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MAJOR ARTICLE

Isoniazid Adherence Reduces Mortality and Incident Tuberculosis at 96 Weeks Among Adults Initiating Antiretroviral Therapy With Advanced Human Immunodeficiency Virus in Multiple High-Burden Settings

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Background. People with human immunodeficiency virus (HIV) and advanced immunosuppression initiating antiretroviral therapy (ART) remain vulnerable to tuberculosis (TB) and early mortality. To improve early survival, isoniazid preventive therapy (IPT) or empiric TB treatment have been evaluated; however, their benefit on longer-term outcomes warrants investigation.

Methods. We present a 96-week preplanned secondary analysis among 850 ART-naive outpatients (≥13 years) enrolled in a multicountry, randomized trial of efavirenz-containing ART plus either 6-month IPT ($n = 426$) or empiric 4-drug TB treatment ($n = 424$). Inclusion criteria were CD4 count <50 cells/mm^3 and no confirmed or probable TB. Death and incident TB were compared by strategy arm using the Kaplan-Meier method. The impact of self-reported adherence (calculated as the proportion of 100% adherence) was assessed using Cox-proportional hazards models.

Results. By 96 weeks, 85 deaths and 63 TB events occurred. Kaplan-Meier estimated mortality (10.1% vs 10.5%; $P = .86$) and time-to-death ($P = .77$) did not differ by arm. Empiric had higher TB risk (6.1% vs 2.7%; risk difference, −3.4% [95% confidence interval, −6.2% to −0.6%]; $P = .02$) and shorter time to TB ($P = .02$) than IPT. Tuberculosis medication adherence lowered the hazards of death by ≥23% ($P < .0001$) in empiric and ≥20% ($P < .035$) in IPT and incident TB by ≥17% ($P \leq .0324$) only in IPT.

Conclusions. Empiric TB treatment offered no longer-term advantage over IPT in our population with advanced immunosuppression initiating ART. High IPT adherence significantly lowered death and TB incidence through 96 weeks, emphasizing the benefit of ART plus IPT initiation and completion, in persons with advanced HIV living in high TB-burden, resource-limited settings.

Keywords. isoniazid adherence; isoniazid preventive therapy; strategy trial; tuberculosis and HIV; tuberculosis prophylaxis.

Despite the scale-up of antiretroviral therapy (ART), tuberculosis (TB) remains the leading cause of death among people with human immunodeficiency virus (PWH) worldwide, accounting for 208 000 deaths in 2019 [1]. The risk of early mortality after initiating ART is particularly high in resource-limited settings and remains largely TB-related, with approximately 10% mortality during the first 3 months [2–6]. Reconstitution of the immune system with ART alone lowers the risk of TB infection by up to 65%, yet PWH remain especially vulnerable to TB in high-burden settings [7–9]. A CD4 count below 50 cells/mm^3 confers the highest risk for early mortality [3, 5]. People with HIV with advanced immunosuppression continue to seek HIV care in various settings [10, 11], underscoring the critical need for TB control strategies beyond ART to improve survival in this highly vulnerable population and to achieve 2030 global

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TB targets, namely, an 80% decrease in TB incidence and a 90% decrease in TB deaths compared with 2015 levels [1].

Isoniazid preventative therapy (IPT) in PWH is one such TB control strategy, with mounting evidence describing the independent and synergistic impact of IPT and ART to reduce the risk of TB and death [12–15]. World Health Organization guidelines now recommend ART initiation and at least 6 months of isoniazid prevention therapy (IPT) for all persons presenting for HIV care after excluding active TB, regardless of CD4 count or tuberculin skin test [16]. Overall, the population receiving TB prevention has expanded since 2015, growing from 1 million to 4.1 million in 2019, and PWH comprise the majority (3.5 million in 2019) [1]. However, coverage of PWH initiating ART with IPT varies from <1% to 89% in high TB- or HIV/TB-burden countries, with scale up predominantly localized to India (25%), United Republic of Tanzania (19%), South Africa (15%), Malawi (5%), and Zambia (5%) [1]. Despite the expanding body of evidence supporting IPT, concerns about unreliable TB diagnostics, poor adherence, and the potential for isoniazid resistance using a 1-drug regimen have contributed to persistently suboptimal global implementation and uptake [17–20].

Given the aforementioned concerns, providing preemptive 4-drug TB treatment at ART initiation has been investigated as an alternative strategy. Our group previously reported no early survival advantage of empiric 4-drug TB treatment over 6-month IPT in the 24-week analysis of the AIDS Clinical Trials Group (ACTG) A5274 REMEMBER (Reducing Early Mortality and Early Morbidity by Empirical Tuberculosis Regimens) trial (ClinicalTrials.gov Identifier NCT01380080) [21]. This randomized, open-label, phase IV strategy trial enrolled outpatients initiating ART with CD4 counts below 50 cells/mm^3 in 10 resource-limited, high TB-burden countries spanning sub-Saharan Africa, the Americas, and Asia. We now present the 96-week analysis of death and incident TB and include the important effect of adherence to TB medications through 24 weeks from this trial.

