STUDY PROTOCOL

Integrated management of cryptococcal meningitis and concurrent opportunistic infections to improve outcomes in advanced HIV disease: a randomised strategy trial [version 1; peer review: 3 approved with reservations]

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Abstract

Background: Mortality associated with HIV-associated cryptococcal meningitis remains high even in the context of clinical trials (24–45% at 10 weeks); mortality at 12-months is up to 78% in resource limited settings. Co-prevalent tuberculosis (TB) is common and preventable, and likely contributes to poor patient outcomes. Innovative strategies to increase TB preventative therapy (TPT) provision and uptake within this high-risk group are needed.

Protocol: The IMPROVE trial is a nested open label, two arm, randomised controlled strategy trial to evaluate the safety (adverse events) and feasibility (adherence and tolerability) of two ultra-short course TPT strategies, in the context of recent diagnosis and treatment for cryptococcal meningitis. We will enrol 205 adults with HIV-associated cryptococcal meningitis from three hospitals in Uganda. Participants will be randomised to either inpatient initiation (early, week 2) or outpatient initiation (standard, week 6) of 1HP (one month of isoniazid and rifapentine). Participant follow-up is to include TB screening, pill counts and tolerability reviews on alternate weeks

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until week-18. The trial primary endpoint is TB-disease free 1HP treatment completion at 18-weeks, secondary endpoints: 1HP treatment completion, 1HP discontinuation, grade ≥3 adverse events and serious adverse events, drug-induced liver injury, incident active TB, 18-week survival; rifapentine, fluconazole and dolutegravir concentrations will be measured in a drug-drug interaction sub-study of 15 eligible participants.

Discussion: The IMPROVE trial will provide preliminary safety and feasibility data to inform 1HP TPT strategies for adults with advanced HIV disease and cryptococcal meningitis. The potential impact of demonstrating that inpatient initiation of 1HP TPT is safe and feasible amongst this high-risk subpopulation with advanced HIV disease, would be to expand the range of clinical encounters in which clinicians can feasibly provide 1HP, and therefore increase the reach of TPT as a preventative intervention.

ISRCTN registration: ISRCTN18437550 (05/11/2021)

Keywords
HIV, cryptococcus, meningitis, TB, preventive therapy

Medical Center: Strong Memorial Hospital, Rochester, USA

Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Cryptococcus is the most common cause of HIV-associated meningitis globally, accounting nearly 20% of all AIDS-related deaths[1]. Despite antifungal therapy, 10-week mortality in sub-Saharan Africa remains between 24 and 45%, even in the context of clinical trials[2–4]. Due to advanced immunosuppression, mortality continues beyond hospital discharge particularly in those with CD4<50 cells/μL[5], and mortality at 12-months after cryptococcal meningitis diagnosis is between 40% and 78% in resource limited settings[6]. The key drivers of this persistently high mortality are not known; however, recent data suggest that co-prevalent opportunistic infections including tuberculosis are common and likely contribute to poor patient outcomes[7–9]. A broader pre-emptive anti-infective package now warrants investigation.

Tuberculosis (TB) is treatable and preventable, yet it remains the most frequent cause of AIDS-related deaths worldwide[10,11]. All people living with HIV (PLHIV) should be systematically screened for active TB disease at every clinical encounter; and following exclusion of active TB disease, TB preventive therapy (TPT) should be provided for all PLHIV, irrespective of anti-retroviral therapy (ART) status and CD4 count[11]. Despite clear recommendations from the World Health Organization (WHO), and robust data that TPT prevents TB disease and deaths[12–14], provision of TPT has been sub-optimal globally. In 2019, of the 38 high TB and TB/HIV burden countries only 23 reported provision of TPT for those receiving ART; coverage varied considerably from less than 1% in Thailand to 89% in Zimbabwe[10]. Dramatic scale up of TPT for PLHIV is one of the WHO's key pillars to meet the 2030 and 2035 End TB Strategy targets[15]. Innovative delivery strategies to increase TPT provision are urgently needed.

Barriers to TPT implementation are multi-factorial and include concerns about TPT adherence, loss to follow-up, and drug toxicity[13]. These concerns are pertinent given the historically long duration of TPT regimens (six or nine months of isoniazid (6H/9H). In 2019 however, the landmark BRIEF TB/A5279 trial demonstrated that one month of rifapentine plus isoniazid (1HP) was non-inferior to 9H for preventing active TB disease in PLHIV. Additionally, treatment completion rates were the highest ever reported in a TPT trial (97%), with a lower incidence of adverse events in the 1HP arm[13]. 1HP is a short, efficacious, well-tolerated, and safe TPT regimen, and was endorsed by WHO as a TPT option in 2020[11]. 1HP – if combined with innovative delivery strategies to increase TPT uptake – offers a major potential breakthrough in the prevention of TB amongst PLHIV globally.

Ultra-short course 1HP TPT may have particular advantages over longer course TPT for patients with advanced HIV disease (AHD), in whom risk of TB disease is greatest. In the context of AHD, expedited completion of TPT has clear benefits with respect to pill burden, drug-drug interactions (DDIs) and in rapid sterilisation of latent TB infection (LTBI)[11,16]. TPT with 1HP is of particular interest in cryptococcosis. In HIV-associated cryptococcal meningitis, ART initiation is delayed due to the risk of cryptococcal-immune reconstitution inflammatory syndrome (IRIS)[3]. The risk of unmasking TB-IRIS, however, remains following ART initiation at 4–6 weeks, with most incident IRIS events occurring within the first month of ART initiation[12,17,18]. Completion of 1HP TPT prior to ART initiation has the potential to reduce incidence of TB-IRIS, active TB disease, and TB deaths amongst this subpopulation[12,19].

The IMPROVE trial will evaluate the safety and feasibility of two strategies for the delivery of 1HP TPT in adults with AHD and cryptococcal meningitis: inpatient initiation (early, during week 2 of anti-fungal therapy for cryptococcosis) or outpatient initiation (standard, during week 6 of anti-fungal therapy for cryptococcosis) of 1HP. Currently, the majority of TPT globally is provided in the outpatient setting. We propose that initiation of 1HP prior to hospital discharge has the potential to increase the reach of TPT as an intervention, and to reduce losses from the LTBI preventive care cascade (identification of at-risk populations, exclusion of active TB, provision of TPT, monitoring for adverse events, adherence and completion of treatment)[20]. The potential benefit of inpatient initiation of TPT, however, should be carefully balanced against the risk for drug-related adverse events including risk of DDIs with antifungals or ART, and poor adherence due to additional pill burden. The optimal TPT strategy to prevent TB disease in HIV-associated cryptococcal meningitis therefore needs to be determined.

Study design

The IMPROVE trial is an open label, two arm, randomised controlled strategy trial to evaluate the safety and feasibility of two 1HP TPT strategies for adults with HIV-associated cryptococcal meningitis. The IMPROVE trial is nested within an observational cohort study screening for concurrent opportunistic infections (OIs) in patients undergoing treatment for cryptococcal meningitis.

All consenting adults (≥18 years) will be screened for active TB disease with urine (Alere TB-LAM, Fuji SILVAMP TB LAM and Xpert Ultra), blood (mycobacteria growth inhibitor tube (MGIT)) culture and chest x-ray (CXR) as part of the ongoing prospective observational cohort study. Study participants in whom active TB disease has been systematically excluded will be randomized (1:1) to inpatient initiation or outpatient initiation 1HP TPT (Figure 1).

This trial has been registered on ISRCTN (ISRCTN18437550) on 5th November 2021. This article follows the SPIRIT guidelines[21].

Hypothesis

Our primary hypothesis is that inpatient initiation of 1HP TPT will be non-inferior to outpatient initiation of 1HP TPT with respect to "TB-disease free 1HP treatment completion", and that inpatient 1HP TPT is safe (adverse events) and feasible (adherence and tolerability) in patients with HIV-associated cryptococcal meningitis.

