Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Le T, Van Kinh N, Cuc NTK, et al. A trial of itraconazole or amphotericin B for HIV-associated talaromycosis. N Engl J Med 2017;376:2329-40. DOI: 10.1056/NEJMoa1613306

A Trial of Itraconazole or Amphotericin B for HIV-associated Talaromycosis

Supplementary Material

Contents

Section 1 – IVAP Investigators List

1. The Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam: Nguyen Huu Chi, M.D., Vo Minh Quang, M.D., Prof. Nguyen Tran Chinh, M.D., Ph.D, Nguyen Quoc Hung, M.D., Le Duc Vinh, M.D., Nguyen Thanh Liem, M.D., Ly Quoc Cong, M.D., Vo Trieu Ly, M.D., Nguyen Phu Huong Lan, M.D., Dinh Nguyen Huy Man, M.D., Nguyen Thi Quynh Nga, M.D.

2. The National Hospital for Tropical Diseases, Hanoi, Vietnam: Ta Thi Dieu Ngan, M.D., Nguyen Thi Hoai Dung, M.D., Nguyen Kim Thu, M.D., Ph.D., Pham Thi Khuong, M.D., Dang Thi Bich, M.D., Nguyen Van Long, M.D., Do Minh Hoang, M.D., Hoang Thi Thanh Tu, M.D., Le Xuan Luat, M.D., Nguyen Thi Dung, M.D., Nguyen Thi Lan, M.D., Tran Bang Huyen, M.D.

3. Bach Mai Hospital, Hanoi, Vietnam: Nguyen Quang Tuan, M.D., Doan Thu Tra, M.D., Le Thi Hoa, M.D., Tran Minh Hanh, M.D.

4. Viet Tiep Hospital, Hai Phong, Vietnam: Nguyen Thi Phuong, M.D., Tran Thi Lien, M.D., Dao Trong Hoang, M.D., Vu Thi Sinh, Chu Thi Nga, M.D., Lai Thi Quynh

5. Vietnam-Sweden Uong Bi Hospital, Quang Ninh, Vietnam: Tran Viet Tiep, M.D., Ph.D., Ha Van Hien, M.D., Trinh Thu Hoan, M.D., Nguyen Thi Thu Ha, Le Quang Dong, Nguyen Thi Kim Anh

6. Oxford University Clinical Research Units, Ho Chi Minh City and Hanoi, Vietnam: Prof. Tran Tinh Hien, M.D., Ph.D., Nguyen Thi Mai Thu, M.Sc., Ha Thuc Ai Hien, M.Sc., Ashley Nguyen, Vu Phuong Thao, DPhil., Phan Thi Hong Dao, Hoang Suong Nguyet Anh, Duong Van Anh, M.Sc., James Campbell Ph.D., Nguyen Thi Thanh Thuy, M.Sc., Nguyen Thi Phuong Dung, Ph.D., Ho Van Hien, M.Sc., Nguyen Thanh Tien, Nguyen Thu Van, Hoang Dieu Linh, Tran Thi Kieu Huong, M.Sc., Ngo Thanh Bao, M.Sc., Nguyen Bao Tran, M.Sc., Behzah Nadjim, M.D., Ph.D., Rogier van Doorn, M.D., Ph.D.

7. Oxford University Health Economic Centre, Oxford, United Kingdom: Prof. Alastair Gray, Ph.D.

8. University of Liverpool, Liverpool, United Kingdom: Prof. William Hope, M.D., Ph.D.

9. Karolinska Institute, Stockholm, Sweden: Mattias Larsson, M.D., Ph.D

10. Mahidol Oxford Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand: Thomas Pouplin, Ph.D.

Section 2 – Study sites

Study sites	Number of beds and level of care	Number of patients recruited	Authorities providing ethical approval	Authority providing regulatory approval
Hospital for Tropical Diseases, Ho Chi Minh City	550 Tertiary infectious disease referral hospital for southern Vietnam	176	Hospital for Tropical Diseases and Ministry of Heath	Vietnam Ministry of Health and Ministry of Finance
National Hospital of Tropical Diseases, Hanoi	350 Tertiary infectious disease referral hospital for northern Vietnam	147	National Hospital for Tropical Diseases and Ministry of Heath	
Vietnam-Czech Republic Viet Tiep Hospital, Hai Phong	1700 Provincial general medicine referral hospital	50	Viet Tiep Hospital and Ministry of Heath	
Bach Mai Hospital, Hanoi	1900 Tertiary general medicine referral hospital for northern Vietnam	43	Bach Mai Hospital and Ministry of Heath	
Vietnam-Sweden Uong Bi Hospital, Quang Ninh	1100 Regional general medicine referral hospital	24	Uong Bi Hospital and Ministry of Heath	

Section 3 – Data Monitoring and Ethics Committee Charter

Data Monitoring and Ethics Committee
CHARTER for IVAP

Data Monitoring and Ethics Committee (DMEC) Overview

Trial Description and Study Design

- Trial sponsor: **Medical Research Council UK, Department for International Development UK, and Wellcome Trust via the Joint Global Health Trials Scheme (Financial) and University of Oxford (Regulatory)**
- Trial design: **A Randomized, Open-Label, Comparative Study of the Effectiveness of Itraconazole versus Amphotericin B in the Induction Treatment of Penicilliosis in HIV-Infected Adults (IVAP)**
- Phase: **Drug phase IV**
- Number of patients: **440**
- Names of sites: **National Hospital for Tropical Diseases, Hanoi, Vietnam; Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; Bach Mai Hospital, Hanoi, Vietnam; Viet Tiep Hospital, Hai Phong, Vietnam; Uong Bi Hospital, Quang Ninh, Vietnam**
- Principal Investigators: **Dr. Thuy Le, Prof. Nguyen Van Kinh**

DMEC Terms of Reference (from MRC Guidelines of Good Clinical Practice in Clinical Trials 1998)

1. To determine if additional interim analyses of trial data should be undertaken
2. To consider the data from interim analyses, plus additional safety measures for the above named trial and relevant information from other sources
3. In the light of 2., and ensuring that ethical considerations are of prime importance, to report (following each DMEC meeting) to the Trial Steering Committee (TSC) and to recommend on the continuation of the trial
4. To consider any requests for release of interim trial data and to recommend to the TSC on the advisability of this
5. In the event of further funding being required, to provide to the TSC and MRC appropriate information and advice on the data gathered to date that will not jeopardize the integrity of the study.

DMEC Membership

- This charter will be agreed by all DMEC members.
- Composition of membership will be:

  Prof. Diederik van de Beek – DMEC Chairman - Academic Medical Center, Amsterdam, the Netherlands
  Dr. Ronald B Geskus – biostatistician - Academic Medical Center, Amsterdam, the Netherlands
  Prof. Janet Darbyshire, Emeritus Professor of Epidemiology - Medical Research Council Clinical Trials Unit, United Kingdom
  Prof. David Mabey, Professor of Communicable Diseases - London School of Hygiene and Tropical Medicine, United Kingdom

Acronyms

CTU –	Clinical Trials Unit (of OUCRU-VN)
DMEC –	Data Monitoring and Ethics Committee
MRC –	Medical Research Council, UK
OUCRU-VN –	Oxford University Clinical Research Unit – Viet Nam

PI – Principal Investigator
TSC – Trial Steering Committee

Introduction

The purpose of this charter is to define the roles and responsibilities of the Data Monitoring and Ethics Committee (DMEC), delineate qualifications of the membership, describe the purpose and timing of meetings, provide the procedures for ensuring confidentiality and proper communication, and outline the content of the reports.

The DMEC will function in accordance with the MRC guidelines for Good Clinical Practice in Clinical Trials and the approved trial protocol.

The DMEC administration will be coordinated by the OUCRU-VN CTU. All significant communications, meetings and reports will be made in writing, communicated to all relevant parties and maintained with the Trial Master File.

Definitions

The following definitions apply to this protocol:

Ethical Committee of Reference: the lead ethical committee to which all safety reporting and DMEC reports are issued. In the case of this trial, the ethical committee of reference is the Oxford Tropical Research Ethics Committee.

Grade 3 or 4 Adverse Event: any untoward medical occurrence of severity defined as grade 3 or 4 by the National Institute of Health for AIDS grading scheme
http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/daidsaegradingtable.pdf

Serious Adverse Event (SAE): An AE is considered to be "serious" if it results in only one of the following outcomes

- Death,
- Life-threatening event (the subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity (a substantial disruption of a person's ability to conduct normal life functions),
- Congenital anomaly/birth defect
- Important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Unexpected Serious Adverse Event (USAE): Untoward medical events which fit one or more criteria of SAE above and which are not considered a part of normal clinical progression of disease or expected drug reaction. Any event which becomes of concern to the investigators or study doctors during the course of the trial may be reported as a USAE.

