STUDY PROTOCOL

# Impact of Integrated Yoga Practice on Immune Parameters and Quality of Life of Adult People Living With HIV: Protocol for A Randomized Open-Label Trial in Chittoor, India

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## ABSTRACT

**Background:** Yoga therapy can be a promising adjunct to antiretroviral therapy. However, evidence on the effectiveness of Yoga therapy is scanty. The proposed trial will estimate the effect of integrated yoga practice for six months on immune parameters (CD4 (cluster of differentiation 4), viral load) among adult people living with HIV (PLWH) and its cost-effectiveness from the healthcare system's perspective.

**Methods:** In this randomized open-label parallel-group trial, 110 PLWH in stage 2 HIV, between 18 and 49 years in the intervention arm and 220 PLWH in the same stage will be recruited by block randomization. Integrated yoga practice will be given for six months in the intervention arm, and health education on yoga practice in the control arm, besides antiretroviral therapy. After six months, the difference in immune parameters, cardio-metabolic indicators and quality of life (QOL) will be assessed. Besides, an economic evaluation will be done with sensitivity analysis. If found useful, the intervention can be tested at large scale for further confirmation of the outcomes. Irrespective of the study's outcome, the results will be disseminated through peer-reviewed journals.

**Trial registration:** CTRI/22/09/045909 dated 27/09/2022 under the Clinical Trials Registry-India version: 1.0 dated 27/09/2022

**Keywords**: CD4 Counts, HIV, India, Viral Load, Yoga

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## INTRODUCTION

The treatment against HIV infection primarily aims to improve the immune parameters of the body. These immune parameters include the CD4 count, CD8 count, CD4/CD8 ratio, and viral load. These biomarkers have an inverse relationship with the possible opportunistic infections (OI) among the people living with HIV (PLWH).[1,2] In PLWH, immune compromise is primarily due to a decrease in CD4+ T-lymphocyte (CD4) cells, resulting in increased rates of the human immunodeficiency virus (HIV)/ viral load-associated morbidity and mortality.[3] Such OIs not only increase the morbidity and mortality among the PLWH, but also incurs a substantial direct cost burden on the family or the health system.[4,5] Hence, treatment with ART plays a critical role in reducing the burden of OIs and the general well-being of the PLWH.

In India, adherence to ART varies between 73% and 82%.[6,7] Hence, adjunct complementary and alternative medicine besides ART is becoming popular as rehabilitation measures in PLWH.[8] It is cost-effective and easy to implement and offers benefits for emotional, psychological, and physical health. Yoga is one of the most effective and time-tested natural immunity boosters that can lead to a healthy, sickness-free body. It is commonly practiced among the Indian population. Yoga lowers stress hormones, strengthens the nervous system, and stimulates the lymphatic system, which removes toxins from the body. Besides, Yoga calms the mind and can contribute to more profound, regulated sleep, which is crucial for wellness. An improved sleep habit heals and maintains a healthy immune system.[9,10] Even the Government of India started focusing on medical philosophies called AYUSH (Ayurveda, Yoga & Naturopathy, Unani, Siddha and Homeopathy) to prevent illnesses and promote well-being. However, literature is scanty in quantifying the effect of Yoga on the immune parameters of the PLWH. This is in line with the UNAIDS' 95–95–95 goal (95% of PLWH diagnosed, 95% of those diagnosed linked to ART, and 95% of those on ART to achieve viral suppression) by 2025, as a part of improving the target for the last 95. On this background, we would like to assess the effect of integrated yoga practice on immune parameters, cardiometabolic profile and quality of life of PLWH.

## OBJECTIVES:

Primary objective of this study is to estimate the effect of integrated yoga practice for 6 months on immune parameters (CD4 (cluster of differentiation 4), viral load) among the adult people living with HIV (PLWH) who are otherwise healthy, attending ART center.

Secondary objectives are to assess the impact of integrated yoga practice for 6 months on cardiometabolic profile & quality of life and cost effectiveness of yoga therapy inclusion along with ART for the PLWH.

## METHODOLOGY

**Trial design:** This will be a Randomized open-label parallel group trial with 1:2 allocation ratio for cases and controls.

