Effect of isoniazid preventive therapy on risk of death in west African, HIV-infected adults with high CD4 cell counts: long-term follow-up of the Temprano ANRS 12136 trial

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Summary

Background Temprano ANRS 12136 was a factorial 2×2 trial that assessed the benefits of early antiretroviral therapy (ART; ie, in patients who had not reached the CD4 cell count threshold used to recommend starting ART, as per the WHO guidelines that were the standard during the study period) and 6-month isoniazid preventive therapy (IPT) in HIV-infected adults in Côte d'Ivoire. Early ART and IPT were shown to independently reduce the risk of severe morbidity at 30 months. Here, we present the efficacy of IPT in reducing mortality from the long-term follow-up of Temprano.

Methods For Temprano, participants were randomly assigned to four groups (deferred ART, deferred ART plus IPT, early ART, or early ART plus IPT). Participants who completed the trial follow-up were invited to participate in a post-trial phase. The primary post-trial phase endpoint was death, as analysed by the intention-to-treat principle. We used Cox proportional models to compare all-cause mortality between the IPT and no IPT strategies from inclusion in Temprano to the end of the follow-up period.

Findings Between March 18, 2008, and Jan 5, 2015, 2056 patients (mean baseline CD4 count 477 cells per µL) were followed up for 9404 patient-years (Temprano 4757; post-trial phase 4647). The median follow-up time was 4·9 years (IQR 3·3–5·8). 86 deaths were recorded (Temprano 47 deaths; post-trial phase 39 deaths), of which 34 were in patients randomly assigned IPT (6-year probability 4·1%, 95% CI 2·9–5·7) and 52 were in those randomly assigned no IPT (6·9%, 5·1–9·2). The hazard ratio of death in patients who had IPT compared with those who did not have IPT was 0·63 (95% CI, 0·41 to 0·97) after adjusting for the ART strategy (early *vs* deferred), and 0·61 (0·39–0·94) after adjustment for the ART strategy, baseline CD4 cell count, and other key characteristics. There was no evidence for statistical interaction between IPT and ART ($p_{interaction}$=0·77) or between IPT and time ($p_{interaction}$=0·94) on mortality.

Interpretation In Côte d'Ivoire, where the incidence of tuberculosis was last reported as 159 per 100 000 people, 6 months of IPT has a durable protective effect in reducing mortality in HIV-infected people, even in people with high CD4 cell counts and who have started ART.

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Introduction

Based on repeated evidence that isoniazid preventive therapy (IPT) decreases the risk of tuberculosis in HIV-infected people, WHO has consistently recommended since 1993 that people living with HIV who are unlikely to have tuberculosis should receive at least 6 months of IPT.[1] However, some countries still have not adopted IPT 23 years later, and in most countries that have, IPT coverage is low.[2,3]

Among the barriers to adopting IPT at country level are the absence of a common vision between HIV and tuberculosis programmes, and the fear that individuals who start IPT with unrecognised active tuberculosis might develop drug resistance.[3–6] Most randomised controlled trials of IPT were done before the antiretroviral therapy (ART) era or in patients with CD4 counts of less than 500 per µL.[7–10] Because ART also decreases the risk of tuberculosis,[11–14] some physicians might prioritise successful ART and ensure immune recovery as early as possible, rather than implement IPT. Furthermore, all but one randomised controlled trials have shown the benefits of IPT in terms of tuberculosis reduction, not of

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See Online for appendix

Research in context

Evidence before this study

We searched PubMed with search terms "tuberculosis" AND "prophylaxis" AND "HIV", on Aug 1, 2016, for trials published in English. There were no date restrictions. Before this study, evidence from randomised trials suggested that 6–12 months of isoniazid preventive therapy (IPT) decreased the risk of tuberculosis in HIV-infected adults who were or were not on antiretroviral therapy (ART), and the risk of mortality in patients who were not on ART. However, no findings from randomised trials exist on the effect of IPT on risk of mortality in HIV-infected adults who had started ART. Furthermore, some trial results called into question the durability of the beneficial effect of IPT.

Added value of this study

Compared with previous trials that assessed the efficacy of IPT versus a placebo or no IPT, the median baseline CD4 count in our study was substantially higher and the follow-up time substantially longer. In our study, IPT led to a 37% reduction in mortality, and the efficacy of IPT in reducing mortality was independent of ART initiation and baseline CD4 cell count. The benefits of a 6-month IPT appeared to be sustained for up to 6 years of follow-up. These findings support the hypothesis that 6 months of IPT and ART could improve each other's efficacy through complementary mechanisms.

Implications of all the available evidence

6 months of IPT has a durable protective effect in reducing all-cause mortality in people with HIV, even in people with high CD4 cell counts and who have started ART. IPT should be proposed to all adults who start ART at any CD4 cell count and have no evidence of active tuberculosis in sub-Saharan Africa.

mortality.[7–9] Some studies have suggested that these benefits might decrease after the treatment is stopped, leading to the consideration of extending treatment in settings with a high prevalence of tuberculosis.[15–18] Finally, IPT efficacy in patients who had never had ART has been shown to be higher in patients with a positive tuberculin skin test (TST), who represent a minority of HIV-infected individuals who had never had ART.[17,19,20]

Between 2008 and 2015, we did a randomised controlled trial to assess the benefits of early ART and 6-month IPT in HIV-infected adults with high CD4 cell counts. The trial endpoint was severe morbidity at 30 months. The final analysis showed that early ART and IPT independently led to lower severe morbidity than did deferred ART and no IPT.[12] After participants reached 30 months of follow-up in the trial, they continued to be followed up in a post-trial phase. Here we present the results of the analysis of the efficacy of IPT in reducing mortality at the end of the post-trial phase.

