STUDY PROTOCOL

Role of Yoga Therapy in Prevention of Tuberculosis in People Living with HIV Infection: Protocol for A Randomized Controlled Trial

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DOI: 10.55489/njcm.141220233270

ABSTRACT

Background: TB is a common opportunistic infection (OI) among people living with Human Immunodeficiency Virus (PLHIV). PLHIV often resort to the use of traditional and complementary medicine (T&CM) to supplement ART in order to maintain and improve their health. Yoga therapy has vast potential and beneficial effects on lungs. This study will assess the proportion of PLHIV developing TB in intervention group as compared to the control group. The secondary objective is to assess the improvement in CD4 T cell count, development of other OIs and to explore the socio-behavioural factors affecting the adherence to yoga programme and ART.

Methods: We propose a hospital-based RCT comparing the yoga group with usual care control group using quantitative methods for 3 years. A total of 1800 PLHIVs will be studied with 1:2 intervention to control group ratio. Each participant will be involved for 24 months (intervention delivery/follow-up). PLHIV in the intervention group will be given yoga therapy training of 45- minute duration once a month for 3-months followed by self-practice at home. Independent t tests and Z test for proportion will be used to compare the two groups at baseline. Intention to treat analyses will be conducted with participants as originally allocated at randomization to avoid bias. Alpha level will be set at 5%, using two-tailed for all inferences.

Discussion: This study will generate preliminary data about effect of yoga on TB and other opportunistic infections as well as the feasibility and utility of further RCT in the domain.

Trial Registration: ISRCTN74208821

Key words: Yoga therapy, HIV, TB, RCT, opportunistic infections

ARTICLE INFO

Financial Support: WOS-B Scheme, KIRAN Division, Department of Science and Technology, Ministry of Science and Technology, Government of India

Conflict of Interest: None declared

Received: 09-09-2023, **Accepted**: 01-11-2023, **Published**: 01-12-2023

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How to cite this article: Chauhan A, Chandrasekaran A, Kondal D, Sinha A, Prabhakaran D. Role of Yoga Therapy in Prevention of Tuberculosis in People Living with HIV Infection: Protocol for A Randomized Controlled Trial. Natl J Community Med 2023;14(12):849-855. DOI: 10.55489/njcm.141220233270

INTRODUCTION

The World Health Organization declared Tuberculosis (TB) as a global health emergency in 1993.[1] Still, it continues to be a major public health problem in resource limited countries such as India.[2] According to the India TB Report 2021, 40% of the India's population is having latent TB infection with Mycobacteria Tuberculosis (MTB).[3] Active TB disease occurs among these population when there is a breakdown of immune system leading to the dual burden of disease.[4]

TB is also one of the commonest opportunistic infections (OI) among people living with Human Immunodeficiency Virus (PLHIV) infection.[5] As per the HIV estimates 2019, the adult HIV prevalence in India was 0.22% (0.17-0.29%) in 2019[6] and an estimated 71000 (49000-98000) incident HIV-TB co-infected patients were there in India in 2019.[3] Both HIV and TB have potentiating effect on each other which if left untreated results in premature deaths.[7]

Around 25% deaths among PLHIV are attributable to TB.[3] It is the leading cause of mortality from a single infectious agent among PLHIV.[2] HIV disease per se increases the overall risk of PLHIV developing TB due to immunocompromised state. PLHIV has 8 times greater risk of acquiring TB compared to HIV negative people. And this risk increases as the HIV disease progresses and CD4 T cell count decreases.[8]

Anti-retroviral treatment and Tuberculosis: Antiretroviral treatment (ART) is effective in reducing the risk of TB among PLHIV, though this risk remains higher than HIV negative individuals.[8] Further, PLHIV with cured TB are also at increased risk of recurrent TB.[8] Recurrent TB disease occurs when a patient who were previously treated for TB develops a new disease either due to relapse (recurrence of old infection) or reinfection (infection with a new strain). Recurrent TB is associated with poor treatment outcomes and higher mortality rates compared to primary TB.[9] This situation is further compounded by the burgeoning prevalence of drug resistant TB (DR-TB) leading to increase burden on the health care system.[10]

