Efficacy and safety of varenicline for smoking cessation in people living with HIV in France (ANRS 144 Inter-ACTIV): a randomised controlled phase 3 clinical trial

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Summary

Background Tobacco smoking is common in people living with HIV, but high-quality evidence on interventions for smoking cessation is not available in this population. We aimed to assess the efficacy and safety of varenicline with counselling to aid smoking cessation in people living with HIV.

Methods The ANRS 144 Inter-ACTIV randomised, parallel, double-blind, multicentre, placebo-controlled phase 3 trial was done at 30 clinical hospital sites in France. People living with HIV who had smoked at least ten cigarettes per day for 1 year or longer, were motivated to stop smoking, were not dependent on another psychoactive substance, and had no history of depression or suicide attempt were eligible. Using a computer-generated randomisation sequence, we allocated (1:1) the patients to receive either varenicline titrated to two 0·5 mg doses twice daily or placebo twice daily for 12 weeks, plus face-to-face counselling. Patients and investigators were masked to treatment group allocation. Patients who were not abstinent at week 24 were offered open-label varenicline for 12 additional weeks. The primary outcome was the proportion of smokers continuously abstinent from week 9 to week 48. Smoking status was confirmed by carbon monoxide in exhaled air. Primary analyses were done in both the intention-to-treat (ITT) population and modified ITT (mITT) population, which comprised all patients who took at least one tablet of their assigned study treatment. The safety analyses were done in the mITT population. The trial is registered at ClinicalTrials.gov, number NCT00918307. The trial status is complete.

Findings From Oct 26, 2009, to Dec 20, 2012, of 303 patients assessed for eligibility, 248 patients were randomly assigned to the varenicline group (n=123) or the placebo group (n=125). After randomisation, one participant initially assigned to the placebo group was excluded from the ITT analysis for a regulatory reason (no French health-care coverage). 102 patients in the varenicline group and 111 patients in the placebo group received at least one dose of their assigned treatment and were included in the mITT analysis. In the ITT analysis, varenicline was associated with a higher proportion of patients achieving continuous abstinence over the study period (week 9–48): 18 (15%, 95% CI 8–21) of 123 in the varenicline group versus eight (6%, 2–11) of 124 in the placebo group, adjusted odds ratio (OR) 2·5 (95% CI 1·0–6·1; p=0·041). In the mITT analysis, varenicline was also associated with higher continuous abstinence: 18 (18%, 95% CI 10–25) of 102 versus eight (7%, 2–12) of 111 in the placebo group (adjusted OR 2·7, 95% CI 1·1–6·5; p=0·029). The incidence of depression was 2·4 per 100 person-years (95% CI 0·6–9·5; two [2%] of 102) in the varenicline group and 12·4 per 100 person-years (95% CI 6·9–22·5; 11 [10%] of 111) in the placebo group. 14 (7%) of 213 participants had 18 cardiovascular events: six (6%) of 102 people in the varenicline group and eight (7%) of 111 people in the placebo group.

Interpretation Varenicline is safe and efficacious for smoking cessation in people living with HIV and should be recommended as the standard of care.

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Introduction

With the use of antiretroviral therapy (ART), people living with HIV might experience a life expectancy close to that expected for the general population of the same age and sex.[1] Nevertheless, improvements can still be made in terms of non-AIDS-related morbidity and mortality, including cancer, cardiovascular diseases, bacterial pneumonia, and respiratory illnesses.[2,3] Tobacco smoking is a leading cause of these conditions and a worldwide problem in people living with HIV. The prevalence of smoking in people living with HIV is two to three times higher than observed in the general population, both in Europe and North America[3,4] and in middle-income and low-income countries.[5]

High-quality evidence on interventions for smoking cessation in people living with HIV,[6] who are also less likely to quit smoking than are people in the general population, is unavailable.[7] Smoking cessation

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Research in context

Evidence before this study

We used a Cochrane review on behavioural and pharmacological interventions for smoking cessation in people living with HIV, which described all trials published before June 17, 2015, and did a literature search on PubMed with the terms "smoking cessation" AND "HIV" AND "varenicline" for all articles published before July 1, 2017. Previous studies showed that a high proportion of people living with HIV are smokers and they are less likely to quit smoking than smokers in the general population. However, high-quality evidence of the risk-to-benefit ratio of interventions for smoking cessation in the long term (1 year) is scarce in smokers living with HIV. Specifically, varenicline with counselling had never previously been assessed in a randomised clinical trial specifically in the people living with HIV. Varenicline is the most efficacious pharmacological treatment for smoking cessation in the general population.

Added value of this study

We report the first randomised, double-blind clinical trial of varenicline in people living with HIV who are not co-dependent on other addictions. Our trial combines an analysis based on continuous abstinence, which was biochemically documented, over a long follow-up, alongside careful recording of adverse events and monitoring of HIV-1 control. We show that a combination of varenicline and counselling support is associated with sustainable continuous abstinence of smoking, is well tolerated and does not affect the control of HIV-1 infection.