Methods

Study design and participants

Temprano ANRS 12136 was a 2×2 factorial randomised controlled trial done in Côte d'Ivoire. The trial design and results have been previously reported.[12] Briefly, the inclusion criteria were HIV infection, age 18 years or older, CD4 count 800 cells per µL or lower, and no criteria for starting ART according to the most recent WHO guidelines (including the absence of active tuberculosis, as determined by using a clinical algorithm[1,21]). At the end of the 30-month follow-up period, we asked patients for a new written informed consent for participating in the post-trial phase (figure 1). The Temprano protocol (appendix), which included the post-trial phase, was approved by the Côte d'Ivoire National Ethics Committee for Health Research.

Randomisation and masking

For the Temprano trial, participants were randomly assigned (1:1:1:1) to one of four groups: deferred ART (group 1), in which ART was deferred until WHO criteria for starting ART were met; deferred ART plus IPT (group 2), in which ART was deferred and 6-month IPT was prescribed; early ART (group 3), in which ART was started immediately; and early ART plus IPT (group 4), in which ART was started immediately and 6-month IPT was prescribed. Randomisation was done with a computer-generated, sequentially numbered, block randomisation list (block size 12), and was stratified by study clinic.

Procedures

After randomisation, all participants had a systematic chest radiograph and a series of blood tests including CD4 cell count, plasma HIV-1 RNA, and serum amino-transferase concentration. The first 50% of participants also had a QuantiFERON-TB Gold In-Tube test (QTF-GIT; Qiagen, Hilden, Germany). IPT consisted of 300 mg of isoniazid once per day, started at month 1 and stopped at month 7. Patients randomly assigned IPT, but who had images suggestive of active tuberculosis on their baseline chest radiograph, had elevated aminotransferases (more than 2·5 times the upper limit of normal), or developed signs suggestive of tuberculosis during the first month were not prescribed IPT. All participants were followed up for 30 months in the Temprano trial.

The first Temprano participant completed 30 months of follow-up on Sept 13, 2010. From this date on, all patients who reached their 30-month visit were asked to continue being followed up in a post-trial phase until the last patient completed the trial-specified 30 months of follow-up. The post-trial phase was started while the Temprano trial was still running, and the closing date was the same

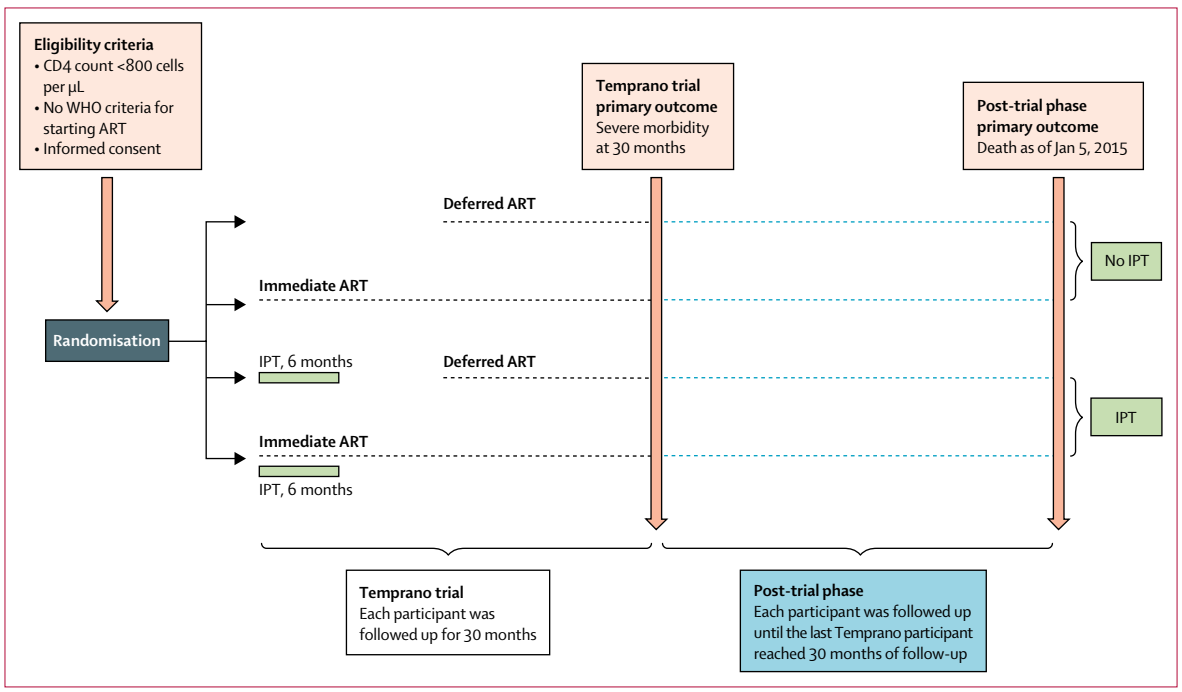

***Figure 1*: Study design of the Temprano trial and post-trial phase**
ART=antiretroviral therapy. IPT=isoniazid preventive therapy.

for both the trial and the post-trial phase. As a consequence, the treatments received during the post-trial phase could not have been influenced by the final results of the trial.

Temprano and the post-trial phase had similar procedures. In the post-trial phase, as in Temprano, patients had quarterly visits to their care centre; CD4 cell count and plasma HIV-1 RNA were measured every 6 months; consultations, CD4 cell count, viral load, and antiretroviral drugs were free of charge; and patients who did not attend a trial visit were traced by experienced social workers. Patients followed up in the post-trial phase had to comply with the same rules regarding ART and IPT prescription as those who were followed up in the trial during the same calendar period. These rules were that patients assigned to the no IPT strategy never received IPT, neither during the trial nor during the post-trial phase; patients assigned to the deferred ART strategy started ART whenever they reached the most recent WHO criteria for starting ART, during the trial if these criteria were met 30 months after enrolment or earlier, or during the post-trial phase if these criteria were met later than 30 months after enrolment. Patients who did not reach these criteria before the closing date did not start ART, during the trial or during the post-trial phase. The most recent WHO criteria for starting ART were WHO 2006 criteria between the beginning of the trial and November, 2009, WHO 2010 criteria between December, 2009, and July, 2013, and WHO 2013 criteria between August, 2013, and the trial and post-trial phase closing date.

