Pulmonary effects of immediate versus deferred antiretroviral therapy in HIV-positive individuals: a nested substudy within the multicentre, international, randomised, controlled Strategic Timing of Antiretroviral Treatment (START) trial

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Summary

Background Observational data have been conflicted regarding the potential role of HIV antiretroviral therapy (ART) as a causative factor for, or protective factor against, COPD. We therefore aimed to investigate the effect of immediate versus deferred ART on decline in lung function in HIV-positive individuals.

Methods We did a nested substudy within the randomised, controlled Strategic Timing of Antiretroviral Treatment (START) trial at 80 sites in multiple settings in 20 high-income and low-to-middle-income countries. Participants were HIV-1 infected individuals aged at least 25 years, naive to ART, with CD4 T-cell counts of more than 500 per μL, not receiving treatment for asthma, and without recent respiratory infections (baseline COPD was not an exclusion criterion). Participants were randomly assigned to receive ART (an approved drug combination derived from US Department of Health and Human Services guidelines) either immediately, or deferred until CD4 T-cell counts decreased to 350 per μL or AIDS developed. The randomisation was determined by participation in the parent START study, and was not specific to the substudy. Because of the nature of our study, site investigators and participants were not masked to the treatment group assignment; however, the assessors who reviewed the outcomes were masked to the treatment group. The primary outcome was the annual rate of decline in lung function, expressed as the FEV_1 slope in mL/year; spirometry was done annually during follow-up for up to 5 years. We analysed data on an intention-to-treat basis, and planned separate analyses in smokers and non-smokers because of the known effects of smoking on FEV_1 decline. The substudy was registered at ClinicalTrials.gov number NCT01797367.

Findings Between March 11, 2010, and Aug 23, 2013, we enrolled 1026 participants to our substudy, who were then randomly assigned to either immediate (n=518) or deferred (n=508) ART. Median baseline characteristics included age 36 years (IQR 30–44), CD4 T-cell count 648 per μL (583–767), and HIV plasma viral load $4 \cdot 2 \log_{10}$ copies per mL ($3 \cdot 5$–$4 \cdot 7$). 29% were female and 28% were current smokers. Median follow-up time was $2 \cdot 0$ years (IQR $1 \cdot 9$–$3 \cdot 0$). We noted no differences in FEV_1 slopes between the immediate and deferred ART groups either in smokers (difference of $-3 \cdot 3$ mL/year, 95% CI $-38 \cdot 8$ to $32 \cdot 2$; p=0·86) or in non-smokers (difference of $-5 \cdot 6$ mL/year, $-29 \cdot 4$ to $18 \cdot 3$; p=0·65) or in pooled analyses adjusted for smoking status at each study visit (difference of $-5 \cdot 2$ mL/year, $-25 \cdot 1$ to $14 \cdot 6$; p=0·61).

Interpretation The timing of ART initiation has no major short-term effect on rate of lung function decline in HIV-positive individuals who are naive to ART, with CD4 T-cell counts of more than 500 per μL. In light of updated WHO recommendations that all HIV-positive individuals should be treated with ART, regardless of their CD4 T-cell count, our results suggest an absence of significant pulmonary harm with such an approach.

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Introduction

Pulmonary complications of HIV-1 infection have been present from the earliest days of the AIDS epidemic, but in the current era of effective combination antiretroviral therapy (ART), such complications have shifted away from opportunistic infections and towards non-infectious complications, especially COPD.[1,2]

Although the most common cause of COPD is cigarette smoking, findings from observational studies have consistently identified HIV infection as an independent risk factor for COPD, even when adjusted for the high smoking prevalence among HIV-positive individuals.[3] Potential mechanisms leading to HIV-associated COPD include respiratory infections, oxidative stress,

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See Online for appendix

Research in context

Evidence before this study

HIV-1 seems to increase the risk for COPD, independent of cigarette smoking status. Although the mechanisms for this increased risk are not clear, use of antiretroviral therapy (ART) has been postulated to potentially reduce COPD risk by decreasing pulmonary inflammatory responses. Conversely, immune reconstitution from ART has also been postulated to increase COPD risk. We searched PubMed for English-language publications containing the terms "HIV" and "chronic obstructive pulmonary disease", restricted to studies published after 1996 when combination ART became available. Our search revealed contradictory data regarding the effect of ART on risk of COPD. Findings from two studies showed a higher risk of COPD with ART use, one study showed a lower risk of COPD with ART use, and four studies showed no association. All these studies were observational and therefore subject to confounding.

Added value of this study

We enrolled 1026 HIV-positive adults naive to ART with CD4 T-cell counts of more than 500 per μL who were then randomly assigned to a strategy of either immediate ART or deferral of ART until either CD4 T-cell counts decreased to 350 per μL or AIDS developed. Participants were enrolled from both high-income countries and low-to-middle-income countries. We measured lung function before randomisation, and then annually. We showed no difference in lung function decline between the two ART strategies.

