Timing of antiretroviral therapy for HIV-infected patients with moderate-to-severe *Pneumocystis* pneumonia: study protocol for a multi-center prospective randomized controlled trial

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Study protocol

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Abstract

Background: *Pneumocystis* pneumonia (PCP) is a common AIDS-related opportunistic infection. Recent reports estimate that more than 400,000 HIV patients develop PCP each year globally. However, the timing of antiretroviral therapy (ART) initiation for HIV infected patients with PCP is still controversial, and the benefits and risks of early initiation of ART are not completely clear. We thus designed this study in order to determine the optimal timing for ART initiation for HIV-positive patients with moderate to severe PCP.

Methods: This study will be an open-labelled, multi-center, prospective, randomized controlled trial. A total of 200 subjects will be randomized to an early ART initiation group (≤14 days after PCP diagnosis), and a deferred ART initiation group (>14 days after PCP diagnosis) at a 1:1 ratio. All subjects will be followed up for 48 weeks after starting ART. The primary outcome is incidence of disease progression (including new opportunistic infections and all-cause mortality) at week 48. The secondary endpoints are the changes in CD4 counts from baseline at week 12, week 24 and week 48, the degree of virological suppression (HIV-RNA<50 copies/mL) at week 24 and week 48, the rate of development of PCP-associated immune reconstitution inflammatory syndrome (IRIS), and adverse events(AEs) at each visit.

Discussion: We hope that the results of this study will reveal the optimal timing for initiation of ART in HIV-infected patients with moderate to severe PCP.

Trial registration: This trial was registered as one of the twelve trials under the name of a general project at chictr.org.cn on February 1, 2019, and the registration number of the general project is ChiCTR1900021195.

Background

Pneumocystis pneumonia, one of the most common AIDS-defining diseases, is caused by the fungal opportunistic organism, *Pneumocystis jirovecii*, and has been effectively controlled in AIDS patients by the widespread use of modern ART. However, the incidence of PCP among undiagnosed HIV patients increased from 48% in 2000 to 67% in 2013 [1]. Reports in recent years estimate that more than 400,000 HIV patients develop PCP globally every year [2, 3]. Mortality of PCP ranges from 10% to 30%, and may be even higher if diagnosis is delayed [4-6]. Although efforts for the early diagnosis and treatment of PCP have been made, the proportion of HIV patients with advanced PCP has not decreased in many high-burden countries [7].

Optimal timing for ART initiation in opportunistically infected patients with HIV infection is controversial. One multi-center randomized clinical trial showed that early initiation of ART had a lower rate of AIDS progression and deaths than deferred ART, without increased adverse events and with optimal viral suppression [8]. In the study, results from both overall analysis of all OIs, and subgroup analysis of PCP were consistent [8]. However, in a recent study investigated the timing of initiation of proteinase-inhibitor ART in HIV-patients with acute AIDS-defining events, enrolling a total of 61 subjects {11 patients with

toxoplasmosis (TE) and 50 patients with PCP}, researchers found that there were no significant immunological or virological differences between the immediate ART initiation group and the deferred initiation group [7]. From the results of the above studies, it is obvious that the timing for ART initiation in HIV-infected persons with PCP remains controversial, and warrants further investigation. We thus designed the present study in order to determine the optimal timing for ART initiation for HIV-positive patients with moderate to severe PCP.

Research Objective

This study aims to investigate the optimal timing for ART initiation in HIV-infected patients with moderate to severe PCP.

Our primary goal is to compare the progression of disease between an early ART initiation group (initiation within 2 weeks of PCP diagnosis), and a deferred ART initiation group (initiation after 2 weeks of PCP diagnosis) at week 48.

Our secondary goal is to compare the safety of the timing of ART initiation between the early-ART initiation group and the deferred-ART initiation group during the 48-week period of this study.

Our tertiary goal is to determine whether there are differences in the long-term effects of early ART initiation as compared to deferred ART initiation with regard to CD4 cell counts and HIV RNA loads in HIV-infected patients with moderate to severe PCP.

