STUDY PROTOCOL

A brief educational video for patients prescribed latent tuberculosis treatment: A randomized trial in an integrated healthcare organization in the United States

Version 1.0

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Version History

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Investigator Roster

Sara Tartof, PhD MPH
Principal Investigator
Research Scientist II, Kaiser Permanente Southern California
Assistant Professor, Kaiser Permanente Bernard J. Tyson School of Medicine

Katia Bruxvoort, PhD MPH
Co-Investigator
Assistant Professor, University of Alabama at Birmingham
Adjunct Investigator, Kaiser Permanente Southern California

Lei Qian, PhD
Co-Investigator
Research Scientist Biostatistician, Kaiser Permanente Southern California

Sally Shaw, DrPH, MPH, MCHES
Project Manager
Lead Senior Research Project Manager, Kaiser Permanente Southern California

Brigitte Spence, MPH
Research Associate
Research Associate II, Kaiser Permanente Southern California

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Summary

Almost 1.7 billion people are infected with latent tuberculosis infection (LTBI)[1] and nearly 10 million people per year develop active TB disease.[2] In 2017, nearly one-quarter of all new active TB cases in the United States occurred in California. LTBI treatment can effectively prevent reactivation and development of TB disease.[3] However, as treatment courses are very long, many patients do not complete treatment. Effective interventions that are low-cost and feasible for large-scale implementation are needed to support efforts to eliminate TB.

Thus, we will conduct a randomized trial of a 3-minute educational LTBI video intervention at Kaiser Permanente Southern California (KPSC), a large integrated health care organization. Web-based patient education videos are used routinely at KPSC to prepare patients for surgery, improve healthy habits, and for other uses. The primary objective of this study will be to determine if the LTBI video intervention improves treatment completion compared to standard care (no intervention).

The study will include adult KPSC members who are prescribed treatment for LTBI, identified using an electronic health record algorithm. At the time of treatment prescription, patients will be randomized to receive the LTBI video intervention or standard care at a ratio of 2 to 1. Those in the intervention group will be sent a secure text message or e-mail with a link to the video. Individuals who watch the LTBI video will also be invited to participate in a brief follow-up survey (4 short questions) about their perceptions of the video accessibility and content.

The primary outcome of the study is LTBI treatment completion (the required number of doses were dispensed) within one year of the prescription order. Secondary outcomes are LTBI treatment initiation (at least one dispensation of LTBI treatment) within one year of the prescription order; initiation and completion within one year of the prescription order stratified by LTBI treatment regimen (if feasible); the proportion of individuals randomized to the intervention group who watched the LTBI video; and the perceptions of those who watched the video.

The primary analysis will be based on intention-to-treat. We will describe and compare characteristics of individuals in the intervention and standard care groups and calculate rates of LTBI treatment completion. To assess the effect of the intervention, we will use Poisson regression with robust standard errors to estimate unadjusted and adjusted rate ratios and 95% confidence intervals. We will also conduct per-protocol analyses, comparing those in the intervention group who watched the LTBI video to those in the standard care group.

We will use similar methods for the secondary analysis of LTBI treatment initiation and analyses stratified by LTBI treatment type (if feasible). For the follow-up survey, we will describe the proportions of participants with each response.

Assuming the completion rate in the standard care group is 0.5 as observed in recent years at KPSC, we estimate that we will need 918 patients (612 for the intervention group and 306 for the

standard care group) to achieve 80% power with type one error 0.05 to detect an intervention effect of 0.10 in the completion rate between groups. As we will conduct trial over 1 year, and approximately 1,950 adult patients per year at KPSC receive an LTBI treatment prescription, we expect that this estimated sample size will be feasible.

Background

In 2015, tuberculosis (TB) surpassed HIV as the number one cause of infectious disease deaths worldwide.[2]Almost 1.7 billion people are infected with latent tuberculosis infection (LTBI)[4] and nearly 10 million people per year develop active TB disease.[5] In 2017, California had the highest incidence and largest number of TB cases in the contiguous United States, comprising nearly one-quarter of all new active TB cases in the nation.[6] The annual TB incidence in California was nearly double the national incidence rate in that year,[6] with a cost of >$78 million spent on medical management.[7] It is estimated that more than 2 million Californians have LTBI.