Implications of all the available evidence

Our data suggest that in HIV-positive individuals who are naive to ART with CD4 T-cell counts of more than 500 per μL, immediate ART causes neither harm nor benefit to lung function decline. In light of updated WHO recommendations that all HIV-positive individuals should be treated with ART, regardless of their CD4 T-cell count, our results suggest an absence of significant pulmonary harm with such an approach, and that timing of ART initiation has no major short-term effect on lung function decline.

monocyte activation, T-cell dysregulation, chronic pulmonary inflammation, and changes in the respiratory microbiota.[2,4]

ART treatment itself has also been implicated as a potential factor in HIV-associated COPD, but the data are conflicting. Findings from two observational studies suggested ART use was associated with an increased risk of COPD,[5,6] results from another study showed a lower incidence of COPD among ART users,[7] and results from other studies showed no association.[8–11] All these studies were limited by their observational designs, in which ART use might be confounded by factors such as socioeconomic status, adherence to medical therapy, and other health behaviours that might affect both the likelihood of ART use and COPD risk.

To address these discrepancies, we did a nested substudy within a randomised controlled trial to test the effect of immediate versus deferred ART on lung function decline in HIV-positive individuals.

Methods

Study design and participants

We did a nested, prospective, controlled, assessor-blinded, substudy within the multisite, international, randomised, controlled Strategic Timing of Antiretroviral Treatment (START) trial at 80 sites in multiple settings in 20 high-income and low-to-middle-income countries. The design, methods, and baseline participant characteristics of the parent START trial and this pulmonary substudy have been previously published[12–14] and the primary results of the parent START trial have been published[15] (for the complete protocol, see appendix). All site institutional review boards or ethics committees approved the substudy.

Briefly, the parent START trial enrolled HIV-1-infected, ART-naive adults aged more than 18 years with CD4 T-cell counts of more than 500 per μL. In addition to the entry criteria for the parent START trial, our additional substudy criteria included the requirement that participants be aged at least 25 years, the age at which lung function begins to decline in most adults. Exclusion criteria were: 1) an episode of respiratory illness within the 6 weeks before baseline spirometry; 2) use of asthma medications for 2 or more consecutive weeks within the 6 months before baseline spirometry; 3) relative contraindications to spirometry, such as chest, abdominal, or eye surgery within the 3 months before baseline spirometry, or known retinal detachment at the time of baseline spirometry; 4) known allergy to albuterol/salbutamol; 5) relative contraindications to albuterol or salbutamol, such as a resting heart rate of more than 110 beats per minute, or a known serious, recurrent or uncontrolled cardiac condition (such as unstable coronary artery disease, decompensated heart failure, or recurrent tachyarrhythmias). Baseline COPD was not an exclusion criterion. We set no limits on enrolment by site, region, sex, or any other factors; all sites had their own methods of recruiting participants. All START substudy participants provided written informed consent specific to their participation in the substudy.

Randomisation and masking

After enrolment and baseline data collection, participants were randomly allocated to an ART treatment strategy of either immediate initiation of ART or deferred initiation until the CD4 T-cell count decreased to 350 per μL or AIDS developed. The

randomisation was determined by participation in the parent START study, and was not specific to the substudy. The study protocol required the use of an approved drug combination derived from the guidelines of the US Department of Health and Human Services as the first ART regimen in both study groups.

Randomisation was stratified by clinical site and permuted blocks of different sizes were used to generate the randomisation schedules. Assignments were obtained from a web-based program that verified participant eligibility. Randomisation schedules were generated only for the parent trial; there was no stratification by substudy participation. Because of the nature of the study as a pragmatic trial to compare HIV treatment strategies rather than specific drugs, site investigators and participants were not masked to the treatment group assignment (in either the parent START trial and this substudy). However, outcomes including lung function test results were reviewed by assessors centrally, who were masked to treatment group and reviewed reports with no indicators regarding ART use or randomised treatment assignment.

Procedures

Before randomisation, study participants did post-bronchodilator spirometry using the EasyOne ultrasonic flow device (ndd Medical, Zurich, Switzerland) after inhalation of 180 μg of albuterol or salbutamol via a metered dose inhaler. During the study, spirometry was done once per year during follow-up for up to 5 years. One of the investigators (KMK) centrally reviewed all spirometry test results. Repeat testing was requested when test results did not meet published quality standards.[16] We used Global Lung Function Initiative 2012 normative equations[17] to determine predicted FEV_1, predicted forced vital capacity (FVC), and the lower limit of normal (5th percentile) of the FEV_1:FVC ratio.

We assessed current and former cigarette use and defined current smokers as having smoked more than ten cigarettes in the past 30 days. We defined lifelong non-smokers as having reported smoking fewer than 120 cigarettes in their lifetime. We calculated smoking pack-years as (average self-reported number of cigarettes smoked per day/20)×number of years smoked.

We administered the St George's Respiratory Questionnaire for COPD (SGRQ-C). The SGRQ-C is a validated, participant-completed, 40-item measure of respiratory health status,[18] scored from 0 to 100 points, for which higher scores reflect worse respiratory health status. SGRQ-C questionnaires were scored according to the standardised SGRQ-C algorithm, which converts SGRQ-C responses to equivalent scores on the 50-item full version of the SGRQ. The minimal clinically important difference in SGRQ scores is 4 points.[19] Certified SGRQ-C language or dialect translations were available for most countries, but not all. In Israel, Thailand, and Peru, the full 50-item version of the SGRQ had been translated and certified for use in these countries, but not the SGRQ-C. Therefore in these countries, we shortened the SGRQ to the SGRQ-C and translations and back-translations were done before site opening. In Cape Town, South Africa, we did new translations and back-translations for Xhosa and Zulu from the original English version of the SGRQ-C. For sites in several countries (India, Nigeria, and Uganda, representing 18% of study participants), there were too many dialects to do timely translations for all participants, so the SGRQ-C was not administered at these sites. We assessed use of respiratory medications (eg, inhalers, oral leukotriene inhibitors, or theophylline) and bronchitis events by self-report annually.