In case of a morbidity event in the Temprano trial phase, transportation for unscheduled visits, investigations, hospital admission, and non-antiretroviral drugs were free of charge. However, in the post-trial phase, patients had to pay for treatment, just as any other patient followed up in routine condition in the same care centre.

Regardless of the similarities and differences between the trial and post-trial phases, individuals randomly assigned IPT and those randomly assigned no IPT had exactly the same assessments and clinical management (especially evaluation for active tuberculosis and ascertainment of death) at the time of enrolment, during the trial phase, and during the post-trial phase.

Outcomes

The primary endpoint of the Temprano trial was severe morbidity, defined as a combination of all-cause deaths, AIDS diseases, non-AIDS malignancies, and non-AIDS invasive bacterial diseases, whereas it was all-cause mortality in the post-trial phase.

Statistical analysis

We refer to trial groups each time we show separate data for each of the four groups, and trial strategies whenever we show data combining patients assigned to IPT (groups 2 and 4), no IPT (groups 1 and 3), early ART (groups 3 and 4), and deferred ART (groups 1 and 2).

In each group and strategy, we used the Kaplan-Meier method to estimate the cumulative probability of event occurrence. We estimated death rates by dividing the number of events by the cumulative person-time at risk.

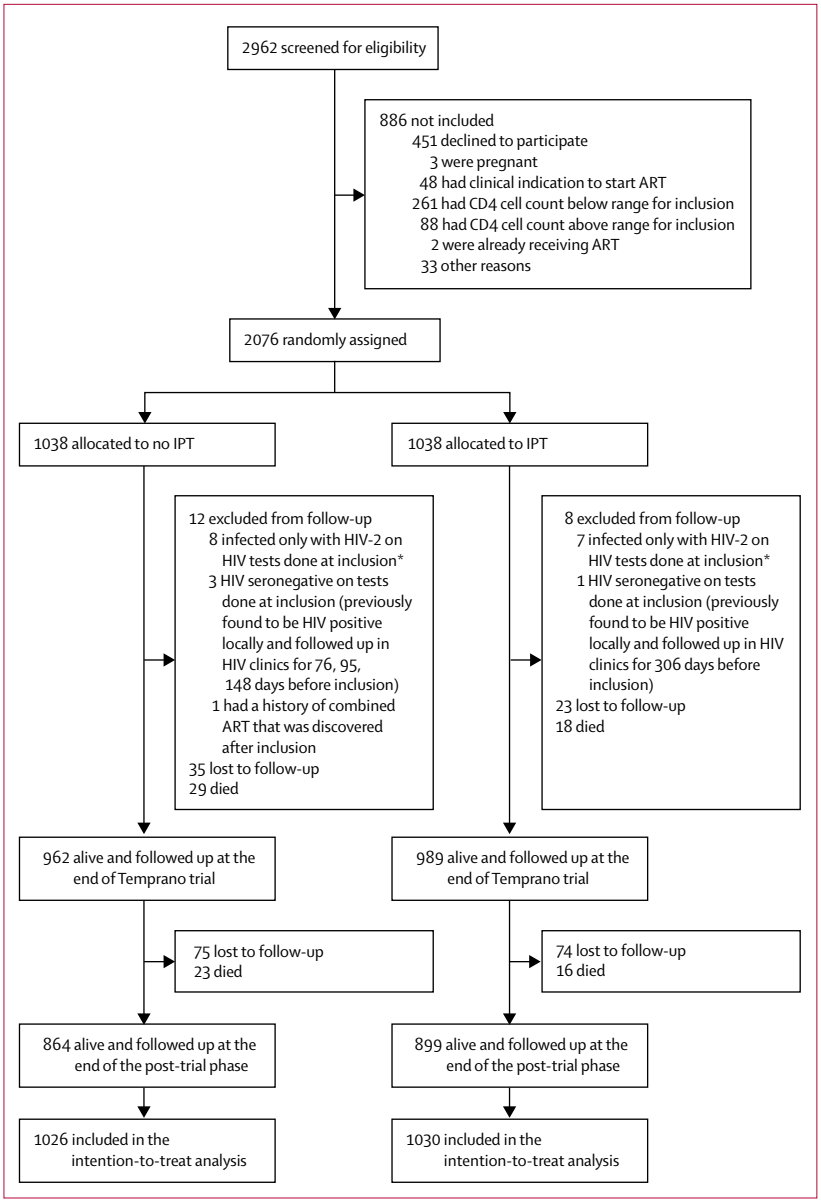

***Figure 2*: Trial profile**
ART=antiretroviral therapy. IPT=isoniazid preventive therapy. *Patients were previously thought to have had dual infection with HIV-1 and HIV-2 on the basis of tests done locally.

The time at risk started at randomisation and ended on Jan 5, 2015. Follow-up data were censored when participants died or were lost to follow-up. Patients were defined as lost to follow-up if they did not attend their last scheduled visit and if no further information on their vital status was available in the 6 months preceding the closing date of the database.

