

Inpatient initiation of tuberculosis preventive therapy with 1 month of isoniazid and rifapentine for adults with advanced HIV disease and cryptococcal meningitis (IMPROVE): a non-inferiority, randomised controlled trial



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Summary

Background Tuberculosis preventive therapy coverage for people with advanced HIV disease (AHD) is poor. Innovative delivery strategies to increase tuberculosis preventive therapy uptake are needed; we sought to evaluate the safety and feasibility of two strategies for ultra-short course tuberculosis preventive therapy with 1 month of daily rifapentine plus isoniazid (1HP).

Methods In this phase-3, open-label, non-inferiority, randomised controlled strategy trial (ISRCTN 18437550), we recruited consecutive adults (aged ≥ 18 years) admitted to hospital with AHD receiving treatment for cryptococcal meningitis who were screened for active tuberculosis during their hospitalisation from three tertiary referral hospitals in Uganda (Mulago National Specialised Hospital, Kiruddu National Referral Hospital in Kampala, and Mbarara Regional Referral Hospital). Adults without evidence of tuberculosis disease and meeting all eligibility criteria were approached for consent and inclusion. Patients were excluded if they had evidence of active hepatitis B infection, abnormal liver function tests, had known chronic liver disease, were jaundiced, were pregnant or breastfeeding, or presented with a clinical syndrome which, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial. After providing informed consent, we randomly assigned participants (1:1) to inpatient initiation of 1HP before hospital discharge or outpatient initiation at 6 weeks after time of cryptococcal meningitis diagnosis. 1HP was standardised across treatment groups, a 28-day course of 600 mg rifapentine plus 300 mg isoniazid daily with adjunctive pyridoxine (25 mg per day). The 1HP regimen was not dose adjusted on the basis of weight. The primary endpoint was tuberculosis disease-free survival and 1HP treatment completion at 18 weeks, powered for a 15% non-inferiority margin; analysis was by intention to treat.

Findings From Jan 24, 2022, to Nov 13, 2024, 419 adults were screened after 210 were found ineligible and four died before random allocation, 205 were randomly allocated (171 in Kampala and 34 in Mbarara, Uganda); 103 to the inpatient group and 102 to the outpatient group. 119 participants (58%) were male and 86 (42%) were female. In the primary adjusted intention-to-treat analysis, 72 participants in the inpatient 1HP group (70%) had tuberculosis disease-free survival and 1HP treatment completion at 18 weeks compared with 63 (62%) in the outpatient 1HP group (adjusted risk difference 7.1%, 90% CI -3.8 to 17.9) confirming non-inferiority. Treatment completion was achieved in 78 (76%) of 103 in the inpatient 1HP group compared to 67 (66%) of 102 in the outpatient 1HP group (site-adjusted risk difference 9.7%, 95% CI -2.4 to 21.8). 170 grade 3 or 4 adverse events occurred in 99 (48%) of 205 participants. Among participants who had taken at least one dose of 1HP the frequency of adverse events across trial groups was similar apart from grade 4 anaemia, which occurred in a higher proportion of participants in the outpatient group (9% vs 2%, $p=0.045$).

Interpretation 1HP initiation before hospital discharge was non-inferior to outpatient initiation among adults with AHD and cryptococcosis. These data suggest that following exclusion of active tuberculosis disease, inpatient 1HP initiation is feasible and comparably safe compared with outpatient initiation.

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Introduction

Cryptococcus is the most common cause of HIV-associated meningitis globally, accounting for 19% of all AIDS-related deaths.¹ Among adults treated for cryptococcal

meningitis, 12-month mortality after hospital discharge is up to 78% in resource-limited settings.²

Tuberculosis is treatable and preventable, but it remains the most frequent cause of AIDS-related deaths

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Research in context

Evidence before this study

Tuberculosis preventive therapy provision is suboptimal, particularly for people with advanced HIV disease (AHD). Ultra-short course tuberculosis preventive therapy with daily rifapentine plus isoniazid for 1 month (1HP) was endorsed by WHO in 2020, irrespective of HIV status. 1HP might have advantages in the context of AHD with respect to pill burden, drug–drug interactions, and in rapid sterilisation of latent tuberculosis infection. Tuberculosis preventive therapy with 1HP is of particular interest in cryptococcosis, as antiretroviral therapy initiation is delayed due to the risk of cryptococcal immune reconstitution inflammatory syndrome. Innovative strategies are needed to increase the reach of the intervention, which may include inpatient initiation of tuberculosis preventive therapy. On March 31, 2025, we searched PubMed from database inception for articles evaluating 1HP use among people with HIV with the terms “([1HP] OR [one month of Isoniazid and rifapentine]) AND [HIV]”. The search was conducted without any language or date restrictions. This yielded 54 studies, of which four studies investigated 1HP in the context of HIV. One randomised controlled trial, the BRIEF-TB trial, evaluated the safety and efficacy of 1HP as compared to 9 months of isoniazid (9H) for preventing HIV-associated tuberculosis disease and death among people living with HIV. The BRIEF-TB trial successfully demonstrated 1HP to

be non-inferior to 9H, but among the 3000 trial participants only 13% had CD4 counts of 250 cells per μL or fewer. Furthermore, in the BRIEF-TB trial tuberculosis preventive therapy was provided in outpatient settings, because that is the standard of care globally. The other three studies identified were small pharmacokinetic studies investigating the drug–drug interaction between rifapentine and dolutegravir, each conducted among participants with well controlled HIV disease.

Added value of this study

To our knowledge, this is the first randomised controlled trial to investigate the safety and feasibility of inpatient initiation of 1HP among hospitalised adults with AHD treated for cryptococcal meningitis. Among 205 randomly assigned participants, inpatient initiation of 1HP before hospital discharge was non-inferior to outpatient initiation in terms of tuberculosis disease-free survival and 1HP treatment completion at 18 weeks following cryptococcal meningitis diagnosis.