Roles and Responsibilities

DMEC Roles and Responsibilities

The DMEC will

- Receive, review and feedback when necessary on USAEs reported in detail within 2 weeks of occurrence and followed until resolution

- Meet periodically (see DMEC Meetings) to review summary tables of serious adverse events (SAEs), grade 3 & 4 AEs and analysis of overall survival. The DMEC may request additional data as required including aggregate and individual subject data related to safety, data integrity and overall conduct of the trial.
- Provide recommendations to continue, modify or terminate the trial depending upon these analyses.
- Communicate other recommendations or concerns as appropriate including requests for additional reviews based on regular reporting and USAE reporting.
- Comply with and operate according to the procedures described in this charter.
- Maintain documentation and records of all activities as described below (see DMEC Chairman, DMEC Meetings, DMEC Reports).

DMEC Chairman will

- Be responsible to archive the interim analysis reports and confidential documentation of rationale for decisions made by the Committee during closed sessions. These will be provided to the Principal Investigator upon completion of the trial.

DMEC Statistician will

- Generate the analysis tables and distribute the interim report amongst the DMEC members as described below (see section "Creation of interim analysis reports" below).

Principal Investigator Roles and Responsibilities

The PIs will directly or through delegation:

- Assure the proper conduct of the study including collection of accurate and timely data.
- Compile and report USAEs to the DMEC as described below.
- Promptly report potential safety concern(s) to the DMEC.
- Communicate with regulatory authorities, ethical committees and investigators, in a manner that maintains patient safety and integrity of the data.

DMEC Participation

Membership will be selected by the PIs and approved by the Joint Global Health Trials administrative representative. If a DMEC member is unable to continue participation on the committee, the reason will be documented and a replacement will be selected by the Principal Investigator with the agreement of the other DMEC members and endorsement of the TSC and the Joint Global Health Trials administrative representative.

DMEC members will declare any existing or potential conflicts of interest to the PI who will report to the Joint Global Health Trials administrative representative. Conflicts of interest will be reduced to the greatest extent that is consistent with assembling a highly competent DMEC. Any questions or concerns that arise regarding conflicts of interest will be addressed by the DMEC Chair (or in the case of the Chair having a conflict, by the TSC Chair) and the Joint Global Health Trials administrative representative as necessary.

A conflict of interest exists or potentially exists when a member has a personal, professional or financial interest which could unduly influence the member's position with respect to the trial or trial related issues. A conflict of interest should also be addressed if an interest could result in the member's objectivity being questioned by others.

DMEC Meetings

Projected Schedule of Meetings

Correspondence with the DMEC will be initiated by the OUCRU CTU prior to any subject enrollment in the trial in order for the members to review the charter, to form an understanding of the protocol, agree to the safety reporting procedures, to establish a meeting schedule and to review the study modification and/or termination guidelines. Subsequent interim and final review meetings will be held to review and discuss interim and final study data according to the schedule below.

Meetings will occur at least annually and additional meetings may be scheduled at the request of the DSMC Chairman, the Trial Steering Committee or the sponsor.

Timeline	*Data Review by*	*Type of Data*
At study initiation	Entire DMEC	Study protocol, safety concerns, DMEC Charter and associated procedures/reports
After the death of 20 enrolled patients or two weeks after the enrolment of the 100th patient – whichever comes first	Entire DMEC	USAE or event reports submitted to the DMEC Enrolment summary Tables of grade 3 & 4 AEs and SAEs Overall survival analysis Any other requested data

Meeting Format

DMEC meetings will generally be conducted by teleconference and coordinated by the administrative coordinator named above. A quorum, defined as a minimum of 3 members will be required to hold a DMEC meeting. Any one member may be absent provided that they are sent the relevant data at least 3 days in advance of the meeting and given opportunity to feedback to other members. Critical decisions of the DMEC should be made by unanimous vote. However, if this is not possible, majority vote will decide. When appropriate, DMEC review sessions may be held by email exchange in lieu of a meeting.

Open and Closed Sessions

Sessions may be open (attended by representatives of the sponsor and study team) or closed (attended only by DMEC members) at the direction of the DMEC. All data presented at the open sessions must be blinded. A report based on each DMEC meeting will be organized by the Chairman and submitted to the Trial Steering Committee. This report will include a recommendation to:

- Continue the trial without modification
- Continue the trial with modification
- Stop the trial due to safety concerns
- Stop the trial for another reason

Reports will be circulated to all DMEC members for their approval before being issued.

Creation of interim analysis reports

The study statistician will generate the code (in the statistical software R) to generate all tables outlined in the Interim Analysis Plan but will remain blinded to the treatment assignment throughout the study.
Prior to each interim analysis, raw data will be transferred from the study statistician to the DMEC statistician together with R code to generate all summary tables. A separate file with the randomization code will be transferred from the pharmacist managing the randomization list to the DMEC statistician. Based on this information, the DMEC statistician will merge the randomization code to the data, generate the tables and distribute the interim report amongst the DMEC members.

Study Review Criteria, Stopping Rules and Guidelines

Safety Analyses

The primary safety endpoint is survival. In addition to the primary safety endpoint, the DMEC will consider grade 3 & 4 adverse events, serious adverse events and unexpected or events concerning to the Investigators at the time points defined above.

Stopping Guidelines / Stopping Rules

The DMEC may recommend termination or modification of the study if preliminary data indicate beyond reasonable doubt that one of the allocated strategies is better than the other in primary outcome. The Haybittle-Peto boundary,

requiring p<0.001 at interim analysis to consider stopping for efficacy, should be used as a guidance. However, the DMEC recommendation should not be based purely on statistical tables but also requires clinical judgment.

Termination or modification may also be recommended for any other perceived safety concern, including but not limited to a higher than anticipated rate of treatment side effects resulting in severe adverse events or unexpected SAEs.

Adaptive Protocol Modification
There is no planned sample size re-estimation or protocol adaption; however if the DMEC reveals a need, a recommendation to re-evaluate the sample size calculation or make other changes may be put forward to the Trial Steering Committee.

Consideration of External Data
The DMEC will also consider data from other studies or external sources during its deliberations, if available, as these results may have an impact on the status of the patients and design of the current study.

DMEC Reports

Monitoring for Safety
The primary charge of the DMEC is to monitor the study for patient safety. Formal DMEC safety reviews will occur as specified above (see DMEC Meetings). The following events will also be reported to the DMEC:

- Unexpected Serious Adverse Events will be reported in detail within 2 weeks of occurrence and followed up until resolution

Safety reporting to regulatory and ethical committees will be in accordance with the requirements of each committee.

Content of DMEC Reports at Formal Interim Analyses
The detailed content of the interim analysis report will be outlined in a separate document, the Interim Analysis Plan.

Monitoring for Study Conduct
The DMEC will be updated during scheduled meetings on study enrolment and major operational issues.

Blinding
As the dissemination of preliminary summary data could influence the further conduct of the trial and introduce bias, access to interim data and results will be confidential and strictly limited to the involved statistician and the monitoring board and results (except for the recommendation) will not be communicated to the outside and/or clinical investigators involved in the trial.

DMEC Communication of Findings and Recommendations
Following each meeting and within 2 weeks of the meeting the chairman will send findings and recommendations of the DMEC in writing to the Trial Steering Committee. The report should include the date of the meeting, participants, data reviewed by the Committee and a recommendation to continue the trial with/without modification or to stop the trial on a specified basis. The report may include minutes of relevant non-confidential discussion points and any requests for clarification of further information.

These findings and recommendations can result from both the open and closed sessions of the DMEC. If these findings include serious and potentially consequential recommendations that require immediate action, the chairperson will promptly notify the Principal Investigator by phone.

Response to DMEC Findings and Recommendations
The Trial Steering Committee will review and respond to the DMEC recommendations. If the DMEC recommends continuation of the study without modification, no formal response will be required. If the recommendations request action, such as a recommendation for termination of the study or modification of the protocol, the Trial Steering Committee or Principal Investigator will provide a response stating whether the recommendations will be followed and the plan for addressing the issues.

Upon receipt, the DMEC will consider the response and will attempt to resolve relevant issues, resulting in a final decision.

The Principal Investigator will disseminate all DMEC reports, responses and final decisions to the relevant ethical committees according to the reporting requirements of that committee.

DMEC Closeout

This study may be terminated under a variety of circumstances including, but not limited to, termination for overwhelming effectiveness, futility, or safety issues per protocol or DMEC monitoring guidelines. A final study report will be issued to the DMEC who may recommend continuing action items to the TSC based upon the report.

Confidentiality

All data provided to the DMEC and all deliberations of the DMEC will be privileged and confidential. The DMEC will agree to use this information to accomplish the responsibilities of the DMEC and will not use it for other purposes without written consent from the TSC. No communication of the deliberations or recommendations of the DMEC, either written or oral, will occur except as required for the DMEC to fulfill its responsibilities. Individual DMEC members must not have direct communication regarding the study outside the DMEC (including, but not limited to the investigators, IRB/EC, regulatory agencies, or sponsor) except as authorized by the DMEC.