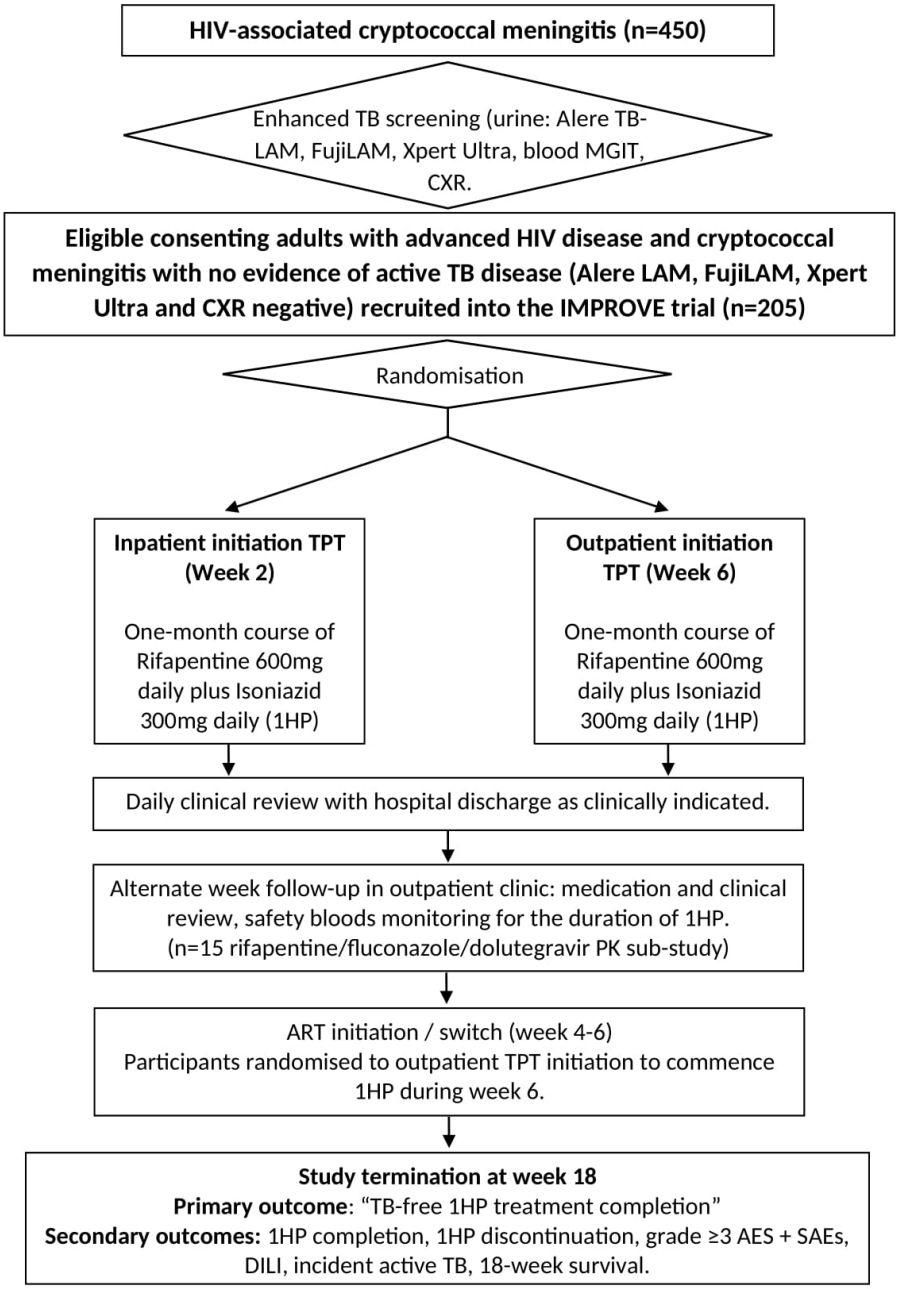

Figure 1. IMPROVE study flow chart. MGIT=mycobacteria growth inhibitor tube; CXR = Chest X-ray; TPT=TB preventative therapy; AEs=adverse events; SAEs=serious adverse events.

Primary objective

- To generate evidence on the safety (adverse events) and feasibility (adherence and tolerability) of 1HP TPT amongst adults with HIV-associated cryptococcal meningitis.

Secondary objective

- To generate preliminary data on potential secondary benefits (reduced loss to follow-up, reduced active TB disease, reduced mortality) of inpatient initiation of 1HP TPT as compared to outpatient initiation of 1HP TPT amongst adults with HIV-associated cryptococcal meningitis.

Study setting

The trial will be set in three hospitals in Uganda: Kiruddu National Referral Hospital, Mulago National Referral Hospital, Kampala and Mbarara Regional Referral Hospital. The study

population will be HIV-positive adults (≥18 years), diagnosed with HIV-associated cryptococcal meningitis.

Primary endpoint

TB-disease free 1HP treatment completion at 18-weeks (after cryptococcal meningitis diagnosis and commencement of anti-fungal therapy). Treatment completion is defined as participant reported adherence to >90% of the study medications, to be completed within 6-weeks from treatment initiation. TB-disease free at 18-weeks is defined as not receiving a diagnosis of active TB disease for the duration of the trial during the 18-week study period.

Secondary endpoints

1. 1HP treatment completion at 18-weeks.
2. 1HP discontinuation of the study drugs for ≥ 5 consecutive days for any reason.
3. Grade ≥3 adverse events (AEs) and serious adverse events (SAEs).
4. Drug-induced liver injury defined as elevation of blood transaminase (ALT) alone ≥ 5x ULN (or ALT ≥ 3x ULN if bilirubin abnormal) or alkaline phosphatase (ALP) alone ≥2x ULN.
5. Incident active TB.
6. 18-week survival.
7. Fluconazole, rifapentine and dolutegravir pharmacokinetics (PK)/ pharmacodynamics (PD) analyses (N=15).

Inclusion criteria

Consecutive hospitalised adults (≥ 18 years) diagnosed with HIV-associated cryptococcal meningitis (confirmed by CSF CrAg testing) will be included in the study. We will include both initial and relapse cryptococcal meningitis episodes. Participants must be HIV-positive. Participants must provide written informed consent or, if unable to consent, have a next of kin who agrees to the patient participating in the study, providing written consent.

Exclusion criteria

Any patient with active TB disease (as evidenced by any positive TB screening test or taking TB therapy at time of screening) will not be eligible for enrolment. In addition, patients with clinical jaundice, abnormal liver function tests (bilirubin > 3.5 mg/dL or alanine aminotransferase (ALT) >200 IU/L), known chronic liver disease, active hepatitis B infection (defined as hepatitis B surface antigen positive) or presenting with a clinical syndrome which in the opinion of the attending clinician, puts the patient at significant risk if he/she were to participate in the 1HP trial will be excluded from the trial. Patients taking any contra-indicated medications including protease inhibitors will not be eligible for inclusion. Hypersensitivity to rifamycins or isoniazid is an exclusion criterion, as are pregnancy and breast feeding.

Consent

Given the nature of cryptococcal meningitis it is anticipated that some patients will lack capacity to consent for themselves. Written informed consent to enter the trial will therefore be obtained from participants or, in the case of those lacking capacity to consent, from next of kin with legal responsibility. Illiterate volunteers will be asked to have a witness present (friend, family or another member of staff independent of the study team) to witness the discussion and thumbprint consent.

The aims, implications, potential benefits and risks associated with the study will be explained in full to all potential participants and/or the next of kin. It will be made clear to potential participants that refusal to participate in the study will not jeopardize their clinical care, and it will be made clear that consent is entirely voluntary and can be withdrawn at any time. Participants enrolled via surrogate consent will be re-consented as soon as their mental status improves and they regain the capacity to consent, with care taken to ensure they understand that they are free to withdraw from the study and if they do so this will not jeopardise their future care.

