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Facilitators and barriers to adolescent participation in a TB clinical trial

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SUMMARY

BACKGROUND: The inclusion of adolescents in TB drug trials is essential for the development of safe, child-friendly regimens for the prevention and treatment of TB. TB Trials Consortium Study 31/AIDS Clinical Trials Group A5349 (S31/A5349) enrolled adolescents as young as

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12 years old. We assessed investigator and coordinator described facilitators and barriers to adolescent recruitment, enrollment, and retention.

METHODS: Interviews were conducted with six investigators from sites that enrolled adolescent participants and six investigators from non-enrolling sites. Additionally, two focus groups were conducted with study coordinators from enrolling sites and two focus groups with non-enrolling sites. Discussions were transcribed, analyzed, summarized, and summaries were reviewed by Community Research Advisors Group members and research group representatives for content validity.

RESULTS: Investigators and coordinators attributed the successful enrollment of adolescents to the establishment and cultivation of external partnerships, flexibility to accommodate adolescents' schedules, staff engagement, recruitment from multiple locations, dedicated recruitment staff working onsite to access potential participants, creation of youth-friendly environments, and effective communications. Non-enrolling sites were mainly hindered by regulations. Suggestions for improvement in future trials focused on study planning and site preparations.

CONCLUSION: Proactive partnerships and collaboration with institutions serving adolescents helped identify and reduce barriers to their inclusion in this trial.

Keywords

adolescents; tuberculosis; trials

Regimens prescribed to treat TB among pediatric patients are often based on extrapolated data from trials conducted with adults.[1] Experts convened by the U.S. National Institutes of Health have recommended the inclusion of children ≥10 years old and adolescents in TB drug trials (phase 2b and later phases) to gather sufficient data on safety, dosing, and drug-drug interactions and to ensure the development of appropriate drug formulations for these populations.[1,2] However, researchers may lack experience, knowledge, motivation, and awareness of how to operationalize the inclusion of children and adolescents in TB clinical trials. These factors are not unique to the TB research community. Approximately one in five pediatric clinical trials fails due to study design, oversights in planning, or inadequate participant enrollment.[3]

Trials that seek to enroll adolescents alongside adult participants must consider the physical differences between these groups, as well as the cognitive, emotional, and social needs of the adolescent participants.[4] The effort required to address these needs are potentially outweighed by the benefits of adolescent participation in clinical trial research. With this in mind, the U.S. Centers for Disease Control and Prevention's (CDC) Tuberculosis Trials Consortium (TBTC) Study 31 (S31) and the National Institutes of Health (NIH) AIDS Clinical Trials Group (ACTG) Study A5349 (S31/A5349) protocol team designed the trial's eligibility criteria to include participants as young as 12 years old (Clinicaltrials.gov: NCT02410772).

S31/A5349 was an international, multicenter, randomized, controlled, open-label, 3-arm, phase 3 non-inferiority trial that compared two 4-month rifapentine-based regimens with a standard 6-month regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol.

Towards the end of S31/A5349, an evaluation was conducted with the aim of having the study investigators and coordinators from multiple global regions reflect upon both the barriers and facilitators to adolescent recruitment, enrollment, and retention in the S31/A5349 trial.

We report factors that influenced clinical research sites' intentions to recruit and enroll adolescent participants into S31/A5349, barriers and facilitators to adolescent participation, and suggestions to improve adolescent participation in future trials.

STUDY POPULATION AND METHODS

Between January 25, 2016, and October 30, 2018, S31/A5349 enrolled 2,516 participants ≥12 years of age with pulmonary TB. Participants were enrolled from 34 trial sites within the following 13 countries: Brazil, China (Hong Kong), Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, the United States, Vietnam, and Zimbabwe.[5,6]

For this evaluation, a total of 12 in-depth interviews were conducted with investigators at three sites that enrolled adolescent participants and three sites that did not enroll adolescents, from each of the two research networks. Additionally, four focus groups were held with a total of 31 study coordinators. Two focus groups (one for each network) were conducted with coordinators representing sites that did not enroll adolescents. Similarly, two focus groups were conducted with coordinators of sites that enrolled adolescent participants.