Amendments to the DMEC Charter

This DMEC charter can be amended as needed during the course of the study. All amendments will be documented with sequential version numbers and revision dates, and will be recorded in the report from the DMEC meetings. Each revision will be reviewed and agreed upon by both the DMEC and the Trial Steering Committee. All versions of the charter will be archived in the Trial Master File.

Archiving of DMEC Activities and Related Documents

All DMEC documentation and records will be retained in the Trial Master File in accordance with local and international regulatory requirements.

Agreement of DMEC Members

Signatures below confirm the agreement of all DMEC members to the contents of this charter and the confidentiality statement above.

Name: **Diederik van de Beek**	Date:	Signature:
Name: **Ronald B. Geskus**	Date:	Signature:
Name: **Janet Darbyshire**	Date:	Signature:
Name: **David Mabey**	Date:	Signature:

Agreement of Trial Steering Committee Chairman

Signatures below confirm the agreement of the TSC with the contents of this charter.

Name:	Date:	Signature:

UNEXPECTED SERIOUS ADVERSE EVENT REPORT FORM

(complete one form for each USAE)

Study Code:	11CN	**CRF/Patient #:**	
Investigator Name:		**Patient Initials:**	
Reporter Name:		**Patient DoB:**	
Site:		**Patient Sex:**	☐ Male ☐ Female
Country:		**Patient Weight :**	kg

1. EVENT:

Name of event or diagnosis: _____

	DD	MMM	YYYY
Date of study enrolment:			
Date of event onset:			
Date when event became serious:			

2. POSSIBLE CAUSES OF THE EVENT: (check all that apply)

Pre-existing/underlying disease – *specify* ☐ _____

Study treatment – *specify which drug* ☐ _____

Other treatment (concomitant or previous) – *specify* ☐ _____

Protocol related procedures – *specify* ☐ _____

Other (accident, new illness, etc) – *specify* ☐ _____

3. EVENT SERIOUSNESS

Why was the event serious? (check all that apply)

Results in death ☐

Life-threatening ☐

Persistent or significant disability ☐

New in-patient hospitalization ☐

Prolonged in-patient hospitalization ☐

Congenital defect ☐

4. SAE OUTCOME

SAE outcome at the time of report:

	DD	**MMM**	**YYYY**
Fatal/Date of death ☐			
Resolved ☐			
Resolved with sequelae ☐			

Improved ☐

Persisting ☐

Worsened ☐

Unknown ☐

5a. STUDY MEDICATION (current dose)

Study Medication Name:	Dose:	Units:	Frequency:	Route:	Dosage Form:

Batch Lot Number:

Dates for study Medication	DD	MMM	YYYY
Start Date:			
Last dose prior to SAE:			

Was the medication unblinded?

Yes ☐ No ☐ N/A ☐

Was the drug regimen altered in response to the event? ☐ YES (specify below) ☐ No

How was the drug regimen altered in response to the event?

Reduced – specify new dose ☐
Temporarily Interrupted ☐
Permanently discontinued ☐

Dates when drug regimen altered:

	DD	MMM	YYYY
Reduced			
Stopped			
Started			
Discontinued			

Details of new dose

New Dose	Units	Frequency

5b. STUDY MEDICATION (previous dose if applicable)

Study Medication Name:	Dose:	Units:	Frequency:	Route:	Dosage Form:

Batch Lot Number:

Dates for study Medication	DD	MMM	YYYY
Start Date:			
Last dose prior to SAE:			

Was the medication unblended?

Yes ☐ No ☐ N/A ☐

Was the drug regimen altered in response to the event?
☐ YES (specify) ☐ No

How was the drug regimen altered in response to the event?

Reduced – specify new dose ☐
Temporarily Interrupted ☐
Permanently discontinued ☐

Dates when drug regimen altered:

	DD	MMM	YYYY
Reduced			
Stopped			
Started			
Discontinued			

Details of new dose

New Dose	Units	Frequency

6. RELEVANT LABORATORY / DIAGNOSTIC TESTS ☐ YES (specify below) ☐ No
(including those preceding the event)

Name of test	Result (Units)	Normal Values / Reference Range	Sample Collection Date			Result Pending
			DD	MMM	YYYY	
1..						☐
2.						☐
3.						☐

7. TREATMENT(S) / PROCEDURES FOR SAE ☐ YES (specify below) ☐ No

Name of treatment/procedure	Total daily dose/unit	Start Date			End Date			Ongoing
		DD	MMM	YYYY	DD	MMM	YYYY	
1.								☐
2.								☐
3.								☐

8. RELEVANT PREVIOUS DISEASE / MEDICAL HISTORY ☐ YES (specify below) ☐ No

Disease / Medical History	Start Date DD/MMM/YYYY			End Date DD/MMM/YYYY			Ongoing
1.							☐
2.							☐
3.							☐
4.							☐
5.							☐

9. RELEVANT PREVIOUS TREATMENT / PROCEDURES ☐ YES (specify below) ☐ No

Treatment History	Start Date			End Date			Ongoing
1.	DD	MMM	YYYY	DD	MMM	YYYY	☐
2.							☐
3.							☐
4.							☐
5.							☐

10. CONCOMITANT MEDICATION ☐ YES (specify below) ☐ No

Name of drug (not drugs used to treat the SAE)	Total daily dose/unit	Start Date DD / MMM / YYYY			End Date DD / MMM / YYYY			Ongoing
1.								☐
2.								☐
3.								☐
4.								☐
5.								☐

11. SAE DESCRIPTION

Detail a chronologic history of the event including: signs and characteristics, severity, dates and outcomes of hospitalization and any other relevant information not captured on this form.

12. Detail any additional forms or section continuations attached to this report

Type of Form/Attachment	Number of Pages

13. Investigator Name and Site

Investigator Signature: _____

Investigator Name: _____ **Date of Signature:** _____

OR Designee Signature: _____

Designee Name: _____ **Date of Signature:** _____

Address of Signatory: _____

_____

Telephone number: _____

14. IRB and Regulatory Reporting

This SAE has been reported to the following authorities:

Authority	Reference Number	Date Sent

Section 4 – Trial Steering Committee Charter

Trial Steering Committee
CHARTER for IVAP

Trial Steering Committee (TSC) Overview

Trial Description and Study Design

- Trial sponsor: **Medical Research Council UK, Department for International Development UK, Wellcome Trust for the Joint Gobal Health Trials Scheme (Financial) and University of Oxford (Regulatory)**
- Trial design: **A Randomized, Open-Label, Comparative Study of the Effectiveness of Itraconazole versus Amphotericin B in the Induction Treatment of Penicilliosis in HIV-Infected Adult (IVAP)**
- Trial Phase: **IV**
- Number of patients: **440**
- Names of sites **National Hospital for Tropical Diseases, Hanoi, Vietnam; Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; Bach Mai Hospital, Hanoi, Vietnam; Viet Tiep Hospital, Hai Phong, Vietnam; Uong Bi Hospital, Quang Ninh, Vietnam**
- Principal Investigator: **Dr. Thuy Le, Prof. Nguyen Van Kinh**

TSC Terms of Reference (from MRC Guidelines of Good Clinical Practice in Clinical Trials 1998)

1. To monitor and supervise the progress of the trial *"Randomized, Open-Label, Comparative Study of the Effectiveness of Itraconazole versus Amphotericin B in the Acute-Phase Treatment of Penicilliosis in HIV-Infected Person (IVAP)"* towards its interim and overall objectives
2. To review at regular intervals relevant information from other sources: protocol, SOPs, ICF. CRFs…
3. To consider the recommendations of the DMEC
4. In the light of 1,2, & 3 to inform the Council and relevant Research Boards on the progress of the trial
5. To advise the Medical Research Council on publicity and the presentation of all aspects of the trial

TSC Membership

- Membership will be approved by the Medical Research Council
- Members will address conflicts of interest and potential conflicts of interest in accordance with provisions in this charter.
- TSC members will agree to this charter and confirm their agreement to the confidentiality statement within this document covering TSC activities.
- Composition of membership will be:
    - **Prof. Nicholas Paton – Chairman - Infectious Diseases Physician** - National University of Singapore, Singapore.
    - **Prof. Robin Grant – Neurologist** - Division of Clinical Neurosciences, College of Medicine and Veterinary Medicine, University of Edinburgh, United Kingdom
    - **Prof. Robin Bailey** – **Professor of Tropical Medicine** - the London School of Hygiene and Tropical Medicine, United Kingdom
    - **Dr. Thuy** Le **- Principal Investigator - Infectious Diseases Physician/Scientist** - Oxford University Clinical Research Unit, Vietnam
    - **Prof. Nguyen Van Kinh** – **Principal Co-Investigator - Director** - National Hospital for Tropical Diseases, Vietnam
- The sponsor representative who will act as an observer to the committee will be**:**
    - **Dr. Marta Tufet** - **International Activities Advisor** - Wellcome Trust, United Kingdom

Acronyms

CTU –	Clinical Trials Unit (of OUCRU-VN)
DMEC –	Data Monitoring and Ethics Committee
MRC –	Medical Research Council, UK
OUCRU-VN –	Oxford University Clinical Research Unit – Viet Nam
PI –	Principal Investigator
TSC –	Trial Steering Committee

Introduction

The purpose of this charter is to define the roles and responsibilities of the Trial Steering Committee (TSC), delineate qualifications of membership, describe the purpose and timing of meetings, provide the procedures for ensuring confidentiality and proper communication, and outline the content of communications.