Cox proportional hazards models were used to compare IPT strategies (IPT *vs* no IPT) with respect to mortality using the intention-to-treat approach. In the main analysis, we adjusted the hazard ratio (HR) for the other trial strategy (early ART *vs* deferred ART) and for the trial centre (as a random effect). In a secondary analysis, adjustment was also made for baseline CD4 cell count, to explore the effect of the extent of immunosuppression on the results; and for variables recognised as risk factors for mortality or tuberculosis, to address potential residual confounding effects of these variables. Finally, we compared IPT strategies with respect to loss-to-follow-up, and death or loss to follow up, to examine the extent to which the primary results could be affected by attrition; we restricted the analyses to the sample of patients who had the QuantiFERON-TB Gold In-Tube test done at baseline, and stratified the analysis for the result of the test; and we used the per-protocol approach to compare IPT strategies with respect to mortality. In the per-protocol analysis, we censored the follow-up of patients assigned to IPT: at 1 month for patients who did not start IPT; and on the date when IPT was discontinued for patients who started IPT, but discontinued it prematurely.

The main analysis comparing IPT strategies with respect to mortality was predetermined in the Temprano trial protocol. The secondary and ancillary analyses are post-hoc analyses.

We tested interaction between strategies, and the assumption of the proportional hazards was examined. All reported p values were two-sided and were not adjusted for multiple testing. Statistical analyses were done with SAS software (version 9.3).

The Temprano trial is registered at ClinicalTrials.gov, number NCT00495651.

Role of the funding source

The funder 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 18, 2008, and July 16, 2012, 2076 patients were randomly assigned to treatment groups; 20 (1%) were subsequently excluded and 2056 were included in the analyses (figure 2; appendix). The first 30-month visit was on Sept 13, 2010, and the last 30-month visit on Jan 5, 2015. All participants who were alive and followed up at the end of Temprano consented to participate in the extended follow-up (n=1951).

Baseline and follow-up characteristics of the 2056 participants according to IPT strategies (IPT and no IPT) are shown in table 1. Characteristics according to the four randomisation groups are shown in the appendix. Between March, 2008, and January, 2015, 2056 participants were followed up for 9404 person-years; 4757 person-years during the trial and 4647 person-years during the post-trial phase. The median follow-up time was 4·9 years overall (IQR 3·3–5·8), 4·9 years (3·5–5·8) in the IPT strategy, and 4·8 years (3·3–5·8) in the no IPT strategy. Of 1030 patients assigned to the IPT strategy, 927 (90%)

	No IPT (n=1026)	IPT (n=1030)
Baseline		
Age (years)	35 (30–41)	35 (30–42)
Sex		
Women	807 (79%)	807 (78%)
Men	219 (21%)	223 (22%)
Body-mass index (kg/m²)	22·6 (20·2–25·5)	22·3 (20·2–25·2)
WHO clinical stage		
1 or 2	931 (91%)	927 (90%)
3 or 4	95 (9%)	103 (10%)
CD4 count (cells per µL)	465 (365–575)	464 (378–573)
CD4 count categories (cells per µL)		
≥500	423 (41%)	426 (41%)
<500	603 (59%)	604 (59%)
Plasma HIV-1 RNA (log_{10} copies per mL)	4·7 (4–5·2)	4·7 (4–5·3)
Plasma alanine aminotransferase >2·5 × ULN	4 (<1%)	6 (1%)
Haemoglobin <95 g/L	116 (11%)	122 (12%)
Past history of active tuberculosis	33 (3%)	28 (3%)
Positive IGRA for tuberculosis*	173/485 (36%)	164/482 (34%)
Immunovirological characteristics at 30 months		
CD4 count (cells per µL)	421 (318–579)	435 (346–581)
Plasma HIV-1 RNA (log_{10} copies per mL)	0 (0–3·5)	0 (0–3·5)
Follow-up		
Follow-up time, overall (patient-years)	4636	4768
Temprano trial	2346	2413
Post-trial phase	2290	2355
Lost to follow-up, overall	110 (11%)	97 (9%)
Temprano trial	35 (3%)	23 (2%)
Post-trial phase	75 (7%)	74 (7%)
Deaths, overall	52 (5%)	34 (3%)
Temprano trial	29 (3%)	18 (2%)
Post-trial phase	23 (2%)	16 (2%)
(Table 1 continues in next column)		
(Continued from previous column)		
Ever started co-trimoxazole	988 (96%)	1002 (97%)
Ever started ART	901 (88%)	930 (90%)
First-line ART regimen		
Tenofovir–emtricitabine plus efaviren	632 (70%)	652 (70%)
Tenofovir–emtricitabine plus LPV/r	200 (22%)	207 (22%)
Other†	69 (8%)	71 (8%)
Time spent on ART (years)		
Temprano trial	1·8 (0·2–2·5)	1·9 (0·4–2·5)
Post-trial phase	2·0 (0·5–3·3)	2·2 (0·5–3·3)
Ever started IPT‡	0 (0)	927 (90%)
Completed 6-month course§	0 (0)	869 (94%)

Data are n (%), n/N (%) or median (IQR). IPT=isoniazid preventive therapy. ULN=upper limit of normal. IGRA=interferon gamma release assay. ART=antiretroviral therapy. LPV/r=lopinavir/ritonavir. *Only the first 967 patients enrolled in Temprano (IPT: n=482; no IPT: n=485) were tested for tuberculosis with an IGRA (QuantiFERON-TB Gold In-Tube); indeterminate results were considered negative. †Other regimens were tenofovir–emtricitabine–zidovudine (n=81), zidovudine–lamivudine–LPV/r (n=25), zidovudine–lamivudine–efavirenz (n=3), zidovudine–lamivudine–nevirapine (n=3), didanosine–lamivudine–efavirenz (n=1), stavudine–lamivudine–efavirenz (n=1), stavudine–lamivudine–LPV/r (n=1), and lamivudine–abacavir–LPV/r (n=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 (n=16), the presence of clinical signs suggestive of tuberculosis at the 1-month visit (n=47), non-attendance at the 1-month visit (n=24), elevated aminotransferase concentrations at baseline (n=6), pregnancy (n=4), death before 1 month (n=1), and other reasons (n=5). §The reasons for stopping IPT prematurely were death from an unknown cause (n=1); discontinuation by patients for personal, non-medical reasons (n=22); discontinuation by physicians because of the presence in the patient of signs or symptoms suggestive of tuberculosis (n=10, of whom 3 were confirmed to have tuberculosis); pregnancy (n=13); and the following 12 adverse events: elevated aminotransferase concentration (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 concentration led to death.