Original signed consent forms will be kept by the investigator, participants will be given a copy of the signed/thumb-printed consent form and a participant information sheet. The patient information sheet and consent form can be found as *Extended data*[21].

Withdrawals

Participants may withdraw from the study at any time by withdrawing their consent. Assessment of vital status up until 18-weeks (secondary outcome) will continue via telephone calls at a minimum, unless consent is completely withdrawn.

Randomisation and treatment allocation

Following screening and enrolment, participants will be randomised individually, based on random block sizes, using a computer-generated programme to either inpatient initiation (early, week 2) or outpatient initiation (standard, week 6) 1HP TPT. Participants will be randomized on the planned day of discharge from hospital; the specific timing of randomisation will be participant specific as it will depend on the clinical condition of the patient as monitored by the attending study physician and their time of hospital discharge. In instances, where the participant remains an inpatient for ≥14 days, randomisation will occur on day 14 rather than on the planned day of discharge. The trial pharmacist at each study site is responsible for conducting the randomisation by sequentially drawing sealed envelopes that contain the treatment assignment for each enrolled patient.

Interventions

A summary of study interventions including timings are detailed below in the schedule of events table (Table 1).

Primary intervention: Participants will be randomised to receive either a 28-day course of rifapentine 600mg daily plus

Table 1. Schedule of events table.

	Day 1	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk11	Wk 12	Wk 13	Wk 14	Wk 15	Wk 16	Wk 17	Wk 18
Cryptococcal meningitis diagnosed	X																		
Commence anti-fungals[1]	X																		
Inpatient TB screening package[2]	X	X	X																
IMPROVE 1HP RCT enrolment		X	X																
Randomisation[3]			X																
1HP initiation (early inpatient arm)[4]			X																
Hospital discharge			X	X															
Follow-up[5]					X		X		X		X		X		X		X		X
Clinical review					X		X		X		X								X
Pill counts[6]					X		X		X		X								X
Liver function tests[7]					X		X		X		X								X
Safety monitoring blood tests[8]					X		X		X		X								X
PK sampling[9]							X	X	X										
1HP initiation (late outpatient arm)							X												
ART initiation / switch[10]					X	X	X												
Primary outcome[11]																			X
Trial completion																			X

1. Participants will receive antifungal for 1–2 weeks as induction therapy for cryptococcal meningitis. Following completion of induction therapy, patients will step down to 800mg Fluconazole (continuation phase) to complete total 10-week course.

2. Clinical samples will be stored for future research

3. In cases, where the participant remains an inpatient for ≥14 days, randomisation will occur on day 14 rather than on the planned day of discharge.

4. 1HP = Rifapentine 600mg daily plus Isoniazid 300mg daily (plus pyridoxine)

5. Follow-up will occur on alternate weeks until week-18.

6. Self-reported adherence will be assessed, and pill counts conducted.

7. Alternate week liver function tests (LFTs) will be performed to screen for drug-induced liver injury for the duration of 1HP.

8. Safety monitoring blood tests will be taken including alternate week full blood count and renal function blood tests for the duration of 1HP. Blood will also be stored for future research studies.

9. Rifapentine / fluconazole / dolutegravir PK sampling will be conducted for 15 participants.

10. We anticipate that ~1/3 of participants will be ART naïve, these patients will start ART at week 4–6, ~1/3 of participants will be on ART but have clinical/immunological/virological failure, these patients will switch ART at week 4–6. Patients newly started on ART (<3-months prior to their cryptococcosis diagnosis) i.e. those with unmasking cryptococcal-IRIS will continue their ART.

11. Treatment completion is defined as participant reported adherence to >90% of the study medications, to be completed within 6-weeks of treatment initiation. TB-disease free is defined as not receiving a diagnosis of active TB disease for the duration of the trial.

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isoniazid 300mg daily (1HP) to be initiated as an inpatient or as an outpatient. Amongst participants in the inpatient initiation arm, 1HP TPT will be started in hospital during the second week after cryptococcal meningitis diagnosis. Amongst participants in the outpatient initiation arm, 1HP TPT will be started in the outpatient clinic during the sixth week after cryptococcal meningitis diagnosis. The initial HP treatment dose will be given as directly observed therapy (DOT) in a healthcare setting for both intervention arms (either in the hospital or in the outpatient clinic), thereafter 1HP will be self-administered. Adjunctive pyridoxine (25mg/day) will be provided for all study participants to reduce the risk of peripheral neuropathy.

Inpatient management: Participants will have a full history and examination at time of cryptococcal meningitis diagnosis and will be reviewed daily whilst admitted. Following completion of induction anti-fungal therapy for cryptococcal meningitis, participants may be discharged at the discretion of the attending study physician. Hospital discharge will typically occur ~7–14 days following cryptococcal meningitis diagnosis and commencement of anti-fungal therapy. Amongst participants in the inpatient initiation 1HP arm at least the first dose of 1HP must be given as in inpatient. Following hospital discharge participants will be followed-up every two weeks until week-18.

Outpatient management: This will include: (1) clinical review with TB symptom screen and full physical examination; (2) 1HP adherence review with pill counts during 1HP receipt; (3) safety monitoring blood tests for the duration of 1HP; (4) additional myco-bacteriological and/or radiological testing for active TB disease at the discretion of the study physician as clinically indicated; (5) ART planning and counselling. Participants randomised to the outpatient initiation arm will commence 1HP during week 6.

Assessment of adherence: Adherence to 1HP treatment will be assessed by means of participant interview and pill counts at follow up visits. 1HP treatment completion will be defined as participant reported adherence to >90% of the study medications, to be completed within 6-weeks from treatment initiation. Discontinuation will be defined as cessation of the study drugs for ≥ 5 consecutive days for any reason.

Blood test monitoring: Blood will be drawn prior to enrolment including liver function tests and hepatitis B surface antigen testing (HbsAg). Safety monitoring blood tests (liver function tests (LFTs), renal function tests, and full blood count) will thereafter be taken on alternate weeks for the duration of 1HP therapy**.** If a participant has abnormal LFTs (LFT above the upper limit of normal, which do not meet the exclusion criteria) at screening, outpatient follow-up with clinical review and safety monitoring blood tests will be weekly. Additional samples will be taken alongside monitoring blood tests for sub-studies, including PK/PD studies.

Anti-retroviral therapy: HIV-positive participants who are ART naïve, or who have virological failure will initiate/switch ART at week 4–6 in line with WHO and Ugandan guidelines. Tenofovir, Lamivudine and Dolutegravir (TDF+3TC+DTG) will be the first line ART regimen as per WHO and Ugandan guidelines; there are no drug-drug interactions (DDIs) anticipated between isoniazid and TDF, 3TC or DTG, nor between rifapentine and TDF and 3TC. There is a potential DDI between rifapentine and DTG which will be evaluated in the PK sub-study. ART initiation/switch will be done in conjunction with the participant's ART clinic with second-line or alternative regimens available as required.

Treatment modifications, interruptions, and discontinuations

Study physicians may interrupt 1HP dosing at physician discretion for a potentially life-threatening adverse reaction. Study participants diagnosed with drug-induced liver injury will stop 1HP and it will not be recommenced. Study participants diagnosed with active TB disease during the study period will stop 1HP and commence treatment for active TB in line with drug-susceptibility testing. If a study participant becomes pregnant whilst receiving 1HP, 1HP will be discontinued and isoniazid preventative therapy (IPT) will be started in line with Ugandan guidelines.

Study participants who are randomised to outpatient initiation 1HP who are diagnosed with active TB disease, become pregnant, or who commence a protease inhibitor prior to week-6, will not initiate 1HP TPT as planned.

Termination of study

Reasons for study termination are study completion (week 18), withdrawal of consent, death, or lost to follow up. At study termination the study follow-up and termination case report forms (CRF) will be completed documenting interval history, vital status, primary and secondary endpoints, and reason for study termination.