METHODS

The A5274 trial methods have been previously described in detail (Supplemental Methods) [21]. In brief, between 2011 and 2015, participants were recruited at 18 outpatient study sites in 10 resource-limited countries (Kenya, Malawi, South Africa, Uganda, Zambia, Zimbabwe, India, Brazil, Haiti, and Peru) characterized by both high TB incidence (>100 per 100 000 person-years) and early mortality after ART initiation (6-month mortality ≥5%). We enrolled ART-naive PWH aged ≥13 years who presented for ART initiation with CD4 counts <50 cells/mm^3 without confirmed or probable TB [21]. Tuberculosis screening was conducted for active TB using signs and symptoms (presence of cough lasting ≥2 weeks, any current fever >38°C, hemoptysis, night sweats within the past 2 weeks, unintentional weight loss >10% in past 30 days, or enlarged axillary or cervical lymph nodes) and locally available diagnostics, such as acid-fast bacilli smear, chest radiography, GeneXpert MTB/RIF assay (only available at 5 sites, $n = 444$), ultrasound, and mycobacterial culture. After June 2013, GeneXpert was required for initial TB screening and was conducted on stored baseline samples collected before this date ($n = 398$). Retrospectively, urine LAM testing was also performed on a subset of stored baseline samples ($n = 566$, $n = 283$ per arm) [22]. Exclusion criteria included exposure to single-dose nevirapine (past 2 years), TB treatment (past 96 weeks), IPT (past 48 weeks), or any household contact of multidrug-resistant TB. Inclusion criteria included liver function tests ≤2.5 times the upper limit of normal, creatinine clearance ≥30 mL/min, and Karnofsky score ≥30 at the time of study entry.

At entry, participants were randomized 1:1 to initiate ART plus either empiric 4-drug TB treatment or IPT; randomization was balanced by study site and stratified according to CD4 count (<25 vs ≥25 cells/mm^3) and the presence of poor prognostic factors (none vs ≥1), namely, reportable hospitalization in past 30 days, body mass index <18.5 kg/m^2, or hemoglobin <8 g/dL. Follow-up visits were scheduled through 96 weeks after randomization (weeks 1, 2, 4, 8, 12, 16, 20, 24, 48, 60, 72, 84, and 96). The primary outcome was survival status at week 24, and a priori secondary analysis outcomes were survival status and incident TB at week 96.

Procedures

All participants received efavirenz-based ART (efavirenz/tenofovir/emtricitabine or efavirenz + locally available nucleoside reverse-transcriptase inhibitors). Empiric TB treatment consisted of weight-based, fixed-dose combination isoniazid/rifampin/ethambutol/pyrazinamide daily for 8 weeks followed by fixed-dose combination rifampin/isoniazid daily for 16 weeks. Isoniazid prevention therapy consisted of 300 mg isoniazid daily for 24 weeks. All participants received medications for self-administration, initiated treatment within 7 days of randomization, received pyridoxine while on isoniazid, and received local standard of care.

A sputum sample from each participant was stored at entry. At all visits, data were collected on signs and symptoms, ART modifications, concomitant medications, and clinical events, as defined by a standardized tool (ACTG Appendix 60) [21]. After enrollment in the study, participants in both groups who developed signs and symptoms were tested for TB using locally available diagnostics and treated accordingly. Self-reported adherence to TB medications and ART was recorded using the ACTG 4-day recall adherence questionnaire administered at week 1, 2, 4, 8, 12, 16, 20, and 24 [23]. Participants were transferred to locally provided care at week

48; data collection continued via telephone and/or chart review at weeks 60, 72, 84, and 96.

Patient Consent Statement

All participants provided written informed consent. The ethics committees and institutional review boards approved the trial methods and procedures at each participating site [21].

Outcomes

Primary outcomes were death and confirmed or probable TB by week 96. Tuberculosis events were classified as confirmed (microbiologically confirmed), probable (compatible clinical and/or radiological presentation [≥1 of the following: radiology consistent with TB; temperature >38°C; weight loss ≥10% of body weight; night sweats; known TB exposure; or absence of another diagnosis] and TB treatment initiated), or clinical (TB treatment initiated). All death and TB events were reviewed and adjudicated by an independent committee. Adherence to TB and ART medications was assessed at each visit and calculated as the proportion of 100% adherence (number of visits with 100% adherence divided by the number of visits with an adherence questionnaire available).

