

## ORIGINAL ARTICLE

# A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa

The TEMPRANO ANRS 12136 Study Group\*

## ABSTRACT

**BACKGROUND**

The members of the writing group, who are listed in the Appendix, assume responsibility for the content and integrity of this article. Address reprint requests to Dr. Anglaret at INSERM Unité 897, Université de Bordeaux, 146 rue Léo Saignat, 33076 Bordeaux, France, or at xavier.anglaret@isped.u-bordeaux2.fr.

In sub-Saharan Africa, the burden of human immunodeficiency virus (HIV)–associated tuberculosis is high. We conducted a trial with a 2-by-2 factorial design to assess the benefits of early antiretroviral therapy (ART), 6-month isoniazid preventive therapy (IPT), or both among HIV-infected adults with high CD4+ cell counts in Ivory Coast.

**METHODS**

\*A list of additional members of the TEMPRANO ANRS 12136 Study Group is provided in the Supplementary Appendix, available at NEJM.org.

We included participants who had HIV type 1 infection and a CD4+ count of less than 800 cells per cubic millimeter and who met no criteria for starting ART according to World Health Organization (WHO) guidelines. Participants were randomly assigned to one of four treatment groups: deferred ART (ART initiation according to WHO criteria), deferred ART plus IPT, early ART (immediate ART initiation), or early ART plus IPT. The primary end point was a composite of diseases included in the case definition of the acquired immunodeficiency syndrome (AIDS), non–AIDS-defining cancer, non–AIDS-defining invasive bacterial disease, or death from any cause at 30 months. We used Cox proportional models to compare outcomes between the deferred-ART and early-ART strategies and between the IPT and no-IPT strategies.

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**RESULTS**

A total of 2056 patients (41% with a baseline CD4+ count of  $\geq 500$  cells per cubic millimeter) were followed for 4757 patient-years. A total of 204 primary end-point events were observed (3.8 events per 100 person-years; 95% confidence interval [CI], 3.3 to 4.4), including 68 in patients with a baseline CD4+ count of at least 500 cells per cubic millimeter (3.2 events per 100 person-years; 95% CI, 2.4 to 4.0). Tuberculosis and invasive bacterial diseases accounted for 42% and 27% of primary end-point events, respectively. The risk of death or severe HIV-related illness was lower with early ART than with deferred ART (adjusted hazard ratio, 0.56; 95% CI, 0.41 to 0.76; adjusted hazard ratio among patients with a baseline CD4+ count of  $\geq 500$  cells per cubic millimeter, 0.56; 95% CI, 0.33 to 0.94) and lower with IPT than with no IPT (adjusted hazard ratio, 0.65; 95% CI, 0.48 to 0.88; adjusted hazard ratio among patients with a baseline CD4+ count of  $\geq 500$  cells per cubic millimeter, 0.61; 95% CI, 0.36 to 1.01). The 30-month probability of grade 3 or 4 adverse events did not differ significantly among the strategies.

**CONCLUSIONS**

In this African country, immediate ART and 6 months of IPT independently led to lower rates of severe illness than did deferred ART and no IPT, both overall and among patients with CD4+ counts of at least 500 cells per cubic millimeter. (Funded by the French National Agency for Research on AIDS and Viral Hepatitis; TEMPRANO ANRS 12136 ClinicalTrials.gov number, NCT00495651.)

**T**HE RECOMMENDED CD4+ COUNT threshold for starting antiretroviral therapy (ART) in asymptomatic human immunodeficiency virus (HIV)-infected adults in lower-resource countries was increased from 200 cells per cubic millimeter in 2006 to 500 cells per cubic millimeter in 2013.<sup>1,2</sup> This change was supported by the results of two randomized, controlled trials.<sup>3,4</sup>

Meanwhile, three types of arguments have emerged to support even earlier initiation of ART. First, there is increasing documentation of inflammation in people with uncontrolled viral replication and of non-acquired immunodeficiency syndrome (AIDS)-defining noninfectious diseases as causes of death in HIV-infected persons<sup>5,6</sup> (with AIDS-defining diseases identified as diseases included in the Centers for Disease Control and Prevention case definition of AIDS<sup>7</sup>). Second, among patients living with HIV in lower-resource countries, the rates of tuberculosis and bacterial diseases are high. These infectious diseases are both common and opportunistic, meaning that their incidence is high in the general population, higher among HIV-infected patients with high CD4+ cell counts, and extremely high among patients with low CD4+ cell counts.<sup>8,9</sup> They have consistently been shown to be major causes of death among HIV-infected patients in settings where access to diagnosis and treatment is low.<sup>10-16</sup> These diseases triggered the question “Should we start ART earlier?” in low-income countries.<sup>17</sup>

Third, ART has been shown to be effective in reducing the risk of HIV transmission.<sup>3</sup> This observation led to the hypothesis that recommending all HIV-infected persons to start ART irrespective of their CD4+ count might help curb the epidemic.<sup>18</sup> This public health argument, however, is acceptable only if earlier ART leads to a favorable benefit-risk ratio at the individual level.

Here we present the results of a trial that assessed the efficacy of early ART in reducing the rate of severe illness among HIV-infected adults in Ivory Coast. Because tuberculosis was expected to be an important target for early ART in this African country, the benefit of combining isoniazid preventive therapy (IPT) with early ART was assessed in the same trial, with the use of a factorial design. In Ivory Coast, the national guidelines do not recommend the use of IPT, owing to the concern that IPT may select resistant bacilli when given to patients with undiag-

nosed tuberculosis.<sup>19,20</sup> The Ministry of Health accepted its use within an experimental framework.

## METHODS

### STUDY DESIGN AND OVERSIGHT

The TEMPRANO ANRS 12136 trial was an unblinded, multicenter, individual-randomized, controlled, 2-by-2 factorial, 1:1 superiority trial that was conducted at nine care centers in Abidjan, the economic capital of Ivory Coast. A description of the full study design is provided in the protocol and statistical analysis plan, available with the full text of this article at NEJM.org.

The protocol was approved by the Ivory Coast National Ethics Committee for Health Research. The sponsor (the French National Agency for Research on AIDS and Viral Hepatitis [ANRS]) had no role in the conduct of the study or the interpretation of the data.

### PARTICIPANTS

Patients were eligible for inclusion in the study if they were 18 years of age or older, had HIV type 1 (HIV-1) infection or dual infection with HIV-1 and HIV-2, had a CD4+ count of less than 800 cells per cubic millimeter, provided written informed consent, and met no criteria for starting ART according to the most recent World Health Organization (WHO) guidelines. The latter included the absence of active tuberculosis, as determined with the use of a clinical algorithm.<sup>21,22</sup> No chest radiography was systematically performed before inclusion. The exclusion criteria are listed in Section 2 in the Supplementary Appendix, available at NEJM.org.