Implications of all the available evidence

In people living with HIV who are motivated to quit and are not co-dependent on other addictive drugs, varenicline with individualised counselling is a convenient and effective option that is safe and has no clinical interaction with antiretroviral drugs. Further research should focus on the discovery of more efficacious smoking cessation treatments and programmes, and on interventions, adapted to people living with HIV in different contexts, able to increase adherence to existing treatments and programmes.

interventions are mostly based on those developed in the general population, including nicotine substitutes, bupropion, and varenicline alongside counselling strategies such as telephone or web-based interventions. Varenicline, a partial agonist of the nicotinic acetylcholine receptor α4β2, is a first-line treatment for tobacco addiction.[8–10] Varenicline exhibits no substantial interactions with antiretroviral treatments (cytochromes P450 are not involved in its metabolism), but a potential risk of varenicline-related depression[11] and cardiovascular complications[12] have been reported, which call for a specific estimation of benefit-to-risk ratio of this treatment in people living with HIV.

We aimed to test whether varenicline treatment alongside face-to-face counselling, an intervention used in the HIV-uninfected population, would be safe and efficacious in the long term for smoking cessation in people living with HIV.

Methods

Study design

The ANRS 144 Inter-ACTIV study is a randomised, parallel, double-blind, multicentre, placebo-controlled, phase 3 trial comparing safety and efficacy of varenicline versus placebo to aid smoking cessation in people living with HIV. The study was done at 30 HIV clinics located in French university hospitals or other referral hospitals that are usually involved in the management of people living with HIV (appendix pp 2–4). The protocol was approved by the Comité de Protection des Personnes Sud-Ouest et Outre Mer III (Bordeaux, France) and the Agence Française de Sécurité Sanitaire des Produits de Santé.

See Online for appendix

For a **summary of the protocol (in French)** see http://www.anrs.fr/fr/actualites/409/anrs-144-inter-activ

Participants

People aged 18 years or older with documented HIV infection were eligible if they had smoked at least ten cigarettes daily for a year or more, volunteered to stop smoking after completing a Q-MAT smoking cessation motivation questionnaire,[13] and were regularly followed up in one of the participating French hospitals. Patients were not eligible if they were co-dependent on a psychoactive substance other than tobacco, had a depressive episode during enrolment diagnosed by a psychiatrist, had ever attempted suicide, were having ongoing treatment with interferon, had been taking efavirenz for less than 3 months, or had had neuropsychological drug-related adverse events while taking efavirenz. Other exclusion criteria were previous treatment with varenicline (or known hypersensitivity to varenicline) or bupropion or ongoing nicotine replacement therapy, being pregnant, or ongoing breastfeeding. Participants were not eligible if they had occupations requiring high vigilance or if they were not affiliated to the health-care system. All participants gave written informed consent (in French). The trial was done in accordance with the Declaration of Helsinki.

Randomisation and masking

Participants were enrolled by investigators and randomly assigned to receive 12 weeks of either varenicline or placebo individually (figure 1). Randomisation (1:1) was done centrally via electronic case report software (CS software, Ennov-Clinsight), on the basis of a list generated with SAS software, version 9.2 (PROC PLAN procedure, block size 8). Randomisation was stratified according to whether the quit-smoking counsellor was

an infectious diseases specialist or tobaccologist and whether or not the centre had participated in an ancillary study on lung ageing. Only the trial statistician (JA) had access to the randomisation list during the trial. JA was involved in the data analysis.

The placebo was biologically inactive. The masking (presentation, colour, taste, and smell) was done by the pharmaceutical vendor (LC², Lentilly, France) in accordance with its internal procedures. Patients and investigators were masked to treatment group allocation.

Procedures

Treatment was given orally at the following doses to minimise nausea: 0·5 mg once daily on days 1–3; 0·5 mg twice daily on days 4–7; and two doses of 0·5 mg twice daily from day 8 to week 12. This 12 week treatment period was followed by a planned 13 week period of no pharmacological intervention, with only the smoking cessation counselling. All participants who resumed smoking before week 24 and were still motivated to quit at week 24 were offered a second, 12 week open-label treatment phase with varenicline if they had not had drug-related serious adverse events and were not using other smoking cessation drugs. Participants and investigators remained masked to treatment groups until the database lock (after week 48), and therefore did not know which group the participant was originally assigned to when they were to receive active varenicline at week 25.

The counselling support was delivered face to face as a programme of assistance in behavioural change by a health-care professional. This programme included an initial counselling session between the smoker and the counsellor in the 4 weeks after screening (from week –4 to week 0). During this initial session, the counsellor explained the programme and the importance for the patient to participate actively in the counselling. The duration of the programme and the precise number of sessions were tailored to patients' needs. At this first session, the counsellor reviewed the patient's smoking status and motivations and fears with respect to quitting smoking and prescribed the trial treatment. During these consultations, each patient set a target date for quitting smoking, in the next 1–2 weeks after the start of trial treatment. The follow-up sessions for this counselling programme aimed to empower participants to maintain smoking cessation by providing moral support and by managing anxiety. The programme aimed to include ten to 15 face-to-face sessions over 1 year.

Each centre had a single specific counsellor who was a tobaccologist or infectious diseases specialist with expertise in counselling. Antiretroviral treatment decisions were made by the local investigators as part of routine management of HIV infection.