Statistical Analysis

Primary outcomes were evaluated using the Kaplan-Meier (KM) method with an intention-to-treat (ITT) approach, analyzing all those who were randomized. Participants who discontinued the study or had unknown survival status before week 48 were censored at the last visit. The Cochran-Mantel-Haenszel test was used to compare each endpoint probabilities between the treatment strategies after stratification by CD4 count (<25 vs ≥25 cells/mm^3) and the prognostic factors (presence of at least 1 prognostic factor vs absence of all prognostic factors). The estimated probability of each endpoint and time to event were compared by TB strategy using the z-test and log-rank test, respectively. The following modified ITT analyses were also conducted: (1) excluding participants retrospectively identified as *Mycobacterium tuberculosis* (MTB) positive at entry using stored baseline samples tested via GeneXpert, urine lipoarabinomannan (LAM) assay, or both assays; and (2) excluding participants who developed confirmed or probable TB (time-to-death analysis only). Competing risk analysis of time to confirmed or probable TB was also performed using the Cox regression method with deaths considered a competing risk. The associations between adherence to TB and ART medications and primary endpoints at 24, 48, and 96 weeks were evaluated using separate Cox proportional hazards models for each TB strategy. Hazards ratios were calculated per 10% increase in the proportion of 100% adherence to TB and ART medications through week 24. Fisher's exact test was used to compare the outcomes of death and incidence TB by cumulative adherence (100% vs <100%). Fisher's exact test was also used to compare the diagnosis of incident TB by 96 weeks among those who were retrospectively identified as having TB at baseline by GeneXpert or urine LAM. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Of 1368 patients screened, 850 eligible participants were randomized to empiric treatment ($n = 424$) or IPT ($n = 426$) and were included in this analysis (Figure 1). The study population was 53% male, 90% were Black African or Black of African origin, the median age was 36 years (interquartile range [IQR], 30–42), and the median CD4 count was 18 cells/mm^3 (IQR, 9–32) (Table 1). No individuals <18 years old were enrolled, and the participant's gender identity information was not collected in this study.

Primary Endpoints

At week 96, 85 deaths, including 2 deaths occurring off study, were recorded (empiric $n = 41$; IPT $n = 44$), including 18 deaths after week 48 (empiric $n = 11$; IPT $n = 7$). Although mortality was higher in those with a CD4 cell count of less than 25 cells/mm^3 and those with poor prognostic factors, the event rates were similar across groups for the stratification factors (Supplementary Table 1). Study groups did not differ by KM-estimated mortality (empiric 10.1% [95% CI, 7.5%–13.6%] vs IPT 10.5% [95% CI, 7.9%–13.9%]), yielding a risk difference of 0.4% (95% CI, −3.8% to 4.6%; $P = .86$) (Table 2), or time to death (log rank $P = .77$) (Figure 2*A*). These conclusions remained unchanged in the modified ITT analyses excluding participants who developed confirmed or probable TB ($n = 36$) or those who were retrospectively identified as MTB positive at entry via GeneXpert MTB/RIF and/or urine LAM assays (GeneXpert $n = 6$; urine LAM $n = 28$; total positive individuals $n = 33$) (Table 2). Five participants (3 in empiric and 2 in IPT) were retrospectively identified as MTB positive and died by week 96.

Overall, 58 participants were diagnosed with 63 TB events (confirmed, probable or clinical) by week 96 (Table 1). Of these, 51 (88%) participants developed TB by week 24; only 2 participants developed TB after week 48 (1 in each arm) (Figure 3*A* and *B*). By week 96, 36 participants developed confirmed or probable TB in empiric and 22 in IPT. There was no difference in the rate of incident TB across groups for the stratification factors (Supplementary Table 1). Among the participants who were retrospectively identified as MTB positive at baseline, there was no significant difference in the diagnosis of incident TB between the 2 arms by 96 weeks (Supplementary Table 2). Compared with IPT, empiric treatment had a higher probability of incident TB (6.1% [95% CI, 4.2%–8.9%] vs 2.7% [95% CI, 1.5%–4.9%]), with a risk difference of −3.4% (95% CI, −6.2% to −0.6%; $P = .02$) (Table 2), and a shorter time to TB diagnosis