In the United States, an estimated >80% of active TB disease is due to reactivation, which could be prevented via successful treatment of LTBI.[7,8] Although poor understanding and adoption of screening guidelines contributes to lack of diagnosis and treatment, LTBI treatment regimens are long (3-9 months) and may cause adverse events.[9] Thus, among patients who are prescribed LTBI treatment, initiation and completion of the full treatment course are extremely poor.[10-14]

Kaiser Permanente Southern California (KPSC) is a large integrated health care organization serving more than 4.7 million members, with sociodemographic diversity similar to the underlying population.[15] Members are enrolled through employer-provided, pre-paid, or federally-sponsored insurance plans. KPSC has a substantial burden of latent tuberculosis, with 114,286 adults testing positive for LTBI from 2009-2018 (13,297 in 2018).

Our preliminary data from qualitative interviews at KPSC with 39 patients prescribed LTBI treatment and 10 physicians identified multiple barriers to LTBI treatment initiation and completion. One of the important barriers identified was a lack of knowledge related to LTBI and confusion around the need for taking the full course of treatment.[16,17] Thus, in consultation with an advisory board of culturally and demographically diverse patients recently prescribed LTBI treatment, we developed a brief (3-minute) educational video about LTBI and the importance of treatment completion. Web-based patient education videos are successfully used across KPSC to prepare patients for surgery, improve healthy habits, and for other uses. However, this approach has not yet been used to improve medication adherence, and its efficacy will be assessed through the randomized trial detailed in this protocol.

Study objectives

Primary objectives

1. Determine the efficacy of a simple, brief video ("LTBI video") to increase LTBI treatment completion among adults

   Primary hypothesis: Patients randomized to receive the LTBI video will have higher treatment completion rates than patients randomized to standard care (no intervention)

Secondary objectives

1. Determine the efficacy of the LTBI video to increase LTBI treatment initiation among adults
2. Determine the efficacy of the LTBI video to increase LTBI treatment initiation and completion among adults, by LTBI treatment type (daily isoniazid for 9 months, daily isoniazid for 6 months, daily rifampin for 4 months, daily rifampin plus isoniazid for 3 months, and weekly isoniazid plus rifapentine for 3 months; some of these treatments may be used infrequently, precluding stratified analyses)
3. Assess patient perceptions of the LTBI video

Outcomes

Primary outcome

1. Proportion of patients prescribed LTBI treatment who complete the treatment within one year of treatment prescription

Secondary outcomes

1. Proportion of patients prescribed LTBI treatment who initiate the treatment within one year of treatment prescription
2. Proportion of patients prescribed LTBI treatment who initiate the treatment within one year of treatment prescription, by treatment regimen (if feasible)
3. Proportion of patients prescribed LTBI treatment who complete the treatment within one year of treatment prescription, by treatment regimen (if feasible)
2. Proportion of patients randomized to the LTBI video who watch the full video
3. Proportion of patients who watch the video who report no difficulties watching the video
4. Proportion of patients who watch the video who report understanding the importance of completing LTBI treatment

Pharmacy data will be used to define and assess treatment initiation and completion, as follows:

- Initiation: At least one dispensation* of LTBI treatment
- Completion: The required number of doses of LTBI treatment were dispensed*

*Picked up from pharmacy or sent via mail to the patient

Table 1: LTBI treatment regimens

LTBI treatment regimen	Total doses	Timing of treatment
Isoniazid	180	Daily for 6 months
Isoniazid	270	Daily for 9 months
Rifampin	120	Daily for 4 months
Isoniazid and Rifampin	90	Daily for 3 months
Isoniazid and Rifapentine	12	Weekly for 3 months

Eligibility criteria

Active KSPC members will be eligible to participate in the trial if they are aged ≥18 years and receive an LTBI treatment prescription order.

