INPLASY PROTOCOL

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Conflicts of interest:
None.

Chinese herbal medicine for treatment of HIV/AIDS-associated diarrhea: a protocol of systematic review and meta-analysis of randomized clinical trials

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Review question / Objective: **To assess the beneficial effect and safety of Chinese herbal medicine for HIV/AIDS-associated diarrhea.**
Condition being studied: **Acquired immune deficiency syndrome (AIDS) is a chronic infectious disease caused by human immunodeficiency virus (HIV). HIV mainly invades and damages CD4+T lymphocytes, resulting in impaired immune cells and defects, which may even cause severe opportunistic infections and tumors. Diarrhea is a common symptom of AIDS, generally not fetal but seriously affect the quality of life. However, the treatment approach for HIV/AIDS-associated diarrhea is still very limited. Chinese herbal medicine have been widely used for diarrhea in China including HIV/AIDS-associated diarrhea and clinical trials were published, but not synthesized. This protocol aimed to systematically review the results of randomized controlled trials (RCTs) with Chinese herbal medicine, and to evaluate the benefits and safety of this therapy for HIV/AIDS-associated diarrhea.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 July 2020 and was last updated on 20 July 2020 (registration number INPLASY202070093).

INTRODUCTION

Review question / Objective: **To assess the beneficial effect and safety of Chinese herbal medicine for HIV/AIDS-associated diarrhea.**

Rationale: **The current treatment of HIV/AIDS-associated diarrhea is not ideal. There is a need for Chinese herbal medicine with an approved safety profile, supporting patients with HIV/AIDS-**

associated diarrhea through comprehensive treatment by relieving symptoms and side effects from antiretrovirals. The quality and effects of the clinical trials should be systematically reviewed and appraised.

Condition being studied: Acquired immune deficiency syndrome (AIDS) is a chronic infectious disease caused by human immunodeficiency virus (HIV). HIV mainly invades and damages CD4+T lymphocytes, resulting in impaired immune cells and defects, which may even cause severe opportunistic infections and tumors. Diarrhea is a common symptom of AIDS, generally not fetal but seriously affect the quality of life. However, the treatment approach for HIV/AIDS-associated diarrhea is still very limited. Chinese herbal medicine have been widely used for diarrhea in China including HIV/AIDS-associated diarrhea and clinical trials were published, but not synthesized. This protocol aimed to systematically review the results of randomized controlled trials (RCTs) with Chinese herbal medicine, and to evaluate the benefits and safety of this therapy for HIV/AIDS-associated diarrhea.

METHODS

Search strategy: Terms: (take Pubmed as an example) Acquired Immunodeficiency Syndrome; Acquired Immune Deficiency Syndrome; Acquired Immune Deficiency Syndrome; acquired immuno-deficiency syndrome; acquired immune-deficiency syndrome; AIDS; human immunodeficiency virus; HIV; diarrhea; diarrohea; Chinese medicine; Chinese herbal medicine; Chinese herbs; herbal medicine; medicinal herbs; Chinese patent medicine; herbs; Chinese traditional; Chinese herbal; Chinese medicinal herbs; traditional medicine; traditional Chinese medicine; medicinal plants; herbal drugs; plants extracts; Chinese herbal drugs; herbal preparations; phytotherapy; randomized controlled trial; controlled clinical trial; clinical trail; randomized; randomly; Randomization; RCT; trial; groups; allocated; blind procedure; Crossover procedure; Placebo; Single blind; Double blind; blind. We plan to search the following databases: 1)The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; 2)PubMed; 3)China National Knowledge Infrastructure (CNKI); 4)Wanfang Data; 5)Chinese Biomedical Literature Database (SinoMed); 6)China Science; 7)Technology Journal database (VIP).

Participant or population: People with acute or chronic HIV/AIDS-associated diarrhea, regardless of race, age, gender or economic status will be included. People with diarrhea caused by dysentery, cholera, poisoning and systemic disease will be excluded.

Intervention: Experimental interventions are Chinese herbal medicine, including extracts from herb(s), single herbs or compound formula, administered orally, taken either alone or in combination with other active treatment.Co-intervention is allowed as long as it is applied in both groups. Combination of different Chinese herbal medicine will be excluded.

Comparator: Control intervention can be no treatment, placebo, or other active treatment. Co-intervention is allowed as long as it is applied in both groups. Combination of different Chinese herbal medicine will be excluded.

Study designs to be included: Randomized controlled trials(RCTs).