Ethics

The adolescent recruitment evaluation protocol was approved by the CDC National Center for HIV, Viral Hepatitis, STD and TB Prevention's Associate Director of Science, TBTC Core Science Group, and the ACTG Tuberculosis Transformative Science Group. The trial in which this evaluation was embedded was approved by the U.S. CDC Institutional Review Board (IRB). Each participating institution provided for the review and approval of this protocol and its informed consent documents by a local IRB or ethics committee or relied formally on the U.S. CDC IRB approval. All interview and focus group participants provided verbal informed consent that was audio-recorded. This activity was reviewed by the U.S. CDC (Atlanta, GA, USA) and was conducted in accordance with applicable federal law and CDC policy.

Theoretical framework

The Capability, Opportunity, Motivation, and Behavior (COM-B) model informed the development of in-depth interview and focus group question guides and data analysis.[7] The COM-B Model, developed by Michie and colleagues, was designed to identify what changes are needed in order for a behavior to occur.[8] The model identifies three factors that need to be present to make the behavior more likely to occur: capability, opportunity, and motivation.

Capability entails physical and psychological capacities to engage in a behavior. Per the model, sources of capability include the skills, abilities, proficiencies, as well as knowledge, memories, attention, and decision processes. Capability may be influenced by guidelines,

fiscal issues, or regulations. Interventions to enhance capability include education, rules, and changing the physical or social environment.[8,9]

Opportunity refers to factors external to a person that enable or constrain a behavior. Sources of opportunity arise from the physical environment and social influences such as cultural norms. Legislation, communications and marketing, and designing or controlling the physical or social environment influence opportunities. Suggested interventions include the use of incentives, persuasive communications, and education.[8,9]

Motivation includes the emotional, social, and cognitive forces that enable or constrain behaviors. Motivation arises from beliefs about capabilities and consequences, goals and optimism, as well as emotions and impulses. Regulations, services, and laws influence motivation. Interventions to elicit motivation include skills training, expectations of punishment or costs, and enablers that reduce barriers (e.g., free transportation).[8,9]

Data collection

During the Fall 2018 semi-annual TBTC Meeting, project team members unaffiliated with the consortium met with the TBTC's Community Research Advisors Group (CRAG), a community advisory board to the TBTC whose members work to ensure TBTC research is responsive to the community needs and had identified adolescent enrollment as a priority. The project team introduced CRAG members to the COM-B model and invited CRAG members to help draft questions for data collection tools that would reflect the COM-B model's constructs. TBTC's Research Participant Protection Working Group then reviewed the draft questions and identified the questions most appropriate to ask of site investigators and coordinators. These questions were then sorted and prioritized, with assistance from CRAG members, into two focus group question guides and two in-depth interview guides.

Focus groups

Four focus groups were conducted with a convenience sample of study coordinators.[10] Two focus groups were conducted with coordinators from sites that did not enroll adolescent participants into S31/A5349. One of these focus groups included coordinators from CDC-funded TBTC sites, the second included coordinators from NIH-funded ACTG sites. Similarly, two focus groups were conducted with coordinators from sites that enrolled adolescent participants into S31/A5349. A total of 19 coordinators from ACTG sites and 12 coordinators from TBTC sites participated in the focus group discussions. Participating coordinators were from China (Hong Kong), Haiti, Kenya, Malawi, South Africa, Uganda, the United States, Vietnam, and Zimbabwe.

Focus groups were conducted during each research network's regularly scheduled in-person meetings and led by project team members. Coordinators were invited to participate prior to the consortia meetings. Focus groups lasted between 90 to 120 min and were conducted in English. Discussions were audio recorded and comprehensive field notes were taken.[10]

Interviews

Interviews were conducted with a purposive sample of investigators from 6 sites that did not enroll adolescent participants into S31/A5349; 3 investigators were from CDC-funded TBTC sites and 3 were from NIH-funded ACTG sites. Interviewers sought the reasons sites did not enroll participants between the ages of 12 and 17 years and solicited feedback for enrolling adolescents in future TB trials.

Similarly, 6 interviews (3 each from TBTC and ACTG) were conducted with investigators from sites that did enroll adolescents. These interviews also aimed to understand site decisions regarding adolescent enrollment, why the site was successful, and identify opportunities for improving adolescent enrollment in future trials.

Interviews were conducted by project team members via ZOOM© at a time convenient for the interviewee.[11] Interviews lasted 40–60 min. Conversations were recorded. Interviews were conducted primarily in English. Questions were repeated in French and Spanish as appropriate if an interviewee asked for clarification. Interview participants were from Haiti, Peru, South Africa, Uganda, the United States, Vietnam, and Zimbabwe.