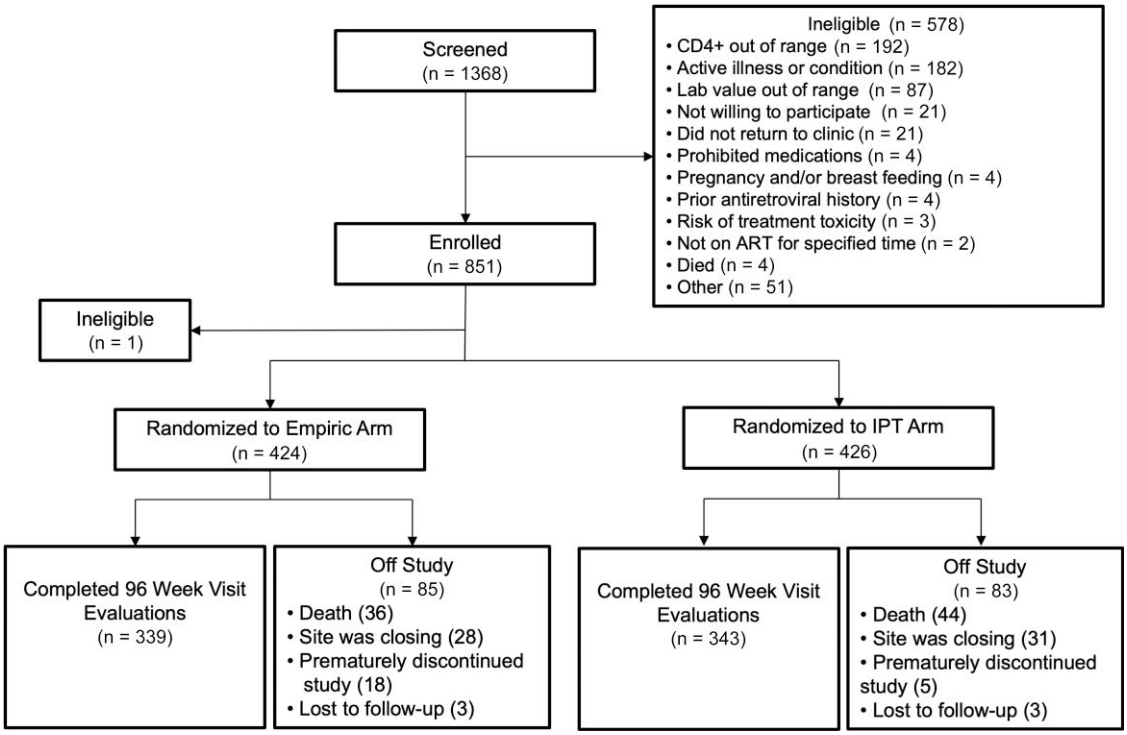

Figure 1. CONSORT study flow diagram. ART, antiretroviral therapy; IPT, isoniazid preventive therapy; Lab, laboratory.

Table 1. Baseline Characteristics and Primary 96-Week Outcomes by TB Strategy[a]

Characteristic/Outcome	Overall ($n=850$)	Empiric TB Treatment ($n=424$)	Isoniazid Preventive Therapy ($n=426$)
Baseline characteristic			
Median age, year (IQR)	36 (30–42)	36 (30–42)	35 (30–42)
Male sex	450 (53)	224 (53)	226 (53)
Race			
Black	768 (90)	380 (90)	388 (91)
Indian	30 (4)	17 (4)	13 (3)
Other	52 (6)	27 (6)	25 (6)
Median CD4 count, cells/mm^3 (IQR)	18 (9–32)	18 (9–11)	19 (9–33)
Median HIV-1 RNA, $\log_{10}$ copies/mL (IQR)	5.3 (4.9–5.7)	5.4 (4.9–5.7)	5.3 (4.9–5.7)
Outcome at week 96			
Death or unknown status	85 (10.0)	41 (9.7)	44 (10.3)
Confirmed or probable TB	36 (4.2)	25 (5.9)	11 (2.6)
Any TB[b]	58 (6.8)	36 (8.5)	22 (5.2)
Total TB events, n	63	39	24
Confirmed pulmonary	20	14	6
Confirmed extrapulmonary	3	1	2
Probable pulmonary	8	5	3
Probable extrapulmonary	6	6	0
Clinical pulmonary	4	1	3
Clinical extrapulmonary	22	12	10

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; RNA, ribonucleic acid; TB, tuberculosis.

[a]Data presented as *n* (%) or median (IQR) unless otherwise indicated.

[b]Any confirmed, probable, or clinical tuberculosis event as per AIDS Clinical Trials Group Appendix 60, including pulmonary and extrapulmonary (more than 1 event possible per participant). Confirmed TB is defined as microbiologically confirmed TB. Probable TB was defined as compatible clinical and/or radiological presentation (≥1 of the following: radiology compatible with TB; temperature >38°C; weight loss ≥10% of body weight; night sweats; known TB exposure; or absence of another diagnosis) and TB treatment initiated. Clinical TB was defined as TB cases where TB treatment was initiated.

Table 2. Kaplan-Meier Estimates for Primary Outcomes With 95% CIs by TB Strategy Using Intention-to-Treat and Modified Intention-to-Treat Approaches