Clinical examinations and laboratory tests were done at screening (week –4), baseline (week 0), and weeks 2, 4, 6, 9, 12, 18, 24, 37, and 48; participants who took part in the second phase of varenicline treatment had additional visits at weeks 27, 29, 31, 34, and 42. Smoking status was assessed by interview at each visit and was confirmed by measuring carbon monoxide in exhaled air with the Tabataba analyser (FIM Medical, Villeurbanne, France). An exhaled carbon monoxide concentration of ten particles per million or less was used to confirm smoking abstinence.[14] Self-assessment questionnaires assessed motivation to quit smoking (Q-MAT) and nicotine dependency (Fagerström test) at screening, and depressive disorders were identified with the hospital anxiety and depression (HAD) scale at screening and

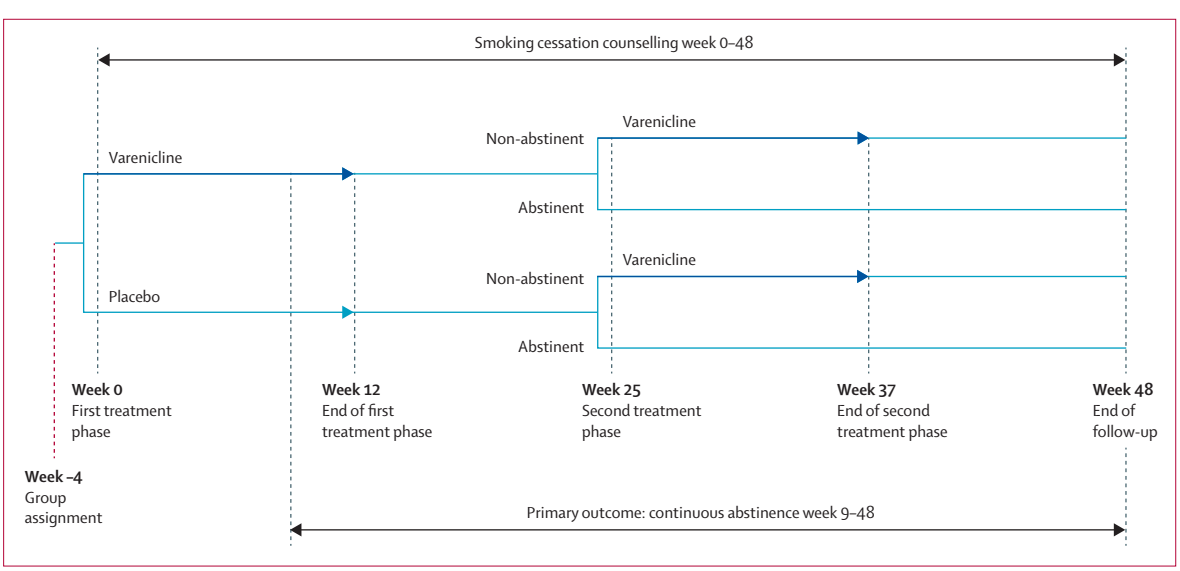

Figure 1: **Study design of the ANRS 144 Inter-ACTIV trial**
Timeline of study with treatment phases from random group assignment (at week –4) to end of follow-up (week 48). First treatment phase: masked treatment with varenicline or placebo. Second treatment phase: varenicline offered to eligible patients who did not remain abstinent and did not have any serious adverse event during the first phase.

during the trial at all follow-up visits. Positive HAD assessments were confirmed by a psychiatrist and quantified with the Montgomery-Åsberg depression rating scale.

Outcomes

The primary endpoint was the proportion of continuously abstinent smokers from week 9 to week 48. Participants were classified as non-abstinent for the primary endpoint when they resumed smoking between week 9 and week 48 or if they took other smoking cessation drugs than the study treatment. All those participating in the second phase of active varenicline were considered non-abstinent.

Prespecified secondary endpoints were the proportion of continuously abstinent smokers from week 9 to week 12; incidence of episodes of depression over the duration of the study; cardiovascular and cerebrovascular events as specifically elicited events for the duration of the study; and the proportion of abstinent smokers after the optional second phase (weeks 34–48). HIV immunovirological changes during follow-up were also monitored. Other objectives described in the protocol will be reported elsewhere.

Clinical and laboratory adverse events were graded with the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) scale for grading adult adverse events.[15] Each investigator assessed the imputability of all adverse events while masked to group assignment. An adverse event was considered serious if fatal or life threatening, causing persistent or significant disability or incapacity, requiring hospital admission or prolongation of existing hospital admission, resulting in a congenital abnormality or birth defect, defined as a laboratory grade 4 event, or other medically important events as defined by the investigator. Participants were considered to be diabetic if they reported a history of diabetes or were receiving treatment for diabetes at screening or baseline. Hypertension was defined as systolic/diastolic blood pressure of 140/90 mm Hg or more at screening. Psychiatric, cerebrovascular, and cardiovascular events were closely monitored throughout the study. Transaminase concentrations, blood pressure, and weight were assessed in post-hoc analyses.

Statistical analysis

Assuming the same efficacy of varenicline as in the general population (continuous abstinence in 10% of participants in the placebo group and 23% in the varenicline group),[9] the targeted number of participants per group was 127, with a two-sided type I error of 5% and a power of at least 80% (χ^2 test).