Methods

Study design

This study will be conducted as an open-labelled, multi-center prospective randomized controlled trial. We will recruit 200 subjects from the following 17 hospitals: Chongqing Public Health Medical Center, Beijing You'an Hospital of Capital Medical University, Harbin Medical University, the Second People's Hospital of Tianjin, the First Hospital of Changsha, the Eighth People's Hospital of Guangzhou, Liuzhou General Hospital, the Third People's Hospital of Guilin, the Third People's Hospital of Shenzhen, Guiyang Public Health Clinical Center, Public Health Clinical Center of Chengdu, Kunming Third People's Hospital, Yunnan Provincial Infectious Disease Hospital, the Fourth People's Hospital of Nanning, Guangxi Longtan Hospital, the First Affiliated Hospital of Zhejiang University, and Xixi Hospital of Hangzhou. This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [9]. The enrolment, intervention and assessment processes are shown in Figure 1. All subjects in each treatment arm of the study will participate voluntarily, after informed consent is obtained. Each individual will be invited to participate in a 48-week follow-up after commencement of ART. Study visits will be scheduled at week 4, week 8, week 12, week 24, week 36, and week 48. Blood and urine samples will be collected for laboratory testing, including haematological analysis, urinalysis, clinical chemistry studies, serum amylase levels, myocardial enzymes, blood gas analysis, 1,3β-D-glucan,

lymphocyte subset and quantitative plasma HIV-1 RNA. Other patient samples to be collected during the follow-up period are listed in Table 1.

Table 1. Measurement items and point of data capture.

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Baseline	Week 4	Week 8	Week 12	Week 24	Week 36	Week 48
Sign consent	×						
Enrolment	×						
Demography	×						
Signs & symptoms	×	×	×	×	×	×	×
Haematological analysis	×	×	×	×	×	×	×
Urinalysis	×	×	×	×	×	×	×
Clinical chemistry studies	×	×	×	×	×	×	×
Serum Amylase levels	×						
Myocardial enzymes	×						
Blood gas analysis	×						
1,3β-D-glucan	×						
Urine pregnancy test	×						

Lymphocyte subset	×	×	×	×	×		×
Quantitative plasma HIV-1 RNA	×				×		×
Chest CT/X-ray	×	×	×	×	×	×	×
IRIS		×	×	×	×	×	×
Drug combination	×	×	×	×	×	×	×
Adverse events		×	×	×	×	×	×

Participants

Diagnostic criteria

The presumptive diagnosis of moderate to severe PCP will have to meet the following criteria:

(1) Progressive exacerbation of dyspnoea;

(2) Diffuse “ground-glass” interstitial infiltrates spreading from the hilum in chest radiograph;

(3) Alveolar-arterial O2 gradient, (A-a)$DO_2 \geq 35$mmHg, or room air arterial oxygen, $PO_2 \leq 70$mmHg.

The definitive diagnosis of PCP requires identification of *Pneumocystis* cysts or trophozoites via staining, or detection of *Pneumocystis* DNA via PCR in sputum samples, bronchoalveolar lavage (BAL) fluid, or biopsy samples, in addition to the criteria for the presumptive diagnosis of moderate to severe PCP.

We define PCP-IRIS as occurring when the subject experiences a paradoxical exacerbation of either clinical symptoms or radiological signs of PCP after the initiation of ART, despite receiving appropriate drug treatment for PCP.

Inclusion criteria

Subjects will be included in our study if they satisfy the following criteria:

(1) Are aged 18 years or over;

(2) Have confirmed diagnosis of HIV-1 infection;

(3) Are diagnosed with moderate to severe PCP presumptively or definitively;

(4) Have not received any antiretroviral treatment;

(5) Be willing to give the informed consent.