***Table 1*: Baseline and follow-up characteristics**

started isoniazid, of whom 869 (94%) completed the 6-month treatment (table 1). No patient assigned to the non-IPT strategy received IPT.

During follow-up, 86 deaths were recorded. The incidence of death was 0·7 per 100 person-years (95% CI 0·5–0·9) in the IPT group and 1·1 per 100 person-years (0·9–1·4) in the no IPT strategy, which ranged from 0·6 per 100 person-years (0·3–1·0) in group 4 (early ART plus IPT) to 1·3 per 100 person-years (0·8–1·8) in group 1 (deferred ART, no IPT). The 6-year probability of death was 4·1% (95% CI 2·9–5·7) in the IPT strategy group and 6·9% (5·1–9·2) in the no IPT strategy group (figure 3A), which ranged from 3·2% (1·9–5·5) in group 4 (early ART plus IPT) to 7·0% (4·7–10·4) in group 1 (deferred ART, no IPT; figure 3B).

There was no statistical interaction with regard to mortality between the IPT and ART strategy ($p_{interaction}$=0·77), between IPT and time ($p_{interaction}$=0·94), or between ART and time ($p_{interaction}$=0·66; appendix). In the intention-to-treat analysis, the HR of death for IPT compared with no IPT was 0·63 (95% CI 0·41–0·97) after adjusting for the ART strategy (early *vs* deferred) and the trial centre (table 2; main analysis); and 0·61 (0·39–0·94) after adjusting for the ART strategy, trial centre, baseline CD4 cell count, sex, age, plasma HIV-1 RNA, haemoglobin, body-mass index, and past history of tuberculosis (secondary analysis addressing potential residual confounding effects). Other factors significantly associated with death were baseline CD4 count (<500 cells per µL *vs* ≥500 cells per µL; HR 1·65 [95% CI 1·00–2·72], p=0·05), haemoglobin (<90 g/L *vs* ≥90 g/L; 2·65 [1·61–4·35], p=0·0001), and plasma HIV-1 RNA (<5 log_{10} copies per mL *vs* ≥5 log_{10} copies per mL; 0·59 [0·38–0·92], p=0·02). In the per-protocol analysis, the HR of death for IPT compared with no IPT was 0·54 (95% CI 0·33–0·87) after

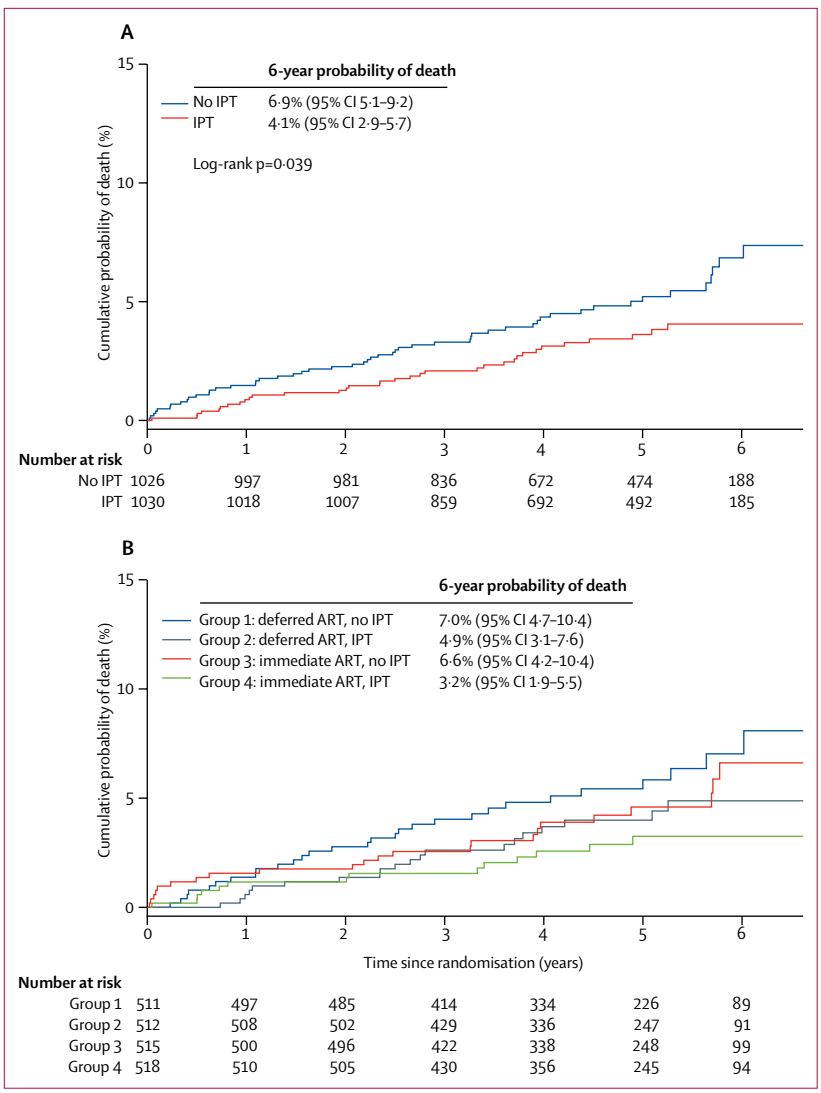

***Figure 3*: Kaplan-Meier curves of probability of death in all patients**
(A) By IPT strategy (n=2056). (B) By randomisation group (n=2056). IPT=isoniazid preventive therapy. ART=antiretroviral therapy.

adjusting for the ART strategy (early *vs* deferred) and the trial centre (main analysis); and 0·53 (0·32–0·86, p=0·01) after adjusting for the ART strategy, trial centre, baseline CD4 cell count, sex, age, plasma HIV-1 RNA, haemoglobin, body-mass index, and past history of tuberculosis (secondary analysis addressing potential residual confounding effects). Cause of death or probable cause of death was recorded in 25 deaths (13 in the IPT strategy group, 12 in the no IPT strategy group; appendix).

