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


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; post-trial phase 39), 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, baseline CD4 cell count, and other key characteristics. There was no evidence for statistical interaction between IPT and ART (pinteraction=0·77) or between IPT and time (pinteraction=0·94) on mortality.

Interpretation In Côte d’Ivoire, where the incidence of tuberculosis was last reported as 159 per 100000 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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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.10–12 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.13,14,20

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.20 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.19 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).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 (QTT-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-specific 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
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