Outcomes

Our primary outcome was rate of lung function decline, expressed as FEV_1 slope in mL/year. Secondary outcomes were the 12-month change in SGRQ scores, use of respiratory medications, and incidence of respiratory illnesses (ie, bronchitis events).

Statistical analysis

Because of the known effects of smoking on FEV_1 slope, we planned analyses in baseline smokers and non-smokers separately. We projected that sample size targets of 400 smokers and 600 non-smokers would have 85% power to detect a difference in FEV_1 slope of
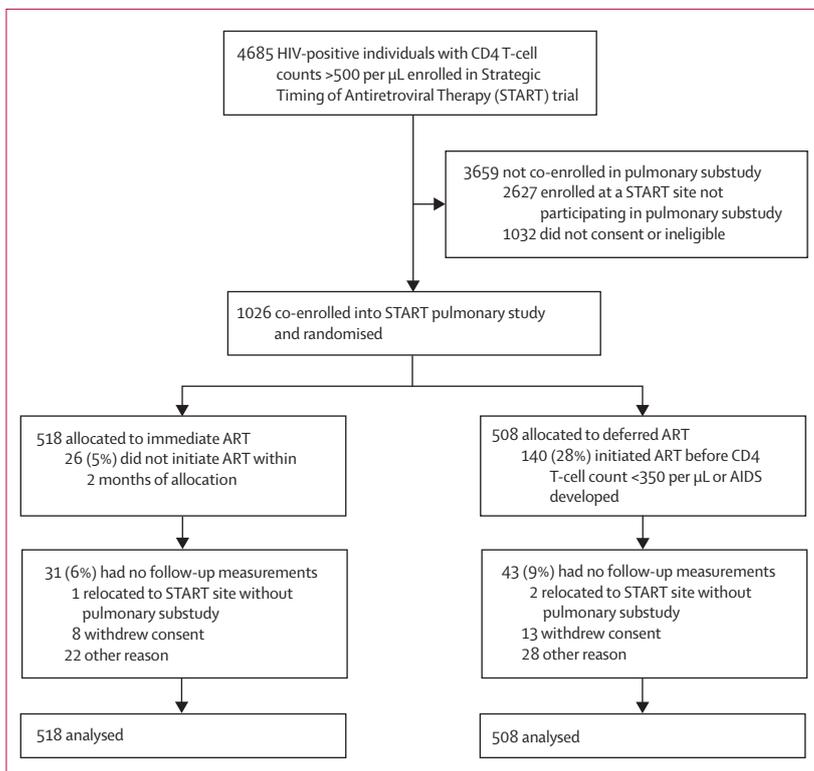

Figure 1: Trial profile

15·5 mL/year in non-smokers and 19·0 mL/year in smokers.[14] Data from the Lung Health Study[20] showed that with smoking cessation, FEV_1 slope tends to be similar to that in non-smokers. Therefore, we analysed former smokers with the non-smoker group in the primary analyses.

The START study's data and safety monitoring board recommended early termination of the parent trial at its May 15, 2015, meeting, because the study showed clear reductions in AIDS events and non-AIDS events in the immediate ART arm. Results were announced by the US National Institutes of Health on May 27, 2015. Therefore, follow-up data were censored on the last day of masked allocation—May 26, 2015,—or the date of last study contact.

For our primary outcome of FEV_1 slope, we used repeated-measures mixed models, with random within-person intercept and slope, with all available spirometry data on a strict intention-to-treat basis by assignment to immediate or deferred ART (see appendix for additional details, including statistical codes). In the case of low-quality spirometry that required repeat testing, we used the most recent test within each study visit window. We tested the linearity of the FEV_1 slopes by adding a time-quadratic term to the primary outcome models

	Immediate ART (n=518)	Deferred ART (n=508)	Total (n=1026)
Age (years)	37 (30–44)	36 (31–43)	36 (30–44)
Female	145 (28%)	154 (30%)	299 (29%)
Race			
Black	198 (38%)	189 (37%)	387 (38%)
Latino or Hispanic	93 (18%)	86 (17%)	179 (17%)
Asian	52 (10%)	53 (10%)	105 (10%)
White	169 (33%)	175 (34%)	344 (34%)
Other	6 (1%)	5 (1%)	11 (1%)
Region			
Africa	168 (32%)	160 (31%)	328 (32%)
Asia	52 (10%)	51 (10%)	103 (10%)
Europe, Israel, or Australia	162 (31%)	151 (30%)	313 (31%)
Latin America	91 (18%)	100 (20%)	191 (19%)
USA	45 (9%)	46 (9%)	91 (9%)
Likely method of HIV infection			
Injection-drug use	9 (2%)	5 (1%)	14 (1%)
Male sexual contact with person of same sex	258 (50%)	247 (49%)	505 (49%)
Sexual contact with person of opposite sex	225 (43%)	225 (44%)	450 (44%)
Other or unknown	26 (5%)	31 (6%)	57 (6%)
Years HIV positive	1·1 (0.4–3.5)	1·2 (0.4–3.6)	1·2 (0.4–3.5)
Laboratory results			
CD4 T-cell count (cells per µL)	650 (587–768)	647 (576–765)	648 (583–767)
CD8 T-cell count (cells per µL)	1026 (757–1381)	1008 (759–1420)	1019 (758–1394)
CD4:CD8 ratio	0·67 (0.48–0.97)	0·66 (0.48–0.91)	0·66 (0.48–0.94)
Nadir CD4 T-cell count (cells per µL)	545 (480–665)	562 (490–651)	552 (486–661)
Log HIV-RNA (copies per mL)	4·2 (3.5–4.7)	4·2 (3.4–4.7)	4·2 (3.5–4.7)
HIV-RNA ≤400 copies per mL	45 (9%)	52 (10%)	97 (9%)
(Table 1 continues in next column)			