Patients with missing data at weeks 9, 12, and 48 were considered to be non-abstinent (ie, treatment failure). For the visits at weeks 18, 24, and 37, if the exhaled carbon monoxide value or declared abstinence status was missing, the participant was considered abstinent only if they were abstinent at the visits immediately before and after.

The primary analysis was based on an intention-to-treat (ITT) analysis of all participants in their originally assigned groups, and a modified ITT (mITT) analysis of all participants who took at least one tablet of their assigned study treatment.

The effect of varenicline was estimated by logistic regression analysis and tested by a two-sided Wald test. The odds ratio (OR) was adjusted for the stratification variables (infectious diseases specialist *vs* tobaccologist and participation *vs* no participation in lung ageing substudy). Cumulative follow-up was computed by summing participants' follow-up duration (time between group assignment date and last contact date before or at week 48).

Safety analysis was done in the mITT population of patients who took at least one tablet of their assigned study treatment, and then according to what treatment was actually received. For randomised comparisons of adverse events in patients who were in the mITT population, the incidence of adverse events was calculated as the number of participants who had at least one event after randomisation, divided by follow-up duration (time between group assignment and last date of follow-up or the date of diagnosis of the adverse event). For the comparison of patients who took varenicline (regardless of the phase) with those who did not take varenicline, the incidence of adverse events was estimated by taking into account only events occurring after the start of varenicline treatment (regardless of the treatment phase). For both comparisons, person-years were computed by summing follow-up since start of varenicline treatment to last date of follow-up or the date of diagnosis of the adverse event.

We did all statistical analyses using the SAS statistical software, version 9.2. The trial is registered at ClinicalTrials.gov, number NCT00918307.

Role of the funding source

The funder had no role in study design, collection, analysis, and interpretation of data, writing the report, or in the decision to submit the paper for publication. PM had full access to all data and had final responsibility for the decision to submit for publication.

Results

From Oct 26, 2009, to Dec 20, 2012, 303 patients were screened. 248 patients were randomly assigned to the varenicline group (n=123) or the placebo group (n=124; one participant initially assigned to the placebo group was excluded from the ITT analysis for a regulatory reason [no French health-care coverage]).

The last visit of the last participant occurred on Jan 20, 2014. 66 (54%) of 123 participants in the varenicline group versus 78 (62%) of 125 participants in the placebo group fully adhered to the 12 week study

treatment and 71 (58%) participants in the varenicline group versus 81 (65%) in the placebo group completed follow-up at 48 weeks (figure 2). The total cumulative follow-up was 181 person-years in the ITT analysis (87 in the varenicline group and 93 in the placebo group; 84% of the expected 216 person-years) and 176 person-years in the mITT analysis (84 in the varenicline group and 92 in the placebo group; 83% of the expected 211 person-years). Most premature treatment discontinuations in both groups were because of participants' decisions (figure 2). Participants attended a median of eight (IQR four to ten) counselling sessions in the varenicline and eight (four to 11) in the placebo group over the course of the trial. Baseline characteristics were similar in the two groups in the ITT (table 1) and mITT (appendix pp 5–6) populations; characteristics were also similar between those who received varenicline and those who did not (appendix pp 7–8).

The mean time since HIV infection diagnosis was 13 years (SD 8) in the varenicline group and 12 years (8) in the placebo group, and most patients were receiving antiretroviral therapy and had less than 50 copies per mL HIV-1 RNA. The mean years of smoking was 27 years (SD 9) in the varenicline group and 25 years (9) in the placebo group, and most patients had already tried to quit smoking at least once (table 1).

In the ITT population (figure 3), 18 (15%, 95% CI 8–21) of 123 patients in the varenicline group were continuously abstinent between week 9 and week 48 compared with eight (6%, 2–11) of 124 in the placebo group (p=0·036). The adjusted OR for continuous abstinence in the varenicline versus placebo group between week 9 and week 48 was 2·5 (95% CI 1·0–6·1; p=0·041). Of the patients who were not continuously abstinent up to week 48, 63 (60%, 95% CI 51–69) of 105 participants in the varenicline group versus 40 (34%, 26–43) of 116 participants in the placebo group were classified as non-abstinent because they missed one or more mandatory follow-up visits. When the smoking counsellor was the infectious diseases specialist, ten (20%, 95% CI 9–32) of 49 patients in the varenicline group versus six (13%, 3–22) of 48 in the placebo group were continuously abstinent; and when the counsellor was the tobaccologist, eight (11%, 95% CI 4–18) of 74 versus two (3%, 0–9) of 76 were continuously abstinent ($p_{interaction}$=0·2183). Between week 9 and week 12, 35 (29%, 95% CI 21–36) of 123 participants in the varenicline group and 14 (11%, 6–17) of 124 participants in the placebo group were continuously abstinent (p=0·0007). The adjusted OR for continuous abstinence of varenicline versus placebo between week 9 and week 12 was 3·2 (95% CI 1·6–6·4; p=0·0009).