During follow-up, 207 patients were lost to follow-up (97 in the IPT strategy group, 110 in the no IPT strategy group), accounting for an overall rate of 2·2 per 100 person-years (95% CI 1·9–2·5). The rate of loss to follow-up was 1·2 per 100 person-years during the trial phase (95% CI 0·9–1·5), and 3·2 per 100 person-years during the post-trial phase (2·7–3·7). The rate of loss to follow-up was 2·0 per 100 person-years in the IPT strategy group (1·6–2·4) versus 2·4 per 100 person-years in the no IPT strategy group (1·9–2·8). The 6-year probability of loss to follow-up was 14·7% (95% CI 12·8–16·9) overall, 13·9 % (11·4–17·0) in the IPT strategy group, and 15·5% (12·8–18·7) in the no IPT strategy group. The 6-year probability of death or loss to follow-up was 17·4% (95% CI 14·7–20·6) in the IPT strategy group and 21·3% (95% CI 18·3–24·7) in the no IPT strategy group (appendix).

There was no statistical interaction between IPT and ART with regard to mortality or loss to follow-up ($p_{interaction}$=0·50). The HR of death or loss to follow-up for IPT compared with no IPT was 0·78 (95% CI 0·62–0·98) after adjusting for the ART strategy (early *vs* deferred) and the trial centre (table 2), and 0·77 (0·61–0·97) after adjusting for the ART strategy, trial centre, baseline CD4 cell count, sex, age, plasma HIV-1 RNA, haemoglobin, body-mass index, and past history of tuberculosis.

Of the 967 patients who had a QTF-GIT test at baseline (482 in the IPT strategy group, 485 in the no IPT strategy group), the test was positive in 337 patients (IPT 164, no IPT 173), negative in 597 (IPT 306, no IPT 291), and indeterminate in 33 (IPT 12, no IPT 21). In patients with baseline CD4 counts of less than 500 cells per µL, 269 (35%) patients had positive tests, 480 (62%) had negative tests, and 27 (3%) had indeterminate tests versus 68 (36%) who had positive tests, 117 (61%) who had negative tests, and six (3%) who had indeterminate tests, in patients with baseline CD4 counts of 500 cells per µL or higher (p=0·95). In patients aged 50 years or older, 30 (35%) patients had positive tests, 50 (58%) had negative tests, and six (7%) had indeterminate tests versus 307 (35%) who had positive tests, 547 (62%) who had negative tests, and 27 (3%) who had indeterminate tests in those younger than 50 years (p=0·16).

The 6-year probability of death was 3·1% (95% CI 1·3–7·3) in the IPT strategy group and 5·2% (2·6–10·4) in the no IPT strategy group in patients with positive baseline QTF-GIT test (figure 4A); and 5·2% (3·2–8·3) in the IPT strategy and 8·5% (5·7–12·4) in the no IPT strategy group in those with negative QTF-GIT test (figure 4B).

There was no statistical interaction between the result of the QTF-GIT test at baseline and the IPT strategy with regard to mortality ($p_{interaction}$=0·96). When stratifying the analysis by baseline QTF-GIT test results, the adjusted HR of death for IPT compared with no IPT was 0·61 (95% CI 0·20–1·86) in patients with positive QTF-GIT and 0·63 (0·33–1·18) in those with negative or indeterminate QTF-GIT.

Discussion

Our findings from the long-term follow-up of the Temprano trial showed that IPT led to a 37% reduction in mortality, which accounted for an absolute reduction of –2·79% in the probability of death 6 years after randomisation. To our knowledge, this is the first evidence

	N	Death				Death or loss to follow-up			
		n	Rate (per 100 person-years)	aHR (95% CI)	p value	n	Rate (per 100 person-years)	aHR (95% CI)	p value
IPT strategy									
No IPT	1026	52	1·12	..	..	162	3·49	..	..
IPT	1030	34	0·71	0·63 (0·41–0·97)	0·04	131	2·75	0·78 (0·62–0·98)	0·03
ART strategy									
Deferred ART	1023	49	1·05	..	..	165	3·54	..	..
Immediate ART	1033	37	0·78	0·74 (0·48–1·13)	0·17	128	2·70	0·76 (0·60–0·95)	0·02

Hazard ratios were adjusted for study centre and for the other strategy. aHR=adjusted hazard ratio. IPT=isoniazid preventive therapy. ART=antiretroviral therapy.

***Table 2*: Rates and hazard ratios of death and death or loss to follow-up**

from a randomised trial showing that IPT decreases mortality in HIV-infected adults with high CD4 cell counts and in the ART era. The only previous randomised trial[9] that showed a mortality reduction with IPT was done in Haiti in the late 1980s, which was in the pre-ART era and done in patients whose CD4 cell counts were unknown.