### RANDOMIZATION TO TRIAL GROUPS AND STRATEGIES

A computer-generated, sequentially numbered, block randomization list, stratified according to study clinic, was drawn up and then included in a software tool that allowed access to the next available trial identification number and treatment group. Participants were randomly assigned to one of four groups: group 1 (deferred ART), in which ART was deferred until WHO criteria for starting ART were met; group 2 (deferred ART plus IPT), in which ART was deferred until WHO criteria for starting ART were met and a 6-month course of IPT was started 1 month after enrollment; group 3 (early ART), in which ART was started immediately; and group 4 (early ART

plus IPT), in which ART was started immediately and a 6-month course of IPT was started 1 month after enrollment. We will refer to trial groups each time we show separate data for each of the four groups and refer to trial strategies whenever we show data combining patients assigned to early ART (groups 3 and 4), deferred ART (groups 1 and 2), IPT (groups 2 and 4), or no IPT (groups 1 and 3).

#### BASELINE TESTS

After the participants underwent randomization, plasma HIV-1 RNA was measured in all participants by means of a real-time polymerase-chain-reaction assay (Generic HIV Charge Virale, Bio-centric; threshold of detectability, 100 copies per milliliter), and systematic chest radiography was performed. The first 967 patients who underwent randomization also underwent an interferon-gamma release assay (IGRA) for tuberculosis (QuantiFERON-TB Gold test, Celestis). Other tests are listed in Section 2 in the Supplementary Appendix. All trial tests were performed in one reference laboratory. Tuberculin skin tests were not performed.

#### TRIAL DRUGS

The first-line ART regimen consisted preferably of tenofovir–emtricitabine plus efavirenz. Patients with contraindications to efavirenz received tenofovir–emtricitabine plus lopinavir–ritonavir, or tenofovir–emtricitabine plus zidovudine. The latter regimen was abandoned in December 2008 owing to increased side effects in the upper digestive tract.<sup>23</sup>

IPT consisted of 300 mg of isoniazid daily, which was started 1 month after enrollment and stopped 7 months after enrollment. All the patients who were randomly assigned to groups 2 and 4 were eligible for IPT irrespective of the results on IGRA for tuberculosis. However, patients who had images suggestive of active tuberculosis on their baseline chest radiograph, those who had aminotransferase levels greater than 2.5 times the upper limit of the normal range, and those in whom clinical signs suggestive of tuberculosis developed during the first month after enrollment were not prescribed IPT.

Trimethoprim–sulfamethoxazole prophylaxis was prescribed in all patients who had a CD4+ count of less than 500 cells per cubic millimeter

and no history of serious side effects from the drug. It was stopped when the CD4+ count rose above 500 cells per cubic millimeter.

Merck Sharp & Dohme donated Stocrin (efavirenz) and Gilead Sciences donated Truvada (tenofovir–emtricitabine) for all participants in the study; these companies had no other role in the study. Nouvelle Pharmacie de Santé Publique of Ivory Coast provided all other antiretroviral drugs, with support from the U.S. President's Emergency Plan for AIDS Relief.

#### EVOLUTION OF TRIAL PROCEDURES

The trial started in March 2008 and ended in January 2015. During this time period, the WHO guidelines for ART changed twice.<sup>1,2</sup> The inclusion criterion of “no WHO criteria for starting ART” and the criteria for starting ART in patients assigned to the deferred-ART strategy were thus updated over time in line with WHO guideline updates (Section 2 in the Supplementary Appendix).

#### END POINTS

Participants were followed for 30 months. Visits were scheduled monthly for 3 months and quarterly thereafter. CD4+ counts and plasma HIV-1 RNA levels were measured every 6 months. Clinical events were reviewed by an event-documentation committee whose members were aware of the randomization assignments; events were classified as definite, probable, or possible according to standardized criteria (Sections 3 and 4 in the Supplementary Appendix).

The primary end point was a composite of death from any cause, AIDS-defining disease, non-AIDS-defining cancer, or non-AIDS-defining invasive bacterial disease (Section 2 in the Supplementary Appendix). The main secondary end point was grade 3 or 4 illness, including all events with a grade of 3 or 4 according to the ANRS grading table (Section 5 in the Supplementary Appendix). Other secondary end points were virologic suppression, which was assessed as the percentage of patients with an undetectable viral load, and adherence to treatment, as assessed by the medication possession ratio (the number of daily doses of antiretroviral drugs dispensed by the pharmacy to each patient, divided by that patient's total follow-up time in days since the initiation of ART).<sup>24</sup> Par-

ticipants were considered to have completed IPT if they attended all six isoniazid prescription visits.

#### STATISTICAL ANALYSIS

We calculated that with 2076 participants enrolled, the study would have 80% power to detect a 40% lower rate of the primary end point with a new strategy (early ART or IPT) than with the corresponding reference strategy (deferred ART or no IPT), assuming a 10% rate of the primary end point in the reference strategy and with correction factors to account for a 4.2% loss to follow-up (on the basis of previous studies) and for testing for interactions (Section 2 in the Supplementary Appendix). Main analyses were performed on an intention-to-treat basis.

For each trial group and strategy, we used the Kaplan–Meier method to estimate the cumulative probability of the occurrence of an event and estimated rates by dividing the number of first events by the cumulative time at risk. Then, considering all groups together, we estimated CD4+–specific rates in the entire trial population by dividing the number of first events that occurred during the time that patients had CD4+ counts within a given stratum by the cumulative time at risk spent in the stratum. Follow-up data were censored when participants were lost to follow-up before their 30-month visit (Section 2 in the Supplementary Appendix).

Multivariate Cox proportional-hazards models were used to compare strategies with respect to event rates for the primary end point and its components and for the main secondary end point. Models systematically included three explanatory variables: IPT status (yes vs. no), ART status (early vs. deferred), and trial center. Hazard ratios were thus adjusted for the other strategy and the trial center. Interaction between strategies was tested. The assumption of the proportional hazards was examined.

Prespecified sensitivity analyses were performed to explore the influence of baseline CD4+ count and the robustness of the results with varying definitions of end points (Section 2 in the Supplementary Appendix). All reported P values were two-sided and have not been adjusted for multiple testing. Statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute).