In the mITT population, 18 (18%, 95% CI 10–25) of 102 patients in the varenicline group versus eight (7%, 2–12) of 111 in the placebo group were continuously abstinent between week 9 and week 48 (p=0·0201; appendix p 9). The adjusted OR for continuous abstinence in the varenicline versus placebo group between week 9 and week 48 was 2·7 (95% CI 1·1–6·5; p=0·029). 42 (50%, 95% CI 39–61) of 84 participants in the varenicline group were classified as non-abstinent as having missed one or more mandatory visits versus 27 (26%, 18–35) of 103 participants in the placebo group. When the smoking counsellor was the infectious diseases specialist, ten (21%, 95% CI 10–33) of 47 patients in the varenicline group versus six (13%, 3–23) of 46 in the placebo group were continuously abstinent; and when the counsellor was the tobaccologist, eight (15%, 5–24) of 55 versus two (3%, 0–11) of 65 patients were continuously abstinent ($p_{interaction}$=0·1796). Between week 9 and week 12, 35 (34%, 95% CI 25–44) of 102 participants in the varenicline group and 14 (13%, 6–19) of 111 participants in the placebo group were continuously abstinent. The adjusted OR for continuous abstinence of varenicline versus placebo was 3·6 (95% CI 1·8–7·3; p=0·0003).

170 participants across the two groups were not abstinent at week 24, and 63 of them received an open-label second phase of varenicline (21 in the varenicline group and 42 in the placebo group). Two (10%, 95% CI 1–30) of these patients who were initially assigned to

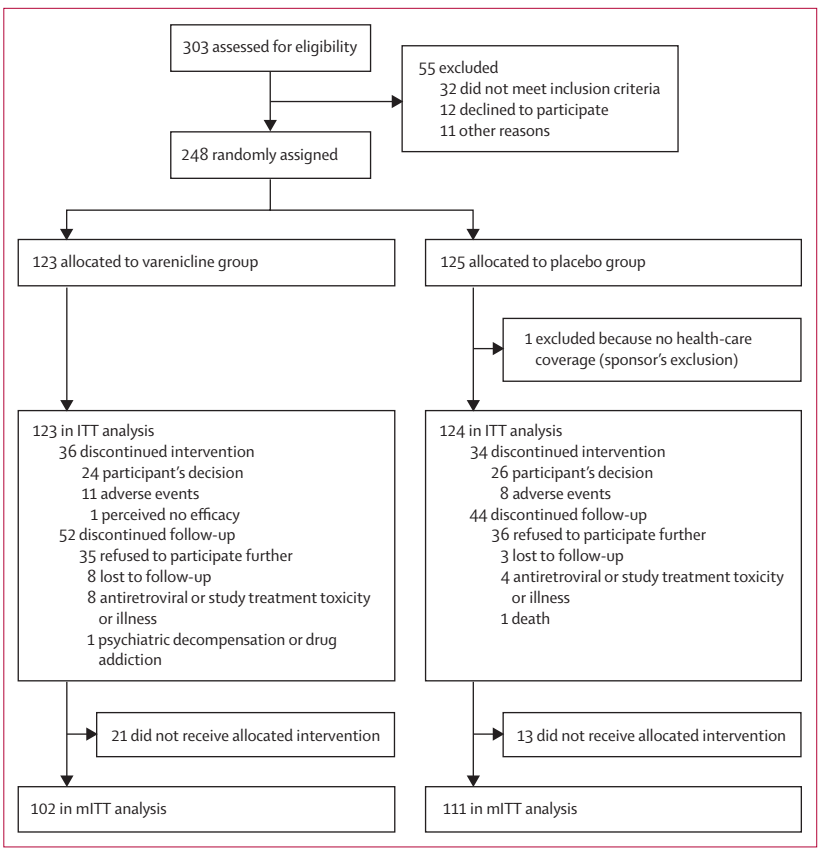

Figure 2: **Flow diagram of the ANRS 144 Inter-ACTIV**
ITT included all randomised participants in their original group. mITT included all randomised participants, in their original group, who took at least one tablet of the study treatment. ITT=intention-to-treat. mITT=modified ITT.

	Varenicline group (n=123)	Placebo group (n=124)	Total (n=247)
Age, years	47 (9)	44 (9)	45 (9)
Sex			
Men	100 (81%)	104 (84%)	204 (83%)
Women	23 (19%)	20 (16%)	43 (17%)
HIV transmission category			
Homosexual or bisexual	64 (52%)	68 (55%)	132 (53%)
Heterosexual	40 (33%)	36 (29%)	76 (31%)
Other*	19 (15%)	20 (16%)	39 (16%)
Time since HIV-1 diagnosis, years	13 (8)	12 (8)	13 (8)
HIV stage C	33 (27%)	31 (25%)	64 (26%)
Antiretroviral treatment	114 (93%)	117 (94%)	231 (94%)
Efavirenz-containing treatment	17 (14%)	20 (16%)	37 (15%)
HIV-1 RNA, log_{10} copies per mL†‡	1·8 (0·9)	1·7 (0·7)	1·8 (0·8)
HIV-1 RNA <50 copies per mL‡	97 (80%)	90 (73%)	187 (76%)
CD4 count, cells per µL	657 (269)	662 (276)	659 (272)
Years of smoking at group assignment‡	27 (9)	25 (9)	26 (9)
Smoking, cigarettes per day	19 (7)	21 (9)	20 (8)
History of at least one smoking cessation attempt§	101 (84%)	100 (81%)	201 (82%)
Fagerström test score for nicotine dependence¶	5·2 (2)	5·5 (2)	5·4 (2)
Q-MAT score	15 (4)	15 (3)	15 (4)
High blood pressure‖	33 (28%)	17 (14%)	50 (21%)
Diabetes declared by investigator	4 (3%)	5 (4%)	9 (4%)
Hospital anxiety and depression scale score	9 (5)	9 (5)	9 (5)