Timeline

A total of 205 patients will be recruited over a period of 3 years. This is feasible based upon previous experience and rates of trial recruitment at our three clinical sites. IMPROVE study recruitment will be supported by regular sensitisation activities to facilitate referrals where appropriate from surrounding clinics and hospitals.

Statistical methods

The primary endpoint, TB-disease free 1HP treatment completion is a composite measure of safety and feasibility. The primary endpoint will be analysed using a generalised linear model (GLM), with a binomial distribution and an identity-link function, from which the unadjusted risk difference between the treatment groups and its one-sided 95% CI will be presented. If the upper limit of the one-sided 95% CI falls below the non-inferiority margin of 15%, non-inferiority will be declared. Assuming an 80% TB-disease free completion rate in the outpatient initiation 1HP TPT arm, a sample size of 205 will give 80% power, with a one sided 95% confidence interval, to determine whether inpatient initiation of 1HP led to non-inferior TB-disease free completion rates

at a 15% non-inferiority margin, allowing for an 5% rate of loss to follow-up and 10% post-randomisation mortality at 18-weeks.

Secondary endpoints including survival will be compared at trial completion (18-weeks after cryptococcal meningitis diagnosis and commencement of anti-fungal therapy) based on superiority test using a 5% two-sided significance level. Analysis of binary secondary outcomes will be conducted using logistic regression models to calculate the OR and two sided 95% CIs between the treatment groups. Analyses of survival data and incident TB will be conducted using unadjusted Cox regression analysis to calculate the HR and 95% CI between the treatment groups. Unadjusted models are appropriate in the context of randomisation, and given the potential for data sparsity. Kaplan–Meier survival curves from point of cryptococcal meningitis diagnosis through 18-weeks by TPT group will be calculated and displayed.

The safety analysis will be descriptive and the frequency and proportions of participants suffering clinical and laboratory-defined grade ≥3 AEs and SAEs will be generated by treatment arms. The safety analysis will include every participant who received a dose of HP.

Ancillary studies

1. **Drug-drug interactions caused by rifapentine associated CYP450 enzyme induction: implications for clinical management in cryptococcal meningitis and advanced HIV disease.**

   Study population: 15 study participants with HIV-associated cryptococcal meningitis taking 1HP, fluconazole and dolutegravir.

   Hypothesis: Our hypothesis is that neither fluconazole nor dolutegravir will require dose adjustment when co-administered with rifapentine, and therefore a standardized package of care including TPT can be provided for adults with HIV-associated cryptococcal meningitis without need for dose modification.

   Schedule of events: PK sampling will be performed on day 0, 5 and 14 of 1HP therapy. Rifapentine, fluconazole, dolutegravir concentrations will be measured at five time-points on each PK-day using liquid chromatography-tandem mass spectrometry approach.

   Analysis: Non compartmental analysis (Cmax, Cmin, AUC)

Quality control and assurance

Trial oversight will be provided by the trial monitoring group (TMG), trial steering committee (TSC) and an independent data safety and monitoring board (DSMB). The DSMB consists of three independent members: DSMB chair, DSMB statistician, and DSMB clinician; the role of the DSMB is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial. The study sponsor is the London School of Hygiene and Tropical Medicine (LSHTM). LSHTM, Keppel Street, London, WC1E 7HT as the trial sponsor had no role in the trial design, and will not be involved in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

The sites will be monitored at regular intervals with visits by the principal investigator (PI) and the study monitor in order to monitor the conduct of the trial and ensure that the principles of International Conference of Harmonisation (ICH) Good Clinical Practice (GCP) are being adhered to. Recruiting sites will be visited by the study monitor and the PI at the site initiation visit (SIV) prior to recruitment commencement, after the first 10 participants, when 50% of recruitment is complete, and at trial closure. Additional visits will be conducted if required. Monitoring visits will ensure that all training has been completed, that drug supply and equipment are in place and that all staff are up to date on the protocol and procedures.

Central monitoring will be performed in addition to the on-site monitoring procedures. All grade ≥3 AEs, SAEs and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported to the TMG within 24hrs; SAEs and SUSARs must also be reported to the local ethics and regulatory bodies (Mulago Hospital Institutional Review Board and Uganda National Council for Science and Technology) no later than 7 days after the investigators are first aware. Quarterly reports on the progress of the trial, as well as the frequency of The Division of AIDS (DAIDS) grade ≥3 AEs, SAEs and all SUSARs will be compiled by the PI/statistician and reviewed by the TMG and the local ethics and regulatory bodies. These reports will be compiled and presented to the TSC and the DSMB at least once every 6 months. Annual summative reports will be sent to the sponsor for review. The DSMB will also review participants' safety data and frequency and causes of death. Any significant issues/protocol violations/serious breaches will also be communicated to the study monitor, sponsor, and Institutional review board (IRB).

Data collection and management

Study source documents will include CRFs, laboratory results, radiology results and other relevant documents. Data entry will occur via the DataFax system: paper-based CRFs are scanned in by the study team, emailed to a remote server, and participant data is then entered by intelligent character recognition. After an initial automated error-checking, a second review for accuracy is performed by the DataFax team at the Infectious Diseases Institute, Uganda. The DataFax system allows for automated data queries to highlight any missing data in real time. DataFax also allows for remote review by oversight bodies and permanent archiving. CRFs will be harmonized between all study sites enabling multi-site data management. Essential source documents will be retained for 20-years after the completion of the study, as per Ugandan guidelines.

Ethical considerations

Patient confidentiality: All participant-related information (including CRFs, laboratory specimens, reports, etc.) will be kept strictly confidential. Participants will be identified only by means of a coded number specific to each participant. All computerised databases will identify participants by numeric codes only, and will be password-protected. All paper records will be kept in a secure, locked location and only research staff will have access to the records. HIV clinic records will be kept in the local HIV clinic as per local practice.

Sample use and storage: Consent forms also include consent for storage of samples (blood and urine) in accordance with Uganda National Council for Science & Technology guidelines and LSHTM Human Tissue Act Policy. Participant specimens will be stored for current and future research studies related to opportunistic infections and the immune response in the IDI translational laboratory in accordance with local standards and LSHTM Human Tissue Act Policy.

Data sharing with third parties: Upon request, participant records will be made available to the following named parties only: study sponsor, the sponsor's monitoring representative, and applicable regulatory entities, including the Uganda National Council of Science and Technology and Mulago IRB. The anonymised database/protocol will be shared with the journal, if required.

Ethical approval: The investigators have obtained approval from the Research Ethics Committees of the London School of Hygiene & Tropical Medicine (Ref: 24059, approved 07 June 2021), as well as Mulago Hospital IRB (Ref: MHREC 2021-25, approved 28 July 2021), and the Uganda National Council of Science and Technology (UNCST, Ref: HS1607ES, approved 25 August 2021). Any further amendments will be submitted and approved by each ethics committee, and communicated with all study investigators prior to implementation.

Indemnity

The sponsor of the trial is the London School of Hygiene and Tropical Medicine and as such provides indemnity for the trial. All personnel involved in the trial will be expected to be indemnified by their employing authority.

Publication policy

We will share results though presentations at scientific conferences and in peer-reviewed open-access journals.

Study status

The first IMPROVE study participant was recruited on 21 January 2021. The IMPROVE study is actively recruiting.

Discussion

The IMPROVE trial will provide preliminary safety and feasibility data to inform 1HP TPT strategies for adults with advanced HIV disease and cryptococcal meningitis. These data will be used to inform design of a subsequent phase 3 trial to evaluate the efficacy of inpatient 1HP TPT in preventing TB disease and deaths in AHD. The potential impact of demonstrating that inpatient initiation of 1HP TPT is safe and acceptable for this high-risk AHD subpopulation, would be to expand the range of clinical encounters in which clinicians can feasibly provide TPT for PLHIV. Data suggest that amongst PLHIV, of those offered TPT more that 90% agree to start, and reported treatment completion for short course rifapentine-containing TPT regimens (1HP/3HP) is >90%[13,14]; the vast majority of losses from the LTBI care cascade therefore occur up-stream and are driven by health system factors rather than patients. Collapsing the LTBI care cascade during hospitalisation to enable rapid TPT initiation prior to discharge, could significantly increase the proportion of adults with AHD successfully initiated on TPT, and therefore reduce the incidence of active TB disease and TB-associated deaths within this key population.