LTBI treatment regimens (medication ID codes) are listed below. To be included in the trial, patients must also have a prior LTBI diagnosis code and must not have a prior active TB diagnosis code (also listed below).

- Include patients with prescription orders for the following LTBI treatment (medication ID codes):
    - Isoniazid: 12199066, 1214000023, 1216000272, 12022505, 12035328, 12035329, 12035330, 12035331, 12035332, 12035333, 12035334, 12035335, 12035336, 12035337, 12015833, 12032230, 12035338, 12035339, 12035340, 12035341, 12035342, 12035343, 12035344, 12035345, 12024985, 12035346, 12181973
    - Rifampin: 12199042, 121103412, 1214000029, 1214000030, 1214000340, 1214000565, 1215200240, 1206096, 12017860, 1209060, 12011205, 12015920, 190716, 1902899, 190207268, 190210700, 12189972, 12189977, 12189987
    - Isoniazid (see codes above) + Rifampin (see codes above), also: 12032976, 12199041, 12029484, 12189973, 12168828
    - Isoniazid (see codes above) + Rifapentine (121100982, 1206442, 12025808, 12188784, 12189978)
- Include patients with the following LTBI ICD-10 diagnosis codes: R76.11, R76.12, Z22.7

- Exclude patients with the following ICD-10 active TB diagnosis codes: A15, A17, A18, A19

Procedures

Randomization

Eligible patients will be identified in near real-time using an electronic health record algorithm that will be refreshed daily. Randomization will occur sequentially as patients are identified (ideally within <24 hours). For every 2 patients randomized to the intervention group (LTBI video), 1 patient will be randomized to receive the standard of care (no LTBI video). Medical record numbers and demographic characteristics (e.g. age, gender, race/ethnicity, and preferred language) will be captured for all patients.

Intervention

Patients who are randomized to receive standard of care will not receive any messages or have any contact with the research team.

For patients randomized to the intervention group, a SMS text message will be sent with a link to access the LTBI video. The message will be in English or Spanish, depending on the patient's preferred language, as recorded in their electronic health record. The message will be sent from KPSC's Complete Care, a comprehensive health care delivery system with integrated clinical information systems, decision support, workflows, and self-management support.[18] The message, from KAISER (524737), will say "Please watch this important video regarding your recent visit [link]."

Patients who have not opted into text messages from KSPC will receive a secure email with the same message and link.

Patients who click on the link will be directed to REDCap page, with the following text: "Please take 2-3 minutes to watch this educational video" and "You are invited to watch this brief video about latent tuberculosis. By watching, you will be agreeing to participate in a research study to evaluate the impact of this video. Participation in this research study is voluntary." Patients will be asked to enter their initials and birthdate, which will facilitate linkage of individuals who watched the LTBI video with their electronic health records. Patients will then click on the video, which will be physically hosted on the Qumu video platform. After watching, patients will click to confirm they watched the video.

Patients that have not watched the video will be sent a reminder via the same communication the initial outreach was sent, either text message or email. This reminder will be sent one week after they were sent the initial outreach. The reminder will also read, "Please watch this important video regarding your recent visit [link]."

Follow-up survey

Patients who watched the LTBI video will be sent an email invitation with a link to participate in a brief (4 short questions) REDCap survey about the accessibility of the video and their perceptions of the content. Patients will receive a $5.00 e-gift card as renumeration for completing the survey.

Patients will be sent two reminders, one week apart to complete the follow-up survey if they confirmed that they have watched the video. The reminder emails will be sent via REDCap with the contact to the study email: tbstudy@kp.org for any questions or concerns a patient may have.

Analysis

Description of intervention and control groups

We will compare the distribution of demographic and clinical characteristics of patients in the two comparison groups with the t-test for continuous variables and the chi-square test for categorical variables. Among patients in the intervention group, we will describe the proportion who watched the video.