	Immediate ART (n=518)	Deferred ART (n=508)	Total (n=1026)
(Continued from previous column)			
Medical history			
Body-mass index (kg/m²)	24·8 (22.2–28.5)	24·8 (22.2–28.0)	24·8 (22.2–28.4)
Current smoker	135 (26%)	155 (31%)	290 (28%)
Previous smoker	58 (11%)	53 (10%)	111 (11%)
Never smoker	325 (63%)	300 (59%)	625 (61%)
Pack years smoking (current and previous smokers)	7·5 (2.5–15.0)	5·3 (1.7–14.3)	6·0 (2.0–15.0)
Previous cardiovascular disease	2 (<1%)	5 (1%)	7 (1%)
Hypertension	98 (19%)	94 (19%)	192 (19%)
Diabetes	22 (4%)	15 (3%)	37 (4%)
Hepatitis B or C	39 (8%)	33 (6%)	72 (7%)
FEV_1 (L)	3·38 (2.62–3.97)	3·37 (2.69–4.01)	3·38 (2.67–4.00)
FVC (L)	4·10 (3.28–4.92)	4·10 (3.27–4.91)	4·10 (3.28–4.91)
FEV_1:FVC ratio*	0·83 (0.78–0.86)	0·83 (0.78–0.87)	0·83 (0.78–0.86)
<0·7	30 (6%)	24 (5%)	54 (5%)
<lower limit of normal†	40 (8%)	27 (5%)	67 (7%)
FEV_1 as percentage of predicted*‡	95·2 (85.0–104.2)	97·0 (86.2–103.2)	96·2 (85.4–103.9)
≥80%	421 (85%)	431 (87%)	852 (86%)
50%–79%	74 (15%)	58 (12%)	132 (13%)
30%–49%	2 (<1%)	4 (<1%)	6 (1%)
<30%	0	0	0
Respiratory health status (St George's Respiratory Questionnaire score)			
Total	7·2 (4.1–13.6)	7·2 (4.2–13.2)	7·2 (4.2–13.4)
Symptoms	13·5 (0.9–27.0)	12·8 (0.9–26.6)	13·0 (0.9–26.6)
Activity	7·0 (7.0–20.4)	7·0 (7.0–20.1)	7·0 (7.0–20.1)
Impacts	2·2 (2.2–6.8)	2·2 (2.2–6.9)	2·2 (2.2–6.8)

Data are median (IQR) or n (%). ART=antiretroviral therapy. FVC=forced vital capacity. *Restricted to spirometry that met quality standards after central quality review (n=497 in the immediate arm; n=493 in the deferred arm). †<5th percentile as predicted by Global Lung Function Initiative equations. ‡Predicted values from Global Lung Function Initiative equations.

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

separately in smokers and non-smokers; the coefficients for the quadratic terms were non-significant (p>0·10) in both smokers and non-smokers and therefore were not included in the final models.

We also did the following secondary analyses: 1) pooling data from baseline smokers and non-smokers with adjustment for smoking status at baseline; 2) pooling data from baseline smokers and non-smokers with adjustment for smoking status at each study visit; 3) restricting analyses to only spirometry tests meeting acceptable quality standards after central review; and 4) censoring spirometry data after ART initiation in the deferred ART arm. Intention-to-treat analyses might not be the most appropriate method for estimating harm, so to address the potential for ART to worsen lung function decline, we also did a secondary analysis of time on ART (allowing each individual to contribute data both on and off ART), and FEV_1 slope, regardless of treatment assignment. We assessed heterogeneity by high-income versus low-to-middle-income settings by testing for an interaction between treatment assignment and high-income country (in the regions of USA, Europe, Israel, and Australia) and low-to-middle-income country (in the regions of Africa, India, Latin America, and Thailand).

For the secondary outcome of SGRQ change, we compared the difference between the randomised arms in SGRQ change between baseline and month 12 separately for smokers and non-smokers. We defined incident bronchitis events as those associated with two or more symptoms of cough, wheezing, breathlessness, or increase in sputum production. We calculated the odds of reporting bronchitis events since the previous study visit over follow-up. For the use of respiratory medications, we calculated the odds of reporting respiratory medication use since the previous study visit over follow-up.

We did all statistical analyses with SAS 9.4 (Cary, NC, USA). We registered the substudy at ClinicalTrials.gov (NCT01797367).

