New Strategies in Clinical Guideline Delivery: Randomized trial of online, interactive decision-support versus guidelines for HIV treatment selection by trainees

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Brief summary: HIV-ASSIST (www.hivassist.com) provides ART decision-support. In this randomized study, trainees using HIV-ASSIST were significantly more likely to choose appropriate ART regimens for ten case-vignettes compared to those using DHHS guidelines alone. Interactive tools are important to augment guideline implementation.

Abstract

Background: Support for clinicians in HIV medicine is critical given national HIV-provider shortages. Department of Health and Human Services (DHHS) guidelines are comprehensive but complex to apply for antiretroviral therapy (ART) selection. HIV-ASSIST (www.hivassist.com) is a free tool providing ART decision-support that could augment implementation of clinical practice guidelines.

Methods: We conducted a randomized study of medical students and residents at Johns Hopkins University, in which participants were asked to select an ART regimen for 10 HIV case-scenarios through an electronic survey. Participants were randomized to receive either DHHS guidelines alone (with video tutorial), or DHHS guidelines and HIV-ASSIST (with video tutorial) to support their decision-making. ART selections were graded 'appropriate' if consistent with DHHS guidelines, or concordant with regimens selected by HIV experts at four academic institutions.

Results: Among 118 trainees, participants randomized to receive HIV-ASSIST had significantly higher percentage of appropriate ART selections compared to those receiving DHHS guidelines alone (% appropriate responses in DHHS vs HIV-ASSIST arms: median 40% [Q1, Q3: 30%, 50%] vs 90% [80%, 100%], $p<0.001$). This difference was consistent among both medical students (median 40% vs 90%, $p<0.001$) and residents (median 40% vs 90%, $p<0.001$). The effect was seen for all case-types, but most pronounced for complex

cases involving ART-experienced patients with ongoing viremia (DHHS vs HIV-ASSIST: median 0% [0%, 33%] vs 100% [66%, 100%]).

Conclusion: Trainees using HIV-ASSIST were significantly more likely to choose appropriate ART regimens compared to those using guidelines alone. Interactive decision-support tools may be important to ensure appropriate implementation of HIV guidelines.

Key words: HIV, Guidelines, Decision-Analysis

Introduction

There are currently an estimated 1.1 million people with HIV (PWH) in the United States (US), with nearly 39,000 new HIV diagnoses annually [1-3]. Ongoing scientific advances have led to increased therapeutic options with improved health and life-expectancy of PWH [1, 4-6]. Despite a projected increased need for providers delivering HIV care, there is currently a shortage of HIV care providers in the US [7-9], with nearly 70% of programs funded for early intervention services through the Ryan White HIV/AIDS program facing challenges in recruiting providers [10]. Furthermore, numerous infectious disease fellowship positions in the U.S. remain unfilled, suggesting that HIV care may increasingly be delivered in primary care settings by providers not specifically trained in HIV [11]. In fact, recent studies have reported that more than half of HIV care is already provided by primary care clinicians [12-15]. However, both internal medicine and family medicine residency training programs report that less than half of trainees receive a formal HIV curriculum or feel comfortable providing HIV care [15-18].

Providing care for PWH requires up-to-date knowledge of HIV prevention, screening, diagnosis, and longitudinal treatment. Over 30 antiretroviral (ART) drugs in seven different classes are currently approved by the U.S. Food and Drug Administration (FDA), leading to a wide range of potential drug combinations [19, 20]. Choosing the optimal ART regimen involves complex decision-making taking into account regimen complexity, side-effects, comorbidities, concurrent medications, treatment history, drug resistance, and other clinical and viral characteristics [19, 20]. While current DHHS guidelines are comprehensive, they can be time consuming to navigate and challenging to use in real-time for trainees and non-HIV specialists.