		Death			Confirmed or Probable TB		
Approach	N	Empiric	IPT	Risk Difference[a]	Empiric	IPT	Risk Difference[a]
Intention-to-treat	850	10.1 (7.5–13.6)	10.5 (7.9–13.9)	0.4 (–3.8 to 4.6)	6.1 (4.2–8.9)	2.7 (1.5–4.9)	–3.4 (–6.2 to –0.6)*
Excluded MTB$^+$ at entry[b]							
GeneXpert MTB/RIF only	844	10.0 (7.4–13.4)	10.3 (7.8–13.7)	0.4 (3.8–4.5)	6.2 (4.2–9.0)	2.7 (1.5–4.9)	–3.4 (–6.3 to –0.6)*
Urine LAM only	822	10.4 (7.7–14.0)	10.2 (7.6–13.6)	–0.2 (–4.5 to 4.0)	5.7 (3.8–8.5)	2.8 (1.5–4.9)	–2.9 (–5.8 to –0.1)*
GeneXpert MTB/RIF and/or Urine LAM	817	10.2 (7.5–13.8)	10.0 (7.5–13.4)	–0.2 (–4.4 to 4.1)	5.7 (3.8–8.5)	2.8 (1.5–5.0)	–2.9 (–5.8 to –0.1)*
Excluded incident TB[c]	814	9.0 (6.5–12.4)	10.3 (7.7–13.7)	1.3 (–2.8 to 5.5)	N/A	N/A	N/A

Abbreviations: CI, confidence interval; IPT, isoniazid preventive therapy; LAM, lipoarabinomannan; MTB, *Mycobacterium tuberculosis*; N/A, not applicable; RIF, rifampicin; TB, tuberculosis.

NOTE: Data presented as percentage (95% CI).

[a]Absolute risk difference (IPT—empiric).

[b]Excluded participants who were retrospectively identified as MTB-positive using stored baseline samples tested via: GeneXpert only ($n = 6$); urine LAM only ($n = 28$); or by either assay ($n = 33$).

[c]Excluded participants who developed confirmed or probable TB as per AIDS Clinical Trials Group Appendix 60 ($n = 3$) [21].

*Denotes *z*-test, $P < .05$.

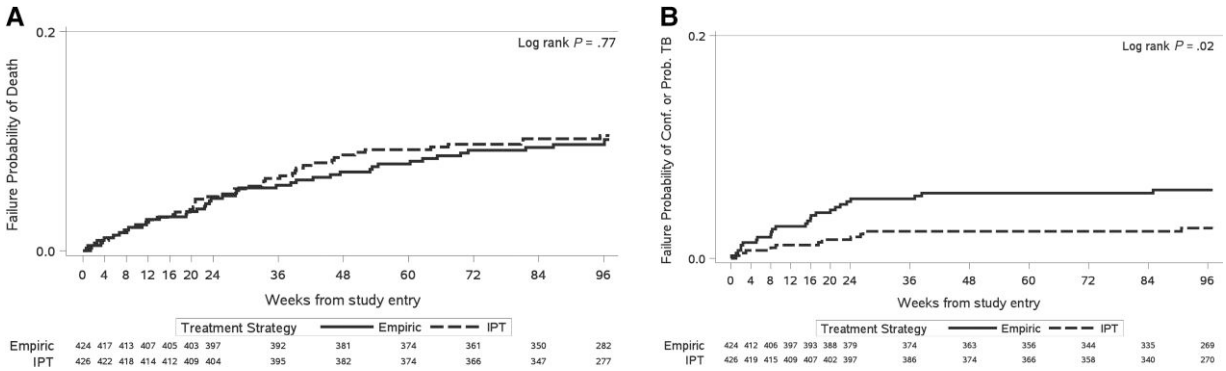

Figure 2. Kaplan-Meier curves comparing time to death *(A)* and time to confirmed (Conf.) or probable (Prob.) tuberculosis (TB) *(B)* by TB treatment strategy. The Kaplan-Meier curves show that time to death did not significantly differ by TB strategy *(A)*, whereas time to incident TB was significantly more rapid among participants randomized to empiric TB treatment (solid line) compared with those who received isoniazid preventive therapy ([IPT] dashed line) *(B)*.

(log-rank $P = .02$) (Figure 2*B*). These conclusions remained unchanged in the competing risk analysis and after excluding participants retrospectively identified as MTB positive at entry (Table 2).

A cause of death was recorded for 83 of 85 deaths (empiric $n = 39$; IPT $n = 44$). Of these, 57 (69%) were HIV-related (30 in empiric and 27 in IPT), including 12 TB-related deaths (8 in empiric and 4 in IPT). Twelve (14.5%) were diagnoses unrelated to HIV diagnoses (empiric $n = 4$; IPT $n = 8$), 12 (14.5%) were classified as unknown (empiric $n = 5$; IPT $n = 7$), and the remaining 2 deaths (2%) were due to drug toxicity and treatment failure (both in IPT) (Table 3). The monthly death rate decreased over the analysis period. Most deaths (93%) occurred by week 48; 61% of all deaths (51 of 83) occurred by week 24, 31% occurred between 24 and 48 weeks, and 7% occurred after week 48 (Figure 3*A* and *B*). Most TB-related deaths occurred by week 48 and were most common between week 24 and 48 (6 of 12; 50%); there were 3 TB-related deaths after week 48 (all in empiric) (Figure 3*A* and *B*).