Eligibility criteria: Randomized controlled trials(RCTs) comparing Chinese herbal medicine with placebo or other active interventions will be included, regardless of language and publication status.

Information sources: The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; PubMed; China National Knowledge Infrastructure (CNKI); Wanfang Data; Chinese Biomedical Literature Database (SinoMed); China Science and Technology Journal database (VIP).

Main outcome(s): 1)Diarrhea frequency (per day or per week); 2)Fecal character.

Additional outcome(s): 1)Recovery duration of diarrhea; 2)Other symptom such as fatigue and anorexia; 3)Length of hospital stay; 4)Body weight; 5)Recurrence; 6)Nutrition status; 7)Quality of life (measured by validated tool or scale); 8)Adverse effect: the incidence of all adverse events or adverse effects reported, including withdrawal from trial due to some adverse effects and modification of treatment plan.

Data management: Retrieved citations from the various search engines will be imported into EndNote and checked for duplicates. Two review authors will use a pre-piloted data extraction form to extract data on general information (study ID, study author and title); methodological information (study design, the number of groups, sequence generation, allocation sequence concealment, blinding, selective outcome reporting, baseline comparability); participant characteristics (diagnostic criteria, inclusion criteria, exclusion criteria, acute/chronic, total number of intervention groups, number lost during follow-up, age, sex, country, setting and disease duration); intervention (the name of therapeutic drug, its form, dosage and regimen, other treatments given, drug combination, duration of treatment), and outcome measures. We will record relevant data using a pre-defined data extraction form. We will resolve disagreements through discussion, and contact the corresponding trial author in case of unclear and missing data.

Quality assessment / Risk of bias analysis: Two review authors will assess methodological quality using the Cochrane 'Risk of bias' tool and report the results in a 'Risk of bias' table. We will use the criteria for judging risk of bias in the 'Risk of bias' assessment tool in the Cochrane Handbook for Systematic Reviews of Interventions, considering the following: (1)Sequence generation. (2)Allocation concealment. (3)Blinding of participants, personnel and outcomes assessors. (4)Incomplete outcome data. (5)Selective outcome reporting. We hope that trials report adverse event data, survival and disease progression. (6)Other possible sources of bias. We will assess vested interests depending on authors of the trials and the source of funding. If information is unclear or not specified, we will also attempt to contact the trial authors. We will resolve any disagreements by discussion between the review authors or, if necessary, by consulting another author.

Strategy of data synthesis: We will use RevMan Web to analyze the data. We will use RR with 95% CIs and a random-effects model to pool their results in the meta-analyses if there are sufficient clinically similar studies available. For dichotomous outcomes, we will calculate the RR for each study and then aggregate the data. For continuous outcomes, if all the trials measured results on the same scale, we will pool MDs between the treatment arms at the end of the follow-up, otherwise we will pool SMDs. Where a meta-analysis is inappropriate, we will summarize data in tables.

Subgroup analysis: We will perform the following subgroup analyses for people with AIDS-related diarrhea to investigate heterogeneity: (1)Acute or chronic; (2)Diarrhea cause by etiology; (3)Type of interventions including but not limited to individual prescriptions of Chinese herbal medicine; a single herb or compound; dosage regimen; Sex, age and ethnicity.

Sensibility analysis: We will conduct sensitivity analyses to explore the impact of losses to follow-up on the effect estimates for the primary outcomes and to exclude studies considered to be high risk of bias. For dichotomous outcomes, we will vary the event rate within the missing patients from intervention and control groups within plausible limits. For continuous data, we will perform sensitivity analyses using methods described by Ebrahim 2013 and Ebrahim 2014.

Language: No restriction.

Country(ies) involved: China.

Other relevant information: None.

Keywords: Chinese herbal medicine; HIV/AIDS-associated diarrhea; systematic review; meta-analysis; protocol.

Dissemination plans: We plan to publish a systematic review based on this protocol.

Contributions of each author:
Author 1 - Bailin Chen - The author drafted and improved the manuscript.
Author 2 - Mingzhu Zhang - The author improved the manuscript.
Author 3 - Ziwei Huang - The author improved the manuscript.
Author 4 - Hongrui Zhang - The author improved the manuscript.
Author 5 - Chang Xu - The author improved the manuscript.
Author 6 - Jing Li - The author improved the manuscript.
Author 7 - Zhenwei Liu - The author read and provided feedback.
Author 8 - Feng Jiang - The author improved the manuscript.
Author 9 - Xun Li - The author improved the manuscript.
Author 10 - Jianping Liu - The author provided statistical expertise, read, provided feedback, and approved the final manuscript.