Prospective Validation Study of a Antiretroviral Therapy (ARV) Decision Support Tool

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1. Abstract

The Centers for Disease Control and Prevention (CDC) estimate that 1.2 million people currently live with HIV in the United States; however, less than half have been prescribed antiretroviral (ARV) therapy and are virally suppressed [1,2,3]. ARV regimens generally include multiple drugs from various mechanistic classes. There are currently over 25 ARV drugs approved by the U.S. Food and Drug Administration (FDA), leading to a wide array of potential ARV combinations [4,5].

Treatment of HIV with antiretroviral drugs (ARV) requires complex medical decision-making that incorporates multiple individual patient variables. The existing guidelines provided by the Department of Health and Human Services (DHHS) provide excellent recommendations on choosing initial ARV regimens, but they are dense, cumbersome to navigate, especially for inexperienced providers and for patients with significant co-morbidities or drug resistance mutations [4]. This is particularly problematic given that recent studies have shown a large proportion of HIV care is being provided by primary care practitioners, who may not have received specific training in HIV care.[6] There is thus a need for innovation to improve provider knowledge of HIV evidence based practice recommendations and emerging scientific data, and to assist clinicians in decision making when selecting an appropriate ARV regimen.

Faculty at Johns Hopkins have recently created HIV-ASSIST (https://www.hivassist.com/) an online interactive patient-based tool that allows for delivery of tailored educational content that may assist providers to learn HIV treatment principles and support decision making on ARV usage.

Our study design involves a randomized trial of trainees from the Johns Hopkins School of Medicine (SOM) and Residents from Johns Hopkins Medical Institutions, comparing ARV selection for ten hypothetical cases among trainees that have access to the current DHHS guidelines versus trainees that have access to HIV-ASSIST. Our hypothesis is that there will be a statistically significant higher percentage of appropriate ART selection (comparing to a reference standard of HIV experts) in the group using HIV-ASSIST compared to the group using DHHS guidelines alone.

We have previously constructed ten standardized case scenarios in an electronic survey format, and ascertained ARV prescribing preferences from experienced HIV clinicians to serve as the reference standard, to define ‘appropriate ART selection’. We will enroll student and resident trainees from Johns Hopkins, who will be randomized to a control group (with access to current DHHS guidelines) or an intervention group (with access to HIV-ASSIST and current guidelines). We will deliver the same ten case scenarios via electronic survey to study participants, who will be asked to recommend ARV regimens for each case. We will report the percent concordance to the reference standard (i.e percent appropriate ART selection), comparing the intervention group to the control group.

2. Objectives

a) Primary: To determine the difference in percent concordance (with reference standard; i.e. percent appropriate ART selection) between the group using the DHHS guidelines for ARV selection and the group using HIVASSIST for ARV selection.

b) Secondary: To determine the difference in time forARV selection for standardized case scenarios between trainees using HIVASSIST and those using the DHHS guidelines.

3. Background

The Centers for Disease Control and Prevention (CDC) estimate that 1.2 million people currently live with HIV in the United States; however, only less than half have been prescribed antiretroviral (ARV) therapy and are virally suppressed. ARV regimens generally include multiple drugs from various mechanistic classes. There are currently over 30 ARV drugs in 7 different classes that have been approved by the U.S. Food and Drug Administration (FDA), leading to a wide array of potential ARV combinations.

Choosing these drugs is a complex medical decision, and current guidelines advocate individualized therapy that accounts for multiple patient characteristics. Factors that must be considered include: previous ARV treatment, adherence, HIV resistance mutations, viral load, comorbidities (e.g., renal function, cardiovascular disease), and drug interactions. Synthesizing each of these modifying factors is necessary, but complex and time consuming for providers. Challenges in prescribing ARV regimens in a primary care setting become increasingly relevant as HIV continues to become a manageable chronic illness. Recent studies have shown that a large proportion of HIV care is provided by primary care practitioners, and often infectious disease specialists feel uncomfortable managing patient's comorbidities like hypertension and diabetes. With the growing need for increasing involvement of primary care physicians in HIV care management, there is also a growing need to develop tools that allow more effective and efficient learning of HIV treatment principles and that support ARV decision making.

To solve this problem, faculty at Johns Hopkins have created HIV-ASSIST, an online interactive patient-based tool that allows for individualized treatment recommendations through the synthesis of patient-specific factors with existing guidelines and evidence. HIV-ASSIST offers efficient real-time learning of treatment principles and augmented decision support for care providers by delivering informational material about the evidence behind suggested regimens during the use of the tool.