We have previously developed and validated a free, online, interactive tool (HIV-ASSIST, https://www.hivassist.com) designed to augment interpretation of current HIV clinical practice guidelines (CPG) [21]. HIV-ASSIST couples delivery of educational material with real-time, personalized ART decision-support. Employing a multiple-criteria decision analysis (MCDA) framework, HIV-ASSIST evaluates the approximately 2000 possible 2, 3, and 4 drug ART combinations and generates a ranked list of ART recommendations specific to any particular patient encounter [22, 23]. Specifically, HIV-ASSIST algorithmically generates a 'weighted score' for every potential ART regimen by quantitatively evaluating individualized covariates (e.g., resistance mutations, concurrent medications, comorbidities, HIV viral load, treatment history, etc.) to generate a composite utility score that attempts to maximize likelihood of viral suppression while optimizing tolerability (e.g., minimizing drug interactions, pill burden, etc.). The tool's algorithms are rooted in published guidelines (e.g., International Antiviral Society-USA [IAS-USA] and Department of Health & Human Services [DHHS]) and refined based on existing literature and expert opinion of scientific principles [19, 21, 24].

Through a randomized controlled trial, we sought to explore the usability and effectiveness of current published guidelines (DHHS) versus HIV-ASSIST for ART regimen selection among trainees, as assessed by clinical vignettes involving HIV treatment-naïve and treatment-experienced patients. We hypothesized that adjunctive usage of HIV-ASSIST could improve application of current evidence-based recommendations compared to usage of DHHS guidelines alone.

Methods

We conducted a randomized study of trainees to evaluate appropriateness of ART selections for a diverse array of patient scenarios in early 2019. We compared participants with access to DHHS guidelines alone with participants receiving access to both DHHS guidelines and HIV-ASSIST. We constructed ten case-vignettes involving PWH, including scenarios with ART-naïve patients and ART-experienced patients, with and without ongoing viremia, resistance mutations, comorbidities, and concurrent medications (Supplemental Table 1). Recognizing heterogeneity in clinical practice, we surveyed a cohort of experienced HIV clinicians (Johns Hopkins Hospital, Brigham and Women's Hospital, University of California San Francisco, and Massachusetts General Hospital) to determine ART regimen reference standards for each case-vignette. Responses from seventeen clinicians (i.e., ART regimen selected by at least one experienced clinician) were used to define the list of possible "appropriate ART selections". We additionally considered ART selections for ART-naïve scenarios to be "appropriate" if consistent with DHHS guidelines for "Recommended Initial Regimens for Most People with HIV" available at the time of the study(study version in Supplemental Table 1).

We enrolled trainees (medical students and internal medicine (IM) residents at Johns Hopkins University) via electronic survey to provide ART selections for the same ten case-vignettes. All students had completed the school's curriculum on microbiology and infectious diseases, inclusive of lectures on ART pharmacology; IM residents complete clinical rotations on an inpatient HIV unit, during which they receive additional didactics. Trainees were randomized 1:1 to receive support in their decision-making either through electronic access to DHHS guidelines (DHHS-alone arm) or DHHS guidelines in conjunction with HIV-ASSIST (HIV-ASSIST arm). For each arm, the study participants were provided a short (~7 minute) video

tutorial on DHHS guidelines and/or HIV-ASSIST usage, including narrative description of how to navigate online DHHS guidelines to find recommendations on ART-naïve patients, ART-experienced patients, drug-drug interactions, comorbidities, and resistance mutations. All participants were also provided a link to the IAS-USA drug resistance mutation card [25]. Individuals randomized to the HIV-ASSIST arm received an additional video tutorial on how to access and interpret HIV-ASSIST results. Individuals were asked to certify that they did not use any additional resources to make ART selections. For both arms, a test question was provided that required specific usage of DHHS guidelines or HIV-ASSIST to verify that participants had access to and ability to use the provided resources. Participants were asked to provide quantitative feedback (Likert scale 1-5 for 'strongly disagree' to 'strongly agree') and free-response qualitative feedback on the usefulness of each resource. The study received ethics approval by the institutional review board at Johns Hopkins University, and all participants provided informed consent (NCT04080765; Supplemental Table 5, Supplemental Content-Protocol).