Implications of all the available evidence

Following exclusion of active tuberculosis disease, inpatient initiation of 1HP is feasible and comparably safe compared with standard outpatient initiation. Our findings should be used to inform clinical and programmatic guidelines for tuberculosis preventive therapy.

worldwide.³ All people living with HIV should be screened for active tuberculosis disease at every clinical encounter; and, after exclusion of tuberculosis disease, tuberculosis preventive therapy should be provided, irrespective of antiretroviral therapy (ART) status and CD4 cell count.³ Despite clear recommendations and robust data that tuberculosis preventive therapy prevents disease and deaths,^{4,6} provision for adults living with advanced HIV disease (AHD) has been suboptimal. Barriers to tuberculosis preventive therapy implementation are multifactorial and include concerns about adherence, loss to follow-up, and drug toxicity.⁵ Innovative delivery strategies to increase provision are needed.

Ultra-short course tuberculosis preventive therapy, 1 month of daily rifapentine plus isoniazid (1HP), was endorsed by WHO in 2020.⁷ 1HP is non-inferior to 9 months of isoniazid for the prevention of active HIV-associated tuberculosis disease and is associated with fewer adverse events.⁵ 1HP, if combined with innovative delivery strategies to increase uptake, offers a major potential breakthrough in tuberculosis prevention.

1HP might have particular advantages over longer course tuberculosis preventive therapy for patients with AHD: expedited completion provides clear benefits with respect to pill burden, drug–drug interactions and in rapid sterilisation of latent tuberculosis infection.^{3,8} Tuberculosis preventive therapy with 1HP is of particular

interest in cryptococcosis, as ART initiation is delayed due to the risk of cryptococcal immune reconstitution inflammatory syndrome (IRIS).⁹ The risk of tuberculosis-IRIS, however, remains after ART initiation at 4–6 weeks, with most incident IRIS events occurring within the first month of initiation.^{4,10,11} Completion of 1HP before ART initiation might reduce incidence of tuberculosis-IRIS, active tuberculosis disease, and death among this subpopulation.^{4,12}

We conducted an open label, randomised controlled trial (the IMPROVE trial) to evaluate safety and feasibility of two strategies for delivery of 1HP in adults with AHD and cryptococcal meningitis. We used cryptococcal meningitis as a common, easily diagnosed, opportunistic disease representative of hospitalised AHD populations with low CD4 counts and at high risk for future tuberculosis disease.^{13,14} We compared inpatient initiation of 1HP with standard of care (outpatient initiation of 1HP at week 6). We hypothesised that inpatient initiation of 1HP would be non-inferior to outpatient initiation of 1HP with respect to tuberculosis disease-free survival and 1HP treatment completion, and that inpatient initiation of 1HP is safe and feasible in patients with HIV-associated cryptococcal meningitis. A non-inferiority design was chosen as we hypothesised that earlier, inpatient initiation of 1HP might have additional clinical and programmatic benefits, including a reduction in tuberculosis and tuberculosis-IRIS events,

alongside increased reach of tuberculosis preventive therapy as an intervention when compared to outpatient initiation.

Methods

Study design and participants

The trial design has been described previously¹⁵ (ISRCTN 18437550, registered on Nov 5, 2021) and the trial protocol is available online. Consecutive adults (aged ≥ 18 years) admitted to hospital with AHD and receiving treatment for cryptococcal meningitis were screened for active tuberculosis as part of a prospective cohort study at three referral hospitals in Uganda: Mulago National Specialised Hospital, Kiruddu National Referral Hospital in Kampala, and Mbarara Regional Referral Hospital. The protocol was approved by the London School of Hygiene & Tropical Medicine Research Ethics Committee (reference 24059), the Mulago Research Ethics Board (reference MHREC 2021–25), and the Uganda National Council for Science and Technology (reference HS1607ES). An independent data safety monitoring board oversaw the trial and reviewed the trial data regularly. All deaths and incident tuberculosis cases were reviewed by the data safety monitoring board in real time.

Tuberculosis screening included Alere tuberculosis-lipoarabinomannan urine assay (Alere, Waltham, MA, USA), urine Xpert MTB/Rif Ultra (Cepheid, Sunnyvale, CA, USA),¹⁶ BD Bactec Myco/F blood cultures, and chest radiography for all potential participants. Additional Xpert Ultra testing on sputum, cerebral spinal fluid, or both was conducted at the clinician's discretion, depending on the clinical syndrome and sample availability. Additional radiology, including brain imaging and abdominal ultrasound examination, was also performed to evaluate for extrapulmonary tuberculosis or alternative infections at physician discretion.

Adults without evidence of tuberculosis disease and meeting all eligibility criteria were approached for consent and inclusion into the IMPROVE trial. Patients were excluded if they had evidence of active hepatitis B infection (hepatitis B surface antigen positive), had abnormal liver function tests (bilirubin >3.5 mg/dL or alanine aminotransferase >200 international units per L), had known chronic liver disease, were jaundiced, were pregnant or breastfeeding, or presented with a clinical syndrome which, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial. Medication contraindications included protease inhibitors or known hypersensitivity to rifamycins or isoniazid.

All the participants provided written informed consent. If a participant was deemed to lack capacity to provide consent, written informed consent was obtained from the next of kin; if a participant recovered the capacity to provide consent, written informed consent was obtained from that participant.