The TSC will function in accordance with the MRC guidelines for Good Clinical Practice in Clinical Trials and the approved trial protocol. This charter will be approved by all members of the TSC.

The TSC administration will be coordinated by the OUCRU-VN Clinical Trials Unit. All significant communications, meetings and reports will be made in writing, communicated to all relevant parties and maintained with the Trial Master File.

TSC Roles and Management

The role of TSC is to provide overall supervision of the trial on behalf of the MRC. In particular, the TSC will concentrate on progress of the trial, adherence to the protocol, patient safety, and the consideration of new information. Day-to-day management of the trial is the responsibility of the Principal Investigator (PI). The PI is responsible to communicate any new information which arises during the trial which may be relevant to the conduct of the trial.

Membership will be selected by the Principal Investigator and approved by the Medical Research Council. If a TSC member is unable to continue participation on the board, the reason will be documented and a replacement will be selected by the Principal Investigator with the agreement of the other TSC members and endorsement of the Medical Research Council.

TSC members will declare any existing or potential conflicts of interest to the Principal Investigator who will report to the Medical Research Council. Conflicts of interest will be reduced to the greatest extent that is consistent with assembling a highly competent TSC. Any questions or concerns that arise regarding conflicts of interest will be addressed by the TSC Chair and the Medical Research Council as necessary.

A conflict of interest exists or potentially exists when a member has a personal, professional or financial interest which could unduly influence the member's position with respect to the trial or trial related issues. A conflict of interest should also be addressed if an interest could result in the member's objectivity being questioned by others.

TSC Meetings

A meeting of the TSC will be organized by OUCRU-VN CTU before the start of the trial to finalize the protocol, timeline, management, DMEC membership and charter and any other relevant issues. Thereafter, the TSC will meet after each DMEC meeting and at least annually although there may be periods when more frequent meetings are necessary. Meetings will be called by the Principal Investigator or the Chair of the TSC. Information and documentation required for the meetings will be circulated well in advance.

Meeting Format

TSC meetings will generally be conducted by teleconference and coordinated by the OUCRU CTU. A quorum, defined as a minimum of 4 members will be required to hold a TSC meeting. Any one member may be absent provided that they are sent the relevant data at least 3 days in advance of the meeting and given opportunity to feedback to other members. Critical decisions of the TSC will be made by unanimous vote. However, if this is not possible, majority vote will decide.

With the agreement of TSC members, meetings may be attended by consultants, trial team members or other experts who can contribute to the discussion.

All meetings will be minuted. Minutes will be circulated for the approval of all members before being finalized.

TSC and MRC Reporting

The Principal Investigator will write a trial report for the Medical Research Council at least annually. This report will include:

- Progress of the trial
- Adherence to the protocol
- Patient safety
- Consideration of the new information

The reports will inform the MRC of the progress of the trial and of any new information that has a bearing on safety or ethical considerations of the trial or any significant complaint arising, with a justification of any decisions taken on the matter.

Reports will be circulated to all TSC members for their approval before being issued.

TSC Governance

Full details of TSC governance requirements can be found in the MRC guidelines for Good Clinical Practice in Clinical Trials. Details below are extracted from this document.

The TSC will endeavour to ensure that the trial is conducted at all times to the rigorous standards set out in the MRC Guidelines for Good Clinical Practice.

The Principal Investigator is responsible to disseminate and act upon all TSC reports, responses and final decisions.

Patient Safety

In all the deliberations of the TSC the rights, safety and well-being of the trial participants are the most important considerations and will prevail over the interests of science and society. The TSC will ensure that the protocol demands freely given informed consent from every trial participant. The TSC will look closely at the patient information provided and advise the investigators on its completeness and suitability.

Progress of the Trials

It is the role of the TSC to monitor the progress of the trial and to maximize the chances of completing the study within the time scale agreed by the MRC. Actual and planned recruitment rates will be presented at each TSC meeting.

In the event that additional time or funding is required, the TSC will notify the MRC as soon as possible. TSC will provide the information necessary for the MRC to make a decision on additional provisions.

Adherence to Protocol

The full protocol will be presented as an agenda item at the fist TSC meeting to be agreed. If the investigators need to make any changes to the protocol during the course of the trial, approval will be sought from the TSC and if necessary, the MRC.

Consideration of New Information

The TSC will consider new information relevant to the trail including reports from DMEC and the results of other studies. It is the responsibility of the PI and the Chairman and other independent members of the TSC to bring to the attention of the TSC any results from other studies that may have a direct bearing on future conduct of the trial.

On consideration of this information the TSC will recommend appropriate action, such as changes to the trail protocol, additional patient information or stopping of the study. The rights, safety and well-being of the trial participants will be the most important consideration in these deliberations.

It is the responsibility of the investigators to notify the DMEC and relevant regulatory authority (if applicable) of any unexpected serious adverse events during the course of the study. All reports from the DMEC will be sent to the TSC. All reports or requests for changes from the ethical committees or regulatory authorities will be sent to the TSC.

Confidentiality

All reports provided to the TSC and all deliberations of the TSC will be privileged and confidential. The TSC will agree to use this information to accomplish the responsibilities of the TSC and will not use it for other purposes. No communication of the deliberations or recommendations of the TSC, either written or oral, will occur except as required for the TSC to fulfill its responsibilities. Individual TSC members must not have direct communication regarding the study outside the TSC (including, but not limited to the investigators, IRB/EC, regulatory agencies, or sponsor) except as authorized by all members of the TSC.

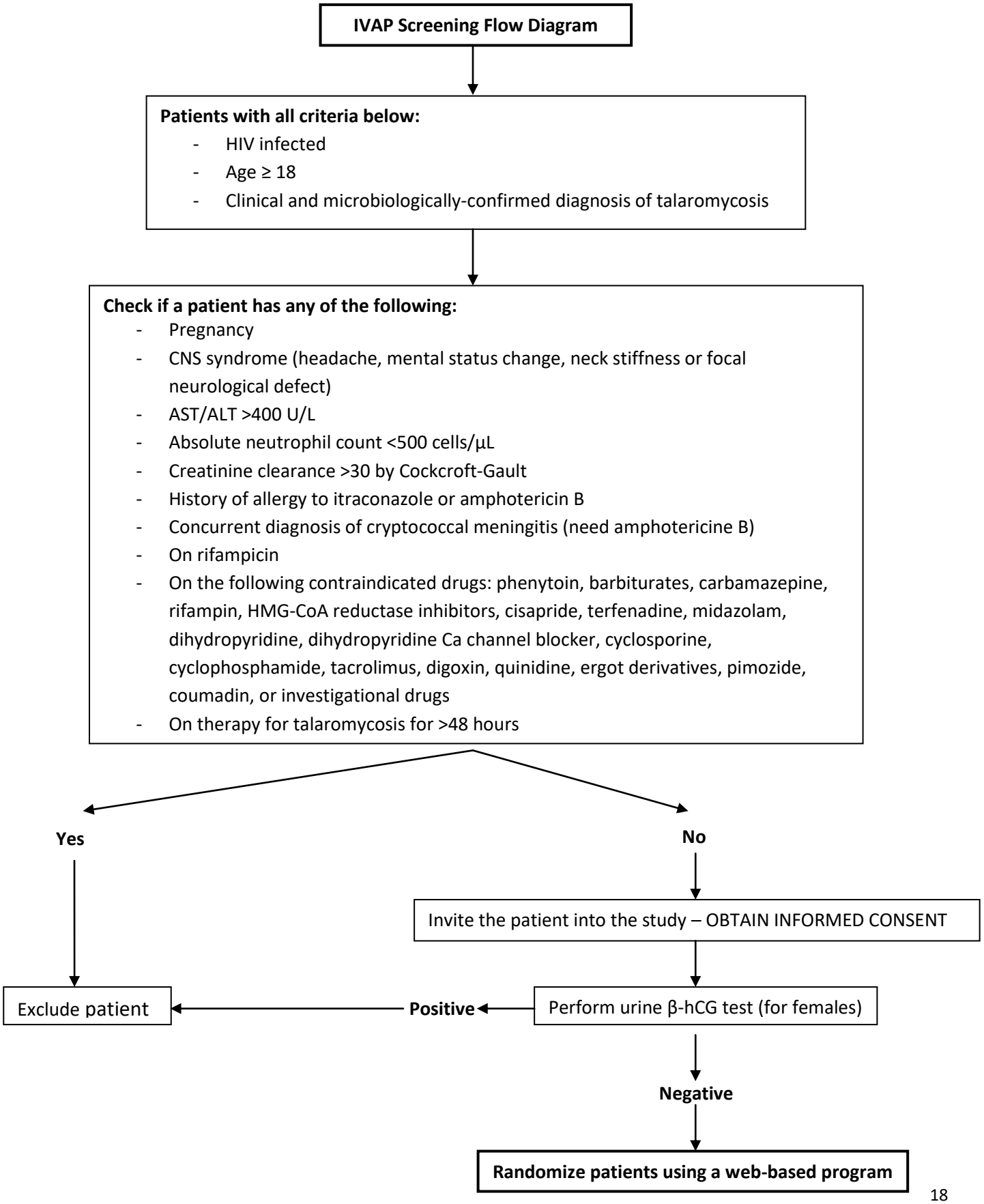
Amendments to the TSC Charter

This TSC charter can be amended as needed during the course of the study. All amendments will be documented with sequential version numbers and revision dates, and will be recorded in the minutes of the TSC meetings. Each revision will be reviewed and agreed upon by TSC members.