Role of the funding source

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

Results

Between March 11, 2010, and Aug 23, 2013, we enrolled 1026 participants in the pulmonary substudy. Participants were randomly assigned to either immediate ART (n=518) or deferred ART (n=508; figure 1). Baseline demographic and clinical characteristics were well balanced between the two groups (table 1). The region with highest enrol-ment was Africa, followed by Europe/Israel/Australia, Latin America, Asia, and the USA. Overall, the cohort was young (median age 36 years [IQR 30–44]), with a recent HIV diagnosis (median time since diagnosis 1·2 years [0·4–3·5]), median baseline CD4 T-cell count 648 per µL (583–767), median HIV plasma viral load of 4·2 $\log_{10}$ copies per mL (3·5–4·7), and 9% had a baseline HIV plasma viral load less than 400 copies per mL despite reporting being ART naive.
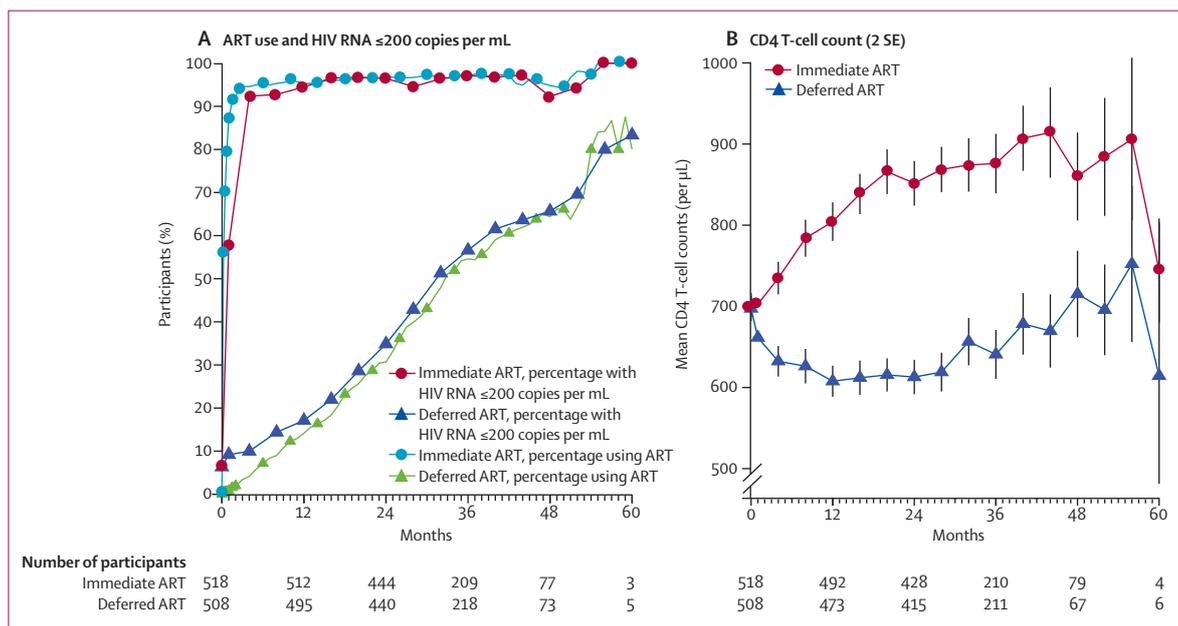

Figure 2: **ART use, HIV RNA, and CD4 T-cell counts**
Differences between randomised treatment arms in frequency of antiretroviral therapy (ART) use (A, blue circles and green triangles), HIV RNA of 200 copies per mL or less (A, red circles and blue triangles), and mean CD4 T-cell counts (B), as a function of follow-up time in study.

29% were female and most study participants reported sexual HIV acquisition (49% men who have sex with men, 44% heterosexual intercourse).

Current smokers comprised 28% of the cohort at baseline, and former and lifelong non-smokers comprised 72%. Of the baseline smokers, 8% quit smoking (reported not smoking at all follow-up visits) and 18% were intermittent smokers (reported smoking at one or more follow-up visits and not smoking at one or more follow-up visits) during follow-up. Of those not smoking at baseline (never smokers or former smokers), 6% reported smoking at one or more follow-up visits. Baseline lung function was generally good (median FEV_1 96·2% of predicted [85·4–103·9]) with COPD prevalence at study entry of 6·8%, as previously reported.[14]

As of the unblinding date (May 26, 2015), ART had been initiated in 99% of the immediate ART arm and 45% in the deferred arm. In the immediate ART arm, mean CD4 T-cell count at the time of ART initiation was 691 per μL (SD 176), mean HIV viral load at ART initiation was 4·1 log_{10} copies per mL (SD 0·9), and 95·0% of follow-up time was spent on ART (there was a time lag between baseline assessments and initiation of ART; figure 2). In the deferred ART arm, mean CD4 T-cell count at the time of ART initiation was 478 per μL (SD 210), mean HIV viral load at ART initiation was 4·5 log_{10} copies per mL (SD 0·9), and 26·3% of follow-up time was spent on ART. The percentage of participants with HIV viral suppression closely mirrored ART use. Average CD4 T-cell counts increased markedly during the first year after randomisation in the immediate ART arm and continued to gradually increase thereafter. Conversely, in the deferred ART arm, average CD4 T-cell counts decreased during the first year, then stabilised and subsequently increased slightly as more participants initiated ART (figure 2).