Exclusion criteria

Subjects will be excluded from the study if they:

(1) Are allergic or intolerant to any of the prescribed therapeutic drugs;

(2) Have hemoglobin (Hb) <60g/L, white blood cell count (WBC) <1.0×10^9/L, neutrophil count (N) <0.5×10^9/L, platelet count (PLT) <50×10^9/L, blood amylase (AMS) >2×upper normal limit (UNL), serum creatinine (SCr) >1.5×UNL, aspartate aminotransferase (AST)/ alanine aminotransferase (ALT)/ alkaline phosphatase (ALP) >5 times of UNL, total bilirubin (TB) >2×UNL, serum creatine phosphokinase (CK) >2×UNL;

(4) Have unstable concomitant opportunistic infections other than PCP;

(5) Have serious heart disease, brain disease, lung disease, kidney disease, tumor disease and other systemic diseases;

(6) Are pregnant or breastfeeding women;

(7) Have severe mental illness;

(8) Are intravenous drug users;

(9) Are not of Chinese nationality.

Randomization

A specific random number sequence will be generated by Medical Research Platform (http://www.51yyt.org/FrontPage/login.aspx?Inviter=) for each subject with consent. Once eligibility has been confirmed, the investigators or designers will randomize the subjects into the early ART initiation group or the deferred ART initiation group at a 1:1 ratio.

Data collection and quality assurance

All of the results will be recorded and double entered independently. All data will be documented on case report forms (CRFs) and immediately recorded in the database through the Medical Research Platform.

Missing values will be checked to ensure data completeness as much as possible. Data that are significantly abnormal or outside the clinically acceptable range (laboratory items exceeding 20% of the normal value) must be explained, and the necessary explanation must be given by the physician. Drop-outs and adverse events will be recorded in time, and drugs used for trial will be supplied, stored, distributed, and recycled in accordance with relevant regulations. After the trial is completed, a data management report meeting will be held to guarantee the validity and authenticity of this trial. The data administrator will perform a database lock after the data lock record is signed by the principal investigator, sponsor, statistical analysts and data managers.

Intervention

All subjects will receive conventional treatment for PCP according to the recommendations of Chinese guidelines for diagnosis and treatment of HIV/AIDS (2018) [10]. TMP-SMZ (trimethoprim-sulfamethoxazole, co-trimoxazole) combined with prednisone will be the preferred regimen. An alternative regimen may be used if the preferred regimen is intolerable, or if the patient is allergic to the preferred regimen. Those who have no obvious improvement after a full course of treatment or deteriorate during the course of treatment will be considered for replacement therapy or extension of treatment. Secondary prophylaxis will be initiated immediately after successful treatment, and maintained until CD4 cell counts are >200 cells/μL for at least six months. Once diagnosed, subjects will be randomly assigned to the early ART initiation (≤14 days after PCP diagnosis) arm or the deferred ART initiation (>14 days after PCP diagnosis) arm based on the random number sequence generated by the Medical Research Platform. As per the local guidelines [10], TDF (300mg/d) +3TC (300mg/d) +EFV (600mg/d) is preferred for ART, and other regimens are optional.

Study endpoints

The primary endpoint is incidence of disease progression (including new opportunistic infections and all-cause mortality). The secondary endpoints are the changes in CD4 counts from baseline to week 12, week 24 and week 48, virologic suppression (HIV-RNA<50 copies/mL) rate at week 24 and week 48, as well as rates of development of PCP-associated IRIS, and adverse events at each visit, including: (1) grade 3 or 4 adverse events; (2) serious adverse events; (3) adverse events related to discontinuation of medication or regimen change.

Sample Size

The sample size will be 100 subjects per treatment arm in order to provide at least 80% power, and an overall two-side alpha level of 0.05. We hypothesize that the proposed study will observe a 20% survival benefit in the early initiation arm, and the expected lost-to-follow-up rate will be 15%.

Data analysis

The primary outcome analysis will be conducted using the Intent-to-Treat Exposed (ITT-E) population, which consists of all randomized patients, whether they are in full compliance with the study protocol or

not. ITT-E will be used to assess the primary efficacy endpoints. We also plan to analyse the primary outcome using the per-protocol (PP) analysis set, which excludes subjects who do not follow the treatment regimens. If any data is not recorded, the last observation carried forward (LOCF) method will be used. Baseline will be defined as the date of randomization. We will compare the primary endpoint in the two groups using time-to-event methods with Cox proportional-hazards models. Categorical variables will be analysed using Fisher's exact test. To explain the competing risk of death, the cumulative incidence function will be used to compare adverse events and IRIS between the two groups [11]. A *p*-value of <0.05 will be considered to be statistically significant.

