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**THE AUTHORS REPLY:** Lopez-Cortes and colleagues question our conclusions on the basis of the results of the START study. Regarding the choice of end points (a question that was also raised by Corrao and colleagues), we included serious AIDS and non-AIDS conditions as part of the primary end point in part because the presence of HIV infection and the use of antiretroviral therapy may affect these life-threatening outcomes, for which the expected incidence was greater than that for AIDS outcomes, as has been shown in previous studies, including the Strategies for Management of Antiretroviral Therapy (SMART) study.[1] The fact that we observed a consistent benefit for immediate initiation of antiretroviral therapy for both serious AIDS and serious non-AIDS events shows the clinical benefit of such an approach for a wide range of conditions. Regarding the analytic approach, we opted for an intention-to-treat method, since it could not induce bias against deferred treatment. However, we can confirm that we have also carried out analyses that included only follow-up time during which patients strictly adhered to their assigned strategy. As would be expected from such an analysis, the benefits of early antiretroviral therapy were even more pronounced than in the intention-to-treat analysis.

Only 21 of the 2359 patients in the deferred-initiation group (not 118) started therapy with a latest CD4+ cell count of 178 cells per cubic millimeter or less (5th percentile of the study population) (Table S1 in the Supplementary Appendix, available with the full text of our article at NEJM.org). More important, in the deferred-initiation group, only 5 patients had a primary event when their latest CD4+ count was less than 350 cells per cubic millimeter. In 59% of the patients with a primary event, the event occurred when the latest CD4+ count was more than 500 cells per cubic millimeter (Fig. S4 in the Supplementary Appendix of our article). Thus, our study provides strong evidence of a clinically relevant benefit for the initiation of antiretroviral therapy when the CD4+ count is more than 500 cells per cubic millimeter and hence supports the recommendation that such therapy should be offered to all HIV-positive patients regardless of the CD4+ count.

Corrao et al. comment on the use of antiretroviral therapy and the length of follow-up in our study. Data on the use of therapy are provided in Figure 1A of the article, which also shows a high level of adherence to therapy. We do not see how the length of follow-up could lead to biased findings, particularly since the hazard ratio did not vary significantly during follow-up.

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Since publication of their article, the authors report no further potential conflict of interest.

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# Randomized Trial of Reduced-Nicotine Standards for Cigarettes

**TO THE EDITOR:** Donny and colleagues (Oct. 1 issue)[1] found that, as compared with the use of standard-nicotine cigarettes, the use of reduced-nicotine cigarettes was associated with reductions in nicotine exposure and dependence and the number of cigarettes smoked. However, when they smoke reduced-nicotine cigarettes, smokers who are already addicted to nicotine may compensate by blocking the ventilation holes and inhaling longer, harder, and more frequently to get enough nicotine. In doing so, they inhale more tar than they would inhale with regular cigarettes.[2]

In the study by Donny et al., the total puff volume was calculated with the use of a device

that measured the number and volume of puffs of a single cigarette smoked in the laboratory. This is quite different than smoking in real-life conditions and may be insufficient to support the authors' conclusions.

The harms of passive smoking should also be noted. There is evidence that inhaled sidestream smoke, the main component of secondhand smoke, is far more toxic than mainstream smoke.[3]

Messages about overcoming addiction may reduce attempts to quit smoking or delay attempts to quit. Moreover, smokers may be misled by the illusion that reduced-nicotine cigarettes are safer than regular ones, and as a result they may choose reduced-nicotine cigarettes instead of quitting.[2] These messages may reduce the rate of smoking cessation and increase passive exposure to smoke.

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**TO THE EDITOR:** The article by Donny et al. and the accompanying Perspective article by Fiore and Baker[1] have prompted considerable discussion. Until the results of this study are replicated in a population that more closely resembles average smokers and has a longer follow-up period, these discussions are premature.

The study design appears to have involved recruitment of participants who were, as compared with average smokers, less dependent on nicotine and showed no compensatory behavior when nicotine levels were reduced. As shown in Figure 1 of the article, the number of cigarettes smoked by participants who received cigarettes with baseline amounts of nicotine increased from 15 to 20, whereas the number smoked by those who received cigarettes with the lowest amount of nicotine remained at baseline levels.