## RESULTS

### BASELINE AND FOLLOW-UP CHARACTERISTICS

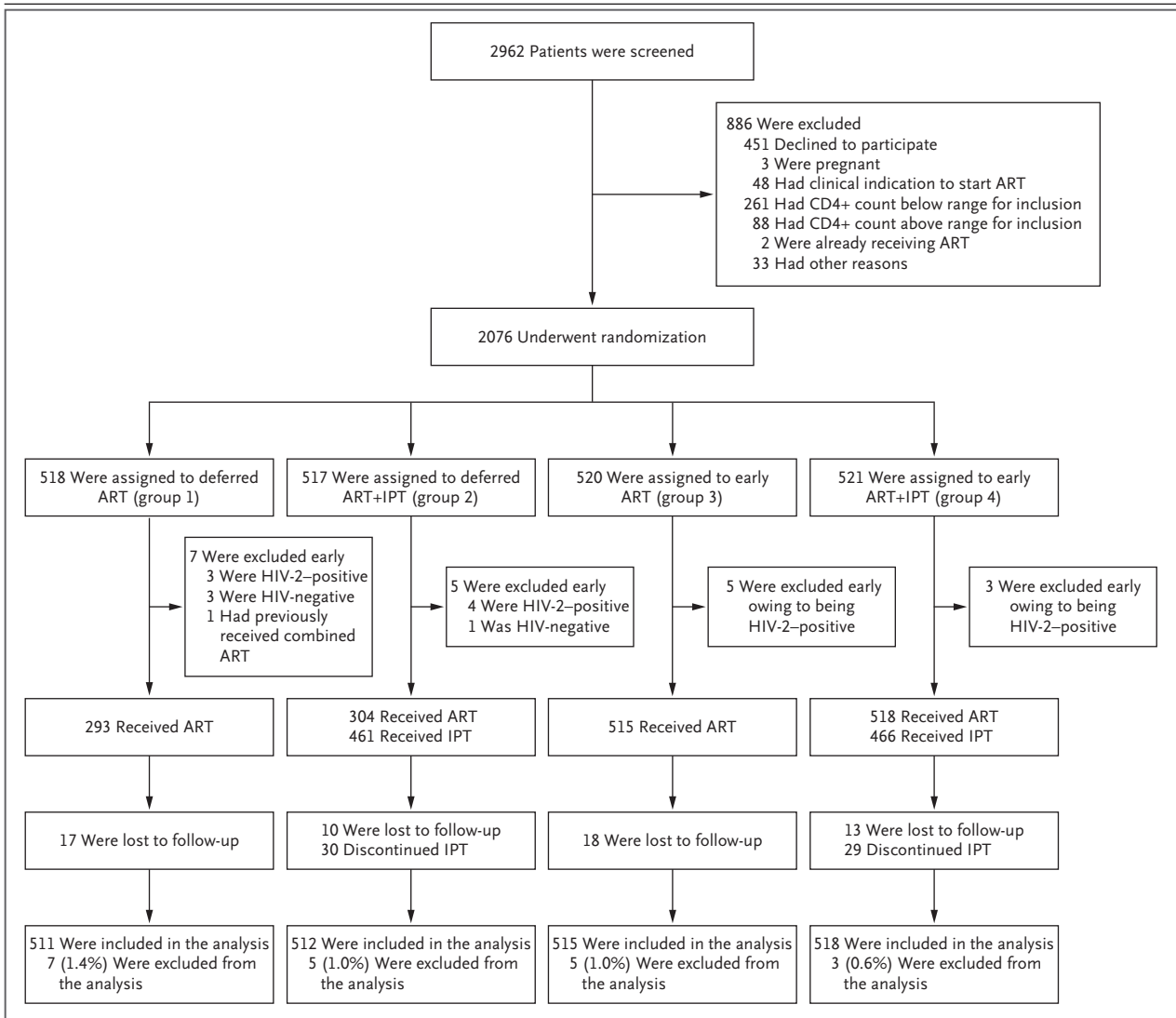
Between March 18, 2008, and July 16, 2012, a total of 2076 patients were randomly assigned to treatment groups; 20 (1%) were subsequently excluded and 2056 (99%) were included in the analyses (Fig. 1). Participants assigned to the deferred-ART strategy were followed for 2382 person-years, and those assigned to the early-ART strategy were followed for 2375 person-years (Table 1). The rate of attendance at scheduled visits was 93% at 3 months and 86% at 30 months (Table S1 in Section 6 in the Supplementary Appendix). At study termination, 47 patients (2%) were known to have died, and 58 (3%) were considered to have been lost to follow-up, with no significant differences among the strategies.

### TRIAL INTERVENTIONS

Among patients assigned to the deferred-ART strategy, the 30-month probability of starting ART was 63% (Fig. S1 in Section 7 in the Supplementary Appendix). Among the 1033 patients assigned to the early-ART strategy, 911 had a viral-load measurement after 12 months, of whom 84% had an undetectable viral load, and 872 had a viral-load measurement after 24 months, of whom 83% had an undetectable viral load. Among the 391 patients assigned to deferred ART who started ART more than 12 months before the 30-month visit, 331 had a viral-load measurement after 12 months of ART, of whom 80% had an undetectable viral load. Among the 70 patients assigned to deferred ART who started ART more than 24 months before the 30-month visit, 63 had a viral-load measurement after 12 months of ART, of whom 81% had an undetectable viral load. Of the 1030 patients assigned to the IPT strategy, 927 (90%) actually started isoniazid, of whom 94% completed the 6-month treatment period (Table 1).

### EVOLUTION OF CD4+ COUNTS

Among patients assigned to the early-ART strategy, the mean CD4+ count increased from 481 cells per cubic millimeter at baseline to 728 cells per cubic millimeter at 30 months. Among patients assigned to the deferred-ART strategy, the mean CD4+ count decreased from 472 cells per



**Figure 1. Randomization, Study Treatments, and Follow-up.**

Clinical indication to start antiretroviral therapy (ART) was irrespective of the CD4+ count. Of the 20 patients who underwent randomization but were excluded from analysis, 15 were infected only with human immunodeficiency virus (HIV) type 2 (HIV-2) on HIV tests performed at inclusion (these patients were previously thought to have had dual infection with HIV-1 and HIV-2 on the basis of tests performed locally), 4 were HIV-seronegative on tests performed at inclusion (these patients were previously found to be HIV-positive locally and were followed in HIV clinics for 76, 95, 148, and 306 days, respectively, before inclusion), and 1 had a history of combined ART that was discovered after inclusion. IPT denotes isoniazid preventive therapy.

cubic millimeter at baseline to 428 cells per cubic millimeter at 12 months and then increased to 511 cells per cubic millimeter at 30 months (Fig. S2, S3, and S4 in Section 7 in the Supplementary Appendix). The evolution of the CD4+ count did not differ significantly between patients assigned to IPT and those assigned to no IPT. On average, patients had CD4+ counts of at least 500 cells per cubic millimeter during 51%

of their follow-up time (Fig. S5 in Section 7 in the Supplementary Appendix).

#### PRIMARY END POINT AND ITS COMPONENTS

During follow-up, 204 primary end-point events were recorded in 175 patients. With all groups considered together, the overall rate of the primary end point was 3.8 events per 100 person-years (95% confidence interval [CI], 3.3 to 4.4),

and the CD4<sup>+</sup>-specific rates of the primary end point for the time during which patients had CD4<sup>+</sup> counts of at least 500 cells per cubic millimeter, between 350 and 499 cells per cubic millimeter, and less than 350 cells per cubic millimeter were 2.8 events per 100 person-years (95% CI, 2.1 to 3.5), 4.1 events per 100 person-years (95% CI, 3.0 to 5.1), and 6.8 events per 100 person-years (95% CI, 5.0 to 8.6), respectively (Fig. S6 in Section 7 in the Supplementary Appendix).