Adherence to Tuberculosis and Antiretroviral Therapy Medications

At week 24, the mean self-reported adherence to IPT was 90.9% (standard deviation [SD] = 17.6%) versus 88.1% (SD = 19.6%) in empiric. Self-reported adherence to IPT was higher than adherence to empiric treatment (Wilcoxon rank-sum test $P = .001$), whereas adherence to ART did not differ by arm (Wilcoxon rank-sum test $P = .73$). Individuals who experienced death were more likely to have <100% cumulative adherence to both ART and TB medications across study visits (Supplementary Table 3). Higher adherence to TB medications through week 24 (10% increase in the proportion of 100% adherence) had a significant impact on mortality (empiric and IPT) and incident TB (IPT only) at each timepoint (24, 48, and 96 weeks), with at least 23% ($P < .0001$) and 20% ($P \leq .0035$) lower hazards of death in empiric and IPT, respectively, and at least 17% ($P \leq .0324$) lower hazards of confirmed or probable TB in IPT (Table 4). Isoniazid preventive therapy participants who survived at week 24 had a higher proportion of 100% IPT adherence at weeks 2, 8, 12, and 20 than those who

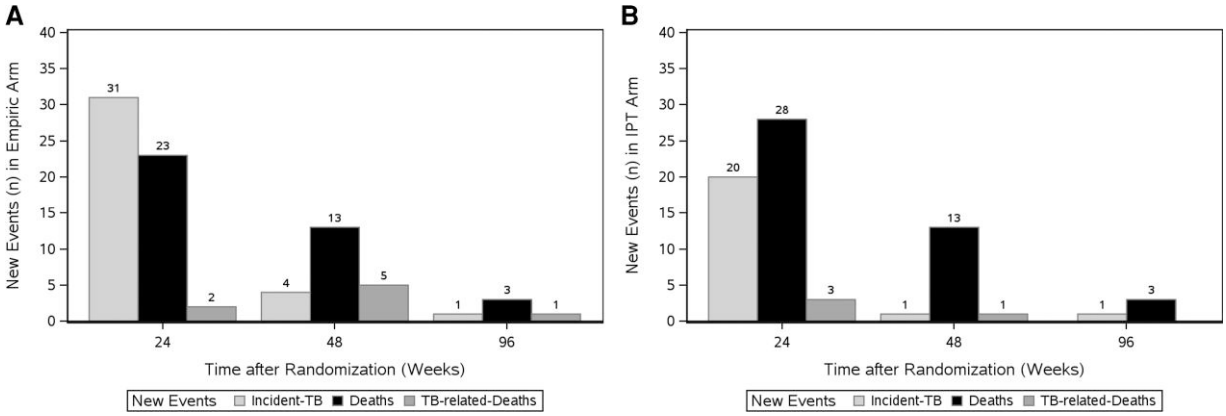

Figure 3. Number of deaths and incident tuberculosis (TB) over the 96-week analysis period by TB treatment strategy. Figure 3 illustrates the progressive decline in the total number of deaths (black bars) per over the 96-week analysis period, with the majority (80%) of all deaths occurring during the first year of follow up—61% by week 24 and an additional 31% between week 24 and 48 (*A* and *B*). Among TB-related deaths (dark gray bars), most (92%) occurred during the first year, yet 50% were recorded between week 24 and 48; 3 TB-related deaths occurred after week 48, all in the empiric arm (*A*). Incident TB (light gray) was most common within the first 24 weeks of follow-up—88% of participants (51 of 58) were diagnosed by week 24; only 2 participants developed TB after week 48 (*A* and *B*). Bar charts show the midpoint of 2 consecutive study weeks. Week 24 included events that occurred after study entry and before week 36, week 48 included events that occurred at or after week 38 and before week 72, and week 96 included events that occurred at or after week 72.

died, and IPT participants with incident TB by 24 weeks had a lower proportion of 100% IPT adherence at weeks 1 and 8 than those without TB. Higher adherence to ART through week 24 reduced mortality and incident TB at each timepoint in both study groups, with at least 27% ($P < .0001$) and 22% ($P \leq .0048$) lower hazards of death and at least 15% ($P \leq .0329$) and 17% ($P \leq .0613$) lower hazards of TB in empiric treatment and IPT, respectively (Table 4).

DISCUSSION

This 96-week analysis of the multicountry A5274 REMEMBER trial indicates no longer-term survival benefit of empiric 4-drug TB treatment compared with 6-month IPT in our outpatient population initiating ART with advanced HIV without confirmed or probable TB. Compared with empiric treatment, IPT had a lower rate of confirmed or probable TB by 96 weeks, and adherence to IPT significantly reduced the hazards of early and longer-term mortality and incident TB through 96 weeks. These findings add to the growing evidence that empiric 4-drug TB treatment may not provide an advantage as a TB control strategy among individuals initiating ART with advanced HIV [24]. More importantly, our data clearly provide evidence supporting the implementation of ART plus 6-month IPT initiation and illustrate that adherence to and completion of IPT is essential to reduce TB and death in high TB-burden, resource-limited settings, even in the context of severe immunosuppression.