We also found no statistical evidence for an interaction between IPT and ART with regard to mortality. IPT and ART had an additive effect, with the maximal benefit in patients who had both therapies, which suggests that receiving both treatments was a better option than receiving either therapy alone. In a placebo-controlled trial[10] done in South Africa in HIV-infected adults receiving ART, who had a median of 216 CD4 cells per µL at baseline, and were followed up for a mean of 2·5 years, IPT decreased the risk of active tuberculosis by 37%. Our finding that IPT decreases mortality independently of CD4 cell count in HIV-infected adults who had a median baseline CD4 count of 465 cells per µL and followed up for a mean of 4·6 years adds to evidence that IPT should be given in patients on ART who have any CD4 cell count.

Apart from these primary conclusions, our data also shed light on two important issues: the durability of IPT's beneficial effect and the effect of IPT in patients with documented latent tuberculosis infection compared with other patients.

In the 1990s, randomised controlled trials of IPT in patients who had never had ART reached contrasting conclusions on the sustainability of the effect of IPT. These findings led to the question of whether continuous IPT was needed to ensure long-term protection in settings with a high incidence of tuberculosis.[7–9,15,16] One randomised controlled trial[17] in Botswana concluded that 36 months of IPT was more effective than 6 months, whereas the other trial[22] in South Africa concluded that continuous IPT taken for a mean duration of 3·9 years was not superior to 6 months of treatment. However, the findings from the trial in South Africa did show benefit of continuous IPT in the per-protocol analysis. Both of these trials therefore support continued protection while patients are on IPT.

In our study, the follow-up time was substantially longer than that in the previous placebo controlled trials of IPT,[7–10,15,16] and the benefits of 6 months of IPT appeared to be sustainable up to 6 years after the intervention, as shown by the Kaplan-Meier probabilities at 6 years and the absence of interaction between IPT and time with regard to mortality. These findings are consistent with those of a study[23] in Brazil, which showed long-term durability of IPT in a setting where ART is widely available. These study findings support the hypothesis that 6 months of IPT and ART could improve each other's efficacy through complementary mechanisms; while the IPT can cure latent *Mycobacterium tuberculosis* infection and prevent new infections during the course of the treatment, ART leads to immune recovery that decreases the risk of both new tuberculosis infection and tuberculosis reactivation in the longer term.[24] That said, when interpreting the efficacy over time of a 6-month course of IPT versus IPT of longer duration, it is important to note the background risk of infection in the area. The incidence of tuberculosis in South Africa, Botswana, and Côte d'Ivoire was last reported in 2014 as 834 per 100 000 people, 356 per 100 000 people, and 159 per 100 000 people, respectively.[25]

Previous randomised controlled trials[7–9,15,16,20] of IPT in patients who were not on ART suggested that the efficacy of IPT was higher in patients with a positive TST. A 2010 meta-analysis[20] suggested that IPT significantly decreases the risk of active tuberculosis and the risk of death in TST-positive, but not TST-negative, HIV-infected people. In the trial[10] of IPT on ART in South Africa, however, subgroup analysis stratified by TST or interferon gamma release assay (IGRA) results showed that the protective effect of IPT against tuberculosis was statistically significant in patients with a negative TST or a negative IGRA and not significant in those with a positive TST or a positive IGRA. Importantly, the HRs of tuberculosis in patients receiving IPT versus those receiving placebo were similar in subgroups of patients with positive or negative IGRA results. The fact that one was significant and the other not was probably because the study was not powered for this ancillary analysis. Our own findings were consistent with this; we also found similar HRs of death in the IPT versus no IPT strategies in subgroup analyses of patients with positive or negative QTF-GIT results. The shape of the mortality curves in