Traditional and complementary medicine: Both HIV and TB share the same anatomical reservoirs such as lungs and immune system.[7] Researcher have observed that PLHIV often resorts to the use of traditional and complementary medicine (T&CM) to supplement ART in order to maintain and improve their health.[12] One such T&CM is yoga therapy with vast potential and beneficial effect on lungs. It improves the psychological and physiological functions.[12] Yoga is known to improve the efficiency of respiratory muscles, endurance time, aerobic capacity, improvement of breathing and medication response.[13] It also has a positive effect on the immune system which in turn can halt the progression of the disease such as HIV.[14] Various studies, case studies and unpublished literature empirically suggest beneficial effect of yoga therapy on HIV and TB.[12] Joseph et al reported an increasing trend in the CD4 cell count in PLHIV practicing Yoga in Maharastra.[15] Naoroibam et al also observed an increase in immunity in PLHIV doing Yoga in Manipur.[14] Mooventhan et al in their case study on new sputum positive pulmonary TB reported better improvement in weight gain, body mass index, symptom scores, pulmonary function and quality of life with conversion of positive to negative sputum smear microscopy in young woman practicing yoga therapy for 8 months.[16] Visweswaraiah et al performed a randomized controlled trial in pulmonary TB patients on yoga as a complementary therapy and they observed patients practicing yoga therapy had a significant reduction in symptom score, weight gain and vital capacity of lungs. Sputum conversion rate was also high in those patients' practicing yoga.[13] Hence, a study was being planned to explore the effect of yoga therapy against TB in PLHIV.

Purpose and objectives: The overarching aim is to assess whether a yoga programme is effective in preventing the occurrence of TB among PLHIV in India as compared to standard care and support for PLHIV infection. Intending to following up this work with a future multi-centric RCT, the subsidiary objective of this early phase study is to determine the feasibility of undertaking the future multi-centric RCT.

The primary objective of this study is to assess the proportion of TB among those practicing Yoga therapy compared to those not practicing Yoga therapy. To compare the improvement in CD4 T cell count amongst those practicing Yoga therapy compared to those not practicing Yoga therapy; to assess the proportion of opportunistic infections other than TB in those practicing yoga therapy compared to those not practicing Yoga therapy; and to assess the socio-behavioural factors affecting the adherence to yoga programme and ART treatment are the secondary objective of the study.

METHODOLOGY

This was a hospital-based feasibility randomised controlled trial.

We propose a feasibility, single center, randomized trial with 2 parallel groups, comparing the yoga group with a usual care control group using quantitative methods of data collection. Figure 1 outlines the sequencing of the study protocol. This is a feasibility RCT since it will be conducted at only one center. We will be assessing the feasibility in terms of recruitment rates, retention rates, assessment completion and adherence to the intervention.

Randomization and blinding: After collecting the key data, eligible participants will be randomized by simple random sampling using computer-generated random number table. This will be done by an independent assessor who does not have any role in trial.