Statistical Analysis

The primary outcome was the proportion of 'appropriate' ART responses, comparing individuals randomized to DHHS-alone versus those receiving access to HIV-ASSIST. The median percent correct were compared using non-parametric tests. In secondary analysis, results were compared by level of training and by type of case-scenario (i.e. ART-naïve, ART-experienced-viremic, ART-experienced-suppressed). We conducted descriptive analysis of quantitative and qualitative feedback.

Results

One hundred eighteen medical students and internal medicine residents consented and completed the study (Supplemental Figure 1), of which 56 were randomized to DHHS-alone (48%) and 62 were randomized to HIV-ASSIST (52%). Participants had similar levels of training between study arms (% medical students, DHHS-alone vs. HIV-ASSIST: 80% vs 76%, p=0.82) (Table 1). In both arms, the majority of participants reported being involved in the care of less than 25 patients with HIV (DHHS-alone vs. HIV-ASSIST: 82% vs 73%, p=0.22).

Trainees randomized to HIV-ASSIST were significantly more likely to select appropriate ART regimens compared to those randomized to using DHHS-alone (DHHS-alone vs. HIV-ASSIST: median 40% [Q1, Q3: 30%, 50%] vs. 90% [80%, 100%], p<0.001) (Table 1, Supplemental Table 1). These results were consistent when evaluating medical students (DHHS-alone vs. HIV-ASSIST: median 40% [30%, 50%] vs. 90% [80%, 100%], p<0.001) as well as medical residents (40% [40%, 50%] vs. 90% [80%, 100%], p<0.001). There was no impact of self-reported prior experience caring for PWH on the effect size (Figure 1).

The impact of HIV-ASSIST was seen among all categories of case-scenarios (Figure 1). Among four case-scenarios describing ART-naïve patients (with and without comorbidities or concurrent medications), the median percent of appropriate ART selections were 75% [75%, 100%] of cases in the DHHS-alone arm compared to 100% [100%, 100%] of cases in the HIV-ASSIST arm (p<0.001). Among three case-scenarios involving ART-experienced, viremic patients, the median appropriate ART selections were 0% [0%, 33%] among participants in the DHHS-alone arm compared to 100% [67%, 100%] in the HIV-ASSIST arm (p<0.001). Among three case-scenarios involving ART-experienced, virologically suppressed patients, the median appropriate ART selections were 0% [0%, 33%] among participants in the DHHS-alone arm

compared to 67% [67%, 100%] in the HIV-ASSIST arm (p<0.001) (Table 1, Supplemental Table 1). Participants randomized to the HIV-ASSIST were able to achieve higher rates of appropriate ART selection despite using significantly less time. The median time to make ART selections in this survey was 1.7 times longer among trainees in the DHHS-alone arm compared to HIV-ASSIST arm (36 vs. 21 minutes, p<0.001).

We collected quantitative feedback on the usefulness of DHHS guidance for making ART selections (Figure 2, Supplemental Table 2). Among participants using DHHS-alone, 89% of participants 'agreed' or 'strongly agreed' that DHHS guidelines were useful in guiding ART selections for ART-naïve patients. In comparison, 98% of participants 'agreed' or 'strongly agreed' that HIV-ASSIST was useful for ART-naïve patients (Figure 2). For cases involving ART-experienced patients, significantly fewer participants considered the DHHS guidelines to be useful compared to HIV-ASSIST (DHHS-alone vs. HIV-ASSIST: 53% vs. 85%). The differences between participant views of the DHHS guidelines and HIV-ASSIST was even more pronounced for complex cases. Thirty-two percent of participants in the DHHS-alone arm 'disagreed' or 'strongly disagreed' that existing DHHS guidelines were useful in making ART selections for ART-experienced-viremic patients, 27% 'disagreed' that DHHS guidelines were useful for patients with comorbidities, 35% for patients with comedications, and 46% for patients with resistance mutations. By contrast, all participants reported that HIV-ASSIST was useful for ART-experienced-viremic patients. Less than 4% 'disagreed' that HIV-ASSIST was useful for making ART selections in patients with comorbidities, comedications, or resistance mutations (Figure 2, Supplemental Table 2). A descriptive summary of representative free-text comments about DHHS guidelines and HIV-ASSIST can be found in Supplemental Tables 3 and 4, respectively, grouped by common themes. Among 56 individuals providing free-response