Data are mean (SD) or n (%). Screening visit (4 weeks before baseline) was used when data from baseline visit were not recorded. Q-MAT=smoking cessation motivation questionnaire. *Other transmission categories were drug users (six in the varenicline group *vs* eight in the placebo group), homosexual or bisexual and drug users (four *vs* one), transfusion or blood-derived products (two *vs* two), and unknown (three *vs* six). †If the viral load measure was undetectable, the viral load threshold value was imputed (usually 20 copies per mL, min–max: [20–60]). ‡Missing data for one patient in varenicline group and one in placebo group. §Three missing data in the varenicline group. ¶13 missing data in the varenicline group and five in the placebo group. ‖Three missing data in the varenicline group and four in the placebo group.

Table 1: **Baseline characteristics in the intention-to-treat population**

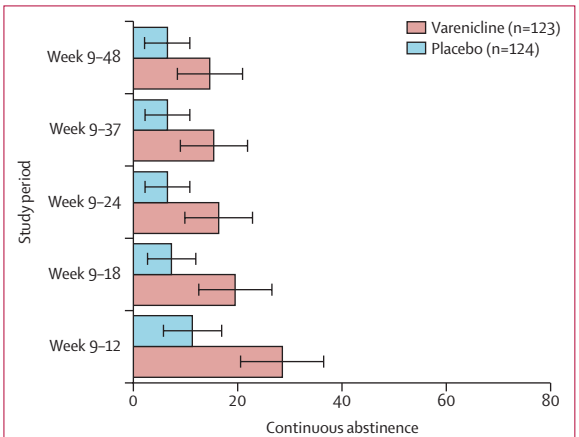

Figure 3: **Continuous abstinence in the intention-to-treat population**
Shaded bars show the proportion of patients who were abstinent in each group over the specified study period and error bars show 95% CI. Abstinence measured from week 9 to week 48.

receive varenicline versus seven (17%, 7–31) who were assigned to placebo were continuously abstinent between week 34 and week 48. Of the 81 participants randomly assigned to the varenicline group who received only the first, masked phase of varenicline, 22 (27%; 95% CI 18–38) remained continuously abstinent between week 34 and week 48.

CD4 cell count and plasma HIV RNA remained stable during the study (appendix p 10). Three participants, who were all from the varenicline group, changed antiretrovirals because of treatment failure. In the varenicline group, mean CD4 counts were 657 cells per µL (SD 269) at screening (week –4) and 612 cells per µL (244) at week 48; in the placebo group, mean CD4 counts were 662 cells per µL (276) and 685 cells per µL (277). Mean HIV-1 RNA load remained stable between 1·8 and 2·0 log_{10} copies per mL in the two groups and 124 (89%) of 139 patients had 50 copies per mL or less at week 48 (57 [88%] of 65 in the varenicline group and 67 [91%] of 74 in the placebo group). Transaminase concentrations and blood pressure remained stable in the two groups throughout the study. Median weight was 68 kg in the varenicline and 70 kg in the placebo group at baseline, and 73 kg in both groups at week 48.

Most adverse events were grade 1 or 2 and were mainly gastrointestinal and psychiatric disorders. 23 (23%) of 102 patients in the varenicline group and 22 (20%) of 111 patients in the placebo group had at least one grade 3 or 4 clinical adverse event (table 2). Seven participants in each group (7% [95% CI 2–12] in the varenicline group and 6% [2–11] in the placebo group) had at least one grade 3 or 4 drug-related adverse event.

The incidence of depression was 2·4 per 100 person-years (95% CI 0·6–9·5; two [2%] of 102) in the varenicline group and 12·4 per 100 person-years (95% CI 6·9–22·5; 11 [10%] of 111) in the placebo group. Regardless of assigned group, the incidence of depression was 5·2 per 100 person-years (95% CI 2·2–12·5; n=5) in participants who received active varenicline at any time and 12·6 per 100 person-years (95% CI 6·3–25·2; n=8) in participants who never received varenicline (p=0·32).

Three participants experienced a total of five adverse events related to efavirenz, including one grade 3 event (anxiety) in a participant who never received varenicline. Of the 18 cardiovascular events reported in 14 participants, one case of grade 2 drug-related hot flushes was reported in the placebo group. No cerebrovascular events were reported. 12 grade 3 or 4 laboratory adverse events were reported in 12 participants, but none were considered drug-related by the investigators (table 2). Of the 29 serious adverse events occurring in 25 participants, one adverse event related to study treatment was reported during the second phase on varenicline in a participant initially assigned to the placebo group: psychiatric hospital admission for behaviour disorder. One participant in the placebo group died after a physical assault unrelated to the study.