Data availability

Underlying data

No underlying data are associated with this article.

Extended data

Zenodo: Integrated management of cryptococcal meningitis and concurrent opportunistic infections to improve outcomes in advanced HIV disease: a randomised strategy trial. https://doi.org/10.5281/zenodo.7858543[21].

This project contains the following extended data:

- IMPROVE 1HP RCT PIS - English V6.0 November 2022.docx
- IMPROVE consent form - English V2 3rd March 2022.docx

Reporting guidelines

Zenodo: SPIRIT checklist for 'Integrated management of cryptococcal meningitis and concurrent opportunistic infections to improve outcomes in advanced HIV disease: a randomised strategy trial'. https://doi.org/10.5281/zenodo.7858543[21].

Acknowledgements

All of the listed authors have contributed significantly to development of the protocol or are directly involved in data collection. All of the listed authors have seen and approved the manuscript. Each author meets the ICMJE authorship criteria. We acknowledge the support offered by the individual sites and staff at Kiruddu National Referral Hospital, Mulago National Referral Hospital, Kampala and Mbarara Regional Referral Hospital; and the TSC & DSMB for monitoring the trial.

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Open Peer Review

Current Peer Review Status: ? ? ?

Version 1

Reviewer Report 02 May 2024

https://doi.org/10.21956/wellcomeopenres.21407.r78401

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Sonal Munsiff
University of Rochester Medical Center: Strong Memorial Hospital, Rochester, NY, USA

The main objective of this study which is going to be an open label, two arm randomized controlled trial, is to assess the safety and feasibility of giving 1 month of isoniazid and rifapentine regimen for TB preventive therapy in adults with recently diagnosed HIV associated cryptococcal meningitis. The objective is laudable and the study worth doing.
Overall the protocol is well written but there are several areas where I think some more detail would be helpful to the reader. In addition, there is a serious flaw in rationale for using the current regimen in light of known sever DDI between dolutegravir and rifapentine, as noted below.
In the introduction, paragraph 4, page 3, the authors state that ultra short course TPT may have particular advantages over longer courses. They state that one clear benefit is respect to Drug drug interactions. However, most of the ART regimens now in use have significant interaction with rifapentine and therefore correct dosing of dolutegravir and rifapentine remains an ongoing challenge.
Further on in that same paragraph they state that “the risk of unmasking TB-IRIS, however, remains following ART initiation at 4-6 weeks, with most incident IRIS events occurring within the first month of ART initiation.” It would be helpful here for the reader to have some data on the risk of TB IRIS in the population being studied, rather than just citing referral references.
Also, the authors state further in that paragraph, that “Completion of 1HP TPT prior to ART initiation has the potential to reduce incidence of TB-IRIS, active TB disease, and TB deaths among this subpopulation.” Again, data on the risk of these events would be helpful.
In the section on Anti-retroviral therapy on page 7 they state that “there is a potential DDI between rifapentine and DTG, which will be evaluated in the PK sub-study.” In fact, there is a very well known interaction between DTG and rifapentine, and numerous studies have shown this, and this is not addressed at all in this protocol. This known DDI should all be addressed.
There is serious concern that using standard dose dolutegravir with rifapentine can lower dolutegravir levels enough to lead to integrase resistance. The current recommendation by WHO is to use double dose DTG (50 milligrams twice a day instead of 50 milligrams once a day), when given with rifapentine 1 HP.
The only way to know that DTG dose is adequate is by looking at outcomes of HIV viral loads,

along with the PK data. The schedule of events that is given does not look at HIV viral load at any time point. Also, an N of 15 for the PK sub study is likely inadequate.
The hypothesis (page 8) that neither fluconazole nor dolutegravir will require dose adjustment when co-administered with rifapentine is therefore not based on the available data.
The authors may want to consider that a good rationale for giving early TB preventive therapy with 1HP regimen is that it could be completed before anti-retroviral therapy is started in ART nauve people with cryptococcal meningitis, at 6 weeks after meningitis treatment, so that drug drug interactions between ART and rifapentine could be avoided.
Another thing to remember is that DTG levels could be affected even after rifapentine is stopped as the effect of rifapentine on the cytochrome P450 system is expected to persist for one to two weeks after stopping the rifapentine. In general, for people on DTG who get 1HP regimen, it is recommended to continue double dose DTG for 2 weeks after stopping rifapentine.

Is the rationale for, and objectives of, the study clearly described?
Partly

Is the study design appropriate for the research question?
No

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Tuberculosis treatment Clinical trials research, tuberculosis program evalaution, HIV and TB co-treatment challenges, HIV Clinical trials

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 28 April 2024

https://doi.org/10.21956/wellcomeopenres.21407.r78395

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Vincent Ganu
Korle-Bu Teaching Hospital, Accra, Ghana

Title:

In the protocol, the opportunistic infection of interest is TB but what the authors are interested in is TPT. And so I suggest we state it as such (i.e. Integrated management of crypto and concurrent TB preventive therapy) in the title rather than stating opportunistic infections which is very broad.

Abstract:
"IMPROVE" should be written in full as it is the first time of mention.

Methods:
Will there be use of standardized questionnaire to collect information about participants? If so, lets state and state the variables that will be collected with the questionnaire

Figure 1:
How did we get the 450 and the 205? And how are the 205 selected from the 450?
DILI should be added to the abbreviation lists and written in full.

Primary Objective:
I thought the aim of the study was to compare the safety and feasibility of 1 HP among 2 groups (i.e. In-patient and outpatient) to establish non-inferiority of both strategies or approaches hence the study design chosen (trial with randomization).
Because for the primary objective currently stated, the current study design is not needed to answer this question. Could have done a cohort study (prospective or retrospective) to answer the primary objective as it is stated now. Need to rephrase to align with the study design/approach.

Study setting:
Kindly give additional information about study sites to demonstrate they have the existing case load of cryptococcal meningitis for the conduct of this study within the study time period as the prevalence of crypto is low among HIV patients. A little more information to put things in perspective will be appreciated. A fair idea of the HIV patient numbers, admission figures and mortality/survival figures relating to each of these facilities.

Primary endpoint:
Need to be specific on the starting time point of calculating the 18 weeks. Is it after diagnosis of crypto or commencement of antifungal therapy as the two may not necessarily occur on the same day due to implementation challenges.
This definition for "treatment completion "does not fit there but rather fits after point 1 under secondary endpoints.

Inclusion criteria:
How do the investigators plan on ensuring that the patients are HIV positive. They should state the steps they will take to ensure this (the tests to be done and the type of tests to be used) so that any other researcher can follow and do same if conducting study elsewhere.

Exclusion criteria:
I think a *major* activity in this study will be the screening of potential participants for TB to rule out active TB.

1. The authors should have a sub-section titled study procedure under which they detail all their activities. One of the main activities to detail will be how the potential participants will be screened for TB.

2. In the flow diagram, several tests have been stated for TB screening. Will each participant be screened using all the tests? If no, who receives what and what is the justification for each test for a participant. The urine LAM is usually best for patients with CD4 cell count <100 or 200. So who gets to do this? GeneXpert will screen sputum. Who gets to do this test and who does not? Is very participant receiving an x-ray? Who gets to do it and who does not?

3. Because this is a study, how will active TB be diagnosed? It must be stated in full as there are different test being proposed to rule out active TB.