feedback on DHHS guidelines, 61% made comments related to difficulty in navigating or finding relevant information within the DHHS guidelines; 38% reported difficulty interpreting or applying the guidelines, and only 14% commented on the usefulness or helpfulness of the guidelines. By contrast, among 61 individuals providing feedback about HIV-ASSIST, 82% made specific comments about the tool being useful or user-friendly.

Discussion/Conclusions

Clinical practice guidelines (CPG) are a core component of medical education and are a key means by which scientific advances are translated into clinical practice. HIV is a representative disease with treatment guidelines that provide evidenced-based recommendations for ART selection [19, 24, 26]. Our results suggest, however, that an interactive, individualized, approach to dissemination of HIV guideline content and treatment principles – HIV-ASSIST (www.hivassist.com) – outperforms the use of national guidelines alone for ART selection. Trainees using HIV-ASSIST with guidelines had significantly higher proportions of appropriate ART selections compared to those using DHHS guidelines alone for a wide range of clinical case-vignettes, consistent across training levels and case complexity. This study has important implications for HIV medicine and for development of CPGs more broadly.

CPGs appropriately place emphasis on developing recommendations based on scientific evidence, which most frequently address well-studied populations. In practice, however, medical decision-making is a nuanced process in which providers weigh numerous considerations that may not fit into neatly studied populations or categories. The DHHS guidelines, as an example, offer a large number of tables to assist clinicians in modifying their ART selections when faced with important comorbidities or comedications. Such approaches offer univariate considerations

(e.g., which ART to avoid with a single comorbidity, such as cardiovascular disease), but may not help clinicians evaluate multiple modifying factors concomitantly. In this context, CPGs may not be the most effective means of helping clinicians synthesize and evaluate multiple considerations simultaneously. We found that when presented with such case-vignettes, most trainees were unable to effectively apply guidelines for ART selection. CPGs also are unable to offer a full framework for decision-making in complex cases, such as those with extensive ART resistance. Current DHHS guidelines explicitly state expert assistance is required in such situations. In contrast, our results suggest usage of HIV-ASSIST effectively supported ART selections for both ART-naïve and ART-experienced scenarios.

Our results support prior findings that indicate that degree of complexity is a barrier to CPG implementation [27]. Ambiguity in recommendations and static, non-interactive guideline dissemination (e.g., publication in a journal) may further limit the effectiveness of CPGs. Our qualitative feedback suggests trainees find this type of guideline presentation to be unwieldy and difficult to navigate, and instead favor flow-diagrams or interactive content. In that context, MCDA may represent a novel approach to assisting clinicians to 'weigh' multiple modifying attributes and outcomes of interest (e.g., viral suppression, tolerability, side-effects, impact on comorbidities, etc.) simultaneously. Our results show that an interactive approach to guideline delivery through HIV-ASSIST was more effective at allowing trainees to apply HIV treatment principles and recommendations and may fill a needed niche for trainees and providers with less experience in HIV medicine.

Our results have implications in facilitating improved uptake of both HIV and other infectious disease CPGs. Others have previously developed tools to address the gap between knowledge and guideline implementation [28]. Limited prior data suggests that adjunctive

measures (checklists, algorithms, etc.) may enhance guideline compliance [29-31]. Educational workshops, paper-based materials, reminders, and order forms have also been studied and shown to be beneficial [32]. A recent study of primary care providers suggests that using more than one resource to implement best practices (e.g., for breast cancer screening) is common [33]. In this context, HIV-ASSIST is a novel approach to clinical education and dissemination of best practice recommendations. This freely available tool couples educational and guideline content with decision-support and provides annotated rationale (with links to supporting evidence) for each step within the decision-making algorithm. In contrast to time-limited educational workshops, online curricula, and other traditional forms of continuing medical education, this approach allows delivery of educational content tailored and relevant to specific patient scenarios, while simultaneously advancing clinical care.

While implementation of CPGs can improve the quality of patient care [34], adherence to guidelines are low, which can lead to poor patient outcomes [35]. The Cabana model identified three factors for why physicians do not follow practice guidelines: knowledge, attitudes, and behavioral skills [36]. A study used this model to identify physician barriers to routine HIV testing, which identified knowledge barriers (lack of awareness of recommendation), attitude barriers (lack of agreement with guidelines), and behavioral barriers (patients, guideline factors, environmental factors) [37]. To help address the knowledge barrier, we show that using a MCDA framework allowed trainees without substantial HIV training to make ART selections that are concordant with a panel of experts at four academic institutions. Outside of the Cabana model, several studies have mentioned limited time and resources as barriers to implementing guidelines into practice [38, 39]. HIV-ASSIST and similar interactive tools have the potential to reduce

time limitations as a barrier to CPG implementation. The impact of such tools in real-world clinical care settings warrants further investigation.

This study has several important limitations. HIV care is not limited to ART selection and entails comprehensive management of HIV and comorbidities, along with delivery of social support and preventive care; cultural competency, decreasing stigma, and understanding of all aspects of LGBTQ care and unique issues that arise from comorbidities are all critical skillsets for an effective HIV provider. Our formative research also focused on trainees to avoid biases and confounding based on background knowledge, pre-existing experience, and established practice patterns. Our results may not be generalizable to other learner groups or more experienced clinical providers, such as ID clinicians. Future directions would include evaluation among primary care providers and others delivering HIV care, including physician extenders. For complex patients currently suppressed with underlying resistance (Supplemental Table 1, Case 8-10), inexperienced users only selected an appropriate ART regimen a median of 67% of the time, even with HIV-ASSIST; in these cases, some participants made selections not expected or recommended by HIV-ASSIST. A newly added interactive wizard feature in HIV-ASSIST that was not available to study participants may address this issue. Participant responses during an electronic survey and clinical vignettes may not be reflective of how they would engage with guidelines or HIV-ASSIST during real patient encounters. Nonetheless, we used a randomized design in which the degree of participant study-engagement is likely to be similar between study arms. Our study design also could not assess the degree to which participants read DHHS guidelines, or the intensity of HIV-ASSIST usage, or if the participants made usage of other materials. While we focused on the proximal outcome of ART

selection, more research is needed to examine the effectiveness of current guidelines and or HIV-ASSIST in improving important patient outcomes such as virologic suppression and quality of life.

These weaknesses are balanced by important strengths of this study. While CPGs are common across the medical field, there is limited data on their effectiveness. We show in a randomized study that, among trainees, an interactive decision-support tool was more effective in supporting clinical decision-making than existing guidelines. Relatively inexperienced trainees with access to HIV-ASSIST made appropriate ART selections (i.e., concordant with experienced HIV providers) in a median of 90% of case-scenarios. Our results provide additional insights into the perceived gaps and barriers to effective delivery of evidence-based practice recommendations for HIV care. These results have significant implications with the projected HIV provider shortage. As HIV medicine is increasingly delivered in primary care settings, we show that HIV-ASSIST may be an important supplement to existing guidelines to ensure that the gains of scientific discovery are translated to the bedside. In this context, however, it is important to recognize that HIV-ASSIST is an adjunctive educational tool to supplement current national guidelines and is not a replacement for clinical judgement.

In conclusion, the shortage of HIV providers threatens the gains made over the past decade for PWH. With an increasing and aging population and prolonged time of ART usage, ART selection must increasingly consider comorbidities, concurrent medications, resistance mutations, and other factors. New tools are needed to ensure that evidence-based recommendations can be effectively implemented. Our results show that HIV-ASSIST, an online, interactive decision-support and educational tool is more effective than current guidelines alone at assisting trainees in ART selection for a variety of case-scenarios. These findings highlight the role that HIV-ASSIST may have in supporting trainee education and the clinical management of PWH. In addition, our results suggest that more research is needed into strategies

for overcoming barriers to CPG interpretation and application across the medical fields. Interactive decision-support tools that are tailored to specific patient conditions may improve application of practice guidelines.

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Figure 1: Appropriate ART selection comparing study arms

Figure Legend: Median (error bars Q1,Q3) percentage of appropriate ART selection for DHHS (blue) and HIV-ASSIST (orange) study arms are shown, by level of training and type of case-scenario. The median for ART-experienced cases was 0%.

Figure 2: Trainee feedback on the usefulness of DHHS guidelines or HIV-ASSIST

Figure legend: Participants were asked to assess whether DHHS guidelines or HIV-ASSIST "was useful for [case-scenario]"; case-scenarios are labeled at the top of stacked bar graphs.

Table 1: Participant characteristics and responses to ten survey-based patient scenarios

		DHHS-alone arm	HIV-ASSIST arm	P
N		56	62	
Training	MS1	14 (25%)	12 (19%)	0.816
	MS2	6 (11%)	11 (17%)	
	MS3	10 (18%)	7 (11%)	
	MS4	15 (27%)	17 (27%)	
	PGY1	4 (7%)	7 (11%)	
	PGY2	4(7%)	4 (7%)	
	PGY3	3 (5%)	4 (6%)	
Self-reported # of patients with HIV	<25	46 (82%)	45 (73%)	0.217
	>25	10 (18%)	17 (27%)	
Minutes to complete ART selections (median, [Q1, Q3])		36 minutes [21, 51]	21 minutes [16, 29]	<0.001
Percent 'appropriate' ART: median [Q1, Q3]	Overall	40% [30%, 50%]	90% [80%, 100%]	<0.001
	MS	40% [30%, 50%]	90% [80%, 100%]	<0.001
	Residents	40% [40%, 50%]	90% [80%, 100%]	<0.001
Percent 'appropriate' ART, by case-scenario: median [Q1, Q3]	ART naïve	75% [75%, 100%]	100 [100%, 100%]	<0.001
	ART experienced—current viremia	0% [0%, 33%]	100 [67%, 100%]	<0.001
	ART experienced—current suppression	0% [0%, 33%]	67 [67%, 100%]	<0.001

Figure 1

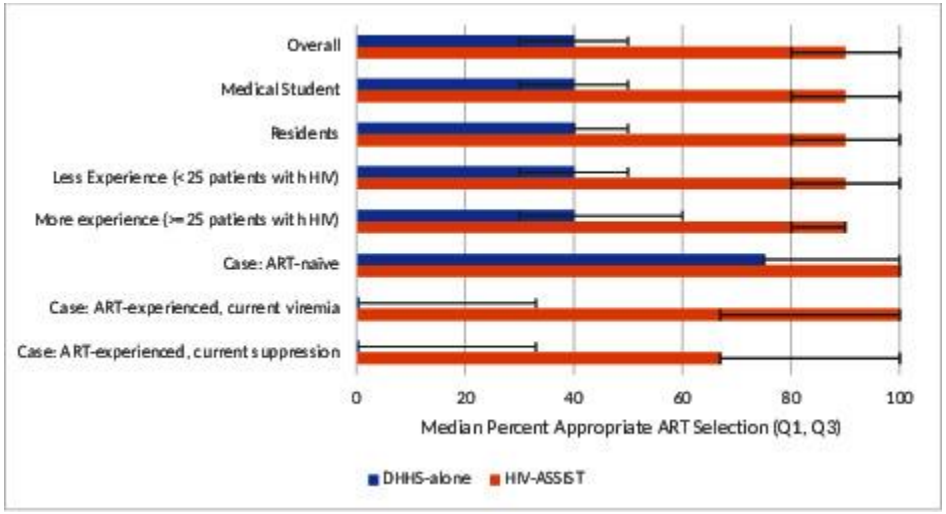

Figure 2