Randomisation and masking

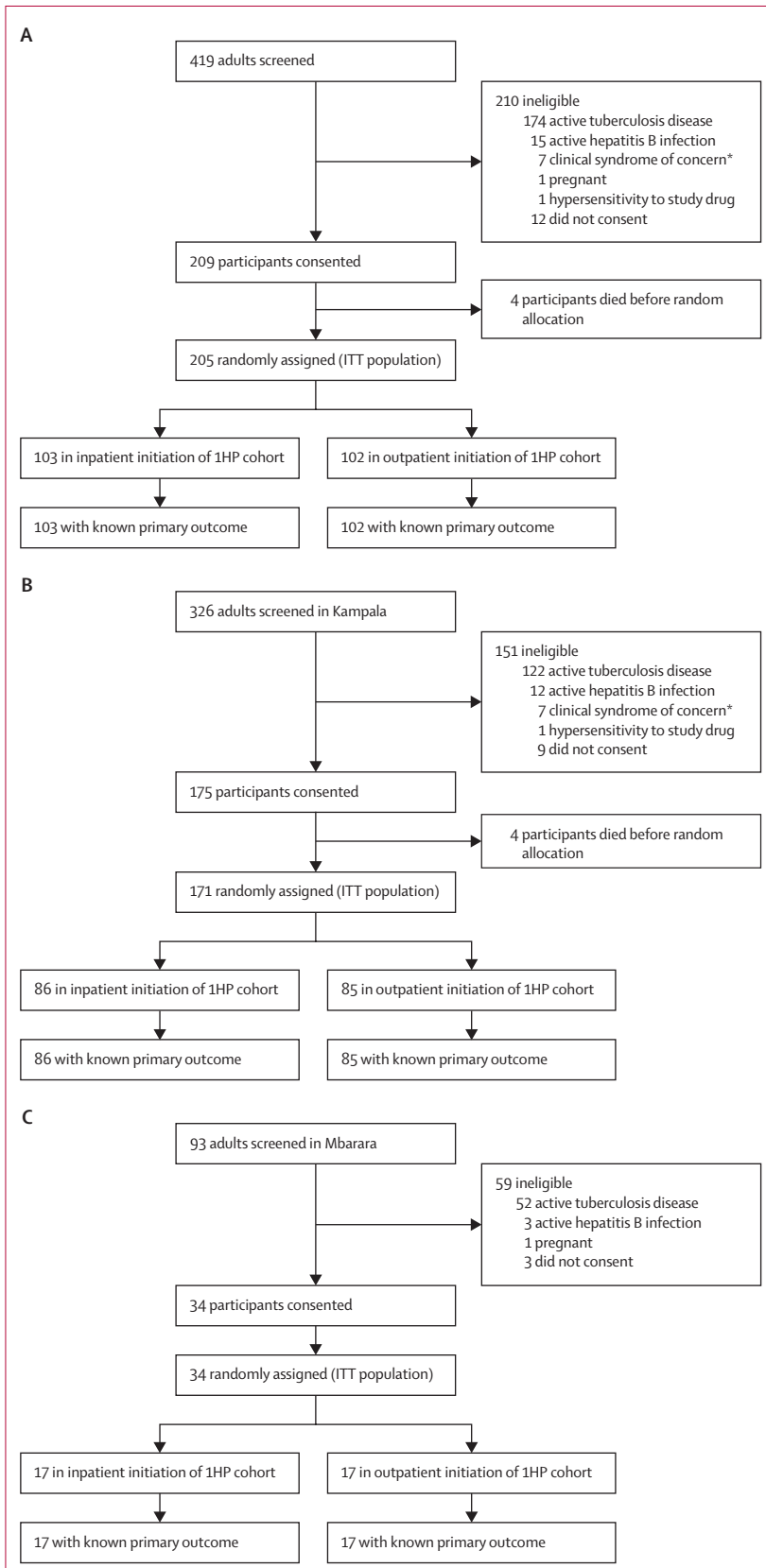
Participants underwent randomisation individually and were assigned (1:1) to either inpatient initiation of 1HP (experimental group) before hospital discharge or outpatient initiation of 1HP at week 6 (standard of care). Random allocation was done with a computer-generated randomisation list in Stata version 16, with random block sizes, stratified according to site (Kampala vs Mbarara). The random allocation sequence was generated by the trial statistician (KF). Random allocation occurred on the day of hospital discharge (or day 14 of antifungal therapy for cryptococcal meningitis, whichever came first). The treatment group assignments were contained in sealed opaque envelopes and provided by the trial pharmacist to recruiting teams after consent had been obtained and participants enrolled to ensure allocation concealment before enrolment.

Procedures

1HP was standardised across treatment groups, a 28-day course of 600 mg rifapentine plus 300 mg isoniazid daily with adjunctive pyridoxine (25 mg per day). The 1HP regimen was not dose adjusted based on weight, in accordance with Ugandan national guidelines and WHO recommendations. The trial medications were administered on an open-label basis. Among participants randomly allocated to the inpatient initiation group, 1HP was started before hospital discharge. Among participants in the outpatient initiation group, initiation of 1HP was delayed until 6 weeks after cryptococcal meningitis diagnosis (ie, approximately 4 weeks after random allocation) at the outpatient clinic. The first 1HP treatment dose was given as directly observed therapy in a health-care setting for both intervention groups (either in the hospital for the inpatient 1HP initiation group or in the outpatient clinic for the outpatient 1HP initiation group), after which 1HP was self-administered.

Timing of hospital discharge was at the discretion of the attending study physician. At time of hospital discharge, all participants received 1200 mg fluconazole once daily for 14 days after cryptococcal meningitis diagnosis, followed by 800 mg fluconazole once daily until week 8 after cryptococcal meningitis diagnosis. Participants were followed up in outpatient clinics for 18 weeks. Follow-up visits were on alternate weeks; in-person visits for the duration of 1HP and telephone visits thereafter. If a participant missed a clinic appointment then follow-up was done by the trial team either by telephone or in person. Follow-up visits included clinical review with a tuberculosis symptom screen; additional mycobacteriological and radiological testing if the tuberculosis symptom screen was positive; 1HP adherence review with pill counts; safety monitoring blood tests (complete blood count, renal function, and liver function) for the duration of 1HP; and ART planning and adherence counselling. ART was initiated, reinitiated, or switched during weeks 4 to 6 in accordance

For the trial protocol see <https://wellcomeopenresearch.org/articles/9-14/v2>



with Ugandan national guidelines.¹⁷ In accordance with WHO and Ugandan national guidelines, dolutegravir dose was not adjusted when co-administered with 1HP; 50 mg dolutegravir once-daily dosing was maintained for participants receiving dolutegravir at baseline, and for those initiating dolutegravir at week 4 to 6. The sequence of initiation of ART and tuberculosis preventive therapy within the outpatient 1HP initiation group was not specified in the protocol and was decided on a case-by-case basis depending on participant choice. Where no specific preference was given by the participant, initiating ART at week 4 with initiation of 1HP at week 6 was the preferred approach.

