol use, depression, and not achieving a suppressed HIV viral load” (Figures 4 and 5).\(^51\)

**How smoking does more damage in people with HIV**

Why does smoking undermine the health of people with HIV more than the health of HIV-negative people? At first the consistently higher prevalence of smoking in HIV-positive people than in the general population appeared to explain the difference in smoking’s impact on morbidity and mortality, suggest Weill-Cornell researchers.\(^49\) But now, they observe, a growing trove of evidence hints that, in people with ongoing HIV-induced inflammation, “smoking may elicit additional inflammatory responses beyond what would be expected in a smoker without HIV infection.”
A CDC study of a nationally representative sample of HIV-positive people in care identified several factors independently associated with higher adjusted smoking prevalence, including viral load (VL) not at or below 200 copies/mL and the other variables shown here and in Figure 4.51

**Figure 4.** In a nationally representative sample of people in care for HIV infection, factors independently associated with higher adjusted smoking prevalence included age 40 to 49 or age 50+ (versus 18 to 29), non-Hispanic white or black race (versus Hispanic), and less than a high school education or a high school education (versus more than high school).51 Figure 5 charts seven other independent predictors.

**Figure 5.** A CDC study of a nationally representative sample of HIV-positive people in care identified several factors independently associated with higher adjusted smoking prevalence, including viral load (VL) not at or below 200 copies/mL and the other variables shown here and in Figure 4.51

continued...
The Weill-Cornell team notes that research unearthed two principal mechanisms of COPD-related lung inflammation or tissue destruction in all smokers: (1) tobacco smoked-induced inflammation, and (2) increased risk of bacterial colonization in remodeled lung.49 But in HIV-positive smokers, studies now suggest seven additional mechanisms may be at play: (1) independent influx of CD8 lymphocytes, (2) increased number of activated macrophages, (3) oxidant-antioxidant imbalance, (4) HIV protein induction of apoptosis in lung endothelial cells, (5) antiretroviral effects, (6) increased susceptibility to bacterial pulmonary infection, and (7) increased susceptibility to *Pneumocystis* colonization after *Pneumocystis* infection.

On top of all that, HIV infection appears to ramp up nicotine metabolism and so heighten the effects of this highly addictive toxin in people with HIV.54 Two of four nicotine metabolites assessed reached plasma concentrations up to 3-fold higher in HIV-positive smokers than in smokers without HIV. Moreover, concentrations of nicotine itself proved 5-fold lower in people with HIV, a finding indicating its faster metabolism in HIV-positive smokers. Enhanced nicotine metabolism, these researcher observe, increases reactive oxygen species and reactive metabolites, which could promote both carcinogenesis and HIV replication.

Notably, nicotine, protease inhibitors, and nonnucleosides all get metabolized via cytochrome P450 enzymes. The resulting interactions can trim antiretroviral concentrations to subtherapeutic levels and contribute to worse viral control in smokers (reviewed under “Smoking, adherence, and viral load” above).55-57

Nicotine is bad news. Everyone who smokes should know just how bad: In animal studies, nicotine killed as readily as strychnine and tripled the lethal impact of arsenic.58

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