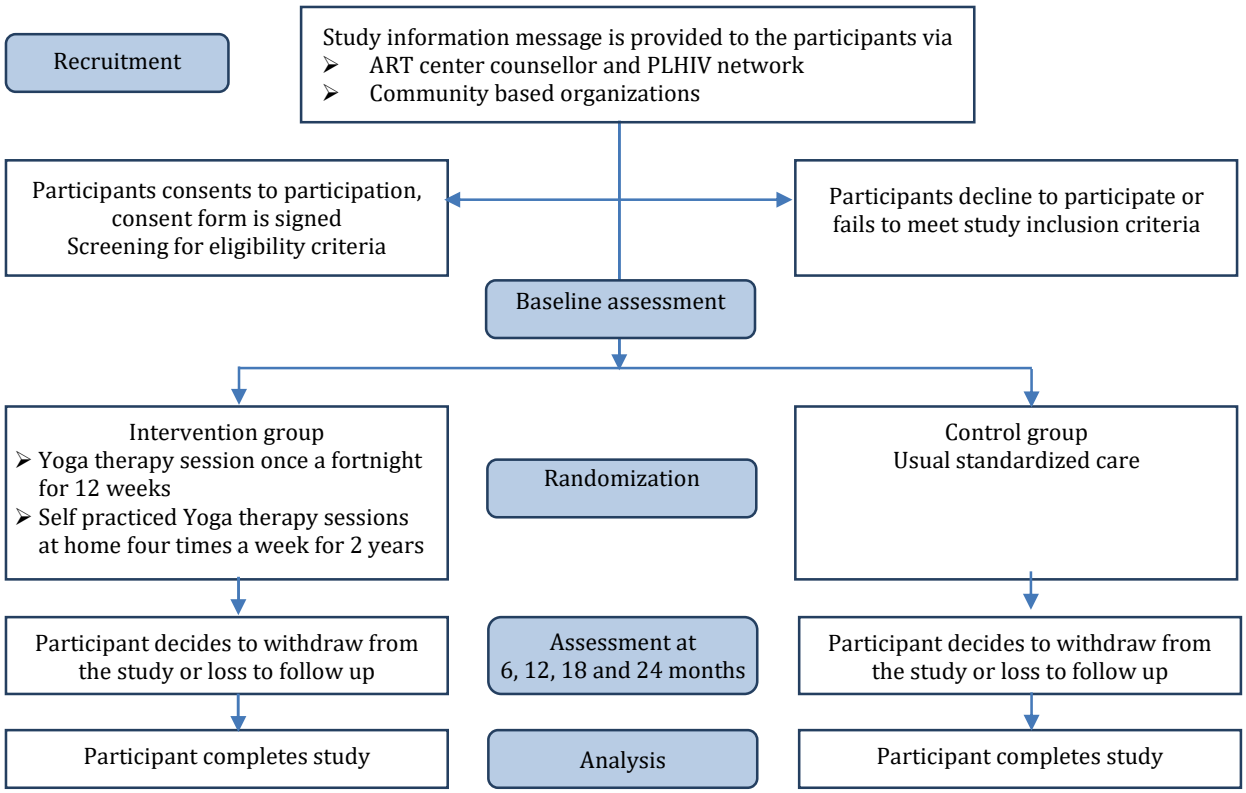

Figure 1: Consort Flow diagram

The exception to this rule will be individuals recruited from the same household. They will be randomised to the same group to avoid contamination. Randomized participants will be age and sex matched. Participants and intervention/control providers cannot be 'blinded' to group allocation, but the outcome assessor will be 'blinded'.

Sampling: According to the India TB Report, 2019[17], 15% PLHIV develop TB over a period of 2 years in India after diagnosis of HIV. So, the sample size required to estimate the real effect at 95% confidence interval, 5% level of significance, will be 395. Taking a drop-out rate of 30% by virtue of death, migration, loss to follow up, etc. the required sample size would be 600 each in the intervention and control group. The ratio of intervention to control group will be 1:2.

Duration of the study and participant involvement

Study Duration: 36 months; (anticipated recruitment period and intervention validation: 3 months, intervention delivery/follow-up: 24 months, final data analysis and writing up: 9 months)

Participant Duration: Each participant will be involved for 24 months (intervention delivery/follow-up). Subsequently, one semi-structured interview will be conducted with some of them.

End of the Study: The end of the study will be the last telephonic follow up at 24 months of the last participant.

Selection and withdrawal of participants

Recruitment

Participants will be recruited after briefing them all the aspects pertaining to participation in the study. Participant information sheet and consent form will be available in the local regional language and Hindi. Participant will be explained about voluntary entry into the study and their decision to be in study won't affect their treatment and care. They will be given options to withdraw from the study at any time but attempts will be made to avoid this occurrence. In case of withdrawal, we will seek consent to use the data in the final analysis.

People living with HIV infection will be referred by the counsellor at the Anti-retro viral treatment centre for participating in the study. Those willing to provide written informed consent will be screened for eligibility criteria.

Eligibility criteria:

Patients diagnosed as HIV positive with available confirmed blood report from a designated laboratory, aged 18-65 years irrespective of gender, receiving/completed Isoniazid Prophylactic Therapy (IPT), and safe to participate in yoga therapy as assessed physically will be included after taking informed written consent.