Data analysis

Focus group discussions and interviews were transcribed verbatim via automated transcription services available through REV.com© (REV, Austin, Texas, USA). Transcriptions were reviewed for accuracy and completeness. Transcriptions were then uploaded into NVivo© Pro 12 v12.1.1 (Lumivero, Denver, Colorado, USA) for analysis.[12] A codebook was developed to organize the analysis of the transcribed interviews and focus group discussions. A subsample of transcripts was selected for team members to individually annotate and develop an initial set of inductive codes. The team met, reviewed, and discussed the inductive codes created by each member to generate an initial set of codes. The initial set of codes was used by the team to independently analyze another transcript. The team meet again to revise code definitions, identify additional codes, assess inter-coder agreement, and attain consensus on how data would be analyzed.

The codebook was refined based on this initial work. Interview and focus group transcripts were analyzed by 2–3 members of the team. Intercoder reliability tests were performed to assess agreement between team members.[13,14] Sections of text with a κ, indicating concordance less than 80% between team members were discussed and coding was reconciled to avoid subjectivity in reports of the analysis. After coding all transcripts, the data were systematically queried to assess the occurrence of individual codes and identify patterns. Queries were organized by data collection approach (interview vs. focus group discussion), research network (TBTC vs. ACTG), and site type (enrolled adolescents vs. no adolescents enrolled). Team members then created initial summaries of patterns identified between codes, including tables and highlighting salient quotes where appropriate. Each summary was reviewed by a second team member to confirm content and ensure clarity. The data were compiled into a full report, and shared with the TBTC's CRAG and consortium representatives, who reviewed and validated the content.

RESULTS

Sixty-eight adolescents were enrolled through 10 sites in seven countries.

Intentions to enroll adolescent participants

When asked about their initial plans regarding adolescent enrollment, investigators at 6 sites indicated that they had planned to enroll adolescents from the outset and obtained Institutional Review Board (IRB) approval to do so. Among the 6 investigators at non-enrolling sites, 3 reported no intention to enroll adolescents prior to the start of the study and 3 reported initial intentions to enroll. Among the 3 with no intention, the opportunity for enrollment was effectively constrained. Two investigators described governmental restrictions barring the inclusion of adolescents in trials. The third site reported the facility in which the site was located restricted care to individuals 18 years and older.

Among the 3 sites that intended to enroll adolescents and sought IRB approvals, an investigator at one site reported their IRB disallowed adolescent enrollment citing a lack of safety data on rifapentine in adolescents. Investigators at the other two sites reported they had obtained IRB approval to enroll adolescents but subsequently encountered barriers that restrained the site's capability.

The first of these two sites noted the site had an adolescent unit from which they could recruit, and clinic staff included adolescent peer educators who were recovered TB patients. The principal investigator attributed the subsequent lack of success in enrolling adolescents to the following factors: 1) the intensity of the study schedule and/or duration of clinic visits, 2) the clinic's operating hours were from 8:00 am to 4:00 pm, which did not accommodate both the study's schedule and participants' school schedules; 3) the additional effort needed to coordinate school schedules along with adolescents' transportation needs, staff/clinic schedules, and timing the collection of sputum specimens to meet courier schedules; 4) many adolescents lost parents to HIV and guardians frequently lack paperwork proving legal guardianship for the consent process; and 5) the stigma surrounding HIV, specifically adolescents' concerns that their parent/guardian would make them leave the house if they tested HIV positive. Notably, these factors were reiterated by coordinators from multiple sites during focus group discussions.

The investigator at the second site reported the IRB that approved the protocol initially imposed an age and weight restriction on the adolescents recruited, which differed from the protocol, but could be lifted once a 'safety indication' had been demonstrated. The investigators noted that the restrictions made recruitment complex and contributed to the lack of success.

Barriers and facilitators to adolescent participation

As a preface to more probing questions, both investigators and coordinators from sites that successfully enrolled adolescents into Study 31/ACTG 5349 were asked to identify the foremost reasons their site accomplished this goal. Three themes emerged 1) actions and behaviors of the study staff, 2) access to adolescents, and 3) recruitment strategies. As shown in Figure 1, partnership was an over-arching subject considered to provide both

opportunity and capability for adolescent enrollment. Participants reported on efforts to not only establish, but also cultivate, partnerships with institutions or organizations where adolescents are present, and then to place staff onsite to conduct recruitment activities.