Archiving of TSC Activities and Related Documents

All TSC documentation and records will be retained in the Trial Master File in accordance with local and international regulatory requirements.

Section 5 – IVAP Screening Flowchart



Section 6 – *Talaromyces marneffei* Quantitative Fungal Count – Standard Operating Procedure

EQUIPMENTS:

1. Citrate tubes 2 mL for collection of whole blood
2. Gilson Pipette – P100 or P200
3. Sterile 200 microL Pipette Tips
4. Sterile eppendorfs (3 per sample)
5. Sabouraud dextrose agar plates (4 per sample)
6. Vortex
7. Safety Cabinet (Class II)

METHODS

Plate preparation

1. Sabouraud dextrose agar with cloramphenicol 50 mg/L
2. Dry in an incubator (30°C) for 30 minutes prior to use
3. Mark each plate into 2 halves using a permanent marker
4. Label each plate with
    a. the study number,
    b. the date the sample was withdrawn from the patient,
    c. the date the sample was processed (this should usually be the same date as the date that the sample was taken)
    d. the dilution strength i.e. 10^0 (neat), 10^{-1}, 10^{-2}, 10^{-3}

Processing samples

1. Samples should be processed the same day they are taken from the patient, and processed within 2 hours
2. Samples should be processed in a class II safety cabinet, since there is an aerosolisation risk because of vortexing
3. Neat samples and diluted samples should be vortexed before every step – ie., before making the next serial dilution and before inoculating the plate.

4. Perform 10 fold serial dilutions 3 times on each sample:

    a. Vortex neat whole blood samples

    b. Withdraw 100 microL (0.1 ml) using a P100 or P200 pipette

    c. Inoculate the aliquot into an eppendorf tube containing 0.9 ml distilled water

    d. Vortex the dilution and repeat 2 times to create 10^{-1}, 10^{-2}, and 10^{-3} dilutions

    e. Use a new pipette tip for each stage of the dilution process

    f. Immediately inoculate the plates

Plate inoculation

1. Label the plates as above
2. Use a P100 or P200 pipette set to 100 microL
3. Use a new pipette tip
4. Start from the most dilute dilution (10^{-3})
5. Vortex the dilution
6. Draw up 100 microL dilution
7. Inoculate one half of the plate with approximately 20 x 5 microL drips from the pipette
8. Vortex the dilution
9. Draw up 100 microL and inoculate the other half of the plate in the same way
10. Repeat for all the other dilutions, working from the weakest to the neat whole blood
11. If at any stage you are concerned that the tip may have become contaminated then use a new tip
12. Incubate at 37°C for a total of 14 days

Reading samples

1. Check the plates every day for growth. The best time for reading *T. marneffei* colony forming units (CFU) is approximately 3-5 days
2. Start a new recording sheet for each patient
3. Record the patients study number on each sheet
4. Count the visible CFUs by holding the plate over a dark background

5. Identify the plate that has between 20 and 250 CFUs. Use this plate to estimate the fungal burden. If there is no plate with more than 20 CFUs, then use the plate with any positive growth to estimate the fungal burden.

6. Count the number of CFUs on each side of the plate and calculate the mean number of CFUs

7. Record the number of CFUs on the plates every day until there is maximum (or confluent) growth. Usually a plate can be record 3-5 times until it reaches maximum growth. Use the maximum number of CFUs for calculation.

8. Determine the fungal burden by the formula, $Y = X * 10^{(n+1)}$

where Y is the number of CFUs in 1 ml of whole blood

X is the mean number of CFUs

n is fold number of dilutions of the plate that is read

Eg., if the plate with CFUs in the range of 20 and 250 CFUs is of the 10^{-2} dilution, and the mean number of colonies is 80, then n = 2 and the fungal burden is $80 X 10^3 = 80\,000$ CFUs/ml.

Storage fungal cultures

1. The first available *T. marneffei* growth for each patient should be stored using Pro lab Microbank beads

2. Use the neat sample from Day 1 (or a later day if Day 1 sample is unavailable)

3. Label each bead tube with the study number, *T. marneffei* and the date of storage. Try not to use a plate if it is contaminated with mold. Subculture first if there are no mold-free plates available

Which other samples should be stored?

Most samples will only need the earliest available sample to be stored. In addition, samples from patients with disease relapse, immune reconstitution inflammatory syndrome, or persistent growth beyond 14 days are also stored.

Potential Hazards

1. Blood-borne pathogens:

The samples come from patients with HIV and potentially other blood-borne viruses. A laboratory

coat and gloves must be worn at all times when working on specimens. The risk of transmission is low, but all patient samples should be handled within the safety cabinet. All staff must be checked for hepatitis B virus immunity prior to commencing work as per local procedures, and vaccinated as appropriate. In the event of a splash or other injury stop work immediately and follow your local guidelines.

2. *Talaromyces marneffei* is category 2 organism. There is no risk of person to person transmission. Biosafety level 2 practices are recommended for propagating and multipulating cultures containing *T. marneffei*.

Section 7 – Supplementary Tables and Figures

Table S1. Clinical and laboratory characteristics of patients at baseline

Characteristic	Amphotericin B (N=217)	Itraconazole (N=218)
Male sex – no./total no. (%)	152/215 (71)	144/217 (66)
Median age (IQR) – year	34 (30-38) [n=215]	34 (29-38) [n=217]
History of intravenous drug use – no./total no. (%)	70/215 (33)	66/217 (30)
Antiretroviral therapy		
On therapy – no./total no. (%)	93/215 (43)	95/217 (44)
Median duration (IQR) – days	141 (60-1014) [n=81]	106 (46-386) [n=87]
On therapy > 6 months – no./total no. (%)	38/81 (47)	29/87 (33)
Prior *T. marneffei* infection – no./total no. (%)	6/215 (3)	8/217 (4)
Median duration of illness (IQR) – days	28 (14-30) [n=215]	30 (14-33) [n=214]
Symptoms – no./total no. (%)		
Fever	196/215 (91)	190/216 (88)
Fatigue/anorexia/weight loss	207/215 (96)	205/216 (95)
Cough	114/215 (53)	116/216 (54)
Diarrhea	85/215 (40)	76/216 (35)
Signs		
Median weight (IQR) – kg	47 (41-51) [n=213]	47 (42-53) [n=214]
Median temperature (IQR) – °C	38.0 (37.4-39.0) [n=211]	38.0 (37.3-39.0) [n=216]
Oropharyngeal ulcers – no./total no. (%)	81/215 (38)	88/215 (41)
Skin lesions – no./total no. (%)	168/215 (78)	177/216 (82)
Dyspnea/requirement for oxygen – no./total no. (%)	22/215 (10)	20/217 (9)
Laboratory data		
Median white blood cell count (IQR) – $x10^9$/L	3.7 (2.3-5.3) [n=210]	3.7 (2.4-5.9) [n=213]
Median hemoglobin (IQR) – g/dL	8.9 (7.7-10.0) [n=210]	8.8 (7.7-10.3) [n=213]
Median platelet count (IQR) – $x10^9$/L	121 (52-228) [n=210]	118 (51-215) [n=213]
Median CD4 cell count (IQR) – cells/µL	10 (6-19) [n=205]	11 (6-27) [n=212]
Median creatinine (IQR) – µmol/L	67 (57-82) [n=210]	69 (57-86) [n=213]
Median AST (IQR) – U/L	121 (72-208) [n=210]	121 (68-193) [n=214]
Median ALT (IQR) – U/L	48 (31-82) [n=210]	48 (30-73) [n=214]
Median LDH (IQR) – U/L	411 (262-730) [n=141]	483 (303-813) [n=136]
Positive HBsAg – no./total no. (%)	38/194 (20)	40/195 (21)
Positive Anti HCV – no./total no. (%)	78/195 (40)	62/194 (32)
Positive skin culture for *T. marneffei* – no./total no. (%)	117/135 (87)	131/148 (89)
Positive blood culture for *T. marneffei* – no./total no. (%)	156/214 (73)	145/216 (67)
Blood fungal count		
Detectable – no./total no. (%)	143/201 (71)	148/200 (74)
Median count – $\log_{10}$ CFU/mL	2.20 (1.54-3.13) [n=143]	2.49 (1.54-3.17) [n=148]
Radiographic data		
Hepatosplenomegaly by ultrasound – no./total no. (%)	138/194 (71)	143/190 (75)
Abnormal chest X-ray – no./total no. (%)	76/184 (41)	84/188 (45)

There were no statistically significant between-group differences at baseline (all P>0.05) according to Fisher's exact test for categorical data or the Wilcoxon rank-sum test for continuous data except for duration of antiretroviral therapy (P=0.047).
n refers to the number of patients with non-missing data. IQR denotes interquartile range (lower and upper quartile), and CFU colony forming unit

Table S2. Multivariable regression models for the risk of death at 2 weeks (primary endpoint) and overall survival until 24 weeks.