Pregnant, active TB cases, seriously ill or moribund PLHIVs will be excluded from the study. PLHIVs currently receiving (or with plans to receive during the study period) any related mind body relaxation techniques other than Yoga therapy (>150 minutes/week) will be also excluded from the study

Active TB will be ruled out by conducting 4S symptom screening consisting of screening for symptoms such as cough, fever, weight loss and night sweats. Those suspected will undergo nucleic acid amplification test by NTEP for confirmatory diagnosis)

Participant withdrawal: Withdrawal of the participant from the study will be either at their own request or at the discretion of the investigator e.g., if diagnosed with pregnancy. In this case the participant will be referred back to the ART centre for standard treatment and care or in case when the participant cannot participate in the physical activities. They will be assured of the fact that their non-participation won't affect their future care. Participant information sheet and consent form will also have information about the fact that if the participant withdraws, the data collected till date cannot be erased and may still be used in the final analysis if required.

Ethical considerations: The study protocol was approved by the Institutional Ethics committee (IEC) Smt NHL Municipal Medical College, Ahmedabad, India and IEC of Public Health Foundation of India, Delhi NCR, India. The procedures will be followed in accordance with the IEC. The trial was registered on ISRCTN (https://doi.org/10.1186/ISRCTN74208821).

Participant confidentiality and autonomy will be maintained throughout the study, and data will be anonymized and secured. The information sheet and the consent form will be available in English, Gujarati and Hindi. Written informed consent will be obtained from all the participants for participation as well as use and retention of the study data.

Intervention Protocols

Yoga Group

Groups of 10-15 participants will engage in a 45-min group-based yoga sessions 1 times per fortnight for 12-weeks under the supervision of a trained yoga instructor (holding a graduate degree). Classes will begin with a 5-min warm-up, which includes joint loosening exercises and Om-chanting. Then, participants will perform 15 min of breathing exercises (Pranayama) and 8 min of yogic postures (Asana), followed by 15 min of guided meditational sleep (yoga nidra). The class will finish with 2 min of Corpse Pose (savasana). The yoga protocol can be seen in Table 1. High-definition videos and audios of yoga therapy will also be given to the intervention group along with the booklet on HIV/AIDs and how to perform yoga therapy. The participants in the intervention group will be asked to practice yoga therapy at home daily for 45 minutes 4 days in a week and they will be followed for a period of 2 years.

Telephonic support and audio-visual aid in the form of yoga videos and yoga booklets will be given to the intervention group participants. Telephonic support will be provided every week for 1-month post intervention delivery, then every month for 2 month and then every 6 months for 2 years. This will include physician support for any untoward event due to yoga therapy, yoga instructor support for proper conduct of yoga therapy and maintaining yoga diary/register for noting type and duration of practice of yoga therapy.

The following yoga therapy asana and pranayama will be taught:

Asanas:	**Pranayama:**
1. Adho mukha savanasana (downward facing dog pose)	1. Udgitha pranayama (OM chanting)
2. Sukhasana (relaxed pose)	2. Bhastrika pranayama (bellows breaths)
3. Salamba sarvangasana (supported shoulderstand:	3. Kapalbhati (Rapid exhalation)
4. Ardha halasana (Half plough pose)	4. Anulom vilom pranayama (alternate breathing technique)
5. Supta baddha konasana (reclined bound angle pose)	5. Ujjayi pranayama (Ocean breaths)
6. Savasana (Corpse pose)	6. Bahya pranayama (external breathing)
	7. Agnisar kriya
	8. Bhramari pranayama (humming bee breath)

Table 1: Intervention module

Time	**Name of practice**	**Details**	**Duration**
Total six sessions: 45-min session once a fortnight for 12 weeks	Joint loosening exercise	Joint loosening practices for hands, legs, neck and trunk	5 minutes
	Breathing practices	Kapalbhati, Anulom vilom, Brahmri pranayam, Bhastrika pranayam, udgeeth pranayam, ujaiyi pranayam, bahya pranayama	15 minutes
Follow-up: self-practice at home for 4 days a week for 21 months with supported supervision (Telephonic and home visits)	Yogic postures	downward facing dog pose, relaxed pose, supported shoulder stand, half plough pose, reclined bound angle pose and corpse pose	10 minutes
	Yoga nidra	Guided imagery	15 minutes

Those who are given intervention, every month a telephonic follow-up will be done. This is to assess the practice of yoga therapy in terms of regularity, frequency, duration and any unseen event towards it. Patients will be asked to maintain a diary, where every time they practice the yoga therapy, they would be required to mention the duration, date and type of yoga therapy practiced. Additionally, once in every three months, a trained peer counsellor (who is a HIV positive patient) will be asked to visit the patient after consultation with the patients (for convenience of visiting home) to supervise the practice of yoga therapy and providing assistance if needed. Patient will be asked to submit their record diary at this time to the peer counsellor.