	Varenicline group (n=102)	Placebo group (n=111)	Total (n=213)
Clinical adverse events			
Patients with clinical adverse events	76 (75%)	85 (77%)	161 (76%)
Patients with drug-related clinical adverse events	49 (48%)	43 (39%)	92 (43%)
Patients with grade 3 or 4 clinical adverse events*	23 (23%)	22 (20%)	45 (21%)
Patients with grade 3 or 4 drug-related clinical adverse events	7 (7%)	7 (6%)	14 (7%)
Number of grade 3 or 4 drug-related events	8	7	15
Sleeping disorders†‡	2	2	4
Depression†	1	1	2
Behavioural disorders†§	2	1	3
Drowsiness†	1	0	1
Headache†	1	0	1
Digestive disorders	0	2	2
Asthenia	1	0	1
Tinnitus	0	1	1
Patients with serious clinical adverse events	12 (12%)	12 (11%)	24 (11%)
Patients with psychiatric disorders (any grade)	38 (37%)	42 (38%)	80 (38%)
Patients with drug-related psychiatric disorders (any grade)	24 (24%)	27 (24%)	51 (24%)
Patients with cardiovascular disorders	6 (6%)	8 (7%)	14 (7%)
Number of cardiovascular disorders	8 (8%)	10 (9%)	18 (8%)
Laboratory adverse events			
Patients with laboratory adverse events	78 (77%)	84 (76%)	162 (76%)
Patients with grade 3 or 4 laboratory adverse events	3 (3%)	9 (8%)	12 (6%)
Number of grade 3 or 4 events (none drug-related)	3	9	12
Hyperbilirubinaemia	0	2	2
Increased alanine aminotransferase	1	1	2
Increased γ-glutamyltransferase	0	2	2
Leucopenia	1	0	1
Thrombocytopenia	0	1	1
Hepatic cytolysis	1	0	1
Hyperglycaemia	0	1	1
Hypertriglyceridaemia	0	1	1
Hypophosphataemia	0	1	1
Patients with serious laboratory adverse events	0	1 (1%)	1 (1%)

The investigator was masked when assessing the imputability of all adverse events. *One death unrelated to study treatment (following a physical assault). †Neuropsychiatric adverse events. ‡Sleeping disorders: one sleeping disorder (varenicline), two reports of nightmare (one varenicline and one placebo), and one insomnia (placebo). §Behavioural disorders: one hallucination combined with nightmares (varenicline), one affective disorders (varenicline), and one behavioural disorder without specifications (placebo; considered by the investigator to be a serious adverse event related to study treatment).

Table 2: **Clinical and laboratory adverse events in the modified intention-to-treat population**

Discussion

Our trial showed that varenicline with individual tailored counselling is an efficacious smoking cessation treatment in people living with HIV, with short-term and long-term continuous abstinence. Varenicline, which obtained marketing authorisation in France in May, 2007, was well tolerated, specifically in terms of cardiovascular and neuropsychiatric events, and did not affect the control of HIV-1 infection.

In an open-label study of varenicline and counselling in 36 people living with HIV by Cui and colleagues,[16] 42% of patients remained abstinent from week 9 to week 12 of the study. No serious adverse events were documented, although frequent non-serious adverse events were observed, including nausea (in 36% of patients) and sleeping disorders (abnormal dreams [31%] and insomnia [19%], and affect lability [19%]). HIV viral load remained stable. In our randomised trial with a larger sample size and longer follow-up, the incidence of these adverse events was lower and reassuring. Although a potential benefit of varenicline on CD4 counts was shown in the study by Cui and colleagues,[16] our results did not show significantly increased counts compared with placebo.

The safety of varenicline in smokers living with HIV had not previously been assessed in a randomised, placebo-controlled trial. In the general population, safety concerns had been raised regarding neuropsychiatric or cardiovascular drug-related adverse events.[11,12] However, two recent meta-analyses found no evidence of an

association with suicide, suicidal ideation, depressive syndromes, or death,[17,18] but a link with insomnia and abnormal dreams.[18] In the EAGLES study,[10] a large controlled randomised trial (n=8144) comparing varenicline or bupropion with nicotine patch or placebo in smokers with and without psychiatric disorders, most of the frequently reported adverse events were similarly associated with insomnia and dreams. 67 (7%) of 1026 patients with psychiatric disorders had moderate and severe neuropsychiatric events in the varenicline group (with no significant differences between the varenicline and placebo group or patch group) compared with 13 (1%) of 990 participants without psychiatric disorders.[10]

Regarding serious cardiovascular events, a 2016 meta-analysis of 38 trials in smokers in the general population reported no difference between varenicline and placebo (relative risk 1·03, 95% CI 0·72–1·49).[19] In the general population, the risk of recurrent coronary events decreases in the first 3 years after quitting smoking, and the risk of death from myocardial infarction is reduced by more than 50% after 3–5 years compared with smokers, suggesting that varenicline use for smoking cessation might have more cardiovascular benefits than harms.[20,21] In people living with HIV on effective ART, the risk of losing years of life because of smoking is higher than the risk associated with HIV.[22] Mortality resulting from cardiovascular disorders and non-HIV-related cancers is indeed significantly higher in HIV-infected smokers (mortality rate ratio 6·28) than in HIV-infected non-smokers (2·67).