4. And who does the TB diagnosis to ensure agreement on what is TB and what is not TB? It is best if there are 2 or more experts reviewing the tests outcomes to agree on what is considered active TB and what is not.

5. What about sputum negative TB diagnosis as occurs in clinical practice? Are they excluded from the study as well?

6. For standardization purposes, where will the various TB tests be done and the procedure for each test should be clearly outlined. This is to ensure that the study is reproducible if other researchers want to pursue same study in other jurisdictions.

7. As part of the patient screening, will each patient do liver function test, hepatitis B surface antigen? These must be clearly stated as part of study activities.

8. Based on the above, then it means there will be a screening phase for the study so patient's samples are taken for analysis. Then based on the outcomes of the test results, there will be the enrolment phase where those eligible will be included in the study. I think these should be clearly outlined under the study procedure in a systematic way that every reader can follow

Withdrawals:
I think if the patient says they have withdrawn from the study, then there is no need to do any follow up. There is nothing like partially withdrawn or incomplete withdrawal.

Randomization or treatment allocation:
"In instances, where the participant remains an inpatient for ≥14 days".
This should be clarified as it will have an impact on randomization and the patient's treatment outcomes. Is it 14 days from initial admission? Or 14 days after diagnosis of crypto meningitis? Or 14 days after start of treatment for crypto meningitis? This is important because there will be a time lag between patient presenting to the hospital, carrying out a lumbar puncture procedure and then a turn-around time for getting results of CSF analysis. And patient is still on admission when all these are being done.

Table 1:
- What antifungals are being used? Are these antifungals be administered via intravenous route or via oral route or a mixture? Will it be standard for all patients? Is the study

providing these antifungals for the patients as part of the study for standardization purpose? It's important to clarify the above as it will have an impact on patient treatment outcomes and be a confounder of the study. Reason why all the above needs to be taken into consideration and stated in the protocol.

- What will the pill count be assessing? Fluconazole or 1HP or both or drugs for other co-morbidities? These need to be stated clearly. Assessment of adherence to all medications is key as it has an effect or impact on treatment outcomes and may be confounders. We are looking at integration of management. Another reason why we should monitor for adherence on all medications.

- What drug will the patient be taking after completing the 10 week continuation phase? This should be stated in the study procedure sub-section as the study follow up period is for 18 weeks.

"**We anticipate that ~1/3 of participants will be ART naïve, these patients will start ART at week 4–6, ~1/3 of participants will be on ART but have clinical/immunological/virological failure**"
What are these anticipations based on? What is the evidence for this or is it an educated guess? Is it from literature or from figures at the study sites? Too much has been summarized in this tables and needs to be explained under the methods section above

Inpatient management:
" **Following hospital discharge participants will be followed-up every two weeks until week-18"**
What measures are the authors putting in place to reduce lost to follow up during the follow-up period? All these should be stated clearly? Are there incentives such as tokens for transport purposes for patients to increase their chances of coming for review? Are information on their phone contacts and those of caregivers being taken to do follow-up? Who will be one doing the follow-up? All these should be clearly outlined in the protocol

Outpatient management (point 4):
The study physician is part of the research group and there must be a guideline or protocol to be followed for ruling out active TB. This should be stated. It cannot be at the discretion of the study physician as it affects the rigorousness of the study

Sample size:
- What is the justification for this sample size? How was it calculated and what were the basis for the calculation?

- Since there are 2 groups, is it 205 per group OR the 2 groups make up the 205?

- Will be good to state the formula used or the software used and the reference for readers to follow. And this should not be mixed with the statistical analysis methods

- What is the basis for selection of 5% as the loss to follow up rate and not 10% or 15%?

Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 May 2024

Jayne Ellis

Dear Vincent Ganu, Thank you for taking the time to review the IMPROVE protocol - your feedback is very much appreciated. Please find below responses to each of your comments raised:

Title: In the protocol, the opportunistic infection of interest is TB but what the authors are interested in is TPT. And so I suggest we state it as such (i.e. Integrated management of crypto and concurrent TB preventive therapy) in the title rather than stating opportunistic infections which is very broad. Thank you for this feedback but we cannot change the IRB-approved study title at this stage.

2. Abstract:
"IMPROVE" should be written in full as it is the first time of mention. Thank you, this has been amended.

3. Methods:
Will there be use of standardized questionnaire to collect information about participants? If so, lets state and state the variables that will be collected with the questionnaire Thank you, the following has now been included "Case report forms (CRFs) detailing baseline demographics, clinical details including symptoms, clinical examination findings, ART history, TB and TPT history, and laboratory parameters will be collected." **4. Figure 1:**
How did we get the 450 and the 205? And how are the 205 selected from the 450? DILI should be added to the abbreviation lists and written in full. 450 adults with HIV-associated cryptococcal meningitis will have enhanced TB screening as part of the parent study. Only those with no evidence of active TB disease, will be eligible for consent and recruitment into the IMPROVE TB preventive therapy trial (n=205). A footnote has been

added to the figure to explain this more clearly.

5. Primary Objective:
I thought the aim of the study was to compare the safety and feasibility of 1 HP among 2 groups (i.e. In-patient and outpatient) to establish non-inferiority of both strategies or approaches hence the study design chosen (trial with randomization). Because for the primary objective currently stated, the current study design is not needed to answer this question. Could have done a cohort study (prospective or retrospective) to answer the primary objective as it is stated now. Need to rephrase to align with the study design/approach. Thank you, the primary objective has been amended to read: "To generate comparative data to compare the safety (adverse events) and feasibility (adherence and tolerability) of inpatient vs. outpatient initiation of 1HP TPT amongst adults with HIV-associated cryptococcal meningitis."

6. Study setting:
Kindly give additional information about study sites to demonstrate they have the existing case load of cryptococcal meningitis for the conduct of this study within the study time period as the prevalence of crypto is low among HIV patients. A little more information to put things in perspective will be appreciated. A fair idea of the HIV patient numbers, admission figures and mortality/survival figures relating to each of these facilities. Our team have been conducting cryptococcal meningitis studies across these sites 2006, and these recruitment estimates were based on our trial experience in this setting. To give you some contemporaneous data, in the last 3-months, we have recruited 26 adults with HIV-associated cryptococcal meningitis at Mulago National Referral Hospital, 14 from Kiruddu National Referral Hospital, and 12 from Mbarara Regional Referral Hospital (i.e. ~17 per month in total across all sites).

7. Primary endpoint:
Need to be specific on the starting time point of calculating the 18 weeks. Is it after diagnosis of crypto or commencement of antifungal therapy as the two may not necessarily occur on the same day due to implementation challenges. Thank you for this feedback. This is 18-weeks from when the participant is recruited into the parent study, and we therefore refer to diagnosis of cryptococcal meningitis and commencement of anti-fungal within the study. We appreciate that if a patient was referred to our team with a suspected diagnosis of cryptococcal meningitis, there may be, as you describe a lag-period, however for study purposes we do not confirm the diagnosis of cryptococcal meningitis until study-team performed CSF CrAg has been confirmed as positive. Within the study, we always ensure that anti-fungal medications are started on the same day as the diagnosis is made. **This definition for "treatment completion "does not fit there but rather fits after point 1 under secondary endpoints.** 1HP adherence (defined as adherence to >90% of the 1HP study medications, to be completed within 6-weeks from treatment initiation) is a key component of the primary outcome, and key to assessing the feasibility of giving 1HP to this patient population. We have therefore left maintained this definition within the primary end-point heading, but have additionally included it as well alongside the secondary endpoints as suggested.