Subsequent questions during interviews and focus groups with investigators and coordinators from enrolling and non-enrolling sites sought to examine factors that would influence sites' motivation, capability, and opportunity. Specifically, questions addressed rules and policies, the structure and operations of the research site, study requirements, creating youth-friendly environments, staff knowledge and skills, and navigating interactions with adolescents, parents, and guardians. Both barriers and facilitators to adolescent recruitment, enrollment, and retention emerged throughout these discussions and are summarized in Supplementary Table S1.

The topic of partnerships arose frequently in response to a variety of questions throughout the interviews and focus group discussions. Institutions and facilities that provide health-related services or are involved in healthcare were the most frequently cited partners or potential partners. Respondents also talked about the importance of engaging with individual physicians, nurses, physician assistants, and other clinical care workers working within these facilities to elicit motivation. Engagement approaches included providing education about the protocol and eligibility criteria, addressing concerns such as the safety of the study and benefits of the study; as well as illustrating the overall benefits of enrolling adolescents into the trials being conducted. Figure 2 summarizes described partners and their potential roles.

Suggestions to improve adolescent participation in future trials

Investigators and coordinators at both enrolling and non-enrolling sites made several recommendations to optimize site's and staff member's motivation, capacity and opportunity to recruit, enroll and retain adolescents in future drug trials. These recommendations have been organized by activities that occur during the various stages of a clinical trial, along with the COM-B components potentially impacted and corresponding intervention targets (See Supplementary Table S2).[15]

A first step may be to specify in a study protocol that adolescents must be recruited. As noted by one investigator at a non-enrolling site:

> I think we as sites have a responsibility to try and overcome those barriers to ensure that there isn't added discrimination against kids when these drugs eventually become available or proven to be better than the existing. I would think that the protocol should have a threshold for recruitment of patients. If it's clearly set out up front that a third of the patients need to be adolescents, I think that it would focus the minds of the principal investigators as well as the investigators on the sites, to make sure that this is the business … adolescents have to be recruited and that a certain proportion of the entire patient population has to be adolescents.

Further, both investigators and coordinators noted unique aspects of working with adolescent participants. In addition to special considerations surrounding the consent process and adapting activities around school schedules, respondents cited the importance of creating youth-friendly environments and keeping adolescents engaged during their clinic visits.

Respondents noted ongoing conversations are an important way to engage adolescent participants. Suggested conversation topics include talking with adolescent participants about their future goals, how to achieve their goals, and helping the participants understand or recognize how TB could impact those goals if they did not undergo treatment. Staff also answered questions related to drug and alcohol use, sexually transmitted diseases, and safe sex practices. Respondents observed that it is important for staff at a study site to know how to approach these topics with sensitivity to the adolescent's comfort level and respect for cultural norms. Some relayed that adolescents often want to be assured that they are not the only ones of their age who have been diagnosed with and require treatment for TB. Two sites described small group sessions held to discuss the study, which afforded adolescent participants opportunities to become acquainted with each other and learn that they are not alone in their experiences with TB.

Some respondents spoke to the period of adolescence as a transition from child to adult, noting it was important for study staff to be skilled at navigating this transition and achieving a balance with each participant. While adolescents often want to be treated as adults, respondents explained that adolescents may require closer monitoring, frequent/daily reminders, and frequent check-ins similar to what would be provided to a younger child. Respondents explained that describing the goals of the study in the context of what adolescents would appreciate or value; encouraging adolescents to ask their questions during and after the consent process, and at each visit; stressing the opportunity to have open conversations; explaining that engaging in study activities is part of making decisions for themselves; taking time to inquire about their day-to-day activities and asking follow-up questions; and clearly outlining what is expected during the study can help convey consideration for, and recognition of the adolescent participant.

Finally, investigators and coordinators acknowledged negative perceptions associated with adolescent study participants, including concerns that adolescents 1) require more work to enroll because staff need to approach both the parent(s) or guardian(s) and adolescent, 2) are more likely to forget about appointments, are less likely to follow directions or follow through, and 3) more likely to withdraw from a study. Staff from enrolling sites advised that both these perceptions and approaches to mitigate potential problems should be discussed as a team during initial planning. These discussions can influence a team's motivation.