Primary analyses

The primary analyses will be based on intention-to-treat. The treatment completion rate will be compared between intervention and standard care groups. If necessary, we will use chart review to validate treatment completion based on pharmacy data for a sub-set of patients who received all doses in a single dispensing. The chart-confirmed rates by intervention group and control group can be accounted for in the analyses. To assess the effect of the intervention on treatment completion, we will estimate rate ratios (RR) and 95% confidence intervals using Poisson regression with robust variance, adjusting for covariates based on scientific relevance and/or significantly different distribution between groups. Missing data, which are expected to occur infrequently, will be handled using the missing data indicator approach.

Secondary analyses

Using similar methods as for the primary analyses, we will compare the initiation rate between intervention and standard care groups. Similarly, we will compare the initiation and completion rate between intervention and standard care groups by treatment type (if feasible, depending on the number of individuals receiving each type of LTBI treatment). We will also conduct per-protocol analyses to compare the initiation rate and the completion rate between those in the intervention group who watched the LTBI video and those in the standard care group. For the follow-up survey, we will report describe the distribution (number and percentage) for each response option.

Analyses will be conducted in SAS (Version 9.4 for Unix; SAS Institute, Cary, NC).

Sample size and power

Based on data in recent years, we estimate that there are approximately 1,950 adult patients per year at KPSC with an LTBI treatment prescription. Using SAS 9.4 PROC Power test for two proportions, we calculated sample size estimates for a 1:2 randomized efficacy trial, given a range of completion rates based on other studies of 0.3, or 0.4, and a range of effect size (rate difference) of 0.05, 0.10, 0.15, and 0.2 to achieve 80% power, with type one error 0.05. If the completion rate in the control (standard care) group is 0.5, we need 918 patients (612 for intervention group and 306 for control group) to achieve 80% power to detect an intervention effect of 0.10 in the completion rate between two groups. As we will conduct the randomized efficacy trial over 1 year, this estimated sample size will be feasible.

Table 2. Sample size calculation for a 1:2 randomized trial – completion

Completion rate in control group	Completion rate in intervention group	Rate difference	Sample size of control group	Sample size of intervention group	Sample size (total)
	0.4	0.1	282	564	846
0.3	0.45	0.15	132	264	396
	0.5	0.2	78	156	234
	0.5	0.1	306	612	918
0.4	0.55	0.15	140	280	420
	0.6	0.2	81	162	243
	0.6	0.1	306	612	918
0.5	0.65	0.15	137	274	411
	0.7	0.2	77	154	231
	0.7	0.1	281	562	843
0.6	0.75	0.15	124	248	372
	0.8	0.2	68	136	204

Data management and quality assurance

Data management and quality assurance activities will be performed by the study team.

The algorithm for randomization will be piloted before beginning the trial to ensure that it accurately identifies all eligible patients and only eligible patients. Additionally, chart reviews will be conducted to confirm patients were correctly identified among those who watched the video and confirmed watching via REDCap. Validity and accuracy of REDCap survey data will be subject to range and consistency checks.

Baseline characteristics and outcomes will be extracted from the KPSC electronic health records. KPSC programmers and/or biostatisticians will develop the study datasets and conduct data quality checks, which include data integrity control and program review. Data integrity control will include checks such as sample size, duplications, formatting, etc. All decisions made during data extraction and data quality checks will be documented.

Ethical considerations

The study has been reviewed and approved by the KPSC Institutional Review Board (IRB# 12324). All study staff with access to protected health information (PHI) are trained in procedures to protect the confidentiality of subject data. Individuals who receive the intervention will provide agreement to participate in the research study. We will also obtain a waiver of informed consent, as all other aspects of the study are captured as part of routine clinical care.

The HIPAA Privacy Rule governs the use and disclosure of personally identifiable information from covered entities. Throughout the course of this study, PHI will be accessed through the electronic health record by authorized study team members, but no PHI will be disclosed outside of the KPSC study team. As this access presents no more than minimal risk to individuals and the research could not be practically done if required to obtain written authorization for usage, we will obtain a waiver for written HIPAA authorization for research involving use of the EHR.

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