8. Inclusion criteria:

How do the investigators plan on ensuring that the patients are HIV positive. They should state the steps they will take to ensure this (the tests to be done and the type of tests to be used) so that any other researcher can follow and do same if conducting study elsewhere. To be suitable for screening for the IMPROVE trial, a patient needs to be receiving treatment for HIV-associated cryptococcal meningitis i.e. the diagnosis of HIV and cryptococcal meningitis is performed by the parent cryptococcal meningitis study prior to IMPROVE screening. IMPROVE screening, consent and randomisation occurs just prior to hospital discharge. In terms of HIV screening within the parent study, where HIV status is unknown, counselling and HIV testing is performed using a fourth generation point-of-care test HIV antigen/antibody test. If a participant is known HIV-positive e.g if taking ART at admission, repeat HIV testing is not repeated.

Exclusion criteria:
I think a *major* activity in this study will be the screening of potential participants for TB to rule out active TB.

- **The authors should have a sub-section titled study procedure under which they detail all their activities. One of the main activities to detail will be how the potential participants will be screened for TB.**

Thank you, the following "eligibility screening" section has now been added to the manuscript: All potential study participant screened for the IMPROVE trial have the following TB diagnostics performed: urine Alere TB-LAM, urine Xpert Ultra, TB blood culture, and chest radiology. Additional laboratory (including Xpert Ultra on clinical samples (sputum / CSF / lymph node aspirate), and radiological tests may also be undertaken dependent on clinical presentation.

- **In the flow diagram, several tests have been stated for TB screening. Will each participant be screened using all the tests? If no, who receives what and what is the justification for each test for a participant. The urine LAM is usually best for patients with CD4 cell count <100 or 200. So who gets to do this? GeneXpert will screen sputum. Who gets to do this test and who does not? Is very participant receiving an x-ray? Who gets to do it and who does not?**

Yes, as per my paragraph above, all potential participants get urine Alere TB-LAM, urine Xpert Ultra, TB blood culture, chest radiology +/- additional TB diagnostics depending on the clinical presentation.

- **Because this is a study, how will active TB be diagnosed? It must be stated in full as there are different test being proposed to rule out active TB.**

In terms of screening for IMPROVE eligibility, this is as stated in the exclusion criteria: "any patient with active TB disease (as evidenced by any positive TB screening test or taking TB therapy at time of screening) will not be eligible for enrolment." i.e. a TB diagnosis may be microbiological (definite TB disease), or clinical TB disease (empirical treatment based on a clinical and/or radiological syndrome without a confirmed microbiological diagnosis).

- **And who does the TB diagnosis to ensure agreement on what is TB and what is not TB? It is best if there are 2 or more experts reviewing the tests outcomes to agree on what is considered active TB and what is not.**

Screening for IMPROVE eligibility is performed by the study team and any complex cases are discussed during a weekly team meeting. Any clinical or microbiological evidence of TB disease must be considered as an exclusion criteria. Only if the screening study doctors believe that the patient does not have active TB disease, should they be consider for

inclusion into the trial.

- **What about sputum negative TB diagnosis as occurs in clinical practice? Are they excluded from the study as well?**

Yes clinical TB disease is also an exclusion criteria.

- **For standardization purposes, where will the various TB tests be done and the procedure for each test should be clearly outlined. This is to ensure that the study is reproducible if other researchers want to pursue same study in other jurisdictions.**

All TB tests (are performed in accredited laboratories and/or using accredited tests following standard procedures and manufacturers guidelines.

- **As part of the patient screening, will each patient do liver function test, hepatitis B surface antigen? These must be clearly stated as part of study activities.**

This is as per current stated under "Blood test monitoring: Blood will be drawn prior to enrolment including liver function tests and hepatitis B surface antigen testing (HbsAg)."

- **Based on the above, then it means there will be a screening phase for the study so patient's samples are taken for analysis. Then based on the outcomes of the test results, there will be the enrolment phase where those eligible will be included in the study. I think these should be clearly outlined under the study procedure in a systematic way that every reader can follow.**

Thank you, as per the above a section entitled eligibility screening has been added to the manuscript.

Withdrawals:

I think if the patient says they have withdrawn from the study, then there is no need to do any follow up. There is nothing like partially withdrawn or incomplete withdrawal. Although these participants will not contribute to the primary end-point analysis, it will still be important to describe survival status amongst those withdrawn if consent is given.

Randomization or treatment allocation:

"In instances, where the participant remains an inpatient for ≥14 days".

This should be clarified as it will have an impact on randomization and the patient's treatment outcomes. Is it 14 days from initial admission? Or 14 days after diagnosis of crypto meningitis? Or 14 days after start of treatment for crypto meningitis? This is important because there will be a time lag between patient presenting to the hospital, carrying out a lumbar puncture procedure and then a turn-around time for getting results of CSF analysis. And patient is still on admission when all these are being done. This is ≥14 days from study-confirmed diagnosis of cryptococcal meningitis and being recruited into the parent study.

Table 1:

- **What antifungals are being used? Are these antifungals be administered via intravenous route or via oral route or a mixture? Will it be standard for all patients? Is the study providing these antifungals for the patients as part of the**

study for standardization purpose? It's important to clarify the above as it will have an impact on patient treatment outcomes and be a confounder of the study. Reason why all the above needs to be taken into consideration and stated in the protocol.

All IMPROVE participants receive amphotericin-based induction anti-fungal therapy. The induction regimen received however, does depend upon drug availability and whether the participant received induction anti-fungal therapy as part of a randomized controlled trial. These data are collected, however given this is an RCT we expect all baseline co-variates including anti-fungal regimens to be well balanced across treatment arms at time of randomization into IMPROVE.

- **What will the pill count be assessing? Fluconazole or 1HP or both or drugs for other co-morbidities? These need to be stated clearly. Assessment of adherence to all medications is key as it has an effect or impact on treatment outcomes and may be confounders. We are looking at integration of management. Another reason why we should monitor for adherence on all medications.**

Pill counts refers to 1HP only. This has been clarified in the text.

- **What drug will the patient be taking after completing the 10 week continuation phase? This should be stated in the study procedure sub-section as the study follow up period is for 18 weeks.**

200mg of fluconazole. This has been added to the text. **"We anticipate that ~1/3 of participants will be ART naïve, these patients will start ART at week 4–6, ~1/3 of participants will be on ART but have clinical/immunological/virological failure" What are these anticipations based on? What is the evidence for this or is it an educated guess? Is it from literature or from figures at the study sites? Too much has been summarized in this tables and needs to be explained under the methods section above** This is based on our experience working at the study sites.

Inpatient management:
" Following hospital discharge participants will be followed-up every two weeks until week-18"
What measures are the authors putting in place to reduce lost to follow up during the follow-up period? All these should be stated clearly? Are there incentives such as tokens for transport purposes for patients to increase their chances of coming for review? Are information on their phone contacts and those of caregivers being taken to do follow-up? Who will be one doing the follow-up? All these should be clearly outlined in the protocol Thank you for these points. The following have been included within the follow-up section:

- At time of discharge contact details for participants are recorded to facilitate follow-up.
- Follow-up visits are performed by the IMPROVE study team.
- Participants are reimbursed for travel to outpatient visits.

Outpatient management (point 4):
The study physician is part of the research group and there must be a guideline or protocol to be followed for ruling out active TB. This should be stated. It cannot be at the discretion of the study physician as it affects the rigorousness of the study. Thank you for this point. The following has been added: At each study visit IMPROVE participants

will undergo systematic TB screening using WHO TB 4-symptom screen (WHO4SS) and if screen positive will undergo microbiological investigation with urine Alere-LAM, and sputum Xpert Ultra if able to produce sputum. If microbiological investigations are negative this will be followed up with a chest radiograph to further investigate for TB.

- A diagnosis of confirmed TB disease will be assigned in cases with any positive microbiological TB test at any point during the study period, whether TB treatment is initiated or not.
- Participants treated for tuberculosis but without microbiological confirmation will be assigned by a clinical end-point adjudication committee as either probable – if radiological and/or clinical features (which could include consideration of treatment response) are considered compatible with active TB – or possible – if radiological and clinical features are not deemed sufficient for a diagnosis of active TB (which could also include a lack of information such as a missing chest radiograph or radiograph report).
- Participants not treated for active TB will be assigned as 'not tuberculosis' except in the circumstance in which TB treatment is withheld from an individual determined to have active TB but in whom treatment is not deemed appropriate (for example in end-of-life care) when they will be assigned as confirmed, probable or possible according to criteria above.