Control Group

The control group will be asked to continue with its regular routine, and the group will be asked to not make any changes during the study. They will follow up telephonically every 6 months for 2 years to record the CD4 count, 4S screening, other opportunistic infections, ART side effect and adherence, practice of yoga therapy, etc.

Outcome variable and measurement tools:

The primary outcome for this study is the proportion of TB among PLHIV practicing yoga therapy compared to those not practicing it. This will be assessed by "4S" i.e., four symptoms screening which includes presence of any one of cough, fever, weight loss>10% of body weight and night sweats irrespective of their duration. This will be a screening tool and it will be done at the baseline, 6 months, 12 months, 18 months and 24 months. Those who are positive on screening will undergo diagnostic nucleic acid amplification test, chest x-ray and sputum smear microscopy. This test will be conducted by the National TB Elimination program (NTEP) and National AIDS Control Organization (NACO) at the ART center and patient's clinical case record form will be checked for specific diagnosis. If patient is positive by any of the three diagnostics methods, then he/she will be considered as having TB. This will include patients of both pulmonary and extra pulmonary TB. Patients who are diagnosed as active TB during the recruitment period will be excluded from the study whereas those diagnosed during the follow-up period, they will not be further followed up, i.e., it will be the endpoint of the study for those participants. Time-trend analysis will be done for each PLHIV who develops TB so as to determine effect of yoga therapy on TB.

The secondary outcome of this study is to assess the change in the CD4 T cell counts and proportion of other Opportunistic infections (other than TB) between the intervention and the control group. CD4 count measurements are done at the ART center at every 6 months interval routinely. The patients will be asked about their recent CD4 count at the baseline, at 6 months, 12 months, 18 months and 24 months. History of other opportunistic infections (OI) will be taken at baseline, 6 months, 12 months, 18 months and 24 months. This will be self-reported by the patients and their clinical case record file will be checked for specific diagnosis of the OI.

Another important secondary outcome of the study is to assess the socio-behavioral factors responsible for adherence to the yoga therapy and ART treatment. Adherence to ART treatment will be measured as self-reporting by the patients and MIS patients by NACO. While adherence to yoga therapy interventions will be measure in terms of number of yoga sessions attended (on site and virtual), loss to follow up at 6, 12, 18 and 24 months and compliance rate of 60% of the trial. Telephonic follow up (6, 12, 18 and 24 months) and maintenance of yoga register/diary will be used as indicators of participation and study compliance. Few of the participants will undergo in-depth interview by semi-structured questionnaire and socio-behavioral factors determining adherence to ART and the intervention will be explored.

Qualitative Data:

Semi-structured in-depth interviews will be conducted with few of the participants. Semi-structured in-depth interviews will be conducted to help in understanding the feasibility of conducting such trainings on large scale i.e., multi-centric. In-depth interviews with patients will also help in knowing their perspective about the training.

A maximum variety sample will be recruited, with participants varying on age, gender, place of residence, education, and adherence to scheme.

In order to make this qualitative phase as informative as possible, the participants of this phase should have received on-site training and given written informed consent to the proposed study.

Conduct of qualitative phase: In-depth interviews will be carried out by trained qualitative researchers using topic guides, data will be captured with field notes or through digital voice recording and verbatim transcription with anonymization. Final sample size will be determined by saturation sampling; that is, we will continue investigating until no new information is forthcoming. Interviews will be conducted virtually as well as face to face, when possible, as per the participant's convenience. They will also be evaluated for their knowledge and practice related to HIV/AIDs, sexually transmitted infections and practice of T&CM. Before, starting the interviews, it is expected to have "a interview guidance" previously developed. The broad domains will be their experience with the yoga therapy, facilitators and barriers associated with it, social support garnered and acceptance. . Interview guide will be prepared in consultation with the counsellors and yoga instructors. With consent, these will be noted and digitally-recorded. Feasibility, here means participation rate, retention rate, completion of the assessments and adherence to the training. We will measure participation rate from the number of PLHIVs willing to undergo yoga therapy. Retention rate will be number of

participants remaining at the end of the trial. Assessment completion will be number of participants whose complete assessment is available at the end of the trial. Adherence will be assessed as number of participants practicing at least one, two or all forms of yoga therapy for the desired duration of 3 times a week for at least 30 mins a day.