**Study Setting:** The study will be carried out at ART center Chittoor, Andhra Pradesh, India. The ART center is attached with the government district hospital and a medical college having over 3,000 registered PLWH and has the capacity to test their immune status and treat for any other health conditions.

**Study participants:** study participants will be adult PLWH (18 to 49 years), in the second stage of the illness but otherwise healthy, are registered with ART center for treatment.

**Eligibility criteria:** All adult PLWH in stage 2 (CD4 count between 350 cells/mm$^3$ to 499cells/mm$^3$) between 18 and 49 years who come to Chittoor ART center for Anti-retro viral therapy will be eligible for participating in the study. The participants must be willing to spare 1 hour daily for six months for yoga training and practice. PLWH belonged to other stages, already practising Yoga, pregnant women, and those diagnosed with other ailments like locomotor disabilities, opportunistic infections, and tuberculosis will be excluded from the study.

**Interventions:** Integrated Yoga practice will be the intervention. Integrated Yoga is defined as practising loosening and breathing exercises followed by yoga asanas namely: Sun salutation, Padmasana, Vajrasana, Bhujangasana, Chakrasana, Ardhachakrasana, Ustrasana, Paschimothanasana, Savasana and finally Pranayama, and Meditation for one hour every day for six months (Table 1).[11,12] Initially, supervised training will be at a designated place, followed by practice at home.

**Table 1: Types of Yoga (Asanas) under integrated Yoga Practice**

| Name of Yoga | Duration (Min) |
|---|---|
| Body warmup | 5 |
| Breathing practices | 15 |
| Sun salutation | 10 |
| Yogic postures | 20 |
| Pranayama | 5 |
| Meditation | 5 |
| **Total** | **1 hour** |

**Methods of implementing the yoga practice by study participants in the intervention arm:**

After the recruitment of the participants, one month of supervised yoga training will be given at a designated place, maintaining all measures to prevent

COVID-19 infection. A dedicated yoga trainer will conduct the training session. Regular attendance will be maintained during training. Participants attending <70% of the sessions will be excluded from the analysis. However, they will be encouraged to continue the Yoga practice. At the end of the training, the trainer will ask all participants to re-demonstrate yogic practice ('Asanas').

After the completion of training, a pictorial module will be provided to the participants, and they will continue the same practice daily at home. Compliance with the yoga practice will be ensured by making a phone call or a video call twice a week. If the compliance is <70% in a given month, the participants will be considered non-compliant. Appropriate reasons for non-compliance will be documented. If needed, the yoga trainer will help the participants at their convenient place, either at home or at the ART centre.

The participants in the control arm will receive health education at the ART centre based on the same pictorial diagram. A twice-weekly telephonic phone call will be made to ask about the general health condition, compliance to ART and physical exercise including yoga practice.

If participants develop any health conditions during the trial, they will be referred to the attached tertiary care hospital for further management. Details of additional physical activities will be noted for both groups during the trial period. All participants will be followed at the ART centre for clinical evaluation at the end of months three and six of training initiation for the intervention arm or health education for the control arm. Standard treatment Anti-retroviral therapy (ART) will be continued for all the participants as planned.

Laboratory methods: Flow cytometry-based CD4 cell count will be done in the ART centre according to the laboratory guidelines prescribed by NACO. [13] Routine viral load testing for HIV-1 RNA (Ribonucleic Acid) will be done for all the participants during recruitment and at the end of six months by real-time Polymerase Chain Reaction (PCR) as per the NACO guidelines. [14]

**Outcomes:**

The primary outcome (Surrogate outcome) in this trial is CD4 count and viral load measured at the baseline, end of months three and six.

The secondary outcomes include surrogate outcomes such as cardiac profile measured by body mass index (BMI), lipid profile; biochemical parameter HbA1C and clinical examinations & laboratory tests, cost-effectiveness of the intervention and the soft outcome such as quality of life. The quality of life will be enquired at home or at the convenient place of the participants. Direct and indirect costs related to the intervention will be estimated concurrently.