The mean ( $\pm$ SD) CD4<sup>+</sup> count at the onset of a first primary end-point event was 414 $\pm$ 162 cells per cubic millimeter among patients assigned to the deferred-ART strategy and 547 $\pm$ 239 cells per cubic millimeter among patients assigned to the early-ART strategy. The 30-month probability of a primary end-point event was 11.4% among patients assigned to the deferred-ART strategy, 6.6% among patients assigned to the early-ART strategy, 10.7% among patients assigned to the no-IPT strategy, and 7.2% among patients assigned to the IPT strategy (Fig. S7 in Section 7 in the Supplementary Appendix). Probabilities according to treatment group are shown in Figure 2. The hazard ratio for a primary end-point event was 0.56 (95% CI, 0.41 to 0.76) with early ART as compared with deferred ART (Fig. 3) and 0.65 (95% CI, 0.48 to 0.88) with IPT as compared with no IPT (Fig. 4). There was no significant interaction among the strategies ( $P=0.45$ ). These findings were robust to adjustment for baseline CD4<sup>+</sup> count, the exclusion of patients enrolled before December 2009, the censoring of follow-up data at the time a first CD4<sup>+</sup> count of less than 350 cells per cubic millimeter was measured, consideration of only events classified as definite, consideration of each end-point component separately, and stratification according to baseline CD4<sup>+</sup> count, as well as in an analysis in which patients with missing data were categorized as having treatment failure and a per-protocol analysis (Fig. 3 and 4, and Table S6 in Section 6 in the Supplementary Appendix).

The primary end-point component that occurred most frequently was tuberculosis (42%), followed by invasive bacterial diseases (27%), death from any cause (23%), AIDS-defining or non-AIDS-defining cancers (4%), and other AIDS-defining diseases (3%) (Table 2). Drug-sensitivity testing was performed in 40 of the 41

patients with culture-confirmed tuberculosis: 4 had multidrug-resistant tuberculosis (1 had been assigned to the IPT strategy, and 3 had been assigned to the no-IPT strategy), 5 had isoniazid monoresistance (3 had been assigned to the IPT strategy, and 2 had been assigned to the no-IPT strategy), and 5 had another resistance profile (1 had been assigned to the IPT strategy, and 4 had been assigned to the no-IPT strategy). Of the 967 patients who had a serum test for tuberculosis, 597 had a negative test, 337 had a positive test, and 33 had an indeterminate test result. Of the 597 patients with a negative test, 16 went on to have tuberculosis. Of the 337 patients with a positive test, 26 went on to have tuberculosis. Among patients with a positive test, those who were assigned to IPT had significantly fewer tuberculosis events than those assigned to no IPT (adjusted hazard ratio, 0.43; 95% CI, 0.19 to 0.99). Among patients with a negative test, those who were assigned to IPT also had fewer tuberculosis events than those assigned to no IPT, but the difference was not significant (adjusted hazard ratio, 0.58; 95% CI, 0.21 to 1.61).

#### GRADE 3 OR 4 ADVERSE EVENTS

During follow-up, 165 grade 3 or 4 events were recorded in 144 patients (Table 2). The cumulative probability of a grade 3 or 4 event over a 30-month period was 7.7% among patients assigned to the deferred-ART strategy, 7.1% among patients assigned to the early-ART strategy, 8.2% among patients assigned to the no-IPT strategy, and 6.6% among patients assigned to the IPT strategy (Fig. S7 in Section 7 in the Supplementary Appendix). The risk of grade 3 or 4 events was 2.6 times as high among patients assigned to early ART as among patients assigned to deferred ART during the first 6 months and 2.1 times as low among patients assigned to early ART as among patients assigned to deferred ART thereafter. The risk of grade 3 or 4 events did not differ significantly between patients assigned to IPT and those assigned to no IPT (Fig. 4).

#### PARTICIPANTS WITH A BASELINE CD4<sup>+</sup> COUNT OF AT LEAST 500 CELLS PER CUBIC MILLIMETER

A total of 849 patients had a CD4<sup>+</sup> count of at least 500 cells per cubic millimeter at baseline. Among patients with these baseline CD4<sup>+</sup>

**Table 1. Baseline and Follow-up Characteristics.\***

Characteristic	Group 1: Deferred ART (N = 511)	Group 2: Deferred ART plus IPT (N = 512)	Group 3: Early ART (N = 515)	Group 4: Early ART plus IPT (N = 518)
<b>Baseline</b>				
Female sex — no. (%)	400 (78)	391 (76)	407 (79)	416 (80)
Age — yr				
Median	35	35	35	35
Interquartile range	29–41	30–42	30–42	29–42
Educational level — no. (%)				
Primary school or less	275 (54)	270 (53)	282 (55)	287 (55)
Secondary school or more	236 (46)	242 (47)	233 (45)	231 (45)
WHO clinical stage of HIV infection — no. (%)				
1	340 (67)	326 (64)	333 (65)	322 (62)
2	126 (25)	134 (26)	132 (26)	145 (28)
≥3	45 (9)	52 (10)	50 (10)	51 (10)
CD4+ count — cells/mm <sup>3</sup>				
Median	460	459	467	466
Interquartile range	359–560	364–575	369–584	394–572
CD4+ count stratum — no. (%)				
≥500 cells/mm <sup>3</sup>	201 (39)	212 (41)	222 (43)	214 (41)
350–499 cells/mm <sup>3</sup>	189 (37)	193 (38)	188 (37)	211 (41)
<350 cells/mm <sup>3</sup>	121 (24)	107 (21)	105 (20)	93 (18)
Plasma HIV-1 RNA — log <sub>10</sub> copies/ml				
Median	4.6	4.6	4.7	4.7
Interquartile range	4.0–5.2	4.0–5.3	4.0–5.3	4.0–5.3
Dual infection with HIV-1 and HIV-2 — no. (%)	10 (2)	12 (2)	15 (3)	14 (3)
Creatinine clearance <50 ml/min — no. (%)	6 (1)	9 (2)	4 (1)	9 (2)
Plasma alanine aminotransferase >2.5 ×ULN — no. (%)	1 (<0.5)	4 (1)	3 (1)	2 (<0.5)
Hemoglobin <95 g/liter — no. (%)	52 (10)	48 (9)	64 (12)	54 (10)
Positive test for hepatitis B surface antigen — no. (%)	42 (8)	48 (9)	49 (10)	54 (10)
Positive IGRAs for tuberculosis — no./total no. (%)†	89/244 (36)	88/241 (37)	84/241 (35)	76/241 (32)
<b>Follow-up</b>				
Duration of follow-up — mo				
Median	29.9	29.9	29.9	29.9
Interquartile range	29.9–30.0	29.9–30.0	29.9–30.0	29.9–30.0
Lost to follow-up — no. (%)	17 (3)	10 (2)	18 (3)	13 (3)
Total duration of follow-up — patient-yr	1168	1213	1177	1199
Ever started trimethoprim–sulfamethoxazole — no. (%)	467 (91)	476 (93)	451 (88)	455 (88)
Ever started ART — no. (%)	293 (57)	304 (59)	515 (100)	518 (100)
First-line ART regimen — no./total no. (%)				
TDF–FTC plus EFV	205/293 (70)	216/304 (71)	362/515 (70)	354/518 (68)
TDF–FTC plus LPV/r‡	70/293 (24)	68/304 (22)	115/515 (22)	124/518 (24)
Other§	18/293 (6)	20/304 (7)	38/515 (7)	40/518 (8)

Table 1. (Continued.)