	Risk of death at 2 weeks OR (95% CI)	P value *	Overall survival until 24 weeks HR (95% CI)	P value†
Itraconazole treatment (vs. amphotericin B)	1.10 (0.44-2.78)	0.84	1.86 (1.09-3.19)	0.023
Intravenous drug user: Yes	1.66 (0.63-4.25)	0.30	1.08 (0.62-1.88)	0.79
Undetectable fungal count at enrolment ‡	1.79 (0.48-6.33)	0.37	1.56 (0.84-2.89)	0.16
Enrolment fungal count (by +1 log10 CFU/ml) §	2.18 (1.43-3.45)	0.0002	1.45 (1.13-1.86)	0.004
Dyspnoea requiring oxygen: Yes	3.11 (0.98-8.99)	0.05	1.87 (0.91-3.85)	0.09
Oropharyngeal ulcers: Yes	1.73 (0.68-4.54)	0.25	1.28 (0.76-2.15)	0.36
Antiretroviral therapy : Yes	1.26 (0.50-3.19	0.62	1.13 (0.67-1.89)	0.65

* OR: odds ratio. Calculated based on logistic regression including all participants with non-missing covariates and outcome (n=396).

† HR: hazard ratio. Calculated based on the Cox proportional hazards model including all participants with non-missing covariates (n=399).

‡ Compared to a detectable fungal count of 100 CFU/ml.

§ For subjects with a detectable fungal count at enrolment (i.e. the covariate was set to 0 for those with undetectable fungal count).

Table S3. Summary of clinical grade 3 and 4 adverse events until 24 weeks.*			
Event	**Amphotericin B (n=217)**	**Itraconazole (n=218)**	**P value**
Any event			
At least one adverse event – no. of patients (%)	119 (54.84)	110 (50.46)	0.39
No. of adverse events	180	160	0.27
T. marneffei complications – no. of patients (%)	19 (8.76)	57 (26.15)	<0.0001
Respiratory failure	10 (4.61)	12 (5.50)	0.83
T. marneffei relapse	3 (1.38)	15 (6.88)	0.006
T. marneffei poor treatment response	1 (0.46)	13 (5.96)	0.002
T. marneffei IRIS	0 (0.00)	14 (6.42)	<0.0001
Wasting syndrome due to *T. marneffei*	5 (2.30)	6 (2.75)	1.00
Allergic and immune disorders – no. of patients (%)	52 (23.96)	3 (1.38)	<0.0001
Infusion reaction	49 (22.58)	1 (0.46)	<0.0001
Skin rash	1 (0.46)	1 (0.46)	1.00
Drug-induced hepatitis	1 (0.46)	0 (0.00)	0.50
Drug-related hemolytic anemia	1 (0.46)	0 (0.00)	0.50
Hives (platelet transfusion)	0 (0.00)	1 (0.46)	1.00
Skin rash (suspect due to cotrim)	1 (0.46)	0 (0.00)	0.50
Skin rash (suspect due to itraconazole)	1 (0.46)	0 (0.00)	0.50
AIDS-associated stage IV diseases – no. of patients (%)	19 (8.76)	22 (10.09)	0.74
Extrapulmonary TB	7 (3.23)	5 (2.29)	0.58
Wasting syndrome due to HIV	4 (1.84)	4 (1.83)	1.00
Disseminated TB	3 (1.38)	5 (2.29)	0.72
CMV retinitis	3 (1.38)	4 (1.83)	1.00
PCP	2 (0.92)	4 (1.83)	0.69
Toxoplasmosis	0 (0.00)	2 (0.92)	0.50
CMV polyneuritis	1 (0.46)	0 (0.00)	0.50
Disseminated MAC infection	0 (0.00)	1 (0.46)	1.00
AIDS-associated stage III diseases – no. of patients (%)	21 (9.68)	23 (10.55)	0.87
Pulmonary TB	19 (8.76)	22 (10.09)	0.74
Oral herpes	2 (0.92)	0 (0.00)	0.25
Abdominal lymphadenitis	0 (0.00)	1 (0.46)	1.00
TB IRIS	0 (0.00)	1 (0.46)	1.00
Other infections – no. of patients (%)	12 (5.53)	19 (8.72)	0.26
Pneumonia	6 (2.76)	6 (2.75)	1.00
Sepsis (*Salmonella* spp.)	0 (0.00)	4 (1.83)	0.12
Suspect Parvovirus B19 infection	1 (0.46)	1 (0.46)	1.00
Infectious diarrhea	1 (0.46)	1 (0.46)	1.00

Sepsis	1 (0.46)	1 (0.46)	1.00
Shock	2 (0.92)	0 (0.00)	0.25
Buttock abscess	1 (0.46)	0 (0.00)	0.50
Fever	0 (0.00)	1 (0.46)	1.00
Scabies	0 (0.00)	1 (0.46)	1.00
Sepsis (ESBL *Klebsiella pneumoniae*)	0 (0.00)	1 (0.46)	1.00
Sepsis (*Streptococcus pneumoniae*)	0 (0.00)	1 (0.46)	1.00
Urinary tract infection	0 (0.00)	1 (0.46)	1.00
Viral infection	0 (0.00)	1 (0.46)	1.00
Nutritional and metabolic disorders – no. of patients (%)	9 (4.15)	3 (1.38)	0.09
Hypokalemia	4 (1.84)	2 (0.92)	0.45
Hypomagnesemia	3 (1.38)	0 (0.00)	0.12
Anasarca	1 (0.46)	0 (0.00)	0.50
Fatigue	1 (0.46)	0 (0.00)	0.50
Hypocalcemia	0 (0.00)	1 (0.46)	1.00
Blood and lymphatic disorders – no. of patients (%)	16 (7.37)	3 (1.38)	0.002
Anemia	8 (3.69)	2 (0.92)	0.06
Neutropenia	2 (0.92)	0 (0.00)	0.25
Pancytopenia	1 (0.46)	1 (0.46)	1.00
Phlebitis	2 (0.92)	0 (0.00)	0.25
Thrombocytopenia	2 (0.92)	0 (0.00)	0.25
Epitaxis	1 (0.46)	0 (0.00)	0.50
Thrombophlebitis	1 (0.46)	0 (0.00)	0.50
Central nervous system (CNS) disorders – no. of patients (%)	1 (0.46)	3 (1.38)	0.62
Meningoencephalitis	1 (0.46)	1 (0.46)	1.00
CNS syndrome of unclear etiology	0 (0.00)	1 (0.46)	1.00
Encephalophathy	0 (0.00)	1 (0.46)	1.00
Cardiovascular disorders – no. of patients (%)	2 (0.92)	0 (0.00)	0.25
Hypotension	1 (0.46)	0 (0.00)	0.50
Stroke	1 (0.46)	0 (0.00)	0.50
Respiratory disorders– no. of patients (%)	2 (0.92)	1 (0.46)	0.62
Dyspnea	2 (0.92)	0 (0.00)	0.25
Hemoptysis	0 (0.00)	1 (0.46)	1.00
Gastrointestinal disorders – no. of patients (%)	8 (3.69)	10 (4.59)	0.81
Diarrhea	3 (1.38)	2 (0.92)	0.69
Gastrointestinal bleeding	2 (0.92)	3 (1.38)	1.00
Abdominal distention	1 (0.46)	1 (0.46)	1.00
Nausea/vomiting	1 (0.46)	1 (0.46)	1.00
Peritonitis	1 (0.46)	1 (0.46)	1.00

Esophageal stricture	0 (0.00)	1 (0.46)	1.00
Hepatitis – cholestasis	1 (0.46)	0 (0.00)	0.50
Suspect drug-induced liver failure	0 (0.00)	1 (0.46)	1.00
Renal disorders	10 (4.61)	1 (0.46)	0.006
Renal failure	10 (4.61)	1 (0.46)	0.006
Bone and joint disorders – no. of patients (%)	1 (0.46)	0 (0.00)	0.50
Acute gout	1 (0.46)	0 (0.00)	0.50
Psychiatric disorders – no. of patients (%)	1 (0.46)	2 (0.92)	1.00
Delirium	0 (0.00)	1 (0.46)	1.00
Depression	0 (0.00)	1 (0.46)	1.00
Manic episode	1 (0.46)	0 (0.00)	0.50
Accident	1 (0.46)	0 (0.00)	0.50
Traffic accident	1 (0.46)	0 (0.00)	0.50
Death of unknown cause – no. of patients (%)	0 (0.00)	3 (1.38)	0.25
Death of unknown cause	0 (0.00)	3 (1.38)	0.25

*Listed are the numbers of patients who had at least one adverse event of the respective type. All comparisons are based on Fisher's exact test, except for the comparison of the total number of adverse events which was based on a quasi-Poisson regression model with treatment as the only covariate.