Ethics and dissemination

The study was approved by The Ethics Committee of the Chongqing Public Health Medical Center (2019-003-02-KY), and duly registered at the Chinese Clinical Trial Registry (ChiCTR1900021195). We will share the results through published medical journal articles and at conference presentation after completion of the study.

Discussion

The decision as to when to initiate ART in patients with moderate-to-severe PCP continues to cause confusion and frustration in clinical practice. On the one hand, patients desperately need suppression of HIV replication, as most are severely immunocompromised due to their high viral loads. The sooner the initiation of ART in these patients, the more favourable the chances of survival they would have, notwithstanding concerns regarding drug toxicity and IRIS. On the other hand, the complications relating to the administration of a multitude of medications intended to treat both PCP and HIV infection to such systemically unwell patients makes it inevitable to have to consider the emergence of IRIS, or the overlapping toxicities of various drugs, and complex drug-drug interactions among various drugs. The earlier that ART is initiated, the higher the risk of subsequently developing IRIS, and of arousing drug toxicities, and of initiating unfavourable drug-drug interactions.

Previous studies have investigated the timing of ART initiation in patients with OIs, including PCP. The PISCIS cohort study (conducted from 1998 to 2006) found that patients with AIDS-defining diseases, including those with PCP, were significantly more likely to progress to a new AIDS-defining disease or death if ART initiation was deferred >30 days after HIV infection diagnosis, compared with early ART initiation patients (<30 days after HIV infection diagnosis) [12]. The AIDS Clinical Trials Group (ACTG) reported in 2009 that AIDS progression and death of HIV patients with non-tuberculous OIs are decreased if they initiated ART early (within 14 days of starting acute OI treatment) [8]. Previous studies show that patients with OIs, including PCP, may be able to benefit from early ART initiation. However, a recent study investigating the timing of initiation in HIV-patients with acute AIDS-defining events, enrolling 50 patients with PCP, found that there were no significant differences in safety, efficacy and quality of life between the immediate ART initiation group (initiation within 7 days of PCP diagnosis and treatment) and the deferred initiation group (after the treatment for PCP was over) [7]. The above conflicting studies clearly

indicate that the optimal timing for ART initiation in patients with PCP remains controversial, and further investigation of this issue is warranted, especially for those with moderate-to-severe PCP, which is associated with high mortality.

Herein, we designed a multi-center prospective randomized controlled trial in China, in which all eligible subjects will be randomized into an early ART initiation group (≤14 days after PCP diagnosis) and a deferred ART initiation group (>14 days after PCP diagnosis). We will collect data of survival, immunological reconstitution, virological suppression, AEs, and IRIS emergence in HIV-infected patients with moderate-to-severe PCP, with the aim to investigate the safety and benefits of early ART. We speculate that subjects in the early ART initiation group will have lower new OI incidence rates and all-cause mortality than those in the deferred ART group. We hope that our results will provide unequivocal clinical evidence as to the optimal timing to initiate ART in HIV-infected patients who are diagnosed with moderate-to-severe PCP.

Trial Status

This trial is currently in the recruitment phase. Patient recruitment began in March 2019 and is expected to be completed in May 2020. (protocol version 5, 28 August 2019).

Abbreviations

ACTG: AIDS Clinical Trials Group; AEs: adverse events; AIDS: acquired immune deficiency syndrome; ART: antiretroviral therapy; BAL: bronchoalveolar lavage; CRFs: case report forms; HIV: human immunodeficiency virus; IRIS: inflammatory syndrome; ITT-E: Intent-to-Treat Exposed; LOCF: last observation carried forward; PCP: *Pneumocystis* pneumonia; PP: per-protocol; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; TE: toxoplasmosis; UNL: upper normal limit

Declarations

Acknowledgements

Not applicable.