Outcomes

The primary endpoint was tuberculosis disease-free survival and 1HP treatment completion at 18 weeks from cryptococcal meningitis diagnosis. To meet the primary endpoint participants needed to have completed 1HP (participant-reported adherence of >90% of the study medications, completed within 6 weeks from treatment initiation) and to be tuberculosis disease-free and alive at 18 weeks. The 18-week primary endpoint was chosen to ensure sufficient time to assess 1HP adherence, to detect incident tuberculosis and tuberculosis-IRIS, and to capture early mortality. Secondary endpoints by trial group were 1HP treatment completion at 18 weeks, discontinuation of study drugs for 5 or more consecutive days, percentage of participants with clinical or laboratory-defined adverse events of grade 3 or above or serious adverse events (according to the criteria of the Division of AIDS), percentage of participants with drug-induced liver injury (defined as elevation of blood alanine transaminase [ALT] alone $\geq 5 \times$ the upper limit of normal [ULN], or ALT $\geq 3 \times$ ULN if bilirubin abnormal, or alkaline phosphatase $\geq 2 \times$ ULN), all-cause mortality, and percentage of participants diagnosed with tuberculosis disease up to 18 weeks. Tuberculosis outcome status was categorised as confirmed active tuberculosis, probable active tuberculosis, possible active tuberculosis, or non-active tuberculosis, with adjudication by an independent infectious diseases expert (TSH).

Statistical analysis

Assuming an 80% tuberculosis disease-free survival and 1HP treatment completion in the outpatient group, we calculated that a total sample size of 205 would provide 80% power to show non-inferiority of inpatient 1HP initiation, with a non-inferiority margin of 15% (the lower

Figure 1: Trial profile

1HP=1 month of daily rifampine plus isoniazid. ITT=intention-to-treat. *A clinical syndrome which, in the opinion of the attending clinician, puts the patient at significant risk if they were to participate in the 1HP trial.

boundary of the one-sided 95% CI of the absolute difference in the primary endpoint), allowing for a 5% rate of loss to follow-up and 10% mortality at 18 weeks after randomisation. A 15% non-inferiority margin was chosen after discussion with relevant clinicians or stakeholders. The primary analysis was performed in the intention-to-treat population, which included all participants who had undergone random allocation. A generalised linear model with an identity link function was used to calculate the risk difference in the primary endpoint by trial group, adjusting for randomisation site, based on 90% and 95% CIs. Further prespecified adjustments for age, sex, CD4 count, and ART status to correct baseline imbalances between groups were done, consistent with the statistical analysis plan. Given there were missing data for CD4 counts a post-hoc decision was made to conduct multiple imputation. The primary analysis, therefore, has used multiple imputation and is adjusted for site, baseline imbalances, and additional factors used in the imputation model. A complete case analysis was also reported.

We conducted one prespecified sensitivity analysis in which participants diagnosed with probable or possible tuberculosis disease diagnosed during follow-up were excluded from the primary endpoint analysis. We conducted two prespecified subgroup analyses; reported past medical history of tuberculosis and ART status at baseline.

Secondary endpoints were also analysed by use of a generalised linear model with an identity link function, adjusted for site only. Safety analyses were conducted for the intention-to-treat population, and then for a safety population, which included only participants who had taken at least one dose of 1HP. Analyses were conducted in STATA version 18.5. The full statistical analysis plan is provided in the supplementary appendix (pp 11–25). The trial has been reported in line with the 2025 CONSORT guidelines.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, and writing of the report or review of the final manuscript.

Results

From Jan 24, 2022, to Nov 13, 2024, 419 adults were screened after 210 were found ineligible and four died before random allocation, 205 were randomly allocated (171 in Kampala and 34 in Mbarara, Uganda; figure 1, appendix p 9). More men than women were enrolled: this imbalance was reflected in the inpatient group but not the outpatient group (table 1). Participants in the inpatient group were less likely to be currently receiving ART, were more likely to report a history of tuberculosis disease, and had lower median baseline CD4 counts compared with participants in the outpatient 1HP group (table 1). No participants were lost to follow-up.

	Inpatient initiation of 1HP before hospital discharge (N=103)	Outpatient initiation of 1HP (N=102)
Sex		
Male	68 (66%)	51 (50%)
Female	35 (34%)	51 (50%)
Median age, years	35.0 (30.0–40.0)	36.0 (30.0–43.0)
ART status		
Currently receiving ART	19 (18%)	28 (27%)
Tenofovir–lamivudine–dolutegravir	16 (16%)	27 (26%)
Median time on ART, months	2.9 (0.9–18.6)	3.6 (0.9–18.9)
Median baseline CD4 count*, cells per μ L	18.0 (8.0–45.0)	28.0 (11.0–54.0)
Median weight, kg	52.0 (47.0–60.0)	55.0 (50.0–60.0)
Baseline WHO4SS		
Fevers	62 (60%)	53 (52%)
Weight loss	54 (52%)	56 (55%)
Night sweats	45 (44%)	36 (35%)
Cough	31 (30%)	31 (30%)
History of TPT	4 (4%)	4 (4%)
History of tuberculosis disease	9 (9%)	5 (5%)
Haemoglobin, g/dL	11.9 (10.8–13.3)	11.9 (10.3–13.8)
CSF Xpert Ultra performed	27 (26%)	26 (25%)
Sputum Xpert Ultra performed	17 (17%)	17 (17%)
Ultrasound abdomen performed	29 (28%)	31 (30%)
Site		
Kampala	86 (83%)	85 (83%)
Mbarara	17 (17%)	17 (17%)
Median time on antifungal therapy before random allocation, days	10.5 (8.0–13.0)	10 (7.0–13.0)

Values are n (%) or median (IQR). 1HP=1 month of daily rifampentine and isoniazid. ART=antiretroviral therapy. WHO4SS=WHO four symptom screen. TPT=tuberculosis preventive therapy. CSF=cerebrospinal fluid. *23 patients missing quantitative CD4 counts (17 participants missing baseline counts and six with counts <200 cells per μ L per Visitect).