It is envisioned that, after the project, the activities launched through the project will continue to operate and expand if the outcomes are effective. We will consider the following aspects to the project sustainability in order to inculcate the culture of Yoga as one of the therapeutic modules along with ART, such as:

1. Availability of the training module with the video to all adult PLWH attending ART.
2. Inclusion of yoga component in the counseling sessions of the PLWH.
3. Continuation of the service of the yoga teacher/ or train a staff at the ART center to train the PLWH attending ART center based on the availability of the fund.

**The duration of the study** duration is 18 months.

**Sample size:** Assuming 60% of the PLWH can show improvement in the CD4 count with 6 months of Yoga & ART compared to only 40% improvement in CD4 counts in the control arm (only ART), with a superiority margin of 5%, power 80% at 5% significance level, and with 1:2 allocations for cases and controls, and 10% of attrition in each group, the sample size is estimated to be 110 participants in the intervention arm and 220 participants in the control arm. (Reference: Chow S-C, Shao J, Wang H, Lokhnygina Y. Sample size calculations in clinical research. Third ed: Chapman and Hall/CRC; 2017).

**Recruitment:** Participants' eligibility will be assessed in the ART centres based on the registers' information. After the informed consent process, block randomization will be done using mixed blocks to control predictability with a block size of 6 to allocate 2 participants in the intervention arm and 4 participants in the control arm and a block size of 9 to allocate 3 participants in the intervention arm and 6 participants in the control arm. Thus, 28 blocks of size 6 and 18 blocks of size 9 will be required to complete the randomization process. Computer generated sequences will be used for randomization. To ensure allocation concealment, sequentially numbered opaque sealed envelopes will be used and the blocks/envelopes will be selected randomly to determine the participants' allotment. Outcome assessor that is data analyst will be blinded to overcome detection bias.

**Data collection:** Data collection will be done by research assistant and field staff recruited for this study. They will be trained in the Good Clinical Practice (GCP) guidelines and Standard Operating Procedure (SOP) of the study. The supervisor will do a 10% validation. The data collectors will collect the following data.

**Baseline information:** After recruitment, baseline details, including socio-demographic details, clinical parameters (CD4, viral load), quality of life, & laboratory parameters (HbA1C, lipid profile), will be collected at the ART centre using pre-tested electronic case report forms (CRF).