DISCUSSION

Enrolling adolescents into TB therapeutic trials is essential to the conduct of studies that can inform global policies and treatment guidelines. Success requires research teams to be motivated to think about this population separate from adults and plan accordingly when initially designing a study protocol, developing budgets, and planning for day-to-day logistics. During initial planning of TBTC Study 31/ACTG A5349, CRAG members advocated for lowering the age requirement for inclusion. Subsequent discussions with TBTC and ACTG investigators and coordinators revealed a broad array of facilitators that created motivation, capacity, and opportunity for the successful enrollment of adolescents as well as suggestions that may positively influence these COM-B components. Some facilitators, such as trainings, the establishment and cultivation of partnerships, creation of

youth-friendly study materials and settings, and the accommodation of school schedules, required additional investments of time, energy, and resources.

While some barriers arose from site's capabilities, opportunities, and motivations, others were beyond the control of the study teams (e.g., affiliated with an institution that provides care to adults only). To note, investigators and coordinators at sites that had the approval to enroll adolescents discussed factors that precluded some adolescents from participating despite meeting clinical eligibility requirements (e.g., the requirement to have consent forms signed by both parents). From the standpoint of equity, these requirements warrant further attention.

Finally, some responses provided by investigators and coordinators reflected differences by country or site setting. For example, coordinators from African sites discussed interactions with boarding schools at length, whereas coordinators from other countries did not. To note, information was not stratified by country to retain anonymity. Some facilitators and barriers, as well as suggestions to improve recruitment, enrollment, and retention of adolescents, may not be appropriate for every setting, nor all studies.

Limitations

This evaluation is subject to additional limitations associated with the methods and results. Data collected through the focus group discussions may have been influenced by use of a convenience sample and group dynamics, leading to reports of acceptable approaches in line with rules and regulations. To minimize this, facilitators held separate sessions with participants that enrolled and did not enroll adolescents. Participants were invited to consider different scenarios and approaches that are acceptable in diverse settings. Further, focus group facilitators worked to address the extent to which participants commanded the discussion and ensure input from all participants.

The team that coordinated and led the focus groups included some staff members from the CDC, which funded some of the participating sites. The presence of these staff may have led participants to limit the information that they shared due to concerns of being viewed critically or appearing disrespectful.

In-depth interviews are also susceptible to challenges. The social context, or power dynamic between the interviewer and participant can impact the effectiveness of interviews.[16] To mitigate this, members of the project team who were not CDC employees or affiliated with the TBTC conducted the interviews. Additionally, all participants were provided with the primary questions in the structured interview guide ahead of the scheduled interview. Finally, no data were collected from adolescents. This was beyond the scope and resources of the evaluation. Despite these limitations, the reflections of the investigators and coordinators who participated in this evaluation provide helpful insights for other researchers.

CONCLUSION

The TB Trials Consortium and AIDS Clinical Trial Group successfully enrolled adolescent participants in S31/A5349. Underlying motivation and decisions by study sites to proactively pursue partnerships, accommodate school schedules, create youth-friendly environments, and place recruitment staff near adolescents, created capacities and opportunities that facilitated enrollment of adolescents into the trial. Recognition of these factors can increase adolescent participation in future TB clinical trials. Focused efforts by researchers will enable adolescents to benefit from prospective novel treatments in a timely and equitable manner.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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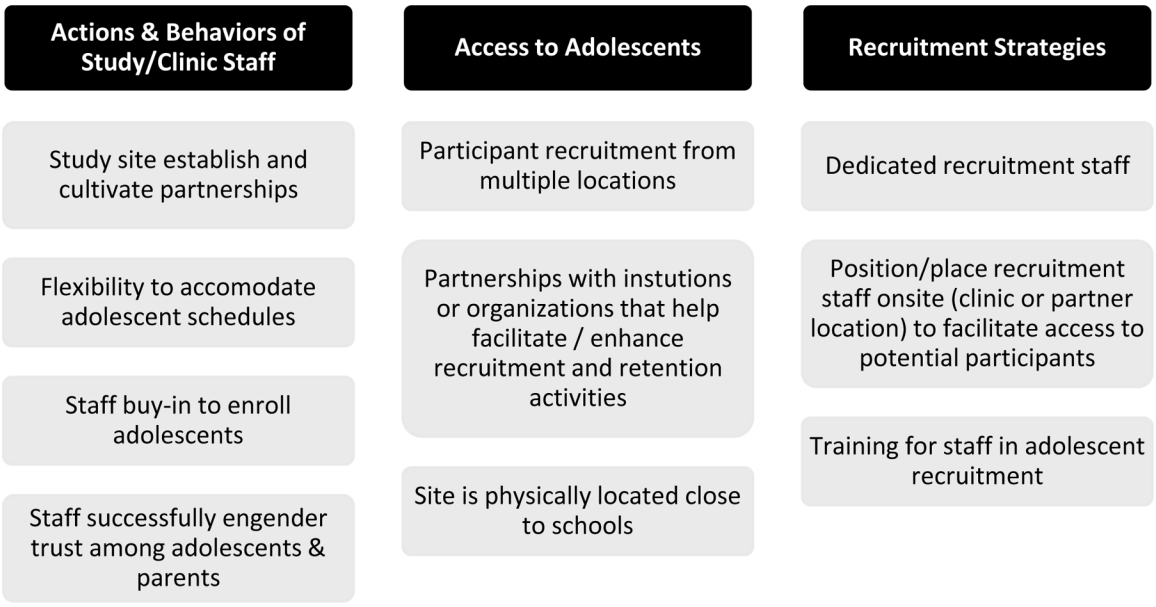