Table 1: Baseline characteristics stratified by 1HP treatment group

In the primary adjusted (for study site, sex, CD4 count, history of tuberculosis, presence of cough at baseline, and ART status) intention-to-treat analysis 70% of participants in the inpatient 1HP group met the primary endpoint of tuberculosis disease-free survival and 1HP treatment completion at 18 weeks compared with 62% in the outpatient 1HP group (table 2, figure 2A). For the primary endpoint non-inferiority analysis, the upper boundary of the one-sided 95% CI was -3.8% , which was greater than the prespecified -15% non-inferiority margin. With a one-sided 2.5% level, generating comparable 95% CI, non-inferiority was still demonstrated. The results of the prespecified sensitivity analyses in which participants diagnosed with probable or possible tuberculosis were excluded were consistent with the primary intention-to-treat analysis. There was no evidence of interaction across prespecified subgroups (figure 2B, appendix pp 1–2).

Overall, there were no significant differences in any secondary endpoint by trial group (table 2). Survival to 18 weeks was similar between participants in the

For Division of AIDS criteria see <https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf>
See Online for appendix

	Inpatient initiation of 1HP (N=103)	Outpatient initiation of 1HP (N=102)	Site-adjusted risk difference* (90% CI)	Site-adjusted risk difference* (95% CI)	Fully adjusted risk difference (90% CI)	Fully adjusted risk difference (95% CI)
Primary endpoint: TB disease-free survival and 1HP treatment completion						
Complete case analysis†	64/90 (71%)	55/92 (60%)	10.9 (-0.5 to 22.2)	10.9% (-2.7 to 24.4)	10.5%‡ (-1.2 to 22.3)	10.5%‡ (-3.4 to 24.5)
Multiple imputation	72/103 (70%)	63/102 (62%)	8.0 (-2.7 to 18.7)	8.0% (-4.7 to 20.7)	7.1%§ (-3.8 to 17.9)	7.1%§ (-5.9 to 20.0)
Secondary endpoints stratified by 1HP treatment group						
1HP treatment completion	78/103 (76%)	67/102 (66%)	..	9.7% (-2.4 to 21.8)
1HP discontinuation ≥5 days	22/103 (21%)	16/81 (20%)	..	0.2% (-11.2 to 11.7)
Diagnosed with tuberculosis disease	8/103 (8%)	13/102 (13%)	..	-5.4% (-13.4 to 2.6)
Alive at 18 weeks	85/103 (83%)	84/102 (82%)	..	1.9% (-8.0 to 11.8)
Any grade 3 or 4 adverse event or serious adverse event	57/103 (55%)	59/102 (58%)	..	-2.4% (-15.8 to 11.0)
Any grade 3 or 4 adverse event or serious adverse event in the safety population¶	57/103 (55%)	40/81 (49%)	..	5.6% (-8.9 to 20.0)
1HP drug-induced liver injury in the safety population¶	10/103 (10%)	7/81 (9%)	..	0.4% (-7.9 to 8.7)

Among participants in the outpatient initiation of 1HP trial group, 21 (21%) of 102 never started 1HP versus none of 103 in the inpatient 1HP group (risk difference 20.6% [95% CI 12.7 to 28.4]; p<0.001). 1HP=1 month of daily rifapentine and isoniazid. ART=anti-retroviral therapy. *Adjusted for site are per randomisation strata (Kampala vs Mbarara). †Complete case analysis restricted to 182 participants with baseline CD4 count available. ‡Complete case analysis adjusted for site, sex, ART status at baseline (two levels), baseline CD4 count (continuous variable based on fractional polynomials). §Adjusted risk difference using multiple imputation to account for 23 missing CD4 counts. Adjusted for site, sex, ART status at baseline (two levels), baseline CD4 count, presence of cough at baseline, and past medical of tuberculosis history. ¶The safety population comprises all participants who took at least one dose of 1HP.

Table 2: Primary and secondary endpoints among 205 adults with HIV-associated cryptococcal meningitis stratified by 1HP treatment group

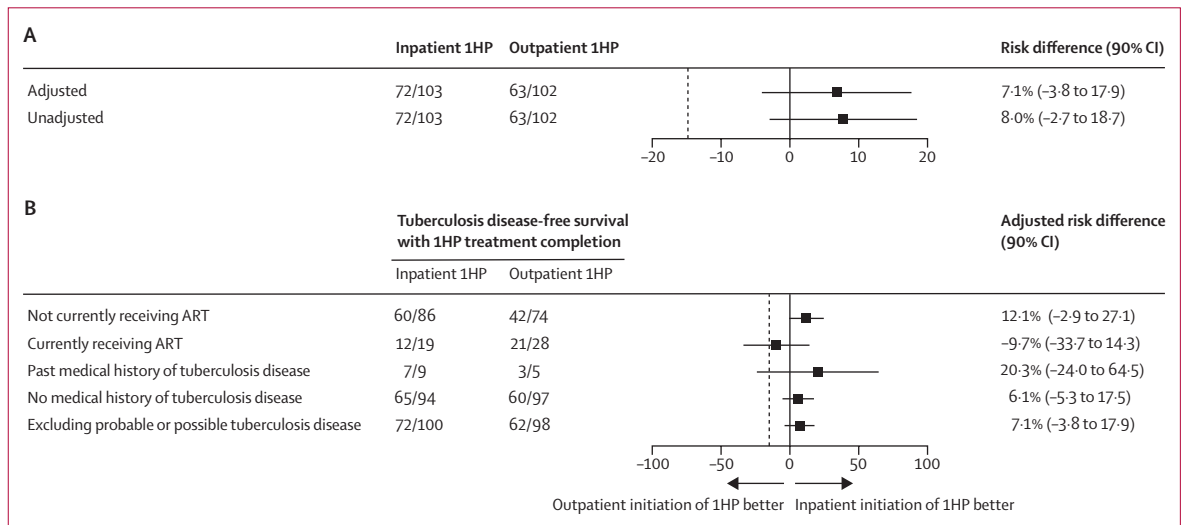


Figure 2: Tuberculosis disease-free survival

(A) Risk difference in the primary endpoint and the prespecified subgroup analysis. The primary outcome was disease-free survival and 1HP treatment completion at 18 weeks after cryptococcal meningitis diagnosis. Risk differences are presented with two-sided 90% CIs based on multiple imputation to account for 23 missing CD4 cell counts. The adjusted risk difference accounts for site, ART status at baseline (yes or no), baseline CD4 cell count (log), the presence of a cough at baseline, and history of tuberculosis. (B) Prespecified subgroup analyses are stratified by ART status at baseline and medical history of tuberculosis; the sensitivity analysis excludes patients who were diagnosed with probable or possible tuberculosis. 1HP=1 month of daily rifapentine plus isoniazid. ART=antiretroviral therapy.