IRIS denotes immune reconstitution inflammatory syndrome; AIDS acquired immune deficiency syndrome; TB tuberculosis; CMV Cytomegalovirus; PCP *Pneumocystis jiroveci* pneumonia; MAC mycobacteria avium complex; ESBL extended spectrum beta-lactamase.

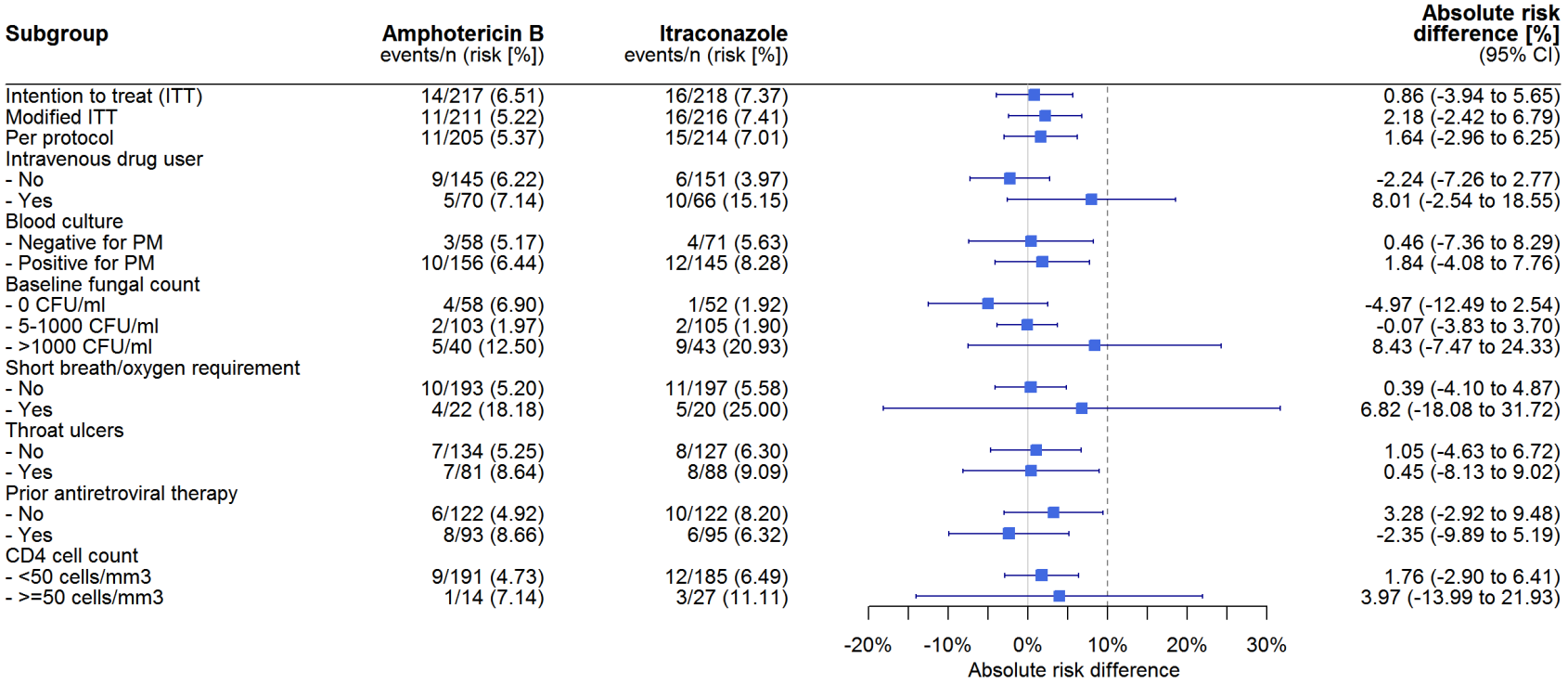
Table S4. Summary of serious adverse events until 24 weeks.*			
Event	**Amphotericin B (n=217)**	**Itraconazole (n=218)**	**P value**
Any serious adverse event			
At least one serious adverse event – no. of patients (%)	58 (26.73)	100 (45.87)	<0.0001
No. of adverse events	72	132	<0.0001
T. marneffei complications – no. of patients (%)	18 (8.29)	52 (23.85)	<0.0001
Respiratory failure	9 (4.15)	12 (5.50)	0.66
T. marneffei relapse	3 (1.38)	15 (6.88)	0.006
T. marneffei poor treatment response	1 (0.46)	13 (5.96)	0.002
T. marneffei IRIS	0 (0.00)	9 (4.13)	0.004
Wasting syndrome due to *T. marneffei*	5 (2.30)	6 (2.75)	1.00
Allergic and immune disorders – no. of patients (%)	3 (1.38)	1 (0.46)	0.37
Skin rash	0 (0.00)	1 (0.46)	1.00
Drug-related hemolytic anemia	1 (0.46)	0 (0.00)	0.50
Skin rash (suspect due to cotrimoxazole)	1 (0.46)	0 (0.00)	0.50
Skin rash (suspect due to itraconazole)	1 (0.46)	0 (0.00)	0.50
AIDS-associated stage IV diseases – no. of patients (%)	14 (6.15)	20 (9.17)	0.37
Extrapulmonary TB	4 (1.84)	4 (1.83)	1.00
Disseminated TB	3 (1.38)	5 (2.29)	0.72
Wasting syndrome due to HIV	4 (1.84)	4 (1.83)	1.00
CMV retinitis	0 (0.00)	2 (0.92)	0.50
PCP	2 (0.92)	4 (1.83)	0.69
Toxoplasmosis	0 (0.00)	1 (0.46)	1.00
CMV polyneuritis	1 (0.46)	0 (0.00)	0.50
Disseminated MAC infection	0 (0.00)	1 (0.46)	1.00
AIDS-associated stage III diseases – no. of patients (%)	11 (5.07)	17 (7.80)	0.33
Pulmonary TB	11 (5.07)	16 (7.34)	0.43
TB IRIS	0 (0.00)	1 (0.46)	1.00
Other infections – no. of patients (%)	10 (4.61)	17 (7.80)	0.23
Pneumonia	5 (2.30)	5 (2.29)	1.00
Sepsis (*Salmonella* spp.)	0 (0.00)	4 (1.83)	0.12
Suspect Parvovirus B19 infection	1 (0.46)	1 (0.46)	1.00
Infectious diarrhea	0 (0.00)	1 (0.46)	1.00
Sepsis	1 (0.46)	1 (0.46)	1.00
Shock	2 (0.92)	0 (0.00)	0.25
Buttock abscess	1 (0.46)	0 (0.00)	0.50
Fever	0 (0.00)	1 (0.46)	1.00

Sepsis (ESBL *Klebsiella pneumoniae*)	0 (0.00)	1 (0.46)	1.00
Sepsis (*Streptococcus pneumoniae*)	0 (0.00)	1 (0.46)	1.00
Urinary tract infection	0 (0.00)	1 (0.46)	1.00
Viral infection	0 (0.00)	1 (0.46)	1.00
Nutritional and metabolic disorders – no. of patients (%)	2 (0.92)	2 (0.92)	1.00
Hypokalemia	1 (0.46)	1 (0.46)	1.00
Fatigue	1 (0.46)	0 (0.00)	0.50
Hypocalcemia	0 (0.00)	1 (0.46)	1.00
Blood and lymphatic disorders – no. of patients (%)	3 (1.38)	2 (0.92)	0.69
Anemia	3 (1.38)	2 (0.92)	0.69
Central nervous system (CNS) disorders – no. of patients (%)	1 (0.46)	3 (1.38)	0.62
Meningoencephalitis	1 (0.46)	1 (0.46)	1.00
CNS syndrome of unclear etiology	0 (0.00)	1 (0.46)	1.00
Encephalophathy	0 (0.00)	1 (0.46)	1.00
Cardiovascular disorders – no. of patients (%)	1 (0.46)	0 (0.00)	0.50
Stroke	1 (0.46)	0 (0.00)	0.50
Respiratory disorders – no. of patients (%)	1 (0.46)	1 (0.46)	1.00
Dyspnea	1 (0.46)	0 (0.00)	0.50
Hemoptysis	0 (0.00)	1 (0.46)	1.00
Renal disorders – no. of patients (%)	4 (1.84)	0 (0.00)	0.06
Renal failure	4 (1.84)	0 (0.00)	0.06
Gastrointestinal disorders – no. of patients (%)	3 (1.38)	6 (2.75)	0.50
Diarrhea	1 (0.46)	2 (0.92)	1.00
Gastrointestinal bleeding	1 (0.46)	1 (0.46)	1.00
Peritonitis	1 (0.46)	1 (0.46)	1.00
Esophageal stricture	0 (0.00)	1 (0.46)	1.00
Suspect drug-induced liver failure	0 (0.00)	1 (0.46)	1.00
Psychiatric disorders – no. of patients (%)	0 (0.00)	1 (0.46)	1.00
Depression	0 (0.00)	1 (0.46)	1.00
Accident – no. of patients (%)	1 (0.46)	0 (0.00)	0.50
Traffic accident	1 (0.46)	0 (0.00)	0.50
Death of unknown cause – no. of patients (%)	0 (0.00)	3 (1.38)	0.25

*Listed are the numbers of patients who had at least one adverse event of the respective type. All comparisons are based on Fisher's exact test, except for the comparison of the total number of serious adverse events which was based on a quasi-Poisson regression model with treatment as the only covariate.