Our group previously reported no early survival benefit of empiric TB treatment and a higher rate of incident TB by 24 weeks compared with 6-month IPT [21]. We now report that these early outcomes are sustained through 96 weeks in our study population at high risk for TB and death. Two recent trials, TB Fast Track [25] and STATIS [26], have similarly reported no early mortality benefit of empiric TB treatment at 24 weeks among PWH with CD4 counts below 150 and 100 cells/mm^3, respectively. The STATIS trial also found no mortality benefit at 48 weeks [26]. Given the limitations of TB diagnostics in PWH, especially with advanced immunosuppression, empiric TB treatment would hypothetically improve survival by providing early TB treatment to patients with undetected active TB and prevent TB activation in those with latent TB infection [9]. However, we found that empiric treatment was not more effective than IPT in reducing longer-term mortality in our population, regardless of whether GeneXpert or urine LAM assays were used at TB screening. Furthermore, the early advantage of IPT to reduce TB risk was maintained through 96 weeks.

Although our results suggest at least a 2-year benefit of IPT, the actual duration of TB protection after initiation of ART plus IPT remains unclear in populations with very advanced HIV. Studies from Africa report TB risk gradually returns to baseline after completing 6-month IPT [27, 28]. A randomized controlled trial from Zambia found that the benefit of IPT (48% lower TB risk compared with placebo) lasted for at least 2.5 years and noted a diminished effect over the maximum follow-up of 7 years [29]. In contrast, recent long-term follow-up of the TEMPRANO (2 × 2 randomized controlled trial of IPT and ART from sub-Saharan Africa) and THRio (cluster-randomized phased treatment trial from Brazil) trials suggests that IPT may provide longer-term protection, specifically a 37% reduction in mortality at 6 years [30], with maintenance of

Table 3. Summary of the Primary Causes of Death in the Overall Cohort and by TB Strategy

Cause of Death	Overall (*n* = 83)	Empiric TB Treatment (*n* = 39)	Isoniazid Prevention Therapy (*n* = 44)
HIV-related	57 (69)	30 (77)	27 (61)
TB-related	…	8	4
Pulmonary TB	…	3	1
Disseminated TB	…	1	1
Extrapulmonary TB	…	0	1
TB meningitis	…	1	1
Pneumonia	…	1	0
Other	…	1	0
Not TB-related	…	22	23
Bacterial infection	…		
Sepsis	…	2	3
Pneumonia	…	2	2
Fungal infection	…		
PCP	…	1	1
Cryptococcal meningitis	…	2	3
Other infection[a]	…	4	4
Kaposi sarcoma	…	2	1
Non-Hodgkin lymphoma	…	0	1
CMV encephalitis	…	0	1
HIV encephalopathy	…	0	1
Terminal AIDS illness	…	1	0
Persistent diarrhea	…	2	1
Anemia	…	1	1
Pulmonary edema	…	2	0
Hypovolemic shock	…	2	0
Other[b]	…	1	4
Non-HIV	12 (14.5)	4 (10)	8 (18)
Unknown	12 (14.5)	5 (13)	7 (16)
Other[c]	2 (2)	0	2 (5)

Abbreviations: AIDS, acquired immune deficiency syndrome; CMV, cytomegalovirus; HIV, human immunodeficiency virus; PCP, *Pneumocystis carinii* pneumonia; TB, tuberculosis.

NOTE: Data presented as *n* or *n* (%).

[a]Respiratory tract inflammation (*n* = 1); aspiration pneumonia (*n* = 2); gastroenteritis (*n* = 1); pneumonia (*n* = 3); meningitis (*n* = 1 isoniazid preventive therapy [IPT]).

[b]Empiric TB treatment (*n* = 1, central nervous system mass lesion); IPT (*n* = 4, cerebrovascular accident, respiratory failure, unknown, disseminated intravascular coagulation).

[c]Treatment failure and toxicity.

Table 4. Effect of Adherence to TB and ART Medications on Death and Incident TB at 24, 48, and 96 Weeks Using Separate Cox Proportional Hazards Models for Each TB Strategy

	Empiric TB Treatment		Isoniazid Preventive Therapy	
Study Week	HR[a] (95% CI)	*P*	HR[a] (95% CI)	*P*
Adherence to TB medications				
Death				
24 weeks	0.71 (.62–.81)	<.001	0.79 (.67–.92)	.004
48 weeks	0.74 (.66–.84)	<.001	0.78 (.69–.88)	<.001
96 weeks	0.77 (.69–.85)	<.001	0.80 (.71–.89)	<.001
Tuberculosis[b]				
24 weeks	0.93 (.79–1.10)	.42	0.80 (.68–.95)	.01
48 weeks	0.93 (.79–1.09)	.38	0.82 (.70–.97)	.023
96 weeks	0.94 (.80–1.10)	.44	0.83 (.70–.98)	.032
Adherence to ART				
Death				
24 weeks	0.68 (.59–.78)	<.001	0.78 (.65–.93)	.005
48 weeks	0.71 (.63–.79)	<.001	0.75 (.66–.85)	<.001
96 weeks	0.73 (.66–.82)	<.001	0.77 (.68–.87)	<.001
Tuberculosis[b]				
24 weeks	0.85 (.73–.99)	.03	0.80 (.66–.97)	.022
48 weeks	0.84 (.73–.98)	.02	0.83 (.68–.01)	.06
96 weeks	0.85 (.73–.98)	.03	0.82 (.68–.99)	.043

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; HR, hazards ratio; TB, tuberculosis.