inpatient 1HP group compared with the outpatient 1HP group (85 [83%] of 103 vs 84 [82%] of 102; site-adjusted risk difference 1.9% [95% CI -8.0 to 11.8]). Treatment completion was achieved in 78 (76%) of 103 in the inpatient 1HP group compared to 67 (66%) of 102 in the outpatient 1HP group (site-adjusted risk difference 9.7% [95% CI -2.4 to 21.8]). All participants in the inpatient 1HP group initiated 1HP as planned, while 21 (21%) of 102 in the outpatient 1HP group never started 1HP (risk difference 20.6% [95% CI 12.7-28.4]; p<0.001). The most frequent reason for 1HP non-initiation was due to

active tuberculosis disease being diagnosed before planned 1HP at week 6 (ten [48%] of 21), followed by death (seven [33%] of 21), participant declining to start 1HP (three [14%] of 21), and alternative tuberculosis preventive therapy started before planned 1HP initiation at week 6 (one [5%] of 21; appendix p 7). Among the 184 randomly allocated participants who started 1HP, 1HP discontinuation for 5 days or more was similar across groups (22 [21%] of 103 in the inpatient group vs 16 [20%] of 81 in the outpatient group; risk difference 0.2 [95% CI -11.2 to 11.7]). 21 tuberculosis

	Inpatient initiation of 1HP (n=103)	Outpatient initiation of 1HP (n=81)	p value
Number of events			
Any grade 3 or 4 event	93	62	NA
Grade 3	73	42	NA
Grade 4	20	20	NA
Number of patients			
Any grade 3 or 4 adverse events	51 (50%)	38 (47%)	0.73
At least one grade 3 adverse event	45 (44%)	31 (38%)	0.46
At least one grade 4 adverse event	17 (17%)	16 (20%)	0.57
Haematological laboratory adverse events			
Anaemia	11 (11%)	11 (14%)	0.56
Grade 3	9 (9%)	4 (5%)	0.39
Grade 4	2 (2%)	7 (9%)	0.045
Neutropenia	21 (20%)	8 (10%)	0.052
Grade 3	17 (17%)	6 (7%)	0.064
Grade 4	4 (4%)	2 (2%)	0.70
Thrombocytopenia	4 (4%)	0	NA
Grade 3	3 (3%)	0	NA
Grade 4	1 (1%)	0	NA
Hepatology laboratory adverse events			
Raised AST	1 (1%)	0	NA
Grade 3	0	0	NA
Grade 4	1 (1%)	0	NA
Raised ALT	1 (1%)	2 (2%)	0.58
Grade 3	1 (1%)	2 (2%)	0.58
Grade 4	0	0	NA
Raised ALP	1 (1%)	1 (1%)	>0.99
Grade 3	1 (1%)	1 (1%)	NA
Grade 4	0	0	NA
Raised bilirubin	2 (2%)	2 (2%)	>0.99
Grade 3	0	1 (1%)	NA
Grade 4	2 (2%)	1 (1%)	>0.99
Renal laboratory adverse events			
Raised creatinine	6 (6%)	4 (5%)	0.79
Grade 3	4 (4%)	3 (4%)	0.39
Grade 4	2 (2%)	0	0.66
Hypokalaemia	2 (2%)	0	NA
Grade 3	2 (2%)	0	NA
Grade 4	0	7 (9%)	NA
Hyponatraemia	14 (14%)	4 (5%)	0.29
Grade 3	7 (7%)	3 (4%)	0.76
Grade 4	7 (7%)	4 (5%)	0.60

(Table 3 continues on next column)

diagnoses were reported from random allocation through to week 18. Participants in the inpatient 1HP group were less frequently diagnosed with tuberculosis disease during follow-up compared to participants in the

	Inpatient initiation of 1HP (n=103)	Outpatient initiation of 1HP (n=81)	p value
(Continued from previous column)			
Clinical adverse events			
Any grade 3 or 4 clinical events	21 (20%)	21 (26%)	0.37
Grade 3	20 (19%)	20 (25%)	0.39
Grade 4	1 (1%)	3 (4%)	0.21
Neurological events	10 (10%)	14 (17%)	0.13
Grade 3	9 (9%)	13 (16%)	0.13
Grade 4	1 (1%)	1 (1%)	0.87
Respiratory events	3 (3%)	0	NA
Grade 3	3 (3%)	0	NA
Grade 4	0	0	NA
Gastroenterological events	3 (3%)	2 (2%)	0.85
Grade 3	3 (3%)	2 (2%)	0.85
Grade 4	0	0	NA
SIRS or sepsis events*	3 (3%)	2 (2%)	0.85
Grade 3	3 (3%)	0	NA
Grade 4	0	2 (2%)	NA
Other events†	5 (5%)	8 (10%)	0.19
Grade 3	5 (5%)	8 (10%)	0.19
Grade 4	0	0	NA

Data are n (%) unless otherwise stated. There were no grade 3 or above clinical adverse effects attributed to hypersensitivity reactions in either study group. 1HP=1 month of daily rifampentine plus isoniazid. ALT=alanine transaminase. ALP=alkaline phosphatase. AST=aspartate aminotransferase. NA=not applicable. SIRS=systemic inflammatory response syndrome. *SIRS or sepsis events includes six cases of extrapulmonary tuberculosis disease. †There were 15 total 3 or 4 clinical events classed as other, occurring in 13 participants (four malaria, one disseminated varicella zoster virus, one bacterial meningitis, one otitis media, one deep vein thrombosis, one fever with unknown cause, one chest pain, one insomnia, one hypovolaemia, one dehydration, one disseminated Kaposi sarcoma, and one urethral stricture).