Data analysis:

Quantitative: Descriptive statistics will be used to characterize the participants. Independent t tests and Z test for proportion will be used to compare the 2 groups at baseline. Both the groups will be matched in terms of age, sex, duration of HIV and CD4 T cell count. If the groups differ at baseline for any variable, then that will be included in the analysis as a covariate. Means of all outcomes, mean change and 95% Confidence interval (CI) will be calculated for each group separately. Intention to treat analyses will be conducted with participants as originally allocated at randomization to avoid bias. Changes in the outcome variable will be examined between groups and within groups. Effect sizes will be reported for each outcome. Alpha level will be set at 5%, using 2-tailed for all inferences and the data will be analyzed by SPSS version 27.0 (SPSS Inc). SD of each outcome will be estimated, to inform the power calculation for a future RCT. Social contextual model of health behavior change will be used to assess the adherence to yoga intervention and ART among participants. We will follow per protocol method for data-analysis.

Qualitative: Once the information from the in-depth interviews has been systematically transcribed a software for qualitative analysis Ethnograph (http://www.qualisresearch.com/) will be used for thematic analysis. We will draw on techniques from the constant comparative method, such as line by line analysis of early interviews, naming each line and segment of data, the use of subsequent interviews to test preliminary assumptions, and discussing deviant cases. Data coding will be done by two investigators independently, which would be then reviewed by the third investigator. The decision on coding rules and theme generation will be done using standard procedures as described by Attride-Sterling. The findings will be reported by using 'Consolidated Criteria for Reporting Qualitative Research.

Dissemination: Study findings will be disseminated to PLHIV, ART center staff, State AIDS control society, National TB Elimination Program, health care providers, community-based organizations, researchers, stakeholders and policy makers. Knowledge translation will take place via publications in high impact peer-reviewed journals, presentations at conferences and newsletters.

Discussion

Study Strengths: This feasibility trial will be the first in low-income countries to investigate the effect of yoga intervention on occurrence of TB among PLHIV. The study will generate preliminary data about effect of yoga on TB and other opportunistic infections as well as the feasibility and utility of further RCT in terms of recruitment and retention strategies especially in COVID-19 pandemic times, assessment of intervention, cross-over issues, etc. Feasibility will be assessed as mentioned above considering both the patient perspective in terms of their acceptance and experiences, facilitators and barriers as well as trial perspectives, i.e., retention rates, participation rate, etc. This research uses a cheap, safe, easily available non-pharmacological intervention i.e., yoga therapy which addresses physical and socio-behavioral impact of HIV. It will help in identifying feasible strategies which may contribute in improving the immune markers of HIV and ultimately reducing morbidity and mortality related to TB among PLHIV.

Anticipated Challenges and Limitations

One of the potential challenges will include the recruitment and retention of participants as it is a 2 year follow up study. We anticipate that by involving a yoga instructor who himself be a PLHIV and imparting yoga training at a familiar community setting, we will be able to recruit the desire number of PLHIV. Although attrition is of concern in such trials requiring health center visit, we anticipate to reduce this by keeping the number of visits at the center to minimum and providing telephonic support as well as audio-visual aid to PLHIV for practicing at home. This will reduce loss to follow up.

Study limitations include lack of measuring quality of life in HIV. Conduct of study at one center and lack of measurements of CD4 count, viral load, and confirmatory diagnosis of presumptive TB case by the study researchers may lead to quality issues and generalizability of findings.

List of Abbreviations

WHO: World Health Organization
TB: Tuberculosis
MTB: Mycobacteria Tuberculosis
PLHIV: People Living with Human Immunodeficiency Virus
OI: Opportunistic Infection
ART: Anti-retroviral treatment
T & CM: Traditional and Complementary Medicine

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