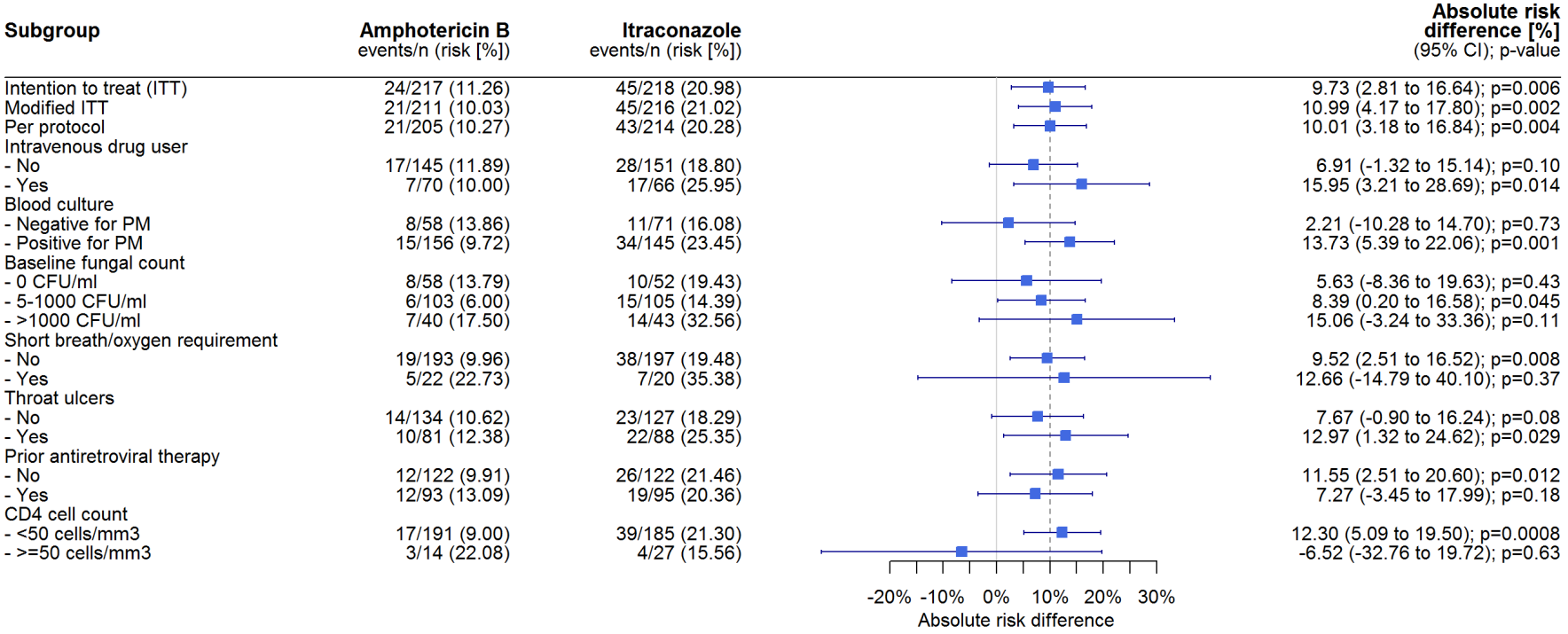
IRIS denotes immune reconstitution inflammatory syndrome; AIDS acquired immune deficiency syndrome; TB tuberculosis; CMV Cytomegalovirus; PCP *Pneumocystis jiroveci* pneumonia; MAC mycobacteria avium complex; ESBL extended spectrum beta-lactamase.

Figure S1. Pre-defined subgroup analyses for the risk of death at 2 weeks (primary endpoint).



The dark-gray dashed vertical line corresponds to the pre-defined non-inferiority margin of Δ=10%. There was no clear evidence that absolute risk differences between treatment groups depend on subgroup levels (P-values of tests for heterogeneity >0.20 for all subgroups, except for intravenous drug use [P=0.09]).

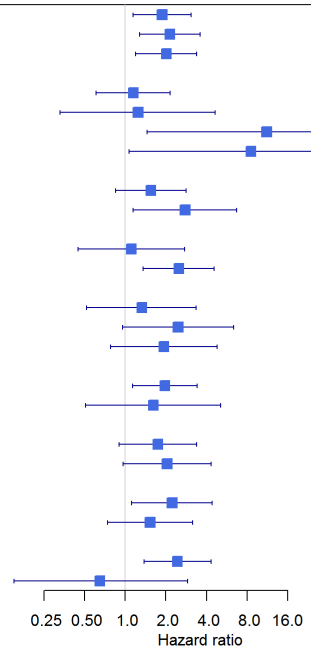
Figure S2. Pre-defined subgroup analyses for the risk of death at 24 weeks.



There was no clear evidence that absolute risk differences between treatment groups depend on subgroup levels (P-values of tests for heterogeneity >0.20 for all subgroups, except for blood culture results [P=0.13] and CD4 cell count stratum [P=0.18]).

Figure S3. Pre-defined subgroup analyses for overall survival until week 24 (time-to-event analysis using Cox regression).

Subgroup	Amphotericin B(n=217) events/n (risk [%])	Itraconazole(n=218) events/n (risk [%])	Comparison HR (95%CI);p-value	Test for heterogeneity p-value
Intention to treat (ITT)	24/217 (11.26)	45/218 (20.98)	1.88(1.15-3.09); p=0.012	
Modified ITT	21/211 (10.03)	45/216 (21.02)	2.15(1.28-3.61); p=0.004	
Per protocol	21/205 (10.27)	43/214 (20.28)	2.02(1.20-3.40); p=0.008	
Time period				0.016
- Weeks 1-4	18/217	21/218	1.15(0.61-2.16); p=0.66	
- Weeks 5-8	4/193	5/194	1.25(0.33-4.64); p=0.74	
- Weeks 9-16	1/189	11/189	11.20(1.45-86.76); p=0.021	
- Weeks 17-24	1/187	8/178	8.55(1.07-68.36); p=0.043	
Intravenous drug user				0.26
- No	17/145 (11.89)	28/151 (18.80)	1.55(0.85-2.83); p=0.15	
- Yes	7/70 (10.00)	17/66 (25.95)	2.78(1.15-6.70); p=0.023	
Blood culture				0.15
- Negative for PM	8/58 (13.86)	11/71 (16.08)	1.11(0.45-2.76); p=0.82	
- Positive for PM	15/156 (9.72)	34/145 (23.45)	2.50(1.36-4.58); p=0.003	
Baseline fungal count				0.65
- 0 CFU/ml	8/58 (13.79)	10/52 (19.43)	1.33(0.52-3.36); p=0.55	
- 5-1000 CFU/ml	6/103 (6.00)	15/105 (14.39)	2.47(0.96-6.36); p=0.06	
- >1000 CFU/ml	7/40 (17.50)	14/43 (32.56)	1.94(0.78-4.82); p=0.15	
Short breath/oxygen requirement				0.88
- No	19/193 (9.96)	38/197 (19.48)	1.97(1.14-3.42); p=0.016	
- Yes	5/22 (22.73)	7/20 (35.38)	1.62(0.51-5.12); p=0.41	
Throat ulcers				0.75
- No	14/134 (10.62)	23/127 (18.29)	1.75(0.90-3.40); p=0.10	
- Yes	10/81 (12.38)	22/88 (25.35)	2.05(0.97-4.34); p=0.06	
Prior antiretroviral therapy				0.46
- No	12/122 (9.91)	26/122 (21.46)	2.23(1.12-4.41); p=0.022	
- Yes	12/93 (13.09)	19/95 (20.36)	1.53(0.74-3.15); p=0.25	
CD4 cell count				0.12
- <50 cells/mm3	17/191 (9.00)	39/185 (21.30)	2.44(1.38-4.32); p=0.002	
- >=50 cells/mm3	3/14 (22.08)	4/27 (15.56)	0.65(0.15-2.90); p=0.57	



The analyis by time period was not pre-defined but was added post-hoc as there was evidence for a time-varying effect of the treatment assignment on the hazard (test for heteroteneity P=0.016).