Table 3: Laboratory and clinical grade 3 and 4 adverse events among 184 IMPROVE participants who took at least one dose of 1HP, stratified by treatment group

outpatient 1HP group (eight [8%] of 103 vs 13 [13%] of 102; risk difference -5.4% [95% CI -13.4 to 2.6]). Eight of the tuberculosis diagnoses (38%) were microbiologically confirmed active tuberculosis, nine (43%) were probable tuberculosis, and four (19%) were possible tuberculosis (appendix pp 8, 10). Ten of the tuberculosis diagnoses were made before week 6 (appendix p 8). Overall, there was no difference in the proportion of participants experiencing grade 3 or above adverse events or serious adverse events by treatment group (57 [55%] of 103 in the inpatient group vs 59 [58%] of 102 in the outpatient group; risk difference -2.4% [95% CI -15.8 to 11.0]).

A total of 77 serious adverse events occurred among 54 (26%) of 205 participants; 35 serious adverse events occurred in 22 (21%) of 103 participants in the inpatient group, and 42 serious adverse events occurred in

32 (31%) of 102 participants in the outpatient group. Among participants who had taken at least one dose of 1HP, serious adverse events occurred in 22 (21%) of 103 in the inpatient group compared with 24 (30%) of 81 in the outpatient group.

A total of 170 grade 3 or 4 adverse events occurred in 99 (48%) of 205 participants. 93 grade 3 or 4 adverse events occurred in 51 (50%) of 103 participants in the inpatient 1HP group compared with 77 grade 3 or 4 adverse events in 48 (47%) of 102 participants in the outpatient 1HP group (appendix pp 4–6). Among participants who had taken at least one dose of 1HP, the frequencies of adverse events across trial groups were similar (table 3), apart from for grade 4 anaemia, which occurred in a higher proportion of participants in the outpatient group (9% vs 2%, $p=0.045$).

Discussion

This non-inferiority randomised, controlled trial showed that initiation of 1HP before hospital discharge among adults admitted to hospital with AHD was non-inferior to outpatient 1HP initiation for 18-week tuberculosis disease-free survival and 1HP treatment completion. 1HP treatment completion was similar across groups, suggesting that despite the increased pill burden and close temporal proximity to a severe acute illness, initiation of 1HP before hospital discharge was feasible and acceptable to patients. Survival to 18 weeks was also similar across groups. Notably, more serious adverse events (eg, rehospitalisation) and significantly more grade 4 anaemia occurred in the outpatient 1HP group than in the inpatient group. Almost half of all patients (48%) had a grade 3 or 4 adverse event during the study.

In addition to being feasible and having a comparable safety profile to outpatient initiation, we hypothesised that an additional benefit of inpatient initiation of 1HP—which allows for tuberculosis preventive therapy completion before ART initiation, or switch of ART at week 6 after cryptococcal meningitis diagnosis—would be a reduction in the incidence of tuberculosis disease and tuberculosis-IRIS events. Although our trial was underpowered to investigate this potential secondary benefit, there were fewer tuberculosis diagnoses in the inpatient 1HP group than in the outpatient group (8% vs 13%, respectively). Because the majority of tuberculosis cases were diagnosed early, this suggests that most of the incident tuberculosis cases could represent either unmasking tuberculosis-IRIS or subclinical tuberculosis that was present but undetected at baseline. Tuberculosis was diagnosed less frequently among participants in the inpatient 1HP group, therefore early initiation of 1HP in this group might have mitigated the risk of tuberculosis-IRIS. The reduction in rehospitalisations with earlier tuberculosis preventive therapy completed before ART initiation might also be due to a reduction in tuberculosis-related unmasking

IRIS, even if not formally diagnosed. Some unmasking IRIS events might self-resolve with continued immune reconstitution.

Our trial builds on the BRIEF-TB trial and adds important data to inform 1HP usage in adults with AHD. BRIEF-TB was a landmark trial demonstrating that 1HP was non-inferior to 9 months of isoniazid for prevention of HIV-associated tuberculosis disease and death; however, among the 3000 trial participants, the median CD4 count was 470 cells per μL , and only 13% had CD4 counts of 250 cells per μL or fewer.⁵ To date, there has been a paucity of clinical trial data to inform 1HP use in the context of AHD. In comparison to BRIEF-TB, our trial participants were notably more immunocompromised, with a median cohort CD4 count of 22 cells per μL , and all participants were recovering from cryptococcal meningitis. To be expected, therefore, tuberculosis preventive therapy treatment completion was lower among IMPROVE trial participants (71% overall), compared with 97% in the 1HP group of the BRIEF-TB trial, which is the highest ever recorded in a trial of tuberculosis preventive therapy.⁵ In addition, although the proportion of IMPROVE participants who had grade 3 and above adverse events and serious adverse events was similar across groups within our trial, the proportion of participants with serious adverse events was higher in the IMPROVE study population (26% overall) than in the 1HP group of the BRIEF-TB trial (6%). These data highlight the complexities of providing clinical care for critically ill people with AHD.

Despite 1HP, post-hospital discharge mortality within the trial population remained high (18% at week 18), with no significant difference by trial group. Although our trial was not powered to investigate for differences in survival across groups, these data highlight that tuberculosis preventive therapy alone is unlikely to be sufficient to significantly reduce post-hospital discharge mortality within this group who are at extremely high risk of death. To improve short-term and medium-term outcomes after AHD-associated hospitalisation, tuberculosis preventive therapy probably needs to be delivered within a multifaceted bundle of care, which might include enhanced outpatient follow-up, nutritional support, and antimicrobial prophylaxis or pre-emptive therapy for other important opportunistic infections to bridge the gap until effective immune reconstitution has been achieved. Despite widespread access to ART in Uganda, it should be noted that only 23% of our study population with AHD and cryptococcal meningitis were receiving ART at time of enrolment. These data highlight ongoing challenges with delivering equitable ART programmes for all people living with HIV in resource-limited settings, and the crucial need for intensive adherence counselling for this population. Although further research is needed, our trial provides data that interventions initiated at the time of hospital discharge are feasible and have acceptable safety.