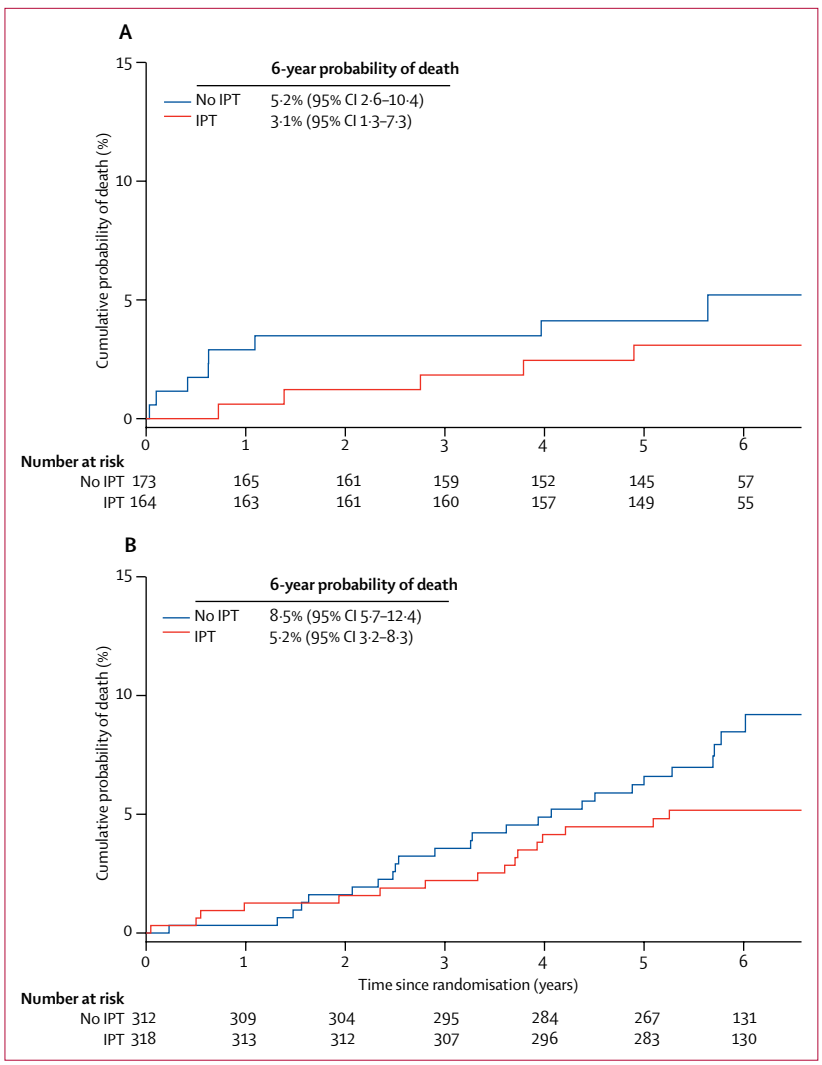

***Figure 4*: Kaplan-Meier curves of probability of death in patients with a QuantiFERON-TB Gold In-Tube test result**
(A) Positive test (n=337). (B) Negative test (n=630). IPT=isoniazid preventive therapy.

both subgroups in our study suggests that the efficacy of IPT was maximal during the early follow-up in patients with positive QTF-GIT test, and during the late follow-up in those with negative QTF-GIT test. Finally, in our study, overall mortality rates appeared to be lower in patients who had a positive QTF-GIT test than in those with a negative test, despite similar distributions of CD4 cell count categories at baseline. This finding suggests that the test might be a measure of immune competence with possible prognostic value, a hypothesis that should be explored further.

Our study has several limitations. First, although we reported severe morbidity events at 30 months in the Temprano study,[12] we did not report long-term morbidity data in this report of the long-term follow-up. During the Temprano trial phase, the event documentation committee used standardised criteria to validate and classify all severe morbidity events. These criteria were a combination of clinical definitions and laboratory and radiological test results. Some clinical definitions included evolution under standardised care and treatment.[12] During the post-trial phase, participants had to pay for tests other than routine ART monitoring tests, and for care and treatment other than ART. Therefore, we did not document morbidity events during the post-trial phase, and focused efforts on recording mortality. 18 papers previously reported the results of primary IPT trials.[7–10,12,15–18,22,26–33] All studies had all-cause mortality as a primary or secondary outcome, and none chose tuberculosis mortality. Causes of death were reported in only four papers. In these four papers, death of unknown cause was frequent.[10,17,30,31] All-cause mortality is a better primary outcome than tuberculosis mortality for an IPT trial. Even if it were feasible to document all causes of death, an intervention that would decrease disease-specific mortality, but that did not decrease all-cause mortality, would not have the same public health impact as one that decreases all-cause mortality. Furthermore, all-cause mortality is much less subject to misclassification bias than disease-specific mortality. Finally, causes of mortality are very difficult to document in HIV trials done in low-resource settings because many patients die at home. Even for individuals who die in hospital settings, fewer facilities are available to document morbidity compared with hospital settings in high-resource countries. Therefore, the causes of death that we report must be considered with caution.

Second, open-label trials are more susceptible to bias than blinded trials because knowledge of treatment allocation can affect post-randomised treatment decisions and reporting of outcomes. In our study, patients in the two strategy groups had similar rates of loss to follow-up, similar percentages of patients on ART over time, similar time spent on ART, and similar percentages of patients on co-trimoxazole over time. These patients also had similar CD4 cell counts and viral load distributions at the end of the Temprano trial phase, when they entered the post-trial phase. These findings suggest that there was no differential care management, although they do not prove it. Additionally, 10% of patients were lost to follow-up in both groups. Among these patients lost to follow-up, undocumented deaths could have been more frequent in patients randomly assigned IPT compared with those randomly assigned no IPT. Because undocumented death could only occur in patients lost to follow-up, and because the rates of loss to follow-up were similar between strategies and even slightly higher in the no IPT group, we do not believe that the risk of under-reported death rates in IPT compared with the no IPT group was high, but we cannot completely rule out this risk. In all cases, the evidence would have been stronger if we had used a placebo.

Third, tests for interaction reject the hypothesis of no interaction if there is strong evidence of an interaction.

Failure to reject does not prove that the effect of ART and IPT are independent. This fact is important in the interpretation of our results, and the reason for which it is more accurate to say that there was no evidence for an interaction between ART and IPT rather than that there was evidence for the effect of both interventions being completely independent.

In conclusion, in these African HIV-infected adults with high CD4 cell counts, 6 months of IPT led to a 37% decrease in mortality, independently of baseline CD4 cell count and with no significant evidence for an interaction between IPT and ART. 6 months of IPT should be proposed to all adults who start ART at any CD4 cell count and have no evidence of active tuberculosis in sub-Saharan Africa, regardless of IGRA or TST status.[34,35]

Contributors

SPE and XA were co-chairs of the Temprano trial. ABad, RM, DG, TN'D-Y, RS, CD, SPE, and XA formulated the hypotheses and research questions. ABad, RM, CG, J-BN, JLC, GMK, EO, EM, AAnz, AM, JG, PG, CRa, BS, GN, LD, AY, SKam, SAm, A-BK, AKoua, EK, MD, DH, SAc, SKo, JS, AAni, FD, FK, MO, NM, OM, CB, NB, GB, MT, A-CK, GS, S-YY, SKar, AKouam, RA, ABak, SKD, KA, CD, SPE, and XA recruited and followed up patients and collected clinical data. MK, AE, T-d'AT, CRo, HA, TO, HM, and AI did biological tests and collected biological data. DG wrote the analysis plan and did the statistical analysis under the supervision of VJ, ABad, CD, SPE, and XA. ABad, ND, CD, SPE, and XA drafted the manuscript. All authors provided critical input into the draft manuscript.

Declaration of interests

XA reports grants from the French National Agency for AIDS and Viral Hepatitis Research (ANRS) during the conduct of the study. All other authors declare no competing interests.

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