Sample size:

- **What is the justification for this sample size? How was it calculated and what were the basis for the calculation?**
- **Since there are 2 groups, is it 205 per group OR the 2 groups make up the 205?**

1HP treatment completion was 97% in the BRIEF-TB trial in the outpatient setting; as the key trial of 1HP amongst PLHIV these were the primary data to inform our power calculations. Given that our cohort have more advanced HIV disease, and given the possibility of poorer adherence in the inpatient arm, we modelled a range of power calculations, but assuming an 80% TB-disease free completion rate in the outpatient 1HP initiation arm, a total sample size of 205 would give us 80% power to determine whether early 1HP led to non-inferior TB-disease free completion rates. **Power calculations detailing a range of possible sample sizes (overall, assuming 1:1 randomisation) depending on non-inferiority margin and TB-free 1HP completion rates.** **TB-free treatment completion in standard 1HP arm (outpatient setting) 80% 82% 84% 86% 90% Non-inferiority margin 10%** 460 425 385 345 260 **12%** 319 295 268 240 180 **15%** **205** 189 172 154 117 Sample sizes are based on 80% power, with a one sided 95% confidence interval, and allowing for 5% LTFU and 10% post-randomisation mortality at 18-weeks.

- **Will be good to state the formula used or the software used and the reference for readers to follow. And this should not be mixed with the statistical analysis methods**

This has been added. Power calculations were conducted using Sealed Envelope Ltd. 2012. Power calculator for binary outcome non-inferiority trial. [Online] Available from: https://www.sealedenvelope.com/power/binary-noninferior/ [Accessed Wed May 01 2024].

- **What is the basis for selection of 5% as the loss to follow up rate and not 10% or 15%?**

This is based on our experience conducting clinical studies across the study sites since 2006. Thank you again for the review Very best Dr Jayne Ellis

Competing Interests: No competing interests were disclosed.

Reviewer Report 26 April 2024

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Ajay Rangaraj
Department of HIV, Hepatitis and STIs, World Health Organisation, Geneva, Switzerland

Thank you for the opportunity to review this well written manuscript.

1. Please do include the rationale for why 18 weeks was chosen as an appropriate end-time period for the study.

2. It would be a great inclusion if the study can report on post-discharge outcomes - not just for TB, but also for CM. And to report the outcomes more systematically such as post discharge status (functional status), whether re-linked to care for ART, LTFU etc., as it is a highly relevant issue in AHD.

3. It would be good to mention what regimen is being used in the antifungal treatment - as they are not all equal - particularly if conventional amphotericin-B is being used and/or then single high dose liposomal amphotericin. This would also mean the study should track kidney parameters.

4. Under "Consent"- please do consider rephrasing the word ïlliterate" - could perhaps be reworded to "those that are unable to read or write".

5. The study's primary endpoint is "Treatment completion is defined as participant reported adherence to >90% of the study medications, to be completed within 6-weeks from treatment initiation." - I think I understand this as all the study medications - could you please clarify this?
   Also if the individual is not conscious during the inpatient stay - how would adherence be calculated? Or would it be the case that it would be 100%?

6. Is there any intention to look at resistance development in the study - would be important to mention if or if not.

7. Could there have been additional arms in this trial to evaluate 3HP? Was there a rationale to not include it?

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I work on synthesising evidence for and coordinating global treatment guidelines updates for HIV treatment and care - particularly ART, Advanced HIV disease, cryptococcal meningitis, histoplasmosis and other opportunistic infections.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 May 2024

Jayne Ellis

Dear Ajay Rangaraj Thank you for taking the time to review the IMPROVE protocol - your feedback is very much appreciated. Please find below responses to each of your comments raised:

- **Please do include the rationale for why 18 weeks was chosen as an appropriate end-time period for the study.**

This end-time was chosen because the risk of mortality, opportunistic infections and immune reconstitution inflammatory syndrome (IRIS) events (including TB-IRIS) are considerably lower beyond 18-weeks following immune reconstitution with predominately DTG-based ART initiation/switch at 4-6 weeks post cryptococcal meningitis diagnosis.

- **It would be a great inclusion if the study can report on post-discharge outcomes - not just for TB, but also for CM. And to report the outcomes more systematically such as post discharge status (functional status), whether re-linked to care for ART, LTFU etc., as it is a highly relevant issue in AHD.**

In parallel to the IMPROVE trial, where consent is given, study participants are also followed up longitudinally as part of our open cohort study (Improving Diagnostics and Neurocognitive Outcomes in HIV/AIDS-related Meningitis) which collects post-discharge outcomes including neuro-cognitive assessments at annual follow-up visits.

- **It would be good to mention what regimen is being used in the antifungal treatment - as they are not all equal - particularly if conventional amphotericin-B is being used and/or then single high dose liposomal amphotericin. This would**

also mean the study should track kidney parameters.

All IMPROVE participants receive amphotericin-based induction anti-fungal therapy. The induction regimen received however, does depend upon drug availability (liposomal amphotericin vs. amphotericin deoxycholate) and whether the participant received induction anti-fungal therapy as part of a randomized controlled trial. Given this is a randomized trial however, we do anticipate any differences in induction regimens to be well balanced between IMPROVE trial arms. Study participants have both in-hospital, and post-discharge protocolized safety monitoring blood tests including kidney parameters, liver function, and complete blood counts.

- **Under "Consent"- please do consider rephrasing the word illiterate" - could perhaps be reworded to "those that are unable to read or write".**

Thank you, this has been amended in the updated version of the protoc.

- **The study's primary endpoint is "Treatment completion is defined as participant reported adherence to >90% of the study medications, to be completed within 6-weeks from treatment initiation." - I think I understand this as all the study medications - could you please clarify this?**

Yes this means that a participant must complete >90% of both isoniazid and rifapentine within 6-weeks from initiation of the 1HP regimen i.e. they cannot miss more than 3 days of treatment. **Also if the individual is not conscious during the inpatient stay - how would adherence be calculated? Or would it be the case that it would be 100%?** Participants are randomised into the IMPROVE RCT at time of discharge (other than in instances, where the participant remains an inpatient for ≥14 days, randomisation will occur on day 14 rather than on the planned day of discharge), therefore participants rarely have reduced level of consciousness during the IMPROVE trial. In cases where a participant does have a reduced level of consciousness such that they are unable to self-medicate, a naso-gastric tube is inserted to ensure adherence with both IMPROVE study drugs, and with anti-fungal medications, and nutritional support.

- **Is there any intention to look at resistance development in the study - would be important to mention if or if not.**

In cases of culture-proven incident TB disease (e.g. blood culture positive TB-cases) drug susceptibility testing is performed. This has been added to the manuscript.

- **Could there have been additional arms in this trial to evaluate 3HP? Was there a rationale to not include it?**

Within IMPROVE, we are specifically interested in investigating whether TB preventive therapy (TPT) can be initiated as an inpatient for patients with advanced HIV disease and cryptococcal meningitis, such that TPT completion (and sterilisation of latent TB infection) can be achieved prior to ART initiation/switch at ~6-weeks post cryptococcal meningitis diagnosis. We hypothesize that TPT completion prior to ART initiation/switch will reduce the risk of unmasking TB-IRIS events in this population. Whilst 3HP would have been an interesting comparator arm (for example reduced pill-burden, +/- reduced risk of drug-drug interactions as compared to 1HP in this group), it would not allow for TPT completion prior to ART initiation/switch. Furthermore the limited budget and therein sample size, necessitated a two-arm trial only. Many thanks again for the review Very best Dr Jayne Ellis

Competing Interests: No competing interests were disclosed.