Figure 1.
Investigator and coordinator-reported "top" reasons for successful enrollment of adolescent participants

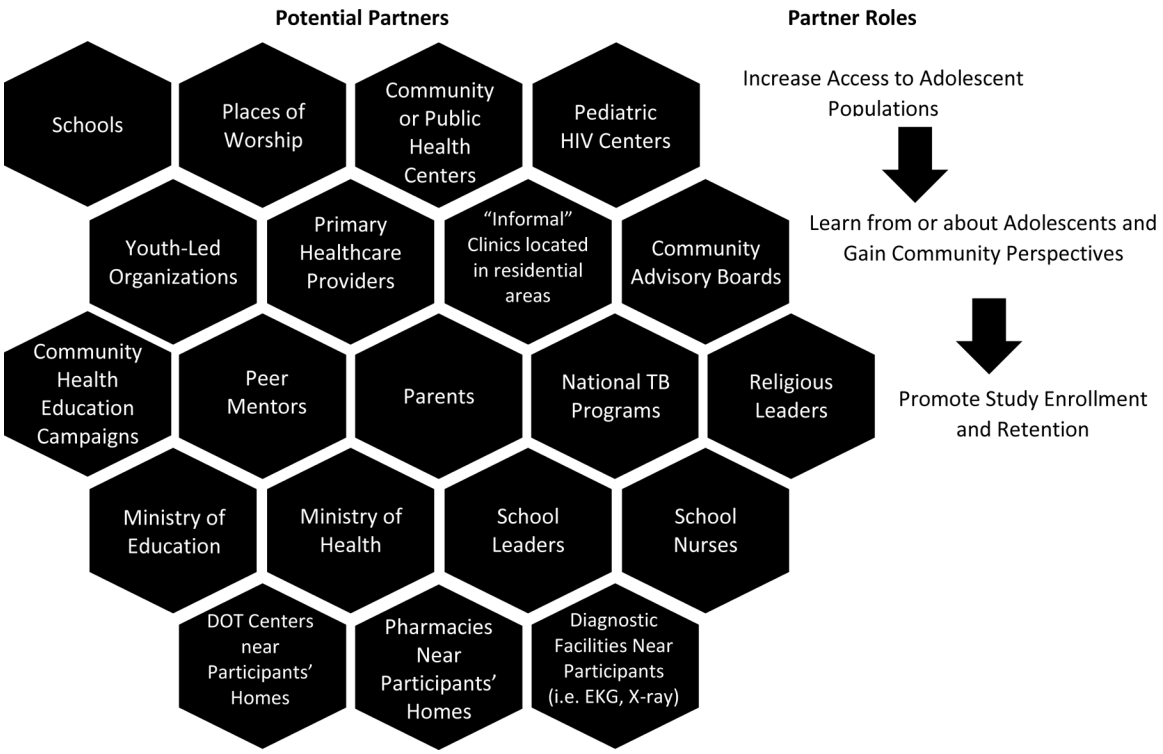

Figure 2.
Potential Partners and Partner Roles