Although none of the participants stated an interest in quitting smoking, a better measure of the participants' intention would have been "no intention to quit smoking in the next 6 months." The majority of current smokers are in this category.[2] Future exploration of this issue and related issues also needs to take into account that the demographic characteristics of smokers have changed: 50% of cigarettes smoked are smoked by persons with mental illness.[3]

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**TO THE EDITOR:** Donny et al. misleadingly report decreased nicotine exposure in participants who were randomly assigned to receive reduced-nicotine cigarettes. Participants assigned to their usual brand of cigarettes smoked an average of 22.2 cigarettes per day, which, at 15.8 mg of nicotine per gram of tobacco, yielded approximately 30 nmol per milligram of creatinine (estimated from Fig. 2 of the article).

The urinary nicotine level scales linearly with the number of cigarettes smoked.[1] That is, participants who smoked cigarettes containing the lowest concentration of nicotine, consuming 14.9 cigarettes per day at 0.4 mg of nicotine per gram of tobacco, should have had a urinary nicotine level of 0.5 nmol per milligram of creatinine. Instead, the level was approximately 15 nmol per milligram.

The most plausible explanation is that participants who were assigned to cigarettes with 5.2 mg of nicotine or less per gram supplemented their low-concentration cigarettes with their (more potent) usual ones. An impressive 81% of participants in this group admitted to doing exactly that. A back-of-the-envelope calculation shows that these participants would have needed to supplement with approximately 11 regular-

strength cigarettes, for a total of 26 cigarettes smoked per day, to deliver the observed nicotine levels. These participants received less nicotine but more smoke — precisely the thing that causes lung cancer.[2]

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**THE AUTHORS REPLY:** In response to Cao et al.: these data are consistent with those of other studies that indicate little compensatory smoking when participants switch to cigarettes with very low nicotine content.[1] Compensation is typically observed when changes to cigarette design increase ventilation but leave the nicotine content unchanged (in what were previously called "light" cigarettes), resulting in an elastic product that enables users to maintain nicotine exposure by changing the way in which they smoke. In contrast, in cigarettes with very low nicotine content, the level of ventilation is not manipulated. There is markedly less nicotine in the tobacco; this greatly limits how much nicotine users can receive by smoking.

With regard to passive smoking, the intent of nicotine reduction is to prevent the development and maintenance of dependence and in doing so to reduce smoking. If fewer people smoked, exposure to secondhand smoke would also be reduced. It is possible that reduced addictiveness or misperceptions of reduced harm could affect attempts to quit smoking. However, these obstacles can be addressed with well-designed communication efforts. Furthermore, the benefits of reduced addictiveness may render treatment and other approaches to tobacco control more effective.

In response to Anselm: our sample of participants reported moderate nicotine dependence; in this respect, our sample was representative of the population in national surveys.[2] Smokers who were interested in quitting also smoked less when they switched to reduced-nicotine cigarettes.[3] Studies involving other populations, including persons with serious mental illness, are under way (ClinicalTrials.gov numbers, NCT01928758, NCT02250664, and NCT02232737).

In response to Anselm and Goldstein and Goldstein: we indicated that the number of cigarettes smoked per day was reduced relative to both internal controls, not baseline, when participants bought their own cigarettes. With regard to the possibility that smokers in the low-nicotine groups were smoking substantially more cigarettes than reported, several alternative sources of nicotine should be considered (e.g., the use of other products and reporting nonstudy cigarettes as study cigarettes). In addition, smokers can extract almost three times as much nicotine from cigarettes with a typical level of nicotine content when access to these cigarettes is markedly reduced.[4] More important, if nicotine regulation is implemented, cigarettes with a typical nicotine content would not be available, and the results suggest that smokers may reduce their smoking (Fig. 1B of our article) and seek other sources of nicotine.

Our findings reinforce what we have known for decades — nicotine is the addictive agent in cigarettes — and reducing levels of nicotine may reduce the addictiveness of cigarettes. Although we agree that additional data will help clarify potential concerns, we urge the medical and public health community to weigh these concerns against the potential benefits of reduced nicotine exposure and dependence and the ongoing devastation caused by combusted tobacco.