Our goal is to evaluate the impact of using HIV-ASSIST compared to DHHS guidelines in making ARV selections (for both ARV naïve and experienced patients) among trainees that are not experts in HIV care. We have previously ascertained ARV preferences for 10 case scenarios from HIV experts to serve as the reference standard. We will the proportion of ARV selections that are concordant with the reference standard (% appropriate ART selection) between a group of trainees using DHHS guidelines, and a group of trainees using HIVASSIST as well as the guidelines

3. Study Procedures

a. Study design: Randomized trial of students and trainees to assess the impact of HIVASSIST utilization on ARV selection for standardized case scenarios compared to usage of DHHS guidelines alone.

b. Study participants and settings: We will enroll up to 200 participants. Students in the Johns Hopkins University SOM or SON (Baltimore, Maryland), and/or internal medicine residents at Johns Hopkins Hospital will be eligible to participate. Participants will be invited to participate via an email to class or program listservs or via flyers posted in the school of medicine or nursing buildings. Individuals that are interested will have a link to a Qualtrics survey where they will receive additional study details.

c. Enrollment/Randomization: An email will describe the study and will contain a link to the survey; the email will also inform them that their participation is completely voluntary, and that their decision to participate (or not) will in no way affect their academic standing. They will also be informed that no information about individual results/surveys will be shared with their school administration. All participants enrolling in the study will be offered an incentive of $50 gift card or equivalent; they will receive a link to this gift card via email after their participation. Study enrollment will take place over 12 months. Participants will be recruited on a rolling basis throughout the study period.

- Qualtrics will be used to deliver the survey, including an initial page explaining the study and asking for consent.
- Qualtrics will automatically randomize participants to different groups as a part of the survey process, using Qualtrics internal random sequence generator. We do not include any stratifications for randomization as limited demographic detail is collected. The participants were not blinded to their allocation, as they were told which decision-support aids they would have available.
- The survey will be conducted in one session, and the time to complete the survey will be captured. Individuals not completing the survey in one session will be excluded. d. Data collection/Survey:
- Development of standardized case scenarios: We have previously designed 10 clinical case scenarios for a range of patient situations, including a) ARV naïve b) ARV experienced, suppressed or c) ARV experienced, failing patients (with and without mutations, comorbidities, and common co-medications). In a prior prospective survey, we have ascertained ARV preferences for each case scenario among a cohort of experienced HIV clinicians. These ARV choices for each case scenario will be considered a reference standard to judge acceptability of ARV selections in the study cohort in this study.
- We will collect basic demographic details of study participant including degree program (NP,MD), level of training (M1, M2), and level of experience with HIV care.
- Each survey will have its own video tutorial briefly explaining how to use the DHHS guidelines and/or HIV-ASSIST. A link to the video will be provided in the survey. The control group will have a link to the DHHS guidelines in the survey. The experimental group will have a link to both the DHHS guidelines, and the HIVASSIST tool. Each participant must acknowledge that they have successfully accessed their respective resources to help inform their ARV regimen selections. A question at the beginning of both surveys will restrict the participants from

advancing until they have filled information from either DHHS guidelines or HIV-ASSIST correctly. This will be a test of the participant's understanding of how to use the survey and the respective regimen selection aid.

- Study participants will be guided through a survey in which the ten standardized case scenarios (vignettes with relevant HIV and patient variables are provided) are presented, and participants will be asked to propose their ARV treatment regimens. The participant's ARV choices will be recorded. Through Qualtrics software, we will also record the time needed to complete the study.

e. Statistical considerations:

Definitions of appropriate ART selection:
Current DHHS guidelines recommend an individualized approach to ARV selection based on multiple considerations. Several regimens are listed as acceptable for ARV-naïve patients as 'regimens recommended for most people living with HIV', with specific instructions on comorbidities or drug interactions that may lead to selection from a list of 'regimens recommended in some clinical scenarios'. For ARV-experienced patients, the guidelines outline a list of general treatment principles to consider, such as including "at least two, and preferably three, fully active agents."

For each case-scenario in the survey, we have previously collected ARV selections from a cohort of experienced HIV clinicians, recognizing that there may be multiple reasonable ARV regimen options for each case scenario. The ARV choices from the prior survey will be used as the reference standard.

Each question will be graded as 'concordant/appropriate' if the ARV regimens selected by the respondent matches an ARV regimen of any HIV expert, or is consistent with current DHHS guidelines (e.g., selection from the list of "regimens recommended for most people living with HIV'' for treatment-naïve case-scenarios; regimens which "include at least two, and preferably three, fully active agents"

Our primary outcome is the proportion of appropriate ARV selection for standardized case scenarios, comparing between trainees and expert HIV clinicians and/or DHHS guidelines. Specifically, we will assess:

a) The difference in percent appropriate/concordant between the control group, and the intervention group that has access to HIV-ASSIST
Hypothesis: There will be a statistically significant higher percent concordance in the group using HIV-ASSIST compared to the group using DHHS guidelines alone.