Characteristic	Group 1: Deferred ART (N=511)	Group 2: Deferred ART plus IPT (N=512)	Group 3: Early ART (N=515)	Group 4: Early ART plus IPT (N=518)
Ever started IPT — no. (%)¶	0	461 (90)	0	466 (90)
Completed 6-mo course of IPT — no./total no. (%)‖		431/461 (93)		437/466 (94)

\* None of the baseline characteristics differed significantly among the groups. ART denotes antiretroviral therapy, EFV efavirenz, FTC emtricitabine, HIV-1 human immunodeficiency virus type 1, IPT isoniazid preventive therapy, LPV/r lopinavir/ritonavir, TDF tenofovir, ULN upper limit of the normal range, and WHO World Health Organization.

† The first 967 enrolled patients underwent an interferon-gamma release assay (IGRA) for tuberculosis (QuantiFERON-TB Gold test, Celestis).

‡ Among the 377 patients who started ART with TDF–FTC plus LPV/r, the reason for not receiving an EFV-based regimen was dual infection with HIV-1 and HIV type 2 (15 patients), a history of prevention of mother-to-child transmission with nevirapine (38), declining to use effective contraception (308), and other reasons (16).

§ Other regimens were TDF–FTC–zidovudine (ZDV) (81 patients), ZDV–lamivudine (3TC)–LPV/r (25), ZDV–3TC–EFV (3), ZDV–3TC–nevirapine (3), didanosine–3TC–EFV (1), stavudine (D4T)–3TC–EFV (1), D4T–3TC–LPV/r (1), and 3TC–abacavir–LPV/r (1).

¶ The reasons for not starting IPT at 1 month were the presence of signs suggestive of tuberculosis on the chest radiograph obtained at baseline (16 patients), the presence of clinical signs suggestive of tuberculosis at the 1-month visit (47), nonattendance at the 1-month visit (24), elevated aminotransferase levels at baseline (6), pregnancy (4), death before 1 month (1), and other reasons (5).

‖ The reasons for stopping IPT prematurely were death from an unknown cause (1 patient), discontinuation by patients for personal, non-medical reasons (22), discontinuation by physicians because of the presence in the patient of signs or symptoms suggestive of tuberculosis (10, of whom 3 were confirmed to have tuberculosis), pregnancy (13), and the following 12 adverse events: elevated aminotransferase levels (two grade 2 events, two grade 3 events, and two grade 4 events), psychiatric side effects (two grade 2 events and two grade 3 events), and pruritus (two grade 2 events). None of the episodes of elevated aminotransferase levels led to death.

counts who were assigned to the deferred-ART strategy, the cumulative 30-month probability of starting ART was 41% (Fig. S1 in Section 7 in the Supplementary Appendix); the mean CD4+ count decreased from 617 cells per cubic millimeter at baseline to 533 cells per cubic millimeter at 6 months and then remained stable. Among patients with baseline CD4+ counts of at least 500 cells per cubic millimeter who were assigned to the early-ART strategy, the mean CD4+ count increased from 617 cells per cubic millimeter at baseline to 810 cells per cubic millimeter at 30 months (Fig. S4A in Section 7 in the Supplementary Appendix). On average, patients had CD4+ counts of at least 500 cells per cubic millimeter during 77% of their follow-up time (Fig. S5 in Section 7 in the Supplementary Appendix). During follow-up, 68 primary end-point events were recorded in 61 patients (3.2 events per 100 person-years; 95% CI, 2.4 to 4.0). The mean CD4+ count at the onset of a first primary end-point event was 542±144 cells per cubic millimeter among patients assigned to deferred ART and 702±287 cells per cubic millimeter among patients assigned to early ART. The hazard ratio for a primary end-point event was 0.56 (95% CI, 0.33 to 0.94) with early ART versus deferred ART (Fig. 3) and 0.61 (95% CI, 0.36 to 1.01) with IPT versus no IPT (P=0.78 for interaction) (Fig. 4).

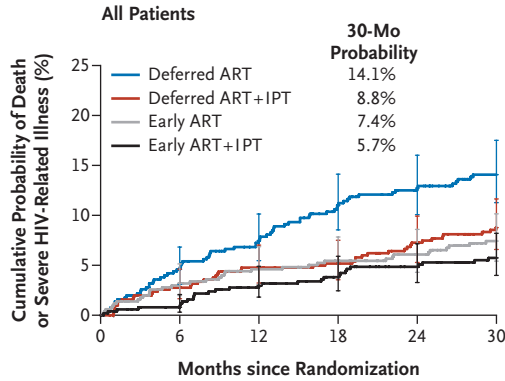
## DISCUSSION

In this study, we recruited 2056 HIV-infected adults who were not eligible to start ART at the time of enrollment according to the current WHO guidelines, in a West African country in which IPT is not recommended. Participants had baseline CD4+ counts evenly distributed on both sides of the CD4+ threshold of 500 cells per cubic millimeter. The early initiation of ART and 6 months of IPT independently resulted in a risk of severe HIV-related illness that was 44% lower and a risk of death from any cause that was 35% lower than the risks with deferred initiation of ART and no IPT. The results were robust across alternate end-point definitions and CD4+ count strata. They were driven mainly by the efficacy of both interventions in preventing tuberculosis; the efficacy of ART in reducing invasive bacterial diseases also played a role.

Our findings suggest that starting ART before the CD4+ count falls below 500 cells per cubic millimeter may be beneficial in patients who live in countries that have a high burden of tuberculosis and bacterial diseases. The efficacy of earlier ART in decreasing the relative risk of severe illness, as estimated by hazard ratios, was similar when CD4+ counts were above and when they were below 500 cells per cubic millimeter, and although the absolute risk of events across

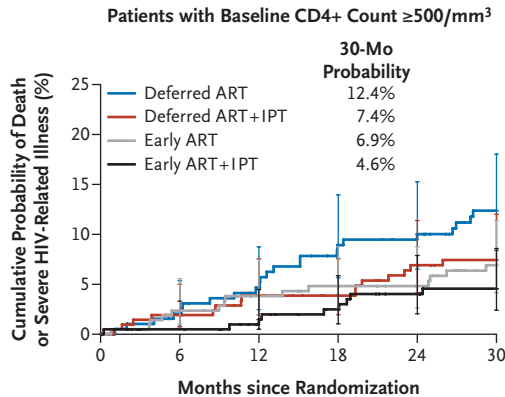


**A Primary Outcome**



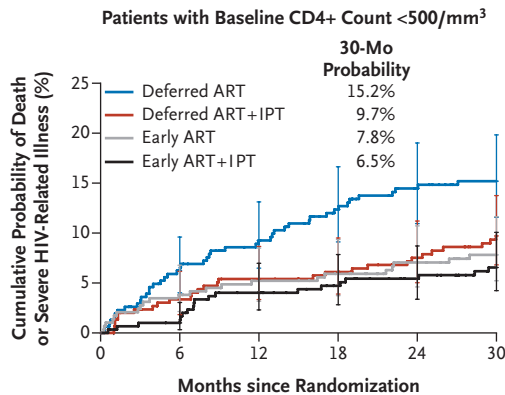
**No. at Risk**

Deferred ART	511	473	448	418	400	366
Deferred ART+IPT	512	489	473	459	440	419
Early ART	515	481	463	452	432	403
Early ART+IPT	518	501	478	459	445	418