We collected 2143 follow-up spirometry tests over a median follow-up time of 2·0 years (IQR 1·9–3·0). Repeat testing for low-quality spirometry was requested for 131 (6·1%) tests, and ultimately 2039 (95·1%) tests met acceptable quality standards. The proportion of acceptable tests did not differ between the immediate and deferred ART arms (p=0·64). As of the unblinding date, 74 (7%) of those randomly assigned had not completed a follow-up spirometry test (31 [6%] assigned to immediate ART and 43 [9%] assigned to deferred ART; figure 3), but all participants were included in the primary analyses.

For the primary outcome of FEV_1 slope, we noted no differences in slopes between the immediate and deferred ART arms either in smokers (difference of −3·3 mL/year, 95% CI −38·8 to 32·2; p=0·86) or in non-smokers (difference of −5·6 mL/year, −29·4 to 18·3; p=0·65; table 2). Analyses pooling baseline smokers and non-smokers, then adjusting for either baseline smoking status or smoking status at each study visit, similarly showed no differences in FEV_1 slopes between immediate and deferred ART arms.
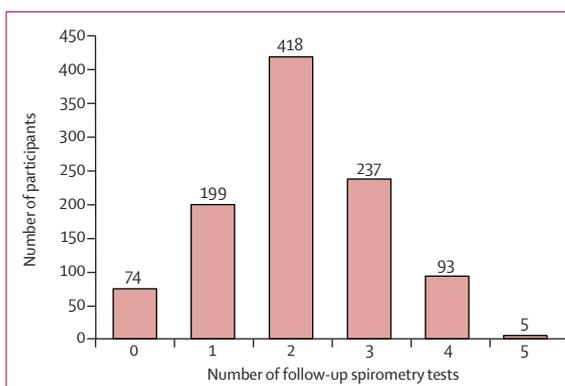

Figure 3: Distribution of number of follow-up spirometry tests collected

	FEV_1 slope (95% CI), mL/year	p value
Baseline smokers		
Immediate ART (n=135)	−32·9 (−58·5 to −7·4)	..
Deferred ART (n=155)	−29·7 (−54·3 to −5·0)	..
Difference	−3·3 (−38·8 to 32·2)	0·86
Baseline non-smokers		
Immediate ART (n=383)	−27·8 (−44·2 to −11·4)	..
Deferred ART (n=353)	−22·2 (−39·6 to −4·9)	..
Difference	−5·6 (−29·4 to 18·3)	0·65
Pooled analysis adjusted for baseline smoking status		
Immediate ART (n=518)	−29·1 (−42·9 to −15·4)	..
Deferred ART (n=508)	−24·5 (−38·6 to −10·3)	..
Difference	−4·7 (−24·4 to 15·1)	0·64
Pooled analysis adjusted for smoking status at each study visit		
Immediate ART (n=518)	−28·8 (−42·6 to −14·9)	..
Deferred ART (n=508)	−23·6 (−37·8 to −9·3)	..
Difference	−5·2 (−25·1 to 14·6)	0·61

Data are from groups of patients randomly assigned to either immediate or deferred ART initiation. ART=antiretroviral therapy.

Table 2: Primary outcome of FEV_1 slope comparisons

Secondary analyses showed no difference in FEV_1 slopes between the two arms when 1) restricting to only spirometry meeting acceptable quality standards, 2) censoring deferred arm data at the time of ART initiation, or 3) restricting to both (appendix). Our secondary safety analysis of time on ART and FEV_1 slope, regardless of treatment assignment, also showed no relationship between time on ART and FEV_1 slope in smokers (p=0·24) or non-smokers (p=0·37). We noted no interaction between the effects of immediate versus deferred ART on FEV_1 slope in high-income versus low-to-middle-income countries in smokers (p=0·65) or non-smokers (p=0·71).

We collected 716 SGRQ-C questionnaires at baseline and month 12, of which 677 had complete information to calculate total SGRQ scores at both timepoints. The proportion of participants missing SGRQ-C data did not differ between the immediate and deferred ART arms (13% vs 16%, respectively; p=0·28). We noted no difference in

	Immediate ART				Deferred ART				Difference in mean change from baseline*	p value	95% CI
	n	Baseline*	Month 12*	Change from baseline†	n	Baseline*	Month 12*	Change from baseline†			
Smokers											
Total	102	11·7 (9·4)	10·6 (10·0)	−1·1 (11·1)	119	12·8 (9·9)	12·3 (10·4)	−0·5 (7·2)	−1·1 (1·1)	0·34	−3·3 to 1·1
Symptoms	111	20·8 (15·4)	17·9 (14·8)	−2·9 (15·6)	122	21·5 (16·5)	23·1 (18·8)	1·6 (15·8)	−4·8 (1·9)	0·01	−8·5 to −1·1
Activity	102	16·7 (14·5)	14·6 (14·3)	−2·0 (14·5)	119	17·5 (14·4)	17·1 (16·0)	−0·3 (11·6)	−2·0 (1·6)	0·23	−5·2 to 1·2
Impacts	103	6·5 (8·5)	6·4 (9·0)	−0·1 (11·4)	119	8·0 (8·9)	6·7 (8·5)	−1·2 (6·7)	0·3 (1·1)	0·76	−1·8 to 2·4
Non-smokers											
Total	241	9·8 (8·9)	8·7 (8·6)	−1·1 (8·4)	215	9·6 (8·9)	10·0 (11·3)	0·4 (10·5)	−1·4 (0·8)	0·08	−3·0 to 0·2
Symptoms	253	15·0 (14·0)	13·2 (15·2)	−1·9 (14·7)	226	14·1 (12·6)	14·5 (15·6)	0·4 (14·9)	−1·9 (1·2)	0·13	−4·3 to 0·5
Activity	246	14·8 (13·5)	13·5 (13·4)	−1·3 (12·4)	222	13·9 (13·7)	14·6 (15·9)	0·7 (15·2)	−1·6 (1·2)	0·17	−3·9 to 0·7
Impacts	248	6·4 (8·4)	5·7 (8·2)	−0·7 (9·5)	218	6·2 (8·2)	6·4 (9·8)	0·2 (10·4)	−0·8 (0·8)	0·33	−2·3 to 0·8