Our secondary outcome will look at the time required for each group to reach a correct answer. Specifically, we will assess:

b) The difference in time to ARV selection for standardized case scenarios between trainees using HIV-ASSIST and those using the DHHS guidelines.
Hypothesis: There will be a statistically significant lower time to correct ARV selection in the group using HIV-ASSIST compared to the group using DHHS guidelines.

Sample Size:
There is limited a priori data to estimate the likely percent concordance between trainees/students and HIV experts. We assumed that those participants using DHHS guidelines alone (control) will have an average of up to 50% appropriate responses, with a wide standard deviation of up to 0.5. We anticipate that there will be approximately 80% appropriate ART selections with a standard deviation of 0.1 among those in the intervention arm. With this assumption, we would need 18 individuals in each arm to be adequately powered to detect a difference (two-sided alpha, 0.05). Table 1 shows needed sample size to have 80% power to detect a difference between the control and intervention arms under varying assumptions. In secondary analysis, we will compare the control and intervention arms, stratified by level of training.

DHHS MEAN % APPROPRIATE RESPONSES	0.3	0.3	0.3	0.5	0.5	0.5	0.3	0.3	0.3	0.5	0.5	0.5
HIVASSIST MEAN % APPROPRIATE RESPONSES	0.7	0.7	0.7	0.7	0.7	0.7	0.8	0.8	0.8	0.8	0.8	0.8
DHHS SD	0.1	0.3	0.5	0.1	0.3	0.5	0.1	0.3	0.5	0.1	0.3	0.5
HIVASSIST SD	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Sample size needed per group for 80% power	1	4	11	4	16	41	1	1	7	2	7	18

Table 1. Sample Size Variations by Expected Group Means and Standard Deviations

4. Drugs/ Substances/ Devices
a. N/A

5. Risks
a. This study only involves a survey with standardized cases to ascertain clinician preferences for a variety of HIV case scenarios. Participants may feel insecure regarding their self-perceived lack of knowledge regarding HIV management. However, all responses to the survey will be visible only to the study members. There are no other biological risks identified.

b. Steps taken to minimize the risks.: Participants will be permitted to stop participating in the survey at any time.

c. Plan for reporting unanticipated problems or study deviations: Participants will be instructed to contact the PI if any problems occur during survey completions. Such problems will be reported to the IRB immediately.

d. Financial risks to the participants: There are no financial risks to participants.

6. Benefits: Once the data are compiled, analyzed, and published, the participants will learn about their collective understanding of HIV antiretroviral management. In addition, the results of this study will allow us to improve HIV-ASSIST, a tool that will greatly expand providers' ability to provide guideline-recommended HIV care. This is particularly important in places where there may not be dedicated HIV training (such as other countries) and in places where there are no HIV providers/a provider with no formal training in HIV care is managing a handful of patients with HIV (which occurs in many rural parts of the United States). Managing HIV in an optimal way not only provides a benefit to patients, it benefits society by reducing patients' viral loads and thus reducing transmission to other persons.

7. Payment and Remuneration

• Participants who complete the study will receive a link through email for an electronic $50 Amazon gift card. There will be no penalties for not completing the study.

8. Costs and Funding

• The only cost of the study is the Amazon incentives that we will offer our participants to complete the study. These costs will be paid using internal Johns Hopkins Institute of Educational Excellence Berkheimer Grant, awarded to Maunank Shah (PI).

9. Trial Registration: clinicaltrials.gov
10. Roles and Responsibilities: The study was designed by Dr. Shah (PI) and Jesus Aaron Ramirez (Co-investigator), who also led protocol development, obtained IRB approval, conducted the study, and led analysis and manuscript writing. The funders had no role in the design, collection, management, analysis or interpretation of data or writing of the report.
11. The study received approval by the Ethics/IRB committee of Johns Hopkins University

Protocol References

1. CDC. HIV in the United States: At A Glance. https://www.cdc.gov/hiv/statistics/overview/ataglance.html [Accessed March 2018].
2. Foundation KF. The HIV/AIDS Epidemic in the United States: The Basics.

https://www.kff.org/hivaids/fact-sheet/the-hivaids-epidemic-in-the-united-states-the-basics/. [Accessed May 2017].

3. Weiser J, Beer L, West BT, Duke CC, Gremel GW, Skarbinski J. Qualifications, Demographics, Satisfaction, and Future Capacity of the HIV Care Provider Workforce in the United States, 2013-2014. Clin Infect Dis 2016,63:966-975.
4. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. 2016. http://aidsinfo.nih.gov/guidelines [Accessed 11/2016].
5. Gunthard HF, Saag MS, Benson CA, del Rio C, Eron JJ, Gallant JE, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. JAMA 2016,316:191-210.
6. Medicine AAoH. HIV Clinician Workforce in the US. https://aahivm.org/wpcontent/uploads/2017/03/FINAL-August-2016.pdf [Accessed March 2018].