**No. at Risk**

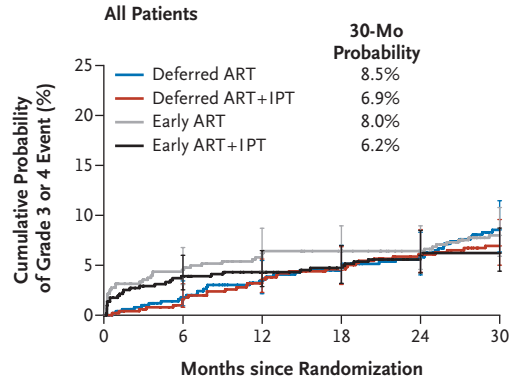
Deferred ART	201	190	181	168	162	145
Deferred ART+IPT	212	204	197	191	182	174
Early ART	222	205	193	189	185	171
Early ART+IPT	214	205	197	190	184	171



**No. at Risk**

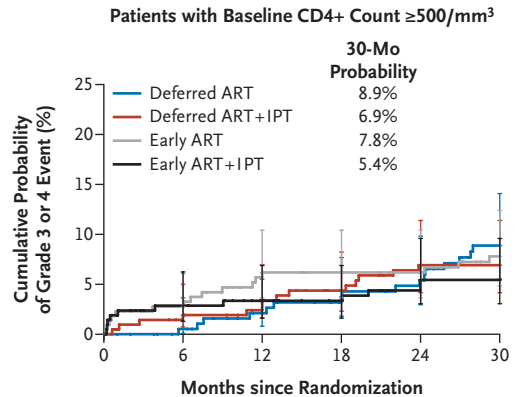
Deferred ART	310	283	267	250	238	221
Deferred ART+IPT	300	285	276	268	258	245
Early ART	293	276	270	263	247	232
Early ART+IPT	304	296	281	269	261	247

**B Main Secondary Outcome**



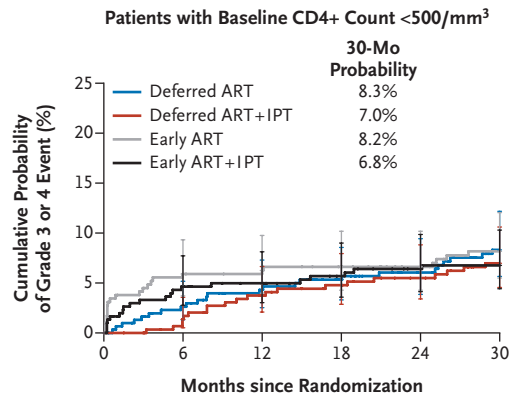
**No. at Risk**

Deferred ART	511	486	464	440	423	385
Deferred ART+IPT	512	495	477	458	442	423
Early ART	515	469	451	442	427	392
Early ART+IPT	518	485	468	451	437	412



**No. at Risk**

Deferred ART	201	192	183	174	168	152
Deferred ART+IPT	212	204	197	189	182	174
Early ART	222	203	188	186	183	167
Early ART+IPT	214	200	192	187	180	167



**No. at Risk**

Deferred ART	310	294	281	266	255	233
Deferred ART+IPT	300	291	280	269	260	249
Early ART	293	266	263	256	245	225
Early ART+IPT	304	285	276	264	257	245

**Figure 2 (facing page). Kaplan–Meier Curves of Probability of the Primary End Point and Main Secondary End Point.**

The primary end point was a composite of death from any cause, AIDS-defining disease, non–AIDS-defining cancer, or non–AIDS-defining invasive bacterial disease. The main secondary end point was events of grade 3 or 4 according to the grading table for severe adverse events of the French National Agency for Research on AIDS and Viral Hepatitis. I bars represent 95% confidence intervals.

CD4+ categories, as estimated by CD4+-specific rates, decreased with increasing CD4+ counts, the risk of events remained clinically significant during the follow-up time when patients had CD4+ counts of at least 500 cells per cubic millimeter. These findings, in patients with CD4+ counts of less than 800 cells per cubic millimeter, confirm and extend those of the HIV Prevention Trials Network 052 study, which showed similar results in patients with CD4+ counts of 350 to 550 cells per cubic millimeter.<sup>25</sup>

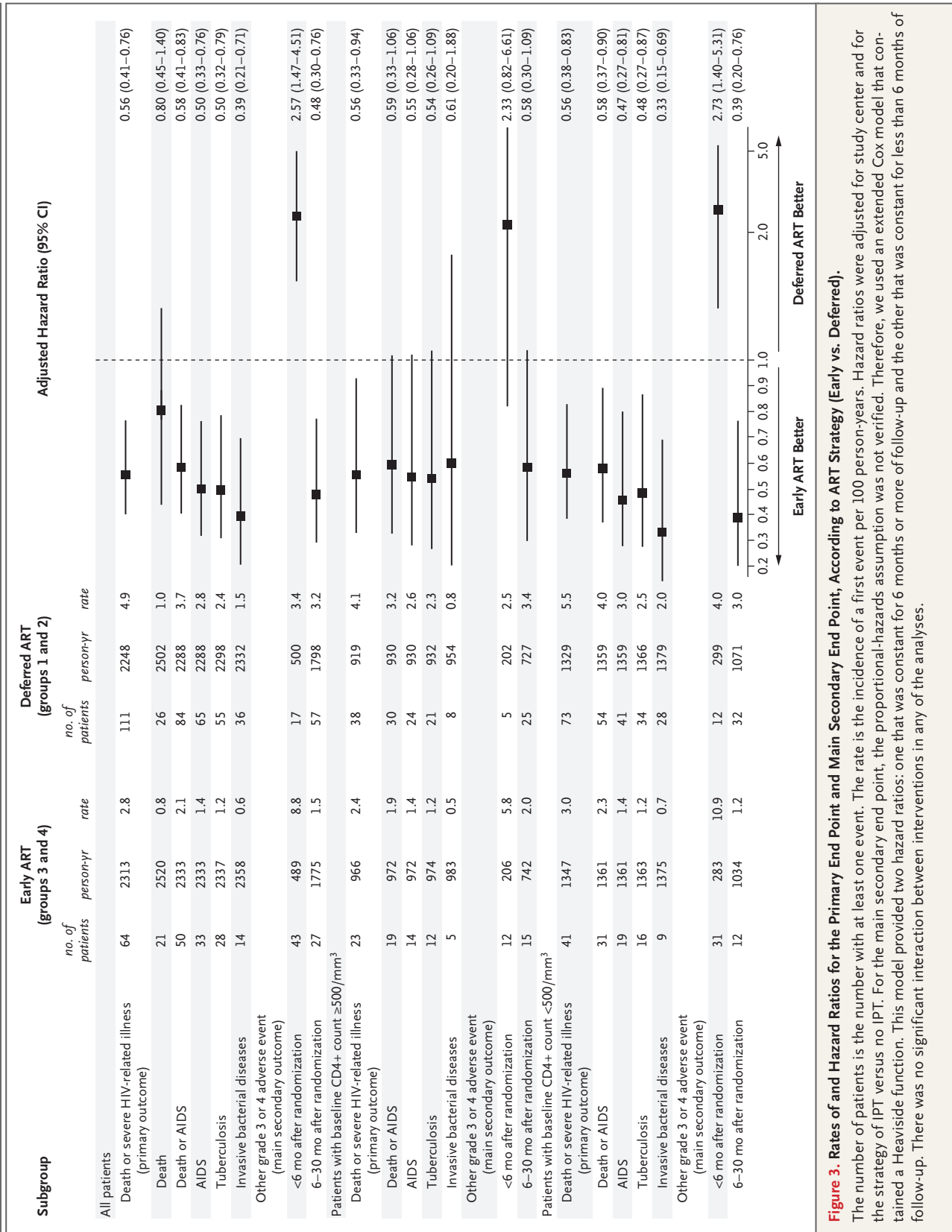
Despite WHO recommendations,<sup>22</sup> many countries with a high tuberculosis burden have not adopted IPT guidelines. In those that have, the coverage remains low.<sup>26,27</sup> Previous evidence of IPT efficacy from randomized trials was derived mostly from studies conducted before the ART era.<sup>22,28–31</sup> Evidence for the added value of IPT in patients receiving ART was mostly from patients with CD4+ counts of less than 500 cells per cubic millimeter.<sup>32–38</sup> Our data are consistent with these previous studies that showed that IPT and ART have additive efficacy with respect to the prevention of tuberculosis and that suggested that the two therapies should be given concomitantly. They also highlight for countries that are reluctant to recommend IPT that isoniazid can be prescribed safely when given early in the course of HIV disease.