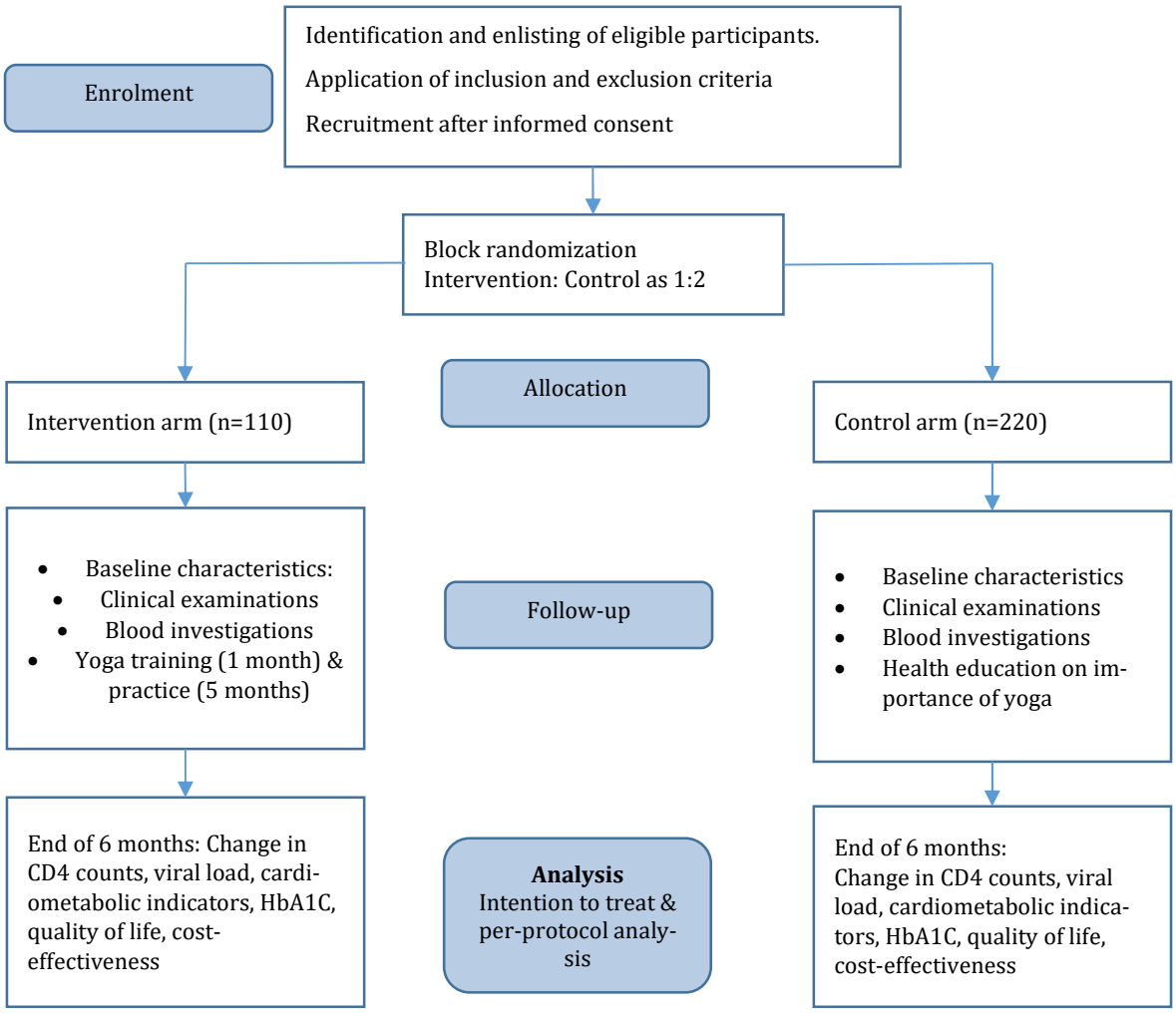


**Figure 1: CONSORT flow diagram of the trial**

**Follow-up:** During weekly telephonic follow-up of the participants, information on- clinical condition and compliance with the ART and yoga practice, problems encountered in yoga practice will be collected for the past week. Additionally, details of any health facility visit other than the scheduled ART centre visit will be collected.

During the scheduled ART visit at the end of the third month of recruitment, clinical examination, cardiometabolic profile, and QOL will be assessed at the ART centres, besides documenting the laboratory parameters.

At the end of six months of recruitment, the assessment will be done on- clinical examination, cardiometabolic profile, quality of life, CD4 count and viral load. The participants' quality of life will be assessed by applying the standard 'EQ-5D (European quality of life) scale' at all stages.[15] In this self-rated questionnaire, participants will be asked to rate their quality of life under five dimensions including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and a combined score to indicate the overall quality of life. If a participant is not reachable during two telephone calls for the weekly follow-up, in-person visits will be attempted to collect the information. Two telephonic reminders will be given for physical follow-up visits at the ART centres. If still unavailable, the trial team will make a home visit before documenting loss to follow-up. A person who fails to comply with at least 70% of the Yoga schedule will be considered non-compliant.

**Nature of data collected:** The questionnaire consists of 3 sections- demographic details, clinical details, and laboratory results. (Table 2). Additional clinical details will be obtained from the participants during the weekly follow-ups.

**Table 2: Types and frequency of data collection**

| Type of data | Frequency of data collection | | |
|---|---|---|---|
| | Base line | End of 3rd month | 6th month |
| Demographic details | ✓ | | |
| Clinical details, Quality of life | ✓ | ✓ | ✓ |
| Biological sample (Blood) | ✓ | ✓ | ✓ |
| Costs incurred for yoga training | Throughout the study period | | |

**Data management:** Data entry will be done electronically through an android application-based case report form (CRF) through dedicated tablets. The data will be stored in the institutional cloud server only accessible to the trial management team (PI/ Trial coordinator/ statistician). The cloud will be appropriately secured to ensure the confidentiality of the participants' information. A weekly consolidated report will be generated to monitor the trial's progress.