A potential benefit of inpatient initiation of IHP at a programmatic level is to increase the reach of tuberculosis preventive therapy as an intervention and to reduce losses from the latent tuberculosis infection preventive care cascade.^{4,8} Supporting this hypothesis, only 79% of participants randomly allocated to outpatient IHP initiated IHP, compared with 100% in the inpatient group. Showing that initiation of tuberculosis preventive therapy in inpatient settings is feasible and safe could expand the range of clinical encounters in which clinicians are willing to provide it. The need to effectively engage people with AHD at the point they initially engage (or re-engage) with care is of crucial importance given the high risk of future disengagement and treatment interruption within this population. The benefits of one-stop shops, a broad term for models that deliver all necessary services at a single location, are well recognised; integrated care services can lead to improved treatment outcomes,^{18–20} retention in care,^{19–21} and patient satisfaction.^{22,23} We argue that for adults with AHD, after systematic tuberculosis screening, initiation of tuberculosis preventive therapy at time of discharge should be part of an AHD integrated care package initiated as part of a one-stop shop during hospitalisation. This might become of increasing importance given the changing financial landscape for HIV services, and the need to optimise efficiency and cost-effectiveness.

Our open-label trial design was unavoidable given the differences in timing of the intervention; however, the trial has several limitations. Although laboratory-defined adverse events and survival could be objectively determined, we relied on participant-reported adherence to study medication, with supplementary pill counts to ascertain treatment adherence. Second, although a consistent approach to tuberculosis diagnosis and use of both urinary point-of-care diagnostics and chest radiography to screen for incident tuberculosis disease was applied throughout the trial, 13 participants were treated for probable or possible tuberculosis disease. These cases reflect challenges with diagnosing tuberculosis in this context of AHD, where, because of the predominance of extrapulmonary tuberculosis disease, patients often present severely unwell with non-specific clinical syndromes. Combined with suboptimal tuberculosis diagnostics and the lack of a confirmatory rule-out test for tuberculosis disease, empirical treatment in the absence of mycobacteriological confirmation remains important. For tuberculosis diagnoses, there is potential for outcome ascertainment information bias, and this might have been different across study groups because of the open-label nature of the trial. For this reason, we conducted an expert adjudication of all tuberculosis cases, and we did a prespecified sensitivity analysis of the primary endpoint in which participants diagnosed with probable or possible tuberculosis disease were excluded. Third, it should be noted that although no evidence of interaction across prespecified subgroups was

detected, we acknowledge that the trial was not powered to detect moderation of the treatment effect, except in the case of very large or qualitative interactions. Fourth, based on IHP adherence data from the BRIEF-TB trial,⁵ and post-discharge mortality data from our earlier cryptococcal meningitis trials,²⁴ we expected that the primary endpoint success rate in the outpatient IHP initiation group would be 80%. The anticipated 80% success rate estimate was too optimistic, and the eventual success rate in the outpatient IHP group was only 62% within the IMPROVE trial. This discrepancy reflects challenges of designing trials in populations with AHD, who remain under-researched, particularly within periods of critical illness. Importantly, despite the lower-than-expected success rate in the control group, the point estimate favoured inpatient IHP, and the lower bound of the 95% CI remained within the prespecified non-inferiority margin. A fifth limitation pertains to the generalisability of our findings. Most importantly, although our trial provides novel data to inform the use of IHP among people with AHD, our study population was restricted to people treated for cryptococcal meningitis and therefore our findings need to be validated within an unselected cohort of hospitalised adults with AHD. Additionally, before enrolment within the IMPROVE trial, all potential participants underwent robust tuberculosis screening to exclude active tuberculosis, including urinary point-of-care diagnostics, traditional mycobacteriology, and radiology. Whether all components of the tuberculosis diagnostics bundle were required to enable safe initiation of tuberculosis preventive therapy and what would be achievable and cost-effective in a non-research setting warrant further investigation.

In conclusion, our trial demonstrated that inpatient initiation of IHP immediately after acute treatment for cryptococcal meningitis was non-inferior to outpatient initiation of IHP among hospitalised adults with AHD. Our data suggest that after exclusion of active tuberculosis disease, IHP can be safely and feasibly initiated before hospital discharge.

Contributors

JE, DRB, KF, DBM, DAJM, and JNJ all contributed to the conceptualisation and methodology of the study, and the acquisition of funding. DRB, KF, DBM, DAJM, and JNJ provided supervision. All other authors contributed to data curation, investigation, or project administration. JE, JNJ, and KF led the formal analysis and data visualisation. JE wrote the initial draft of the manuscript. All authors reviewed and contributed to the final draft of the paper, and all authors were responsible for the decision to submit for publication. All authors had access to the data as presented in the publications. JE, JNJ, and KF accessed and verified the underlying data.

Declaration of interests

JNJ has received research grants from the US Centers for Disease Control and Prevention and UK National Institute for Health and Care Research; is the chair of the Data Safety Monitoring Board (DSMB) for the HARVEST trial (high-dose oral rifampicin to improve survival from adult tuberculous meningitis: a randomised placebo-controlled double-blinded phase 3 trial) and chair of the trial steering committee for the ACACIA trial (single-dose liposomal amphotericin for asymptomatic cryptococcal antigenemia). DAJM has received research grants from the UK National Institutes of Health, and the UK Medical Research Council;

serves on the DSMB for the NewStrat-TB trial (testing novel strategies for patients hospitalised with HIV-associated disseminated tuberculosis), and is an advisor to the National Institute of Allergy and Infectious Diseases; and is a member of the Ugandan Ministry of Health Technical Working Group on Advanced HIV/TB and of MARA (a non-governmental organisation for dealing with meningitis). All other authors declare no competing interests.

Data sharing

Data collected as part of this study will be made available to others upon reasonable request to the IMPROVE trial management group at jayne.ellis1@lshtm.ac.uk. A dataset containing all data required to reproduce the analyses reported in this Article and supplementary appendix will be uploaded to the London School of Hygiene & Tropical Medicine data repository, where it will be freely available.

For the data repository see
<https://datacompass.lshtm.ac.uk/>

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