Short-term adverse events were more common with earlier ART than with deferred ART and involved toxic effects that are expected with antiretroviral drugs — mainly digestive and neurologic effects. The cumulative numbers of other primary end-point components, including AIDS-defining and non–AIDS-defining cancers, and of other grade 3 or 4 events, including hematologic, renal, and hepatic events, were higher among patients assigned to the deferred-ART strategy.

Our study has several limitations. First, the frequency of events such as cancers, cardiovascular diseases, or bone-related toxic effects was probably underestimated, owing to limited diagnostic techniques. Second, this was an open-label study in which investigators were aware of the trial interventions. Third, during the study period, we adapted our criteria for starting ART in patients assigned to the deferred-ART strategy as WHO guidelines evolved. Therefore, the early-ART strategy was not compared with a single, unchanging reference strategy. This is both a limitation and a strength of the study, because it allowed an assessment of the efficacy of the interventions as practice changed. Our data highlight the continued benefit of starting ART earlier than at the CD4+ thresholds recommended by the WHO, even though the threshold was raised over time to 500 cells per cubic millimeter. The robustness of our results in patients with CD4+ counts of at least 500 cells per cubic millimeter suggests that the true effective treatment threshold, if there is any, is at least 800 cells per cubic millimeter.

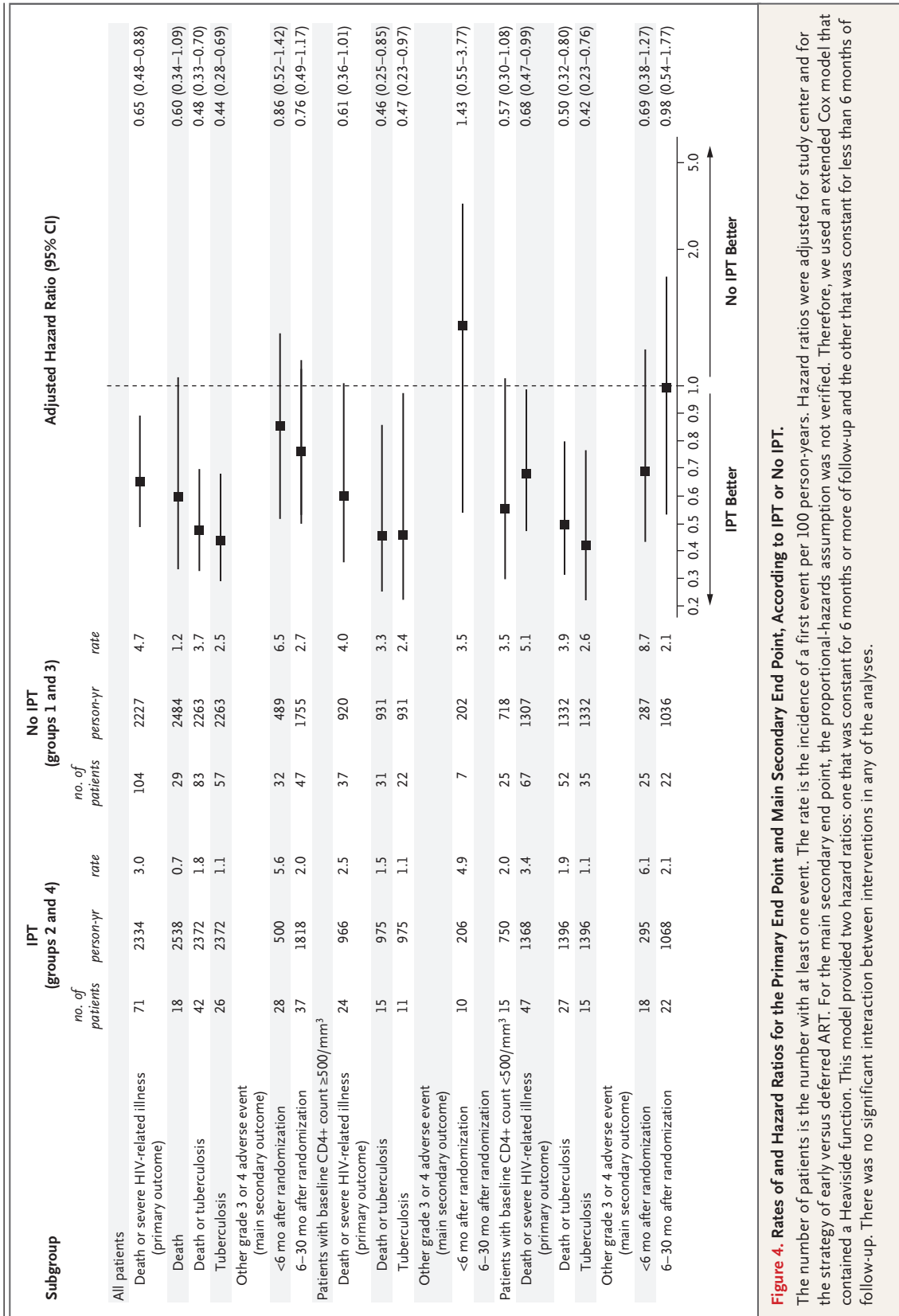
Finally, although our findings suggest that earlier initiation of ART than is currently recommended in Ivory Coast may be beneficial, they do not answer the question of whether higher CD4+ thresholds should be used or whether ART should be recommended to all HIV-infected patients regardless of the CD4+ count. On the one hand, tuberculosis and bacterial diseases are common diseases that act as opportunistic infections in people living with HIV, and we suspect that there is no higher CD4+ threshold that could identify a sharp decrease in risk.<sup>39–42</sup> On the other hand, patients with slow progression of HIV infection, who represent a small minority of patients, may not have the same benefit-risk ratio from earlier ART as other patients.