**Statistical analysis plan:**

The primary outcome CD4 count and viral load will be expressed as the mean with SD or median with IQR. The difference in CD4 count will be estimated between the two groups in absolute number per micro-litre (µL) with a 95% confidence interval (CI). Similarly, viral load (copies/mL) difference will be estimated between the two groups with 95% CI. We will separately calculate the proportion of participants with an increase in CD4 count and viral load from the baseline in both the intervention and control arms. The proportion of CD4 count improvement in both the groups will be expressed with 95% CI. Apart from per-protocol analysis, intention to treat (ITT) analysis will also be done with a best-case and worst-case scenario to adjust for the attrition. An appropriate statistical test will be applied to test the difference between the two groups. A p-value of <0.05 will be considered statically significant for all the statistical tests.

**Viral load:** For both the groups, we will calculate the pre-treatment and post treatment absolute viral load with an appropriate 95% CI and the difference between the two groups by an appropriate statistical test.

**Quality of life:** Mean (SD) or Median (IQR) score will be analyzed for both groups. The difference between the groups will be measured by using ANOVA test.

**Cost-effectiveness analysis:** This economic evaluation will be conducted to ascertain the potential costs and outcomes of adding yoga to the treatment of PLWH along with ART as compared to ART alone and conceptualized from a health care agency and government perspective. Direct (Fixed, semi-fixed, material costs) and indirect intervention cost will be considered for costing.

Cost-utility analysis will also be performed to see the gain in QALY for life/six months' time horizon. Incremental costs per QALY and clinical outcomes will be estimated. ICER-willingness to pay threshold will be determined based on India's GDP at that time. Sensitivity analysis will be done to adjust for the uncertainty.

**Monitoring**

**Data monitoring:** An independent data monitoring committee (DMC) will be consisting of the trial investigators, data managers, and other study team members. The primary role of the DMC will be to review the- recruitment process, data collection, any medical event and subsequent care, withdrawal, and data completeness.

**Harm:** The data collectors will document all medical events during the trial, and the reasons will be evaluated prospectively. In all such situations, the participants will be directed to the government tertiary hospital where the ART centre is located.

**Audit:** The trial will be audited by an external agency independent of the trial team and the study sponsor.

**Human participant protection:**

Institutional ethics committee clearance was taken prospectively from Apollo Institute of Medical Sciences and Research, Chittoor.
(Ref no.: FR001/ IEC/AIMSR/2022)

Written informed consent will be obtained from all the participants. All the source documents will be preserved in the department of the respective site under lock and key. The electronic case report forms' soft copies will be preserved in a password-protected computer for a minimum period of 5 years.

All the study investigators will be trained for ICH-GCP training. Only the trial investigators, including the data manager, will access the data through the password-protected institutional server. Aggregate information about the trial will be uploaded to the institutional website. Similarly, aggregated information about the trial will be shared with the sponsor. Upon completion, a summary of the trial results will be shared with the stakeholders, media, and peer-reviewed journals.

## DISCUSSION

Yoga therapy has proven benefits towards mental and physical benefits. However, the scientific literature has failed to provide robust evidence on the effect of Yoga therapy among immunocompromised individuals like PLWH.[16-20] Yoga therapy is widely practiced in India and other parts of the world. Keeping in mind that HIV infection has a high burden in India, it will undoubtedly be beneficial for the PLWH if Yoga therapy has a proven role in therapy outcomes supplementing the ART. In the current approach of 95-95-95 by the UNAIDS, the goals are mainly directed towards reaching the maximum PLWH by detecting and treating them, besides improving service delivery.[21] However, at the same time, the role of alternative therapies like Yoga can provide an extra edge by improving the mental and physical health of the PLWH.

This trial is expected to provide robust evidence of Yoga therapy as an adjunct to ART in reaching the treatment goals. Besides, the cost-effectiveness component of the study will provide economic evidence in deciding the policy to implement the study on a large scale.

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