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The views expressed in this reply are those of the authors and do not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration.

Since publication of their article, the authors report no further potential conflict of interest.

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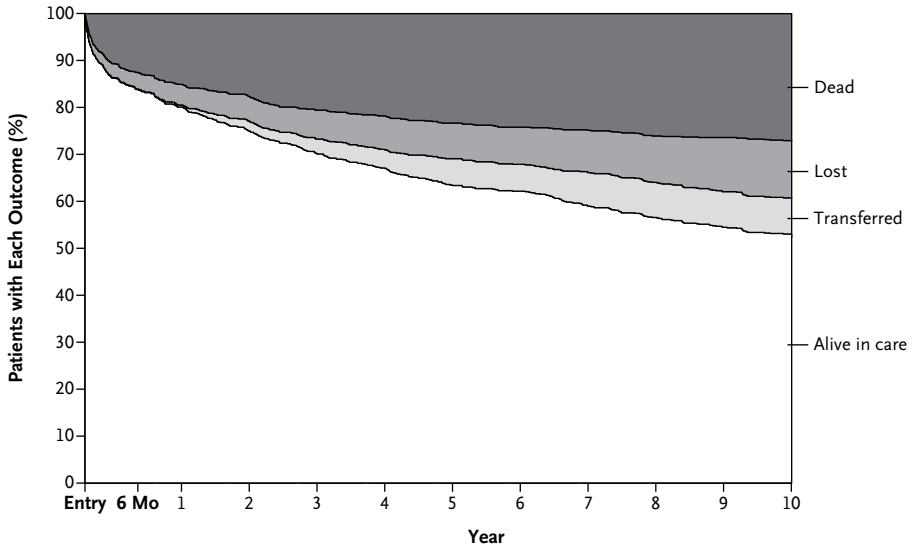
# 10-Year Survival of Patients with AIDS Receiving Antiretroviral Therapy in Haiti

**TO THE EDITOR:** We report the 10-year survival rates in the first cohort of patients with AIDS who consecutively initiated antiretroviral therapy (ART) in Port-au-Prince, Haiti. A total of 910 patients 13 years of age or older who initiated ART from 2003 through 2004 were followed for 10 years; the initiation of ART and follow-up care were performed in accordance with World Health Organization (WHO) guidelines.[1] Details regarding this cohort have been reported previously, and ethics approval for the retrospective study was received from the relevant institutional review boards.[2,3] Death was ascertained from medical records. Data from patients who transferred to another clinic were censored at the time of the transfer. Loss to follow-up was defined as the absence of a clinic visit within 180 days before the 10-year follow-up date.

Three methods were used to assign survival status to patients who were lost to follow-up and to estimate the 10-year survival rate: Kaplan–Meier analysis censors patient data at the time of the loss to follow-up, inverse-probability weighting uses contact-tracing data, and multiple imputation estimates survival on the basis of baseline characteristics among those who are lost to follow-up. Cox modeling was used to identify the characteristics associated with 10-year survival (see the Supplementary Appendix, available with the full text of this letter at NEJM.org, for further details).

Among the 910 patients at baseline, 504 (55%) were female, the median age was 39 years, and the median CD4 count was 131 cells per cubic millimeter (interquartile range, 51 to 212). Approximately half the patients lived in extreme




| Percent of Patients | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Dead | 0 | 11 | 14 | 17 | 20 | 22 | 23 | 24 | 25 | 26 | 26 | 27 |
| Lost | 0 | 3 | 4 | 5 | 6 | 7 | 7 | 8 | 9 | 10 | 11 | 12 |
| Transferred | 0 | 0 | 0 | 2 | 3 | 4 | 5 | 6 | 7 | 7 | 8 | 8 |
| Alive in care | 100 | 86 | 82 | 77 | 72 | 68 | 64 | 62 | 60 | 57 | 55 | 53 |

**Figure 1. Outcomes over 10 Years of Follow-up among 910 Patients Who Initiated Antiretroviral Therapy from 2003 through 2004 in Haiti.**