During the trial period, patients who started ART early and those who deferred and eventually started ART had similar rates of loss to follow-up, attendance at scheduled visits, and virologic success at 24 months. However, all the patients who were assigned to the early-ART strategy received 30 months of treatment, whereas most patients who were assigned to the deferred-ART strategy did not. We thus extended follow-up for patients assigned to the deferred-ART strategy who started ART during the course



**Figure 3. Rates of and Hazard Ratios for the Primary End Point and Main Secondary End Point, According to ART Strategy (Early vs. Deferred).**

The number of patients is the number with at least one event. The rate is the incidence of a first event per 100 person-years. Hazard ratios were adjusted for study center and for the strategy of IPT versus no IPT. For the main secondary end point, the proportional-hazards assumption was not verified. Therefore, we used an extended Cox model that contained a Heaviside function. This model provided two hazard ratios: one that was constant for 6 months or more of follow-up and the other that was constant for less than 6 months of follow-up. There was no significant interaction between interventions in any of the analyses.



**Figure 4. Rates of and Hazard Ratios for the Primary End Point and Main Secondary End Point, According to IPT or No IPT.**

The number of patients is the number with at least one event. The rate is the incidence of a first event per 100 person-years. Hazard ratios were adjusted for study center and for the strategy of early versus deferred ART. For the main secondary end point, the proportional-hazards assumption was not verified. Therefore, we used an extended Cox model that contained a Heaviside function. This model provided two hazard ratios: one that was constant for 6 months or more of follow-up and the other that was constant for less than 6 months of follow-up. There was no significant interaction between interventions in any of the analyses.

**Table 2. Primary End-Point Events and Grade 3 or 4 Adverse Events, According to Trial Group and Strategy.**

Event	Group 1: Deferred ART	Group 2: Deferred ART plus IPT	Group 3: Early ART	Group 4: Early ART plus IPT	Groups 1 and 2: Deferred-ART Strategy	Groups 3 and 4: Early-ART Strategy	Groups 1 and 3: No-IPT Strategy	Groups 2 and 4: IPT Strategy
	<i>number of events</i>							
<b>Primary end-point events</b>								
Total	75	60	41	28	135	69	116	88
Death*	16	10	13	8	26	21	29	18
Tuberculosis†	41	16	17	11	57	28	58	27
Pulmonary	20	4	11	8	24	19	31	12
Extrapulmonary‡	21	12	6	3	33	9	27	15
Invasive bacterial disease§	14	28	7	7	42	14	21	35
AIDS-defining or non-AIDS-defining cancer¶	1	5	1	2	6	3	2	7
Others AIDS-defining disease¶	3	1	3	0	4	3	6	1
<b>Grade 3 or 4 adverse events  </b>								
Total	46	44	42	33	90	75	88	77
Hematologic	26	19	16	10	45	26	42	29
Liver-related	8	7	5	5	15	10	13	12
Renal	5	7	0	1	12	1	5	8
Digestive	0	2	8	9	2	17	8	11
Neurologic	2	3	10	3	5	13	12	6
Cardiovascular	2	4	1	2	6	3	3	6
Cutaneous	1	0	2	1	1	3	3	1
Other	2	2	0	2	4	2	2	4

\* Of the 47 deaths, 22 were considered to be of unknown cause; in the case of 25 deaths, a possible or probable cause of death was identified. Of the latter, 15 were incident events (the main criterion for diagnosing the disease appeared after the patient's enrollment in the study), and 10 were prevalent events (the main criterion for diagnosing the disease was proved to have been present at the time of enrollment). The 15 incident events that were considered to be a possible or probable cause of death were 5 events of tuberculosis, 2 events of hepatitis, and 1 event each of stroke, necrotizing fasciitis, visceral abscess, lymphoma, non-AIDS-defining cancer, cryptococcosis, renal insufficiency, and firearm injury. The 10 prevalent events that were considered to be a possible or probable cause of death were 3 events of tuberculosis, 3 events of non-AIDS-defining cancer, 2 events of renal insufficiency, and 1 event each of bacterial pneumonia and myocardial infarction.

† Of the 85 episodes of tuberculosis, 44 were documented as definite (41 with positive cultures and 5 with histologic evidence, including 2 with positive cultures), 29 as probable, and 12 as possible.

‡ The 42 extrapulmonary cases included 16 cases with both pulmonary and extrapulmonary sites. Documented extrapulmonary disorders were deep lymphadenopathy (16 cases), peripheral lymphadenopathy (9), pleural effusion (8), osteomyelitis (4), miliary disease (2), meningitis (1), pericarditis (1), esophageal ulceration (1), mammary gland infection (1), and pancytopenia (1); several disorders could occur in the same patient.

§ Of the 56 episodes of invasive bacterial diseases, 30 were documented as definite and 26 as probable. The 56 episodes of invasive bacterial diseases were 23 episodes of pneumonia, 12 of isolated bacteremia, 9 of pyelonephritis, 4 of typhoid fever, 2 of prostatitis, 2 of necrotizing fasciitis, 2 of enteritis with bacteremia, 1 of visceral abscess, and 1 of septic shock (for details according to trial group and strategy, see Table S2 in Section 6 in the Supplementary Appendix). Clinically significant bacteria were isolated in 30 episodes, including 18 from blood cultures, 3 from blood and urine cultures, 1 from blood and stool cultures, and 8 from urine cultures. Pathogens were *Escherichia coli* (15 episodes), non-Typhi salmonella (6), *Salmonella enterica* serovar Typhi (4), *Klebsiella pneumoniae* (2), *Streptococcus pneumoniae* (1), *Citrobacter* species (1), and *Acinetobacter* species (1).

¶ AIDS-defining diseases were identified as diseases included in the Centers for Disease Control and Prevention case definition of AIDS.<sup>7</sup> Details on the specific disease events are provided in Table S2 in Section 6 in the Supplementary Appendix.

|| Adverse events were categorized according to the grading table for severe adverse events of the French National Agency for Research on AIDS and Viral Hepatitis. Details on the specific events are provided in Table S3 in Section 6 in the Supplementary Appendix.

of the trial (i.e., within 30 months after inclusion) until they reached 30 months of treatment. Further comparison of adherence and virologic outcomes over a 30-month period of effective treatment will provide additional insights.

In conclusion, our findings suggest that ART has a favorable benefit–risk ratio in patients before the CD4+ count reaches the current treatment threshold of 500 cells per cubic millimeter; we found that 6 months of IPT combined with early ART led to improved outcomes and that the spectrum of diseases for which early ART has a protective effect includes not only tuberculosis but also invasive bacterial diseases. Our data suggest that in low-resource settings, ART pro-

vides substantial clinical benefits in patients who have higher CD4+ counts at the time of initiation than those previously recommended for the initiation of ART.

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#### APPENDIX

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