[a]Per 10% increase in the proportion of 100% adherence to medications through week 24.

[b]Confirmed or probable TB as per AIDS Clinical Trials Group Appendix 60.

the early benefit of IPT (31% reduction in TB risk compared with placebo) through 7 years [31]. TEMPRANO included individuals with higher CD4 counts (41% with CD4 ≥500 cells/mm^3), and THRio was conducted in a medium TB-burden setting among individuals with a positive tuberculin skin test. It is notable that a recent meta-analysis of 3 randomized trials ($n = 2611$ participants with 8584.8 person-years of follow-up) reported the benefit of ART plus IPT to reduce TB risk is not significantly impacted by baseline CD4 count or TB status [15]. Although future studies are needed to understand the precise duration of TB protection from IPT, we identified only 1 additional TB event after week 48 and no TB-related deaths after 9 months, illustrating excellent protection from TB at least during 18 months after completing IPT.

Finally, our 96-week analysis indicates that adherence to IPT significantly improves early and longer-term outcomes, lowering the hazards of death and incident TB by at least 20% and 17%, respectively. To our knowledge, our study is among the first to examine such associations. Isoniazid preventive therapy completion rates ranging from 85% to 95% have been reported in study settings from high TB-burden areas [32–35], which are consistent with IPT adherence reported among our study population. Although these findings suggest high patient acceptability and feasibility of implementation, low IPT uptake and completion rates have been reported from real-world programmatic settings [36], emphasizing the need for national programs to overcome barriers and boost adherence. Potential strategies to improve IPT uptake and completion include integration of TB and HIV care [37], TB training for HIV providers [34], community-based delivery of IPT, video directly observed therapy via smartphone platforms [38, 39], use of adherence devices, such as medication event reminder monitor systems (MERMS), and interventions targeting groups with lower completion rates, such as younger patients and males [35]. In

addition, clinical trials have recently evaluated shorter 3-month and 1-month TB prevention regimens containing isoniazid and rifapentine, which have similar efficacy as 60- to 9-month IPT, but better completion and adherence rates [40], and may alleviate the fear of potential isoniazid resistance (ie, due to poor adherence to a 6-month, 1-drug regimen for prevention).

Our study has several limitations. Treatment assignment was not blinded, which could influence providers' diagnosis and treatment decisions. Second, the length of follow-up limited our ability to fully assess and compare the lasting impact of IPT. In addition, we relied on self-reported adherence instead of using objective measures, such as urine isoniazid levels or pharmacokinetic measurements of rifampicin. Next, due to the low number of culture-confirmed TB cases, we were unable to assess drug resistance at the time of incident TB and could not address concerns about developing isoniazid resistance. Finally, it is unclear why adherence to empiric TB treatment was not also associated with a reduction in incident TB. With the observation that TB was more common in the empiric arm, particularly during the first 24 weeks, it is possible that there was an imbalance in the randomization that could have impacted our findings. A retrospective analysis of A5274 stored urine baseline samples revealed an increased incidence of positive urine LAM assays in the empiric arm compared with the IPT arm, which likely occurred by chance [22]. Finally, given that adherence was self-reported, it could be that the additional pill burden and side effects of the 4-drug regimen led to decreased rates of adherence in actuality. Despite these limitations, we were able to demonstrate the effectiveness of IPT to reduce longer-term mortality and TB risk compared with empiric TB treatment, including the impact of adherence, in a very high-risk study population with advanced HIV.

CONCLUSIONS

In conclusion, empiric 4-drug TB treatment offered no survival advantage over IPT and had a higher rate of incident TB in longer-term follow-up. Furthermore, a higher degree of IPT adherence substantially reduced the incidence of TB and death. These findings highlight not only the importance of TB preventive treatment (TPT) and concomitant ART initiation as an effective strategy to reduce TB and death in individuals with advanced HIV disease and no suspected TB, they also shed light on the necessity of adherence. As we transition to a new era of TPT, with an increasing variety of available treatment strategies, preference for shorter regimens to improve adherence and completion is likely to be associated with greater reduction in TB incidence and mortality. At a minimum, efforts to optimize uptake and adherence to ART and TPT should be prioritized among national ART programs in high-burden, resource-limited settings.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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