SGRQ scores were measured in participants randomly assigned to immediate versus deferred antiretroviral therapy (ART) initiation. Higher SGRQ scores indicate worse respiratory health status. The minimal clinically important difference in the total SGRQ score is 4 points; minimal clinically important differences for the symptoms, activity, and impact domains are not established. *Data are means (SD). †Data are means (SE) adjusted for baseline value.

Table 3: Changes in St George's Respiratory Questionnaire (SGRQ) scores

	Immediate ART		Deferred ART		p value*
	n	Number (%) who had a bronchitis event	n	Number (%) who had a bronchitis event	
Smokers					
Baseline	135	49 (36%)	155	54 (35%)	
Year 1	117	34 (29%)	126	37 (29%)	1·00
Year 2	96	27 (28%)	110	24 (22%)	0·33
Year 3	58	11 (19%)	65	10 (15%)	0·64
Year 4	24	8 (33%)	22	2 (9%)	0·07
Non-smokers					
Baseline	383	96 (25%)	353	76 (22%)	
Year 1	339	62 (18%)	302	55 (18%)	1·00
Year 2	295	45 (15%)	265	37 (14%)	0·72
Year 3	130	20 (15%)	120	17 (14%)	0·86
Year 4	42	11 (26%)	29	4 (14%)	0·25

Effects grouped by treatment and smoking status. Odds ratio from Generalised Estimating Equation with outcome as having any episodes of bronchitis at each follow-up visit: for smokers 1·16 (95% CI 0·66–2·02, p=0·61; for non-smokers 0·89 (0·60–1·32), p=0·57. *From Fisher's exact test.

Table 4: Effect of immediate versus deferred antiretroviral therapy (ART) initiation on bronchitis episodes

total SGRQ score change between the two treatment arms in smokers or in non-smokers (table 3). There were also no differences between the two treatment arms in any of the individual SGRQ domains for either smokers or non-smokers, with the exception that the symptoms domain score in smokers favoured the immediate ART arm.

We showed no difference in the risk of developing self-reported episodes of bronchitis between the immediate and deferred ART arms in smokers or in non-smokers (table 4). We also noted no difference in the odds of self-reported respiratory medication use between the immediate and deferred ART arms in smokers or in non-smokers (table 5).

Discussion

Over a median follow-up of 2 years, the results from our large, multicentre, international randomised trial showed that among ART-naive, HIV-positive individuals with CD4 T-cell counts of more than 500 per μL, the timing of ART initiation had no effect on the rate of lung function decline, for immediate ART compared with deferral of ART until CD4 cell counts were less than 350 per μL. In light of the results from other randomised trials and international HIV treatment guidelines[15,21,22] that support immediate initiation of ART in all HIV-positive individuals regardless of CD4 T-cell count, our data suggest no major benefit or harm to lung function associated with such an approach, although we note that our wide CIs cannot fully exclude either benefit or harm.

Concerns about pulmonary harms from ART were based on findings from two single-centre, cross-sectional studies.[5,6] In one of these studies (n=215), a lower FEV₁:FVC ratio was independently associated with increasing age, more pack-years of smoking, a history of bacterial pneumonia, and use of ART.[5] Findings from the other study (n=167) similarly showed that COPD was independently associated with more pack-years of smoking, a history of intravenous drug use, and ART use (odds ratio 6·22, 95% CI 1·19–32·43).[6] Such potential pulmonary harms of ART were postulated to potentially be related to an immune reconstitution inflammatory syndrome-like phenomenon.

By contrast with these two cross-sectional studies, results from two other prospective, observational studies

suggested that ART might reduce COPD risk in HIV-positive individuals. From administrative data in the US Veterans Aging Cohort Study,[7] ART use was associated with a lower incidence of COPD (incidence rate ratio [IRR] 0·90, 95% CI 0·82–0·99), but when the results were adjusted for smoking the association was no longer significant (IRR 0·93, 0·73–1·18). In the AIDS Linked to the Intravenous Experience cohort,[9] individuals with higher HIV RNA had a faster decrease in FEV_1. However, ART use itself was not associated with a difference in FEV_1 slope. The findings from our randomised trial suggest that the discrepant associations between ART use and lung function decline in observational studies might result from confounding inherent in observational study designs, where ART use might be associated with other factors related to lung function decline such as access to care, self-efficacy, and other confounders, both currently known and unknown.