Although formal pharmacokinetics data from our trial are not available, immunovirological markers of HIV control and clinical HIV progression were not affected over the trial duration, confirming the absence of clinically important interactions between antiretroviral drugs and varenicline in this population of patients with stable antiretroviral treatment.

Our results for continuous abstinence at 48 weeks after an initial 12 week varenicline treatment are in the range of the 19–44% that has been recorded in similar trials in the general population.[8,9,23–26]

In their systematic review, Moscou-Jackson and colleagues[27] identified only five randomised controlled trials, all in the USA, analysing different counselling strategies in addition to nicotine replacement therapy in people living with HIV. Three trials assessed the short-term efficacy of telephone-based interventions.[28–30] A more recent Cochrane review showed no convincing evidence of effective interventions in people living with HIV, both in short-term and long-term assessments,[6] highlighting the need for combining multiple strategies and interventions to maximise efficacy and indicating the need for tailoring interventions.

Interventions involving social support might increase adherence to pharmacological drugs or counselling programmes.[31] In our trial, continuous abstinence was more common in both groups when the counsellor was the infectious diseases specialist rather than the tobaccologist. We believe that these results might reflect the use of a more tailored intervention by the infectious diseases specialist because, for example, they might be able to understand specific barriers faced by people living with HIV, which might be less prevalent in the general population that the tobaccologist is familiar with.

The second open-label phase offered to participants who had resumed smoking after the initial double-blind phase resulted in only small proportions of patients classed as abstinent at week 48. We believe this result might be explained by insufficient motivation not only to quit, but also to be willing to start varenicline again within a very short period of time after failure of the initial 12 week treatment. Our result contrasts with a large multinational, randomised, placebo-controlled trial[32] of retreatment with varenicline (no quit attempt with varenicline in the preceding 3 months) for smoking cessation in 494 smokers, in which 45% in the varenicline group versus 12% in the placebo group were continuously abstinent from week 9 to week 12.

Evidence on interventions to aid smoking cessation in people living with HIV remains scarce. More research is therefore needed to understand determinants of adherence better and to increase adherence of interventions from the start of the smoking cessation intervention to the long term. Additionally, more efficacious innovative products or interventions should be assessed in large trials.

We acknowledge the limitations of our study. First, it was a challenge to enrol the required number of participants and to retain them. 34 participants initially randomly assigned chose not to start study treatment, which weakened the results of the intention-to-treat analysis. We acknowledge that we had incomplete outcome data, as is the case in many other trials analysing the effectiveness of aids for smoking cessation. Given our selection of participants with the aim of maximising safety, our results can be extrapolated to people living with HIV with low risk of neuropsychiatric and cardiovascular events. However, recruitment within a large national network ensures that a diverse population of people living with HIV was recruited in diverse health settings, complementing most published trials done in participants from the USA. The analysis of participants who took at least one tablet of study treatment provides positive findings of efficacy, but intention-to-treat results are much more similar to those seen in practice. Important strengths of our trial are the randomised, blinded comparison versus placebo, and the large sample size. Another strength was the long-term analysis with a primary outcome that was both self-reported and biochemically verified. Additionally, adverse events and HIV outcomes were carefully recorded and described.

This trial shows that a combined intervention of varenicline and individualised counselling support is

effective in assisting people living with HIV to achieve short-term and long-term abstinence. Because smoking is the most common modifiable risk factor worldwide for cardiovascular diseases and malignancies in people living with HIV, smoking cessation interventions should systematically be offered to smokers living with HIV.

Contributors

PM, CK, SF, CS, CD, JR, NW, AB, DZ, XD, J-MM, BS, CF, and GC contributed to study concept or design. PM, CK, SF, CS, CD, JR, NW, DZ, XD, and J-MM were responsible for the acquisition of data. PM, JA, CK, SF, JR, NW, LM, AB, DZ, XD, J-MM, BS, CF, and GC analysed and interpreted the data. PM, AB, LM, and GC supervised or coordinated the study. PM, JA, LM, and GC drafted the manuscript. PM, JA, CK, SF, CD, NW, LM, AB, JR, DZ, XD, J-MM, BS, CF, and GC revised for important intellectual content. PM and GC obtained funding. PM is responsible for sharing the dataset upon request. JA did the statistical analysis.

Declaration of interests

The institution of JR has received funds from Institut national de la santé et de la recherche médicale (Inserm)-France Recherche Nord et sud Sida-hiv hépatites (ANRS). XD has received grant support from Pfizer. J-MM is a member of scientific advisory boards of Merck laboratories, Gilead, Bristol-Myers Squibb, ViiV Healthcare, and Janssen and has received grant support from Merk laboratories and Gilead. BS has received honoraria for seminars from Merck laboratories, Gilead, and Janssen and support for the IAS 2014 conference from Merck laboratories. The institution of CF and GC has received grant support from Inserm-ANRS and Pfizer. GC has received grant support for International Workshop on HIV and Hepatitis Observational Databases from Gilead, Tibotec-Janssen, Roche, Merck laboratories, Janssen Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, ViiV Healthcare, Mylan, Abbvie, and Abbott and grant support for ongoing clinical trials of Inserm-ANRS from Gilead, Tibotec-Janssen, Merck laboratories, Boehringer Ingelheim, and Abbott. All other authors declare no competing interests.

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