Authors' contributions

Y-YQ and Y-QL conceived and drafted the protocol. VH and Y-KC revised the protocol and contributed to finalizing the manuscript. FS and SY contributed to the design and implementation of the study. LY, X-QH and Y-MZ helped to revise the protocol. Y-HZ and S-QT contributed to the statistical analysis and interpretation. All authors contributed to the refinement of the study protocol, and approved the final manuscript.

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Availability of data and materials

The dataset necessary to interpret the findings are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by The Ethics Committee of Chongqing Public Health Medical Center (No. 2019-003-02-KY). Written informed consent will be obtained from each patient before randomization. All subjects will sign informed consent before enrolment in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

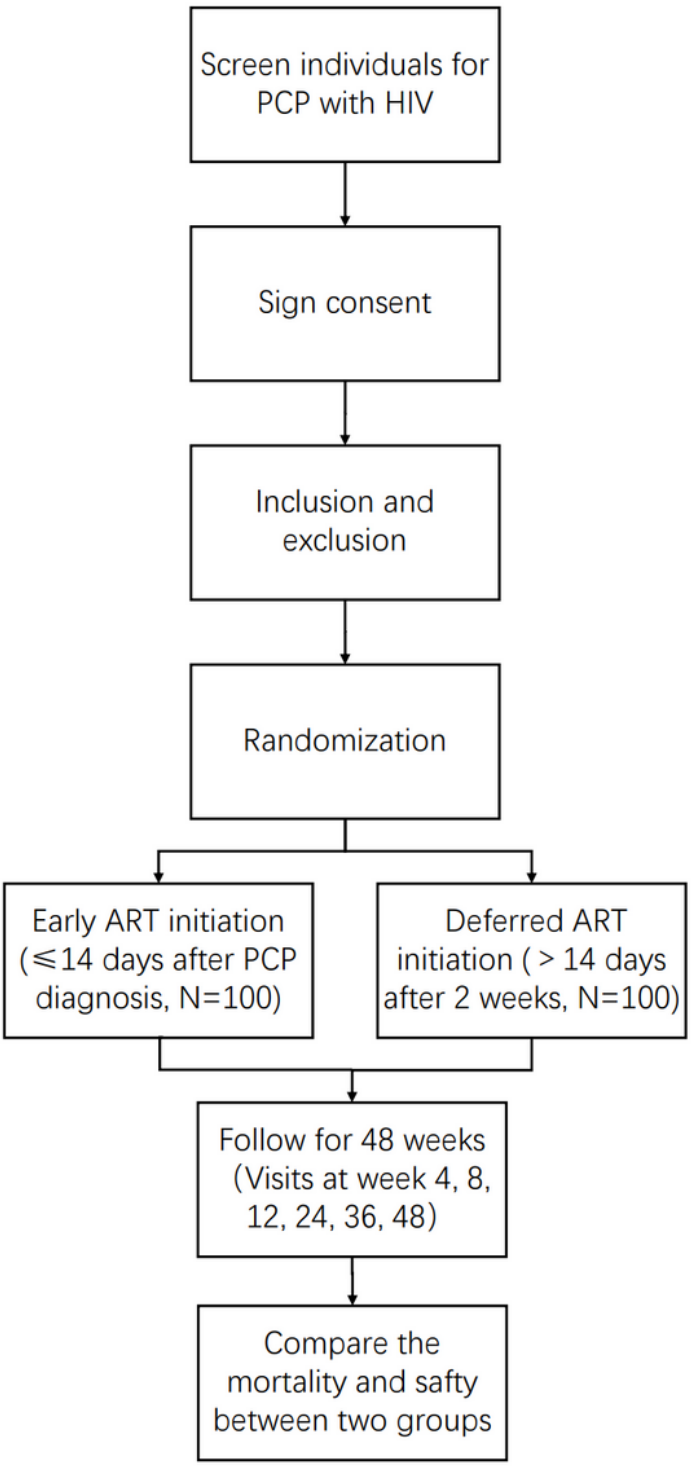

Figure 1

Flow chart of enrolment, intervention and follow-up.

Supplementary Files

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- Additionalfile2Modelconsentform.pdf
- Additionalfile1SPIRIT2013Checklist.doc