Our trial was restricted to participants with initially high CD4 T-cell counts (>500 per µL) and even in the deferred ART arm, average CD4 T-cell counts were more than 600 per µL during follow-up. Therefore, our results cannot be extrapolated to patients who present with, or develop, lower CD4 T-cell counts. Findings from several observational studies suggest that low CD4 T-cell counts are associated with higher COPD risk,[9,23] but low CD4 T-cell counts in observational studies, like ART use, might be associated with other confounders. We also excluded individuals receiving treatment for asthma and those with recent respiratory infection symptoms, so our results are not generalisable to such patients who might be newly initiating ART.

We also noted no differences in respiratory health status, as assessed by the total SGRQ score, between the two ART treatment strategies in either smokers or non-smokers. We noted a difference favouring immediate ART for the SGRQ symptoms domain in smokers, but given the multiple comparisons, the relevance of this finding is unclear. The minimal clinically important difference in the SGRQ symptoms domain is also not established. We also note that in this trial, participants were not masked to treatment assignment, and therefore self-reported measures such as SGRQ and bronchitis events might have been subjected to some degree of bias. The SGRQ was not administered in India, Nigeria, and Uganda, so our SGRQ results do not reflect respiratory health status in those countries.

Results from some studies have suggested a high prevalence of respiratory symptoms in HIV-positive individuals. In a study of 199 HIV-positive men in Canada, the median SGRQ score was 32·0 points (of a maximum of 100 points), which is worse than our median SGRQ score of 7·2 points.[24] This difference might reflect our cohort's young age and recent diagnosis of HIV infection compared with the Canadian cohort, in which the mean age was 49 years and years of known HIV diagnosis was 12 years. The fairly good baseline

	Immediate ART		Deferred ART		p value*
	n	Number (%) who reported respiratory medication use	n	Number (%) who reported respiratory medication use	
Smokers					
Year 1	117	3 (3%)	126	3 (2%)	1·00
Year 2	91	1 (1%)	99	4 (4%)	0·37
Year 3	54	1 (2%)	58	2 (3%)	1·00
Year 4	21	0	21	1 (5%)	1·00
Non-smokers					
Year 1	339	8 (2%)	302	7 (2%)	1·00
Year 2	277	4 (1%)	242	4 (2%)	1·00
Year 3	120	3 (3%)	107	4 (4%)	0·71
Year 4	38	0	26	2 (8%)	0·16

Effects grouped by treatment and smoking status. Odds ratio from Generalised Estimating Equation with outcome as having used respiratory medications since the last study visit: for smokers 0·46 (95% CI 0·15–1·46), p=0·19; for non-smokers 0·56 (0·24–1·31), 0·18. *From Fisher's exact test.

Table 5: **Effect of immediate versus deferred antiretroviral therapy (ART) initiation on self-reported respiratory medication use**

respiratory health status of our study participants might have restricted our ability to detect significant differences in respiratory health status between the ART strategies.

Our study had several strengths. The large sample size and randomised design to immediate *vs* deferred ART is unique and optimised the ability to balance confounders, both currently known and currently unknown. The randomisation to deferred ART will likely never be repeated again in the future, because of findings from the parent START trial that showed that all HIV-positive individuals should be immediately treated with ART. Our international trial enrolled participants from high-income, middle-income, and low-income countries and therefore our findings have broad generalisability to HIV-positive individuals in widely differing HIV treatment settings.

Our study also had several limitations. We measured only post-bronchodilator spirometry, and did not include more time-consuming or sophisticated measures such as prebronchodilator spirometry, single-breath diffusing capacity of carbon monoxide, or quantitative CT of the thorax. We chose to not collect these other measures, partly because of the costs and logistical challenges of an already-complex parent study, and difficulties in implementing and standardising such measures in our 80-site, 20-country trial in both high-income and low-to-middle-income countries. We note that post-bronchodilator FEV_1 is currently the gold standard for assessing lung function loss and diagnosing COPD, which was the primary focus of our study.

Another limitation of our trial was the short follow-up time. Because of the early termination of the parent trial, we had a short median spirometry follow-up time of 2 years. Other studies assessing FEV_1 slope as a primary

outcome have often had longer follow-up times, such as the 4-year UPLIFT trial of tiotropium[25] and the 5-year Lung Health Study of smoking cessation.[26] The SUMMIT trial of inhalers,[27] where FEV_1 slope was a secondary outcome, had a median follow-up time of only 1·8 years, but was very large (n=16 485). Our sample size of 1026 participants and short follow-up time might have limited our study power to detect significant differences in FEV_1 slope, and there was evidence that our truncated follow-up time probably decreased the precision of the slope measures (see appendix for more discussion). Our data exclude, with 95% confidence, treatment differences in FEV_1 slope of more than 39 mL/year in smokers and 29 mL/year in non-smokers, but we were unable to confidently exclude smaller treatment effects. We also could not exclude the possibility that differences might have emerged with longer follow-up.

In conclusion, in treatment-naive, HIV-positive patients with baseline CD4 T-cell counts of more than 500 per μL, immediate initiation of ART seems to have no major effect on short-term rate